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Research and Development in the Synthesis of Cyanoacrylates

A thesis submitted to the University of Dublin for degree of
Doctor in Philosophy

by

Stefano Gherardi

Trinity College Dublin April, 2010

DECLARATION

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Abstract

This dissertation is aimed at developing a new synthetic chemistry suitable for the selective production of highly reactive, high yield and purified electron deficient enes in bulk quantities.

The electron deficient enes in particular belong to the family of 2-cyanoacrylates (CAs) and some related molecules such as 2-cyanopentadienoates and methylidene malonates. CAs represent a special class of highly reactive acrylates capable of instant polymerisation to high polymers at room temperature.

A new synthetic methodology is sought because conventional methods have many limitations. This situation is tolerated in large part, because of the difficulties associated with developing a superior synthetic method suited to mass production, which permits introduction of additional chemical functionality into different esters that will permit augmentation of the suboptimal properties of current poly-cyanoacrylates. Thus, the major challenge of the present work is to develop a new method capable of broad applicability, selectivity and continuous delivery of kilos of pure material in high yield.

This thesis shows the development of a new synthetic approach for the synthesis of CAs. This promising method based on a Mannich reaction was able to produce ethyl cyanoacrylate (EtCA) monomer in good yield. The reaction was later improved and transferred to a task specific ionic liquid (TSIL), thus a new approach was defined ("TSIL Approach") and the reactivity and thermal stability of a new class of inexpensive ionic liquid was studied. This new approach was applied to the synthesis of known CAs, then the focus was centred to the synthesis of thermal sensitive CAs bearing specific functional groups. The scale-up of the reaction was realized by means of a customized short path evaporator (SPE).

In conclusion an original, efficient and inexpensive new method was demonstrated to challenge the Knöevenagel process as the only convenient approach for the preparation of CAs monomers.

Summary

This PhD thesis is about the research and development in the synthesis of CA. The time-line of the project can be divided in five main stages.

1st Bibliographic search; a careful literature search was done in order to explore working methodology for the synthesis of CAs and related high reactive electron deficient enes. This "preliminary work" was important in order to understand the main difficulties associated to these molecules and to learn the strategies used to solve/circumvents problems.

2nd Preparation of EtCA by Knöevenagel process; the experimental work started with the synthesis of a simple monomer by the most common Knöevenagel process. This was an easy way to have a proof of what is reported in the open literature. Moreover the obtained product was purify by distillation and the problems about stabilization towards nucleophilic polymerization in the gas phase were faced.

3rd Alternative crackles synthesis of monomeric EtCA; different approaches were attempted and a new method based on a Mannich reaction was identified ("Imine approach"). This approach was studied in depth but unfortunately the reaction scale-up did not go ahead because of major industrial limitation.

4th The "TSIL approach"; the new chemistry based on a Mannich reaction was applied to a task specific ionic liquid (TSIL). The reaction worked well thus it was thoroughly studied and optimized. This new method ("TSIL approach") showed great potentiality in the synthesis of known CAs in high yield and kilogram scale quantity. Moreover a commercially available short path evaporator (SPE) was customized in order to produce CAs in an efficient and continuous way.

5th Synthesis of functional CAs; the synthesis of thermally sensitive molecules was faced by means of the TSIL approach, in particular great efforts were concentrated in the synthesis of monomers bearing a second functionality on the ester moiety. Last an entire study was dedicated to the identification and rationalization of side-product of reaction.

Acknowledgements

I would like to overstate my gratitude to my University Ph.D. supervisor, Prof. David Grayson. With his deep knowledge in chemistry, ability and enthusiasm, gave to me great critical supports in understanding things.

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Abbreviations

AA: Acetoxyacrylate

AACN: Acetoxyacrylonitrile

AcOH: Acetic acid

AOECA: Aryloxy ethyl 2-cyanoacrylate

BHT: 2,6-di-tert-Butyl-4-methyl phenol

bmim: 1-Butyl-3-methylimidazolium

BSA: Benzenesulfonic acid

CA: Cyanoacrylate

CAA: Cyanoacrylic acid

CAcet: Cyanoacetate

CVC: Cyanovinyl carbonate

DBHT: 4,4'-Methylene bis(2,6-di-tert-butyl phenol)

DEGBE: Diethylene glycol dibutyl ether

DMF: Dimethylformamide

DMSO: Dimethylsulfoxide

EDDA: Ethylendiaminediacetate

EGBCA: Ethylene Glycol Bis (2-Cyanoacrylate)

EtCA: Ethyl cyanoacrylate

EtCAcet: Ethyl cyanoacetate

EWG: Electron withdrawing Group

G: Gibbs Energy

H_0: Enthalpy

HEMA: Hydroxyl ethyl methacrylate

IBC: Isobutyl 2-cyanoacrylate

IL: Ionic Liquid

KSF: Montmorillonite type KSF

LAS: Dodecylbenzene sulfonic acid

MCA: Methylcyanoacrylate

MCPBA: 3-Chloroperbenzoic acid

MM: Methylene malonate

MPA: Metaphosphoric acid

MSA: Methanesulfonic acid

NaX: Zeolite type NaX

N: Normality

NSA: 2-Naphthalenesulfonic acid

ODBCA: Octanediol bis 2-cyanoacrylate

OSA: Octyl sulfonic acid

P(SiMA): Poly(trimehtylsilylmethylmethacrylate

PEG: Polyethylene glycol

PMMA: Polylethylmethacrylate

PPA: Polyphosphoric acid

PTEF: Polytetrafluoroethylene

PTSA: Paratoluen sulfonic acid

PTZ: Phenothiazine

S: Entropy

SAS: 2-pentadecyl sulfonic acid (secondary alkyl sulfonic acid)

SPE: Short path evaporator

Tc: Critical Temperature

TEASY: Triarylphosphate

TEGME: Tetraetylene glycol dimethyl ether

TFA: Trifluoroacetic acid

Tg: Glass Transition Temperature

TMBSA: Tri-methylammonium-butane sulfonate

TOA: Tert-octyl amine

TSIL: Task Specific Ionic Liquid

VdCN: Vinylidene dicyanide

VOC: Volatile organic compounds

Table of Contents

INDEX of Tables

INDEX of Figures

Chapter 1

1 INTRODUCTION

1.1 Cyanoacrylate

1.1.1 History and applications

Cyanoacrylates are very important molecules for applications in many fields. They are widely used as instantaneous adhesive in various industrial fields, in the medical fields, in the leisure fields and, besides, in the household. Cyanoacrylic ester polymers provide excellent adhesive bonds between a wide variety of substrates. These bonds are formed rapidly at room temperature without catalyst's addiction. Other feature is that Cyanoacrylic esters (CAs) can efficiently cement together both living tissues (their use in medicine is approved) or organic materials (plastics, rubber, wood) and inorganic materials (stones, metals, glass, porcelain, ceramics) in various combinations. Apparently only teflon and polyethylene provide exceptions; they can be cemented together only after treatment of their surfaces with special activator (amine, phosphines, etc...).[1]

This unique behaviour was discovered in 1951[2] at the Tennessee Eastman Company research laboratories by H. W. Coover hen the prism of an Abbe refractometer were inadvertently bonded together. This discovery led to the introduction in 1958, of "Eastman 910 adhesive", the first commercial 2-cyanoacrylic ester adhesive. This and a similar adhesive composition (marketed under such brands names as Loctite, Aron Alpha, and Permabond) have subsequently found utility in a broad spectrum of adhesive applications because of their unique great performances.

However, in bonding rubbers, leathers, papers, cloths, fibres and the like, they have had a fault that the cured product (polymer) most common ethyl 2-cyanoacrylate is very hard, and therefore, the bonded part becomes hard and lacks flexibility. Thus, in order to make the cured product flexible, the addition of fine rubber particles, the addition of a plasticizer or a thickening agent, or the like have been proposed. However, a bonded part with improved flexibility is not always satisfactory by these methods, furthermore the additives must be of a very pure and non nucleophilic nature. An alternative way for increasing the flexibility is to modify the ester group.

Moreover, other important property improvements and new functions, such as heat resistance, water resistance and low refractive index, can be obtained by changing the

ester moiety. Indeed unsaturated groups such as allyl or propargyl chains, as well as silicon containing chains, increase the heat resistance. Flexibility and heat resistance are obtained when allyloxy alkyl group are present as ester moieties. Water resistance is increased using bis 2-cyanoacrylate too.
The commercial cyanoacrylic glues features can be summarized as following.

Advantages:

- They are single component easy to use
- They bond rapidly at room temperature without the addition of a catalyst
- They bond very different materials
- They are colorless and transparent
- They give very strong and resistant bond
- They are 100% reactive (do not contain solvents)

Disadvantages:

- They produce bonds with weak hydrolytic and thermal resistance
- Brittleness, they have a lack of toughness, than the commercial produt need of the additions of toughness toughening agents
- Not capable of gap filling, they polymerize in contact with the surface (max 10 μm gap), only viscous formulation bonds up to 40 μm gap
- They are very sensible to the surface preparation, it has to be very clean
- Very quick polymerization on human skin, very careful handling is necessary

In order to improve the cyanoacrylate performance and reduce their limitations it is necessary to discover and optimize a new process capable to produce more complex cyanaocrylates.

1.1.2 Basic properties and polymerisation:

2-Cyanoacrylates (CAs) are electron deficient reactive monomers with the general structure shown in Figure 1.1.

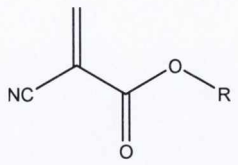


Figure 1.1 General structure of a simple 2-Cyanoacrylate (R typically small alkyl)

The monomers are highly polarised due to the presence of two electron withdrawing groups (EWGs) on the same carbon, and as a consequence are highly susceptible to attack by nucleophilic species at the beta position. Since absorbed monolayers of water are ubiquitous on almost every surface (polyolefins such as polypropylene and polytetrafluoroethylene (PTFE) are typical exceptions), CAs will rapidly polymerise by hydroxyl initiation when a bulk droplet is distorted through the action of spreading the low viscosity monomeric liquid into a thin film confined between two surfaces, each comprising billions of initiation sites. Cyanoacrylic ester polymers provide excellent adhesive bonds between a large diversity of substrates. Than at room temperature these bonds are formed rapidly without the addition of any catalyst. Some typical properties of common CA monomers are given in Table 1.

Table 1.1 Properties of some common Cyanoacrylate monomers[3]

	Methyl	Ethyl	Isopropyl	Allyl	n-Butyl	2-Methoxyethyl
Bpt, °C [1]	85-86	92-93	109-112	120-122	118-120	136-138
at kPa	1.5	1.3	1.6	1.6	1.1	0.1
Viscosity at 25°C (mPa.s)	2	2	2	2	2	3
Density (g/cm^3)	1.10	1.05	1.01	1.05	0.98	1.06
Refractive Index, n_{20}^D	1.44	1.43	1.43	1.46	1.43	1.43
Flash point, °C	83	83	-	82	85	-
Surface Tension,30°C, mN/m [2]	44.5	38.8	34.5	39.5	34.2	41.5
Lap-shear tensile strength[a]	22.0	17.2	20.9	21.5	15.7	18.6

[a] ASTM D1002, steel substrates

Cyanoacrylate monomers also undergo rapid polymerisation in the presence of catalytic amounts of bases like tertiary amines and phosphines. This reaction is inhibited by strong acid and is thus anionic in nature. Base catalysed polymerisation of cyanoacrylates in solution has been investigated extensively using calorimetric studies[4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15]. The results obtained show that in the absence of strong acid the polymerisation has no intrinsic termination reaction. With so-called fast initiators (hydroxyl ions or phosphines), nearly ideal living polymerisation conditions exist and molecular weights approach theoretical values from the monomer/initiator ratio employed[5]. In such cases a classical anionic polymerisation mechanism, such as shown in Figure 1.2, has been postulated. With slow initiators (covalent bases), the initiation step involves one or more reversible monomer addition reactions before the propagation sequence becomes estabilished and polymerisation proceeds via a zwitterionic mechanism[9,10]. For certain initiators a stable zwitterionic initiating species has been isolated [16].

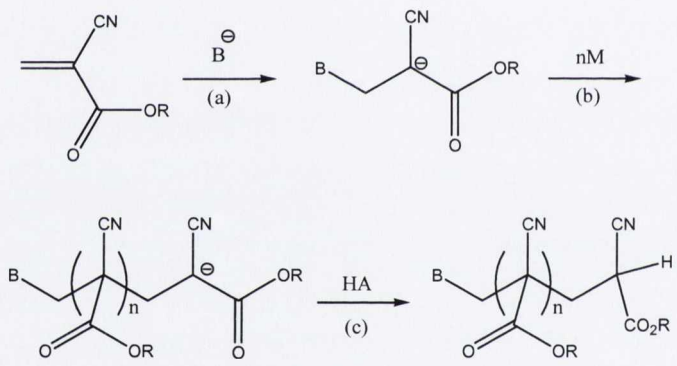


Figure 1.2 Base (B) catalysed anionic polymerisation of cyanoacrylate monomer (M): (a) initiation, (b) propagation, and (c) termination by acid (HA)

Typical thermodynamic parameters for the homopolymerisation of selected alkyl CAs are given in Table 1.2[17,18,19,20]. The data shows that bulk polymerisation of various monomers is thermodynamically favourable from -270 to 160 °C at standard pressure. Ceiling temperatures, T_c, for polymerisation were also derived from thermodynamic data and represent the upper temperature limit for polymerisation. Glass transition temperatures, T_g, were derived from plots of heat capacity with temperature and appear to decrease as the size of the alkyl ester group increases

Table 1.2 Thermodynamic parameters for some Cyanoacrylate Polymerisations at 25 °C and 101.3 kPa[15, 17, 18, 19]

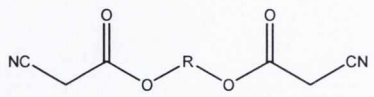
	Ethyl	Allyl	n-Decyl
$-\Delta H_0$, kJ/mol	48	64	69
$-\Delta S_0$, J/mol.K	88	85	141
$-\Delta G_0$, kJ/mol	21	39	39
T_c, °C	267	307	217
T_g, °C	149	122	-78

Several reviews on the chemistry and applications of cyanoacrylates have appeared in the literature the most recent of which in 2007[21, 22, 23, 24, 25].

1.1.3 Specific CA esters for particular application (medical and dental fields)

In the medical and dental field the use of cyanoacrylate has been widely investigated. [26, 27] These applications are quite original and unique, that a brief overview of the field is presented. Early studies showed that polymerization of a thin coating of methyl 2-cyanoacrylate on the occlusal surfaces of teeth resulted in an not efficient sealing of the pits, afforded very little reduction in the incidence of dental caries and occlusal caries. Adhesive bond failure was also found to be the case in the bonding of orthodontic attachments with the methyl, ethyl, and buthyl 2-cyanoacrylates, where the initial good dry bond strengths deteriorated rapidly when exposed to water (1 N saline, 24 hours). As a result of the difficult handing characteristics of the cyanoacrylates (uncontrolled polymerization rates) and sensitivity to moisture, their use in dental applications was essentially precluded. However, experiments showed that when cyanoacrylates formulations were crosslinked the mechanical strength properties increased; the crosslinked cyanoacrylate would impart greater resistance to hydrolytic degradation, higher adhesive bonds to tooth enamel, and improved mechanical properties. The synthesis of a series of new difunctional crosslinkable bis(2-cyanoacrylate) monomers was developed. For e.g. Buck's[27,28] work deals with synthesis of ethylene glycol bis (2-cyanoacrylate), 1,3-propanediol bis (2-cyanoacrylate), 1,4-butanediol bis (2-cyanoacrylate), trans-2-butene-l.4diol bis (2-cyanoacrylate), 1,6-hexanediol bis (2-cyanoacrylate), 2,5-hexanediol bis (2-cyanoacrylate), 1,8-octanediol bis (2-cyanoacrylate), 1,9-nonanediol bis (2-cyanoacrylate), 1,10-decanediol bis (2-cyanoacrylate), 1,12-dodecanediol bis (2-cyanoacrylate), 1,3-bis (hydroxymethyl)

tetramethyldisiloxane bis (2-cyanoacrylate). Unfortunately a main problem of those bis cyanoacrylate is their low solubility in mixture with other "common" monomers, an example of solubility in isobutyl 2-cyanoacrylate (IBC) is reported in Table 1.3.



Bis-CA

Table 1.3. Maximum Solubility of Bis(2-Cyanoacrylate) Monomers in isobutyl 2-Cyanoacrylate (IBC)

Bis-CAs , R =	**Max sol. in IBC (approx.), wt. %**
CH_2CH_2	5
$(CH_2)_3$	9
$(CH_2)_4$	15
$CH_2CH{=}CHCH_2$(*trans*-)	7
$(CH_2)_6$	34
$CH(CH_3)CH_2CH_2(CH_3)OH$	25
$(CH_2)_8$	17
$(CH_2)_9$	32
$(CH_2)_{10}$	7
$(CH_2)_{12}$	6
$CH_2Si(CH_3)_2OSi(CH_3)_2CH_2$	∞

Copolymerization of cyanoacrylates such as IBC/bis(2-cyanoacrylate) blends afforded crosslinked polymers which were not soluble in acetone. Clinical studies[29] and mechanical testing showed that the crosslinked formulations bonded more strongly to teeth and other surfaces and were also more resistant to adhesive bond failure on prolonged contact with moisture than were the noncrosslinked alkyl-2-cyanoacrylate adhesives[30]. As little as 1 wt % bis(2-cyanoacrylate) comonomer provided significant improvements. By utilizing blends of the bis(2-cyanoacrylates) with the alkyl-2-cyanoacrylates, a number of the deficiencies (notably, water sensitivity and erratic polymerization behaviour) of the cyanoacrylates reported in the dental literature[31, 32] have been minimized. After immersion in water at 100°F for 7 days, the crosslinked adhesives showed a higher residual bond strength than those based on IBC and methylcyanoacrylate (MCA) alone (Table 1.4)

Table 1.4 Effect of Aging Time at 37 °C in Water on Breaking Strength

Monomer: isobutyl-2-cyanoacrylate/Ethylene Glycol Bis(2-Cyanoacrylate)(EGBCA) **Filler: Alumina, 72% w**		
Isobutyl-2-Cyanoacrylate/	**Breaking Strength, psi**	
EGBCA (w/w) Monomer Mix	**37 °C/24hrs**	**37 °C/7 days**
100% IBC (Control)	6350	6870
99/1	6520	8140
98/2	6380	7790
96/4	7360	8700
94/6	7600	9300
90/10	8160	-
80/20	8380	-

Furthermore, it can be seen from Table 1.5 that this increase in breaking strength is not limited to polymerized co-monomer blends of bis-CAs and isobutyl-2-cyanoacrylate, but extends to esters of 2-cyanoacrylic acid generally.

Table 1.5 Effect of the Alkyl Group in Alkyl 2-Cyanoacrylate Monomers on Breaking Strength of Crosslinked Alumina Filled Composites

Crosslinking monomer: Ethylene Glycol Bis (2-Cyanoacrylate) (EGBCA) **Filler: 72% w Alumina**		
	Breaking Strengths, psi	
Alkyl Group of 2-Cyanoacrylate Monomer EGBCA	**Alkyl Cyanoacrylate alone**	**Cyanoacrylate + 3.6 mole %**
Ethyl	7290	6060
Isobutyl	5470	7180
n-Amyl	2160	3070
i-Amyl	4590	5060
n-Hexyl	980	1450
n-Heptyl	390	670

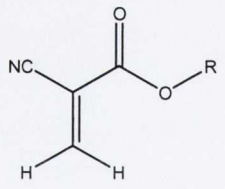
In the past bis-cyanoacrylates have been mentioned in a consistent number of scientific publications and patent applications but they have never been commercialized for dental application or any application, the reason is because up to now no one industrial synthetic method is able to produce those interesting molecule at a reasonable cost in large scale production. Very interesting and recent discovery it has been the use of a new glass-ionomer/cyanoacrylate dental cement[33].

The glass-ionomers are materials widely used in dental field applications[34], they are two component products; a powder which is an acid-decomposable alumino silicate glass and an aqueous solution of a poly acid. The main advantage of a glass-ionomer is to permanently adhering on tooth surfaces, instead others composite resins such as methacrylic polymers and dental amalgams can only be attached to tooth by mechanical mean (they do not have adherent abilities). However, the glass-ionomers has

disadvantages, they are weaker than poly-methacrylate resins and they loose strength quicker. To overcome these disadvantages a new class of resin-modified glass-ionomer cement[35] has been proposed. A blend of glass-ionomer and hydroxyl ethyl methacrylate (HEMA) were mixed together, a better performance material was obtained, however the use of a second component capable to adhere to tooth it was highly desirable. Than cyanoacrylates monomers were tested and a new superior class of cyanoacrylate resin/glass-ionomer cement hybrid has been generated. It has showed to be better than the classic glass-ionomer material in that it sets more rapidly to surfaces, it produces higher bond strength and higher resistance to desiccation. The cyanoacrylate resin/glass-ionomer showed to be superior to conventional resin-modified cement based on methacrylate polymers, because the cyanoacrylate polymers are adhesive, whereas methacrylate polymers are not. This new material showed higher bond strength as well as very good hydrolytic resistance.

1.1.4 Properties of different "special" Cyanoacrylates

Many attempts have been made to improve the properties of cyanoacrylates or to add new functions to them by changing this ester substituent (R) to various substituents or functional groups other than the alkyl groups. An overview of these efforts is shown below.



CAs

Table 1.6 Properties of Cyanoacrylates with new functions.

R (Groups such as)	Improved properties
CH_2=$CHCH_2$- and CH≡CCH_2-	Heat resistance
CH_2=$CHCH_2$-O-CH_2CH_2-	Heat resistance, flexibility
CF_3CH_2-	Low refractive index
CH_2=$C(CN)CO_2$-R'-	Water resistance
Me_2SiCH_2-	Heat resistance

1.1.4.1 Cyanoacrylates with unsaturated groups[36,37]

Cyanoacrylates are generally monofunctional monomers, and so the polycyanoacrylates that are produced by their polymerization are linear chain type thermoplastic polymers with correspondingly low heat resistance. Therefore, it can be expected that crosslinking the linear chain type polymers will result in higher heat resistance. This assumption led to studies on the synthesis of cyanoacrylates with unsaturated groups and evaluation of the heat resistances of the resultant substances. Heating a polymer after the cyanoacrylate has been cured by anion polymerization will induce thermal radical polymerization among the remaining unsaturated groups to produce a crosslinked polymer.

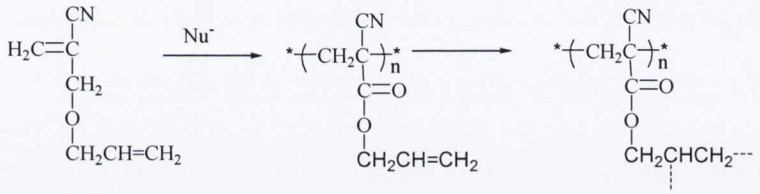


Figure 1.3 Polymerization with Crosslinked Polymer

Table 1.7 shows various cyanoacrylates with unsaturated polymers and the associated heat resistance values.

Table 1.7 Cyanoacrylates with unsatured polymers and adhesion heat resistance[36,37]

	Shearing adesive strength, N/cm^2	
$H_2C=C(CN)COOR$	**Room temperature**	**After heating at 150 °C for 24 hours**
$CH_2=CHCH_2$-	1240	500
$CH\equiv CCH_2$-	1670	400
$CH\equiv(CH_3)CH$-	1140	90
R $CH\equiv C(CH_2CH_2CH_3)CH$-	330	50
CH_3-	1800	0
CH_3CH_2-	1560	0
$CH_3CH_2CH_2$-	930	0

As seen from the above, the introduction of unsaturated groups improved heat resistance. Furthermore, a decrease in adhesive strength and heat resistance was observed with an increase in the number of carbon atoms in a substituent (R). Moreover

the changes in Tg with varied aging temperatures and times indicated that the heat resistance was improved.

1.1.4.2 Aryloxy ethyl 2-cyanoacrylates[38]

It is generally known that flexibility and impact strength may be improved by using the alkoxy ethyl group (R'–O–CH_2CH_2–) for the ester substituent (R). As described in the previous section, heat resistance can be improved by the introduction of unsaturated groups. Therefore, to obtain the combined effects of improved heat resistance and higher impact resistance, aryloxy ethyl 2-cyanoacrylate (AOECA, R: CH_2=$CHCH_2$–O–CH_2CH_2–) was investigated[38].

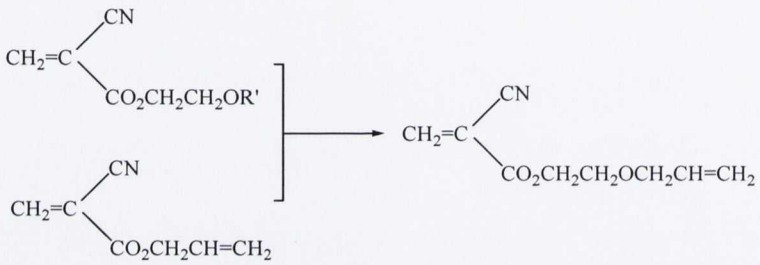
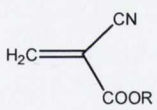


Figure 1.4 Trans-esterification of ester groups in acrylate monomers

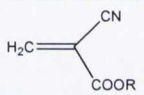
Table 1.8 Changes in impact strength by thermal treatment of AOECA

		**Impact strength after thermal treatment KJ/m^2 {kgf•cm/cm^2}**		
		20 °C, 24 hours	100 °C, 24 hours	150 °C, 5 hours
R	(I) CH_3CH_2-	3.8 {3.9}	2.2 {2.2}	1.2 {1.2}
	CH_2=$CHCH_2$-	5.9 {6.0}	4.1 {4.2}	1.6 {1.6}
	(II) CH_2=$CHCH_2$-O-CH_2CH_2-	5.5 {5.6}	3.0 {3.1}	2.4 {2.4}
	9:1 Mixture of (I)/(II)	7.6 {7.7}	3.6 {3.7}	2.7 {2.8}

1.1.4.3 Fluoroalkyl 2-cyanoacrylates[39]

A sheathed fiber optic cable has a core with refractive index n_0, sheathed by a material with a refractive index of n_1. Since light is reflected and contained inside the core, the refractive indices must satisfy the condition $n_0 > n_1$. Generally, polymers of alkyl 2-cyanoacrylates have refractive indices n_D of 1.48-1.49. Therefore, when such materials are used for sheathing, the core material will be limited to polystyrene or polycarbonates with higher refractive indices (n_D = 1.59-1.60). The use of core materials with superior translucency e.g. polymethyl methacrylate (nD = 1.49) and quartz thus becomes impractical. Thus, to allow the use of such materials with relatively low refractive indices in cores, cyanoacrylates with low refractive indices were developed through the introduction of a fluoroalkyl group as the substituent.

Table 1.9 Refractive indices of fluoroalkyl 2-cyanoacrylate polymers[39]

	**Refractive index of polymer**
CF_3CH_2-	1.439
$HCF_2CF_2CH_2$-	1.430
$HCF_2CF_2CF_2CF_2CH_2$-	1.407
$HCF_2CF_2C(CH_3)_2$-	1.435
$HCF_2CF_2CF_2C(CH_3)_2$-	1.421
CH_3-	1.4923
CH_3CH_2-	1.4868
$(CH_3)_2CH$-	1.4898

1.1.4.4 Bis(2-cyanoacrylate)[27]

As already mentioned above C. J. Buck synthesized a bis (2-cyanoacrylate) having two cyanoacryloyl groups within a single molecule, and confirmed that the use of this monomer improved water resistance. In contrast to above-mentioned cyanoacrylates with unsaturated groups that require heat for crosslinking, the bis (2-cyanoacrylate) crosslinks simply by anion polymerization.

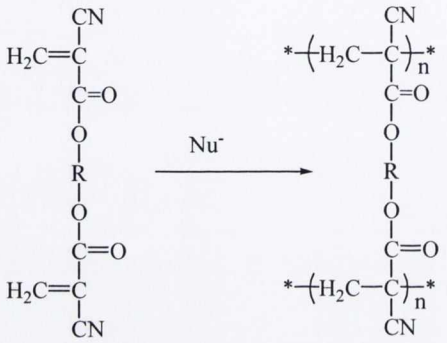
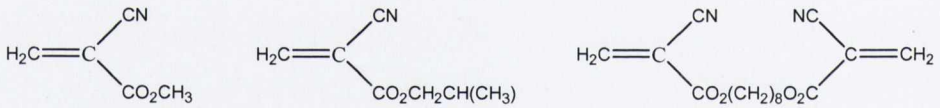


Figure 1.5 Crossinking of bis(2-cyanoacrilates) by anion polymerization

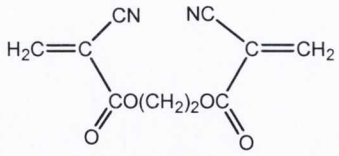


MAC IBC ODBCA

Table 1.10 Bond water resistance values of 2-cyanoacrylates mixed with octanediol bis 2-cyanoacrylate (ODBCA)[27]

Immersion conditions	Shearing adhesive strength, N/cm^2			
	IBC[a] only	9:1 mixture of IBC/DBCA	MCA only	9:1 mixture of MCA/ODBCA
100 °C in air, 1 day	349	420	1794	1373
100 °C in water, 1 day	352	558	1140	1014
100 °C in water, 7 days	360	431	536	794

[a] IBC = Isobuthyl 2-cyanoacrylate



EGBCA

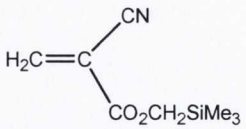
Table 1.11 Mixing ratio of EGBCA and IBC and adhesive Strength[27]

Monomer mixing ratio[a], IBC/EGBCA	Tensile adhesive strength, N/cm^2	
	100 °C in water, 1 day	100 °C in water, 7 days
100/0	4360	4720
99/1	4480	5590
98/2	4380	5350
96/4	5050	5970
94/6	5220	6390
90/10	5600	-
80/20	5750	-

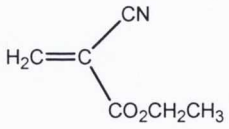
[a] Contains 72% of alumina as filler

1.1.4.5 Cyanoacrylates containing silicon[40]

Organic silicon compounds feature unique reactivity and distinctive physical properties derived from the properties of silicon (Si). Due to these properties, these compounds are widely used as reaction agents or as synthetic powder in synthetic organic chemistry and polymer chemistry. In particular, polysiloxane, due to its superior heat resistance and flexibility at low temperatures, is widely used in several industries as a sealant or lubricant for component parts that are subject to high temperatures. In contrast to such applications, it is possible, synthesizing a cyanoacrylate with silicon as the substituent (R), resulting in the production of a polymer with high heat resistance, particularly good stability at elevated temperatures.



SMCA



EtCA

Table 1.12 Mixing ratios cyanoacrylates containing silicon and alkyl 2-cyanoacrylates and adhesion heat resistance[40]

SMCA/EtCA mixing ratios	Shearing adhesive strength, N/cm^2	
	Room temperature	150 °C[a]
0/100	1260	50
20/80	1220	40
40/60	1100	50
60/40	1050	120
80/20	980	270
100/0	910	440

[a] Measured at 150 °C after heating at 150 °C for 1 hour

As described in the above section, the heat resistance of cyanoacrylates with unsaturated groups can be increased by thermal treatment to crosslink. However, to produce cyanoacrylates with practical heat resistance (Tg), the temperature and duration of the thermal treatment must be higher and longer, respectively, relative to the conditions of actual cyanoacrylate use. Thus, if the bonded parts are heated under load conditions, these parts will peel because the heat resistance is insufficient (i.e. if the crosslinking is insufficient) to maintain the bond. In contrast, polymers of cyanoacrylates containing silicon are inherently good at heat resistant, and so may be used for parts that will be subject to heating under load conditions.

1.1.5 Industrial synthesis of alkyl 2-cyanoacrylate by Knöevenagel reaction

The Knöevenagel reactions is generally carried out in the presence of weak bases such as ethylenediamine, piperidine or the corresponding ammonium salts. Unfortunately when formaldehyde is used as carbonyl group, the alkyl cyanoacrylate product undergoes instantaneous polymerization due to free base. For this reason, the method that forms the current basis for the industrial manufacture of alkyl cyanoacrylates involves condensation of formaldehyde with alkyl cyanoacetates in presence of base catalyst to yield a low molecular weight cyanoacrylic ester polymer; then this pre-polymer is thermally depolymerized in presence of stabilizers[41,42] (mainly strong acids).

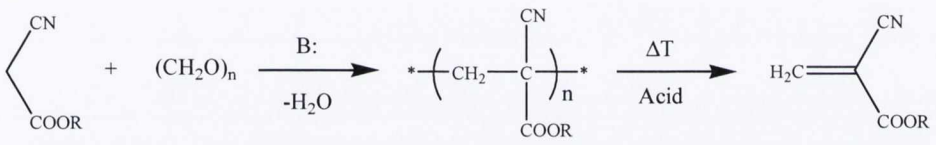


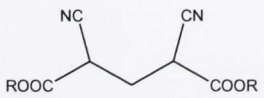
Figure 1.6 Current method for industrial manufacture of alkyl cyanoacrylates)

Improvements in this batch process have increased the yield and the stability of the product. These improvements involve the use of an organic solvent to remove water, the control of cyanoacetate-formaldehyde ratio to obtain an easily depolymerized oligomeric intermediate, neutralizing the base catalyst and processing the product at low water concentrations. Unfortunately the real problem is that depolymerization of oligomeric alkyl cyanoacrylates (CAs) formed in the first stage must be carried out under aggressive conditions, this fact largely restricts the synthetic potential of this method (e.g. it is fairly difficult to synthesize CAs with bulky ester group).

The Knöevenagel process for α-cyanoacrylates production is a well known and a well optimized process, in fact in the last 60 years many synthetic technologic problems have found a solution. The most important are connected with:

- Catalyst of reaction
- Solvent of reaction
- Monomer stabilization
- Reduction of contaminants/side products

A large number of basic catalyst are known to be efficient in the Knöevenagel condensation and any of such materials can in principle be used to catalyze the Knöevenagel process first step. Thus the catalysis can be any basic material, including inorganic bases such as sodium hydroxide, ammonia or ammonium hydroxide, the organic bases such as quinoline, piperidine, diethylamine, sodium or potassium methoxide or ethoxide or similar. The amount of catalyst can be varied as well, usually a percent or less is used, larger amount are may be undesirable, in some cases after thermal depolymerization a contamination of the final product can be obtained with catastrophic consequences. The main target of the basic catalyst optimization has been to reduce the reaction time and reaction temperature as well as to reduce as much as possible the production of 2,4-dicyanoglutarates.



2,4-dicyanoglutarates

This material has a higher boiling point than the correspondent α-cyanoacrylate, nevertheless a carry-over with the final distilled cyanoacrylate is possible and strongly unwanted. In fact such contamination produces a considerable reduction of bench stability of the commercial cyanoacrylate. It is commonly accepted that a quick depolymerization of the paraformaldehyde and a quick reaction between the formaldehyde and the cyanoacetate is necessary in order to minimized the di-cyanoglutarate production. Nevertheless the so called Knöevenagel residue can be a considerable amount of material left in the pot after thermal cracking. This material is most by constituted by glutarates and its recycle is always performed to maximize the yield of reaction. In particular the 2,4-dicyanoglutarate is mixed with paraformaldehyde under basic catalysis performing a Knöevenagel type process[43].

Very important is also the selection of the solvent of reaction, usually low boiling organic solvents suitable for industrial application (cheap, non toxic, non smelly, non corrosive, non halogenated, etc.) and for azeotropical distillation are chosen. Nowadays toluene and heptane are the most used solvent even if some authors proposed the use of high boiling solvents like esters of poly (ethylene glycol) as a medium for either the polymerization and depolymerization reactions steps[44]. In many cases the Knöevenagel process is performed in the presence of highly boiling plasticizers like tertiary

phosphoric acid esters (Triarylphosphate (TEASY)) to give low melting polymer. Then the use of a tricresyl phosphate gives a lower viscosity polymer even if it is not necessary for a successful thermal depolymerization. The polymer inhibitors are usually either high and low boiling. The first type is important for the catalysis of the unzipping stage (or thermal cracking), moreover it does not have to distill and overtabilize the CA, the second for the stabilization of the cyanoacrylate vapors. Then mixture of sulfonic acid, phosphorus pentoxide, hydroquinone, picric acid, maleic anhydride, 1,3-propane sultone, 1,4-butane sultone and many other have been used. At the same time the introduction of a stream of gaseous inhibitor like as sulfur dioxide or boron trifluoride are used. A common practice is to include polymerization inhibitors in the receiving vessel. In recent years the use of cyanoacrylate for biomedical applications has attract more and more interest. In this field the most interesting cyanoacrylates are those with longer ester moieties like n-octyl, heptan, isoheptan and butyl cyanoacrylate. The corresponding poly-cyanoacrylate polymer have lower glass transition temperatures, also they have higher flexibility and compatibility for skin bonding application. Those monomers are high boiling temperatures and need the use of special optimized inhibitor packages[45].

1.1.6 Alternative pathways for the synthesis of Cyanoacrylates

The thermal cracking of the Knöevenagel process is performed under aggressive conditions and so the synthetic potential of this method is restricted. It is possible to state that the preparation of CA esters by mild methods (avoiding the thermal cracking) is a significant problem which many authors were trying to address exploring alternative approaches.

1.1.6.1 Synthesis of 2-cyanoacrylate monomer by Diels-Alder reaction[27,28]

The commercial synthesis of the alkyl 2-cyanoacrylates developed at the Tennessee Eastman Company involved a Knöevenagel condensation of formaldehyde with an

alkyl cyanoacetate in the presence of a basic catalyst. The alkyl 2-cyanoacrylate monomer which formed *in situ* underwent homopolymerization under the reaction conditions. A depolymerization reaction of the homopolymer (carefully dried) in the presence of suitable polymerization inhibitors afforded high purity alkyl 2-cyanoacrylate monomers (e.g. ethylcyanoacrylate). The corresponding Knöevenagel reactions of formaldehyde with an alkylene glycol dicyanoacetate was eliminated as a potential direct route to the bis(2-cyanoacrylates), since any bis(2-cyanoacrylates) or monofunctional 2-cyanoacrylate moieties liberated *in situ* would immediately polymerize to a highly crosslinked polymer which would not be amenable to depolymerization to the desired monomer.

The Buck's study work relates to methods for preparing new bis esters represented in Figure 1.7, where R is an organo linking group and D is a blocking group derived from a cyclic 1,3 diene.

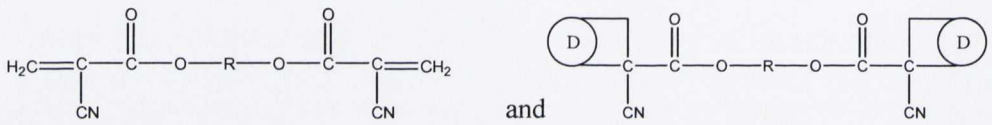


Figure 1.7 Bis-cyanoacrylates studied by Buck[27,28]

These monomers have been found to be particularly useful as adhesives, especially in dental application when incorporated as crosslinking agent for esters of 2-cyanoacrylic acid. The active vinyl group of a 2-cyanoacrylate ester is first blocked by adding a protecting group D through a conventional Diels-Alder reaction until the bis acrylate is formed. The protecting group D is then removed, restoring the active vinyl groups of the bis 2-cyanoacrylate.

The synthetic route using the anthracene adduct is illustrated thus:

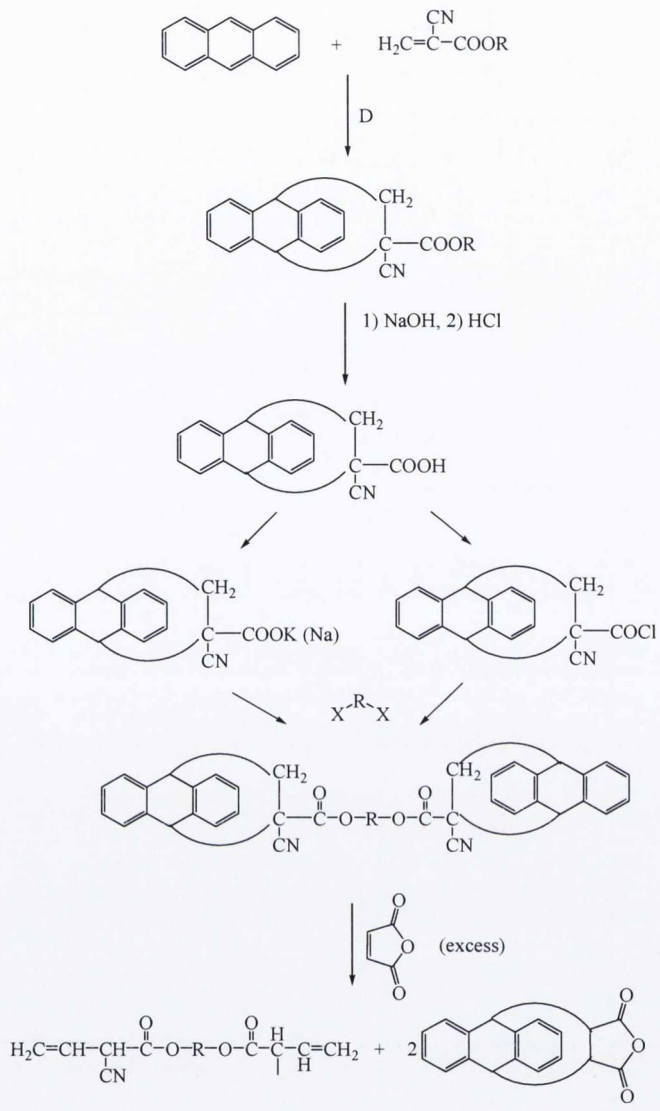


Figure 1.8 Synthetic route for production of bis(2-cyanoacrylates) by Diels –Alder reaction, Buck[27, 28]

High monomer yields were found to be critically dependent on the purity of the bis-adduct and on the use of excess maleic anhydride in the retrograde diene scission step. Besides there were other problems if cyclopentadiene is used instead of anthracene (very toxic) because it must be used only fresh (cracked from dicyclopentadiene) and during the thermal cracking some steps were thermally aggressive inside a long multi-step reaction. Further there were disadvantages such as ethyl ester hydrolysis to acid, the use of benzene as solvent in some steps and of dry acid chloride. In conclusion this method is very labour-consuming, expensive and not suited to industrial processing.

1.1.6.2 Various methods for the synthesis of alkyl 2-cyanoacrylates (CAs)

Several alternative methods for the synthesis of CAs were reported. One of them is based on the thermolysis of alkyl 3-acetoxy-2-cyanopropionates, which are prepared from the sodium derivatives of the corresponding alkyl cyanoacetates and chloromethyl acetate[46].

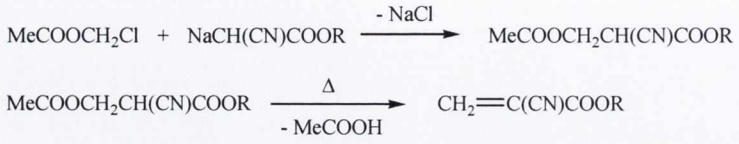


Figure 1.9 Production of cyanoacrylates monomer by thermolysis of alkyl 3-acetoxy-2-cyanopropionates, Gololobov [47]

However, this method has not been adequately studied. Instead the synthesis of the CAs based on the Knöevenagel reaction has been developed in greater detail. This method is the basis for the industrial manufacture of CAs, as is illustrated by numerous publications.[48, 49, 50, 39, 40, 41]

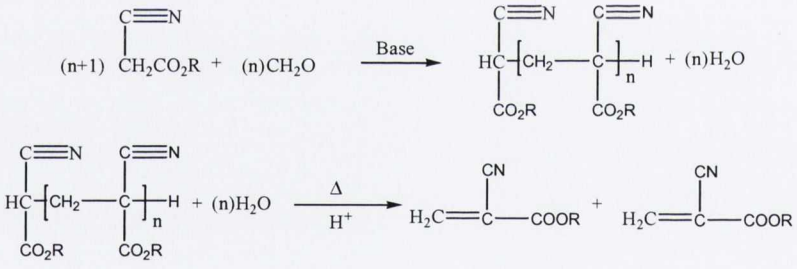


Figure 1.10 Synthesis of cyanoacrylates by Knöevenagel reaction, Gololobov[47]

The monomeric form are produced industrially by reacting a cyanoacetate with formaldehyde or a polymer of formaldehyde (paraformaldehyde, formalin, trioxane) to obtain a crude polymeric condensation product. This crude polymeric product is then depolymerized with heat and acid (phosphoric acid, methane sulphonic acid etc.) to yield the monomeric α-cyanoacrylate. In general the separation of alkyl cyanoacrylate from alkyl cyanoacetate is difficult by distillation because the boiling points fall closer together. In the prior art process, the initial condensation between the cyanoacrylate and formaldehyde is conducted in a low molecular weight volatile organic solvent that is

essentially insoluble in water, such as butyl acetate, benzene, toluene, heptane, or cyanohexane. These organic solvents have been preferred reaction medium because they act as azeotroping solvents (with the water resulting from the condensation reaction) permitting the water to be removed along with the solvent by distillation. The problem with this process is that high molecular weight polymers, which result in a higher grade of purity for the final product, precipitate out of these solvents. In addition these solvents frequently contaminate the final product and are extremely volatile, flammable, thus creating environment and safety problems in practice. For these reasons volatile organic solvents were replaced with esters of poly(ethylene glycol).[53] More recently other methods for synthesis of CAs have been studied starting from methyl acrylate[42,51,52], cyanoacetylene[43,53], ethyl pyruvate[44,54] and esters of 2-cyanopropanoic acid[48,55,56]. However, many of these procedures are limited to laboratory synthesis.

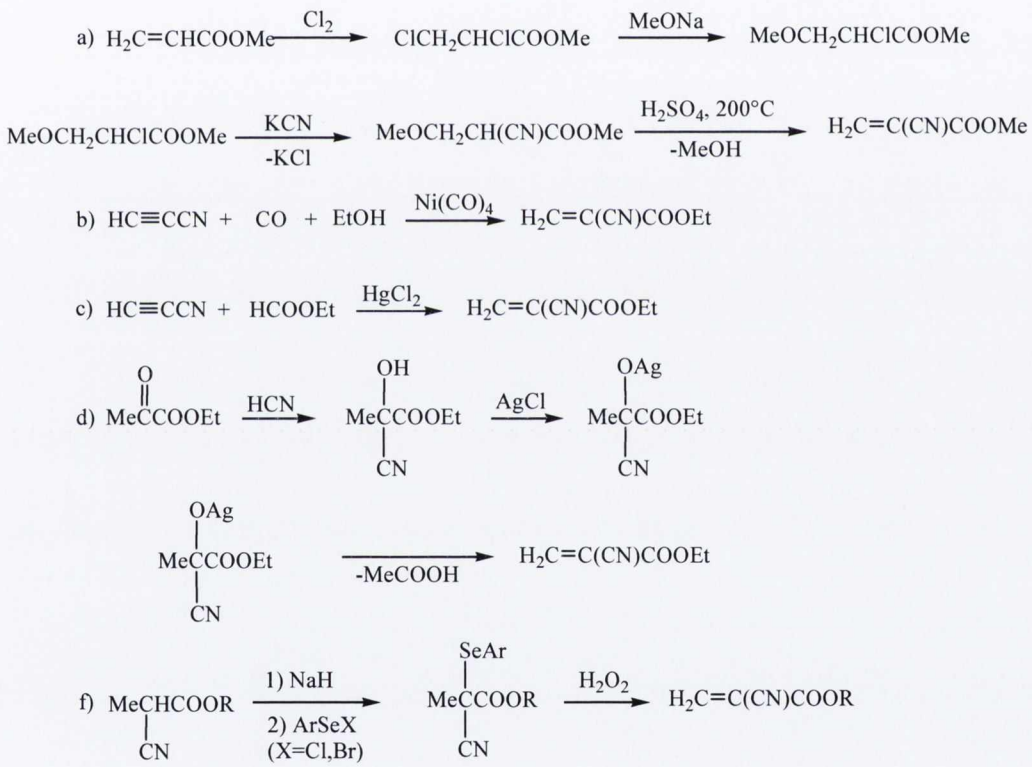


Figure 1.11 Various different ways in the synthesis of cyanoacrylates

All these ways have problems, for example the route described by (c) uses unpleasant reagents not suitable in industrial synthesis (e.g. mercury), route (f) uses selenium that is toxic and malodorous, others are too time-consuming and expensive.

It is possible to transform methyl and ethyl cyanoacrylate into other derivatives of cyanoacrylic acid, or trans-esterification of ethyl 2-cyanoacrylate with butyl or hexyl alcohols in the presence of acid catalyst; this technique can also permit the preparation of bis-cyanoacrylates. However, this target product can be obtained in satisfactory yields only when long chain diols are used. Otherwise an ethyl or methyl cyanoacrylate polymer (poly-cyanoacrylate) can be trans-esterify with an alcohol. Last by depolymerization of the pre-polymer α-cyanoacrylate monomers is obtained (Figure 1.12).

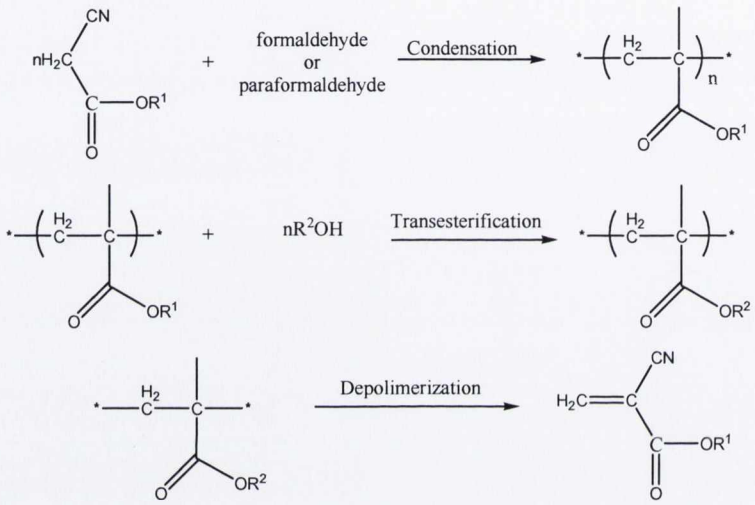


Figure 1.12 Production of cyanoacrylates by pre-polymer trans-esterification B.Malofsky[57].

Even by using this method the significant problem is not solved as thermal cracking is still used.

New opportunity for the synthesis of CAs has been studied by Henkel Ltd., that had patented the thermolysis of ethyl cyanoacrylate as a method for the preparation[56] of free cyanoacrylic acid (CAA) as shown in the following scheme.

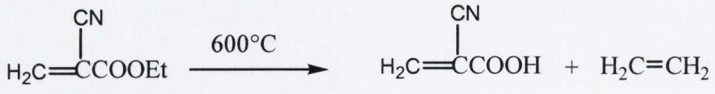


Figure 1.13 Thermolysis of ethyl cyanoacrylates for the preparation of free cyanoacrylic acid, Gololobov[47]

The synthesis of free CAA has stimulated the preparation of new derivatives, first of all, its chloride that by direct esterification or by trans-esterification[58] could be transformed in subsequent derivatives[59] (Figure 1.14)

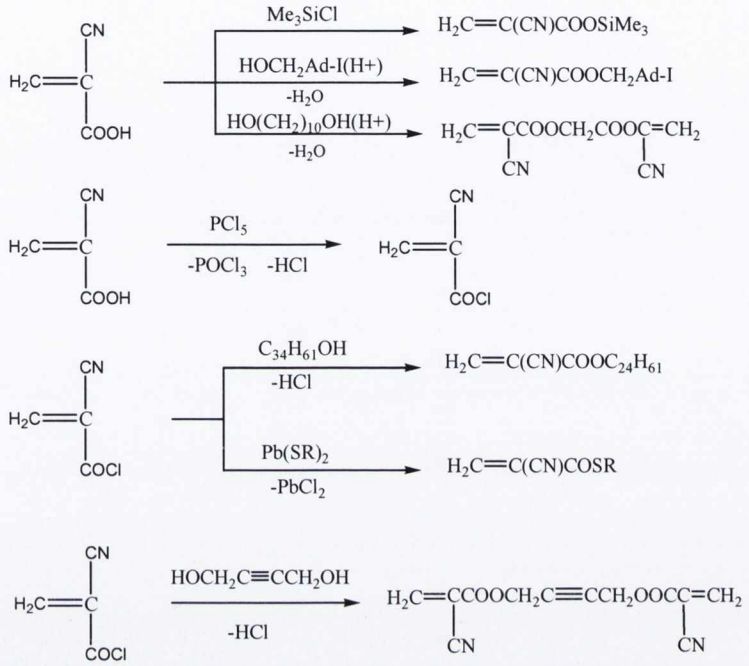


Figure 1.14 Production of different cyanoacrylates by direct esterifications of acrylic acid

1.2 Structural variants of cyanoacrylate

(Non-Cyanoacrylate based electron deficient enes)

1.2.1 Acrylylphosphonates and related compounds

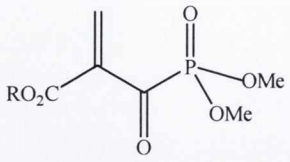


Figure 1.15 Dimethyl (α-ethoxylcarbonyl)propenylolphosphonate[60]

Because of the ease of polymerisation of an olefin with two EWGs on the same carbon atom, many structural variants on the basic CA structure have been proposed with a view to generating commercially important monomers with different properties. However, none of these have been commercialised to date. Tebby and Szpala[61] give a particularly interesting overview of inductive and resonance contributions of various EWGs to Hammet substituent constants directed at the synthesis of acrylylphosphonates (Figure 3) as possible alternatives to cyanoacrylates for biomedical applications. They and their co-workers wished to modify the hydrolytic stability of the resulting polymer for biomedical applications[60] and to propose also[62] synthetic approaches to ketophosphonates. Classic Knöevenagel reaction (see later) was used to prepare these polymers of these materials, however no details have appeared for isolated, reactive monomers[60].

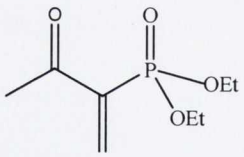


Figure 1.16 Diethyl α-acetovinylphosphonate

The monomer diethyl α-acetovinylphosphonate was reported by a piperidine catalysed Knöevenagel reaction of paraformaldehyde with diethyl acetomethylphosphonate in methanol with an 11% yield[63].

1.2.2 Methyene dialkylmalonates

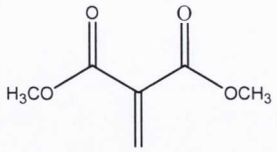


Figure 1.17 Methylene Dimethylmalonate

Methylene dialkylmalonates, or methylene malonates, (MMs) are electrophilic reactive monomers, and have been prepared in several ways. The earliest methods exploited the Knoevanagel reaction in glacial acetic acid with potassium acetate as catalyst. Incorporation of large amounts of metal salts, copper acetate for example, as a polymerisation inhibitor, reportedly enabled direct fractional distillation of monomer in 72% yield (more typically ~40%). However the stability of the monomer prepared under these conditions is not described[64].

D'Alelio[65] reported the base catalysed condensation of dialkylmalonates with aqueous formaldehyde under basic conditions to form a methylol during the course of 24 hours, before dehydrating and fractionally distilling in the presence of copper acetate (Figure 1.18). A variety of symmetrical dialkyl esters were prepared and radically copolymerised with standard acrylates, acrylonitriles and such like. Typical yields were 30%.

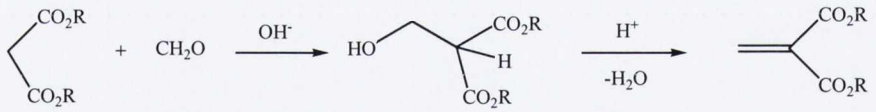


Figure 1.18 Synthesis of Methylene Dilakylmalonates[65]

Higher quality dialkylmalonates (less prone to spontaneous polymerisation; improved yields), including some asymmetrical types (methyl, ethyl and methyl, n-octyl esters) were prepared by the thermolysis of hydrogenated dialkylalkoxymethylene malonates [66, 67] as illustrated in

Figure 1.19. The starting material, for example ethyl ethoxymethylene malonates was first prepared by the zinc chloride catalysed condensation of ethyl orthoformate with ethyl malonate [68].

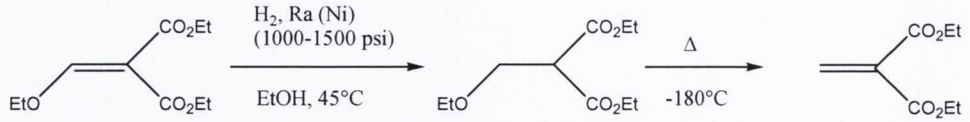


Figure 1.19 Pyrolysis route to Methylene Diethylmalonate[66, 67, 68]

Eck et al. [69] appear to be the first to allude to the production of MMs using thermal cracking of the product directly resulting from a Knöevenagel reaction. They used glacial acetic acid containing acetic anhydride as reaction solvent and achieved higher yields using (zinc) chloroacetates (~86%) as opposed to acetate catalysts (~63%). Titanium alkoxides were added as surprisingly effective stabilisers for the reactive monomers.

Ponticello[70] described a method in which the liable proton in an adduct formed between cyclopentadiene and a common acrylate, was replaced with an additional ester function. The adduct was subsequently pyrolysed as shown in the general scheme in Figure 1.20. Again asymmetrical monomers could be accessed this way.

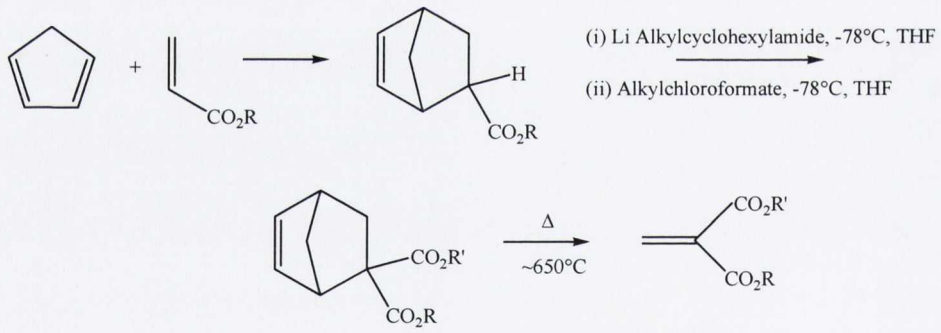


Figure 1.20 Pyrolysis route to methylene dialkylmalonate via simple Diels-Alder adduct of common acrylates[70]

A brief, but comprehensive, overview on the various synthetic routes available for stable methylene malonates is that by Ballesteros et al.[71]. These authors were interested in a multigram route for studies of important synthetic reactions such as Michael and Diels-Alder reactions with electrophilic alkenes, as opposed to the study of polymerisations. Their focus was on the di-t-butyl ester which is much more stable than the simpler alkyl esters. A summary of the various routes to this target is provided in Figure 1.21. The route via sulfoxide elimination, (also employed in CA synthesis), was

described as tedious, and that from the bis-hydroxymethyl product was low yielding (~40%). The preferred method for this particular ester was a Knöevenagel reaction[72].

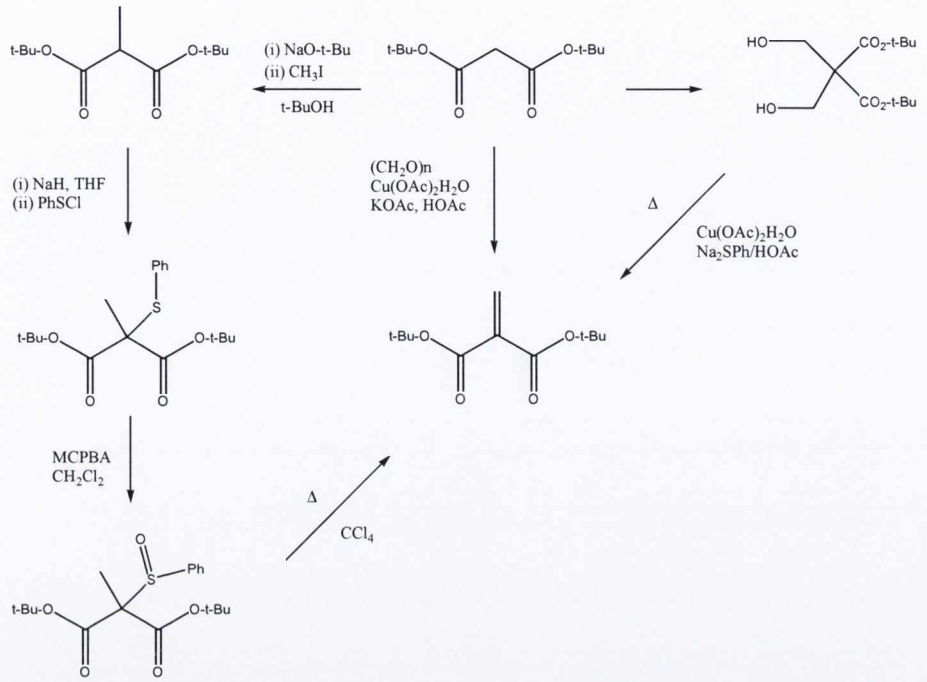
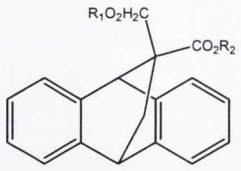


Figure 1.21 Summary of the routes to methylene di-t-Butyl Malonate considered for multigram syntheses[71, 72]

Whereas the multigram route described above is suited to stable derivatives, it is not suitable for other methylene malonates. De Keyser et al.[73,74,75] developed a versatile method building on the copper acetate catalysed Knöevenagel reaction of Ballesteros et al. in conjunction with a Diels-Alder reaction employing anthracene to avoid polymerisation. In this way many crystalline adducts were isolated and readily purified as illustrated in Table 1.13. The corresponding methylene malonates (Table 1.14) were obtained by a retro Diels-Alder thermolysis process in the presence of maleic anhydride at the relatively low temperatures of 200-250 °C. Asymmetric variants were achieved by the half hydrolysis of the symmetric adducts with potassium hydroxide in the corresponding alcohol, with subsequent alkylation of the monoacid salt with alkyl halides. It is interesting to note that the methylene malonates derived from adducts t-w (Table 1.13) were not suited to this mild thermolysis process. The methylene malonates containing methyl and glycidyl functions (w, Table 1.13) were prepared by Ponticello in a 45% yield using the functional group transformation route described above from

cyclopentadiene adducts[76]. This appears to be the only example of an instantly polymerisable monomer containing a polymerisable epoxy functional group, but little detail is provided on its stability or use.



Diels-Alder adduct

Table 1.13. Anthracene Diels-Alder adducts of methylene dialkylmalonates[73] (see text for detail)

Entry	R_1	R_2	Yield (%)	Mpt (°C)
a	CH_3	CH_3	53	161-162
b	C_2H_5	C_2H_5	75	130-131
c	n-C_3H_7	n-C_3H_7	72	104-106
d	n-C_4H_9	n-C_4H_9	55	91-92
e	i-C_3H_7	i-C_3H_7	72	136-137
f	i-C_4H_9	i-C_4H_9	52	94-95
g	n-C_5H_{11}	n-C_5H_{11}	45	75-79
h	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	41	85-86
i	CH_3	n-C_4H_9	51	80-82
j	CH_3	n-C_6H_{12}	53	74-75
k	C_2H_5	n-C_3H_7	82	107-108
l	C_2H_5	n-C_4H_9	46	91-92
m	C_2H_5	$CH_2CH{=}CH_2$	84	88-89
n	C_2H_5	$CH_2C{\equiv}CH$	62	60-61
o	C_2H_5	$C_2H_4OC_2H_5$	47	42-46
p	C_2H_5	$CH_2CO_2C_2H_5$	42	76-77
q	C_2H_5	$(CH_3)_2CO_2C_2H_5$	67	83-84
r	n-C_3H_7	n-C_4H_9	47	91-92
s	n-C_4H_9	n-C_5H_{11}	53	77-79
t	CH_3	$CH_2C_6H_5$	42	109-112
v	C_2H_5	CH_2OCH_3	75	106-107
w	C_2H_5	CH_2CHCH_2O	66	114-115

Table 1.14 Methylene dialkylmalonates derived from Anthracene Diels-Alder adducts by thermolysis [73] (refer to Table 1.13)

Entry	Yield (%)	b.p. (°C) (Torr)
a	54	80-82 (6)
b	67	60-61 (0,25)
c	81	77-81 (0.2)
d	68	76-80 (0.01)
e	64	40-42 (0.1)
f	61	64-65 (0.02)
g	46	99-101 (0.05)
h	48	67-68 (0.3)
i	75	65-68 (0.4)
j	77	80-85 (0.1)
k	63	52-55 (0.25)
l	71	62-63 (0.2)
m	48	52-55 (0.25)
n	2	65-67 (0.3)
o	43	82-84 (0.2)
p	62	98-99 (0.1)
q	32	86-89 (0.06)
r	53	78-80 (0.1)
s	78	95-96 (0.1)

1.2.3 Vinylidene Dicyanide

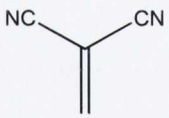


Figure 1.22 Vinylidene Dicyanide

Vinylidene dicyanide (VdCN) is an exceptionally reactive material that is difficult to prepare. It is a low melting solid (mpt ~10°C), toxic and a strong lachrymator. In particular a possible synthesis of vinilydene cyanide was proposed by O. Diels *et al.*[77, 78] which synthesized the 1,1,3,3-tetracyanopropane and 1,1,3,3,5,5-hexacyanopentane from formaldehyde and malononitrile, and suggested the monomer as an intermediate in the synthesis (Figure 1.23).

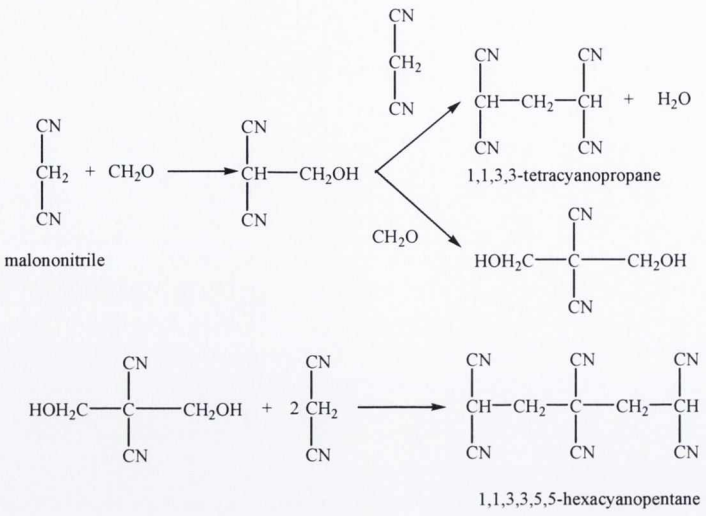


Figure 1.23. Vinylidene cyanide from malononitrile plus formaldehyde, O. Diels[77, 78]

Ardis[79] proposed the synthesis of vinilydene cyanide from thermically decomposition of 1,1,3,3 tetracyanopropane. In particular the authors isolated dimethylol malononitrile by the reaction of malononitrile and formaldehyde, using potassium acetate as catalyst. That dimethylol compound was then treated with malononitrile to yield 1,1,3,3-tetracyanopropane subsequently this product was heated at 150 °C to 200 °C and the production of the monomer occurred.

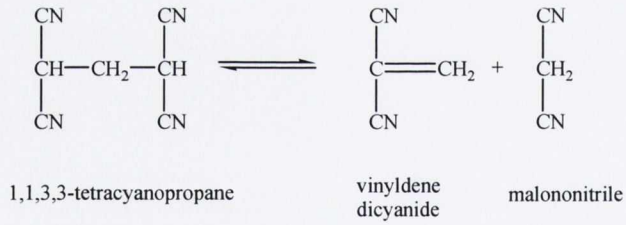


Figure 1.24. Equilibrium between 1,1,3,3-tetracyanopropane and vinilydene cyanide and, Ardis[79]

It was also reported the possible recombination of the monomer with malononitrile in the vapour or liquid phase but it was easily inhibited by traces of sulfur dioxide. Therefore the product monomer was obtained in good yield after separation in a rectification column.

Another way for the production of this monomer was proposed by Ardis *et al.*[66] using the retro Diels-Alder technique.

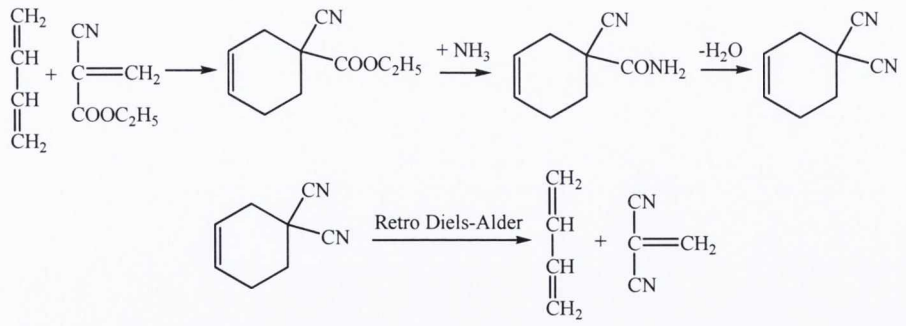


Figure 1.25. Production of vinilydene cyanide by retro Diels-Alder reaction, Ardis[62]

In particular it was observed that the monomer was completely miscible with benzene, nitromethane, trichloroethylene and substantially insoluble in aliphatic hydrocarbons. The monomer polymerized instantly, as expected, upon contact with water, alcohols, amines and a large number of other organic and inorganic nucleophiles; obviously this rapid anionic polymerization is due to the high electron withdrawing effect of the nitrile groups. Homopolymerisation of this monomer has been described by Gilbert et al.[80] and whereas the polymer is inherently unstable and of limited practical value, copolymers, for example with vinyl acetate, display exceptionally interesting piezeoelectric characteristics[81], so a more efficient synthesis of this material is of interest.

1.2.4 Acetoxyacrylonitrile, Acetoxyacrylates and Cyanovinyl Alkylcarbonates

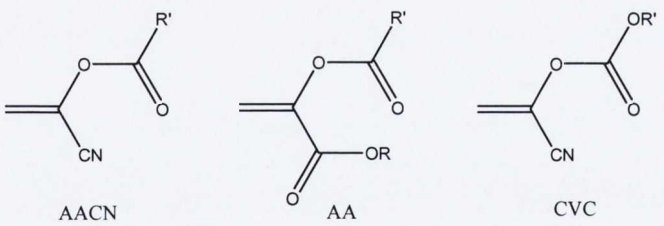


Figure 1.26 Generalised structures of acetoxyacrylonitrile (AACN) , acetoxyacrylate (AA), and cyanovinyl carbonate (CVC)[80, 81, 82, 83, 84, 85, 86, 87]

The synthesis and polymerisation of reverse ester versions of cyanoacrylates and methylene malonates have been described in the literature[82, 83, 84, 85, 86, 87]. In the former, the double electron withdrawing effect is not as pronounced as for the latter and the

reverse ester monomers appear to be more susceptible to radical polymerisation as opposed to anionic polymerisation. One old report indicates however, that pure AAs can only be stored at refrigeration temperatures for few days[84], although the mechanism of polymerisation is not described.

Cyanoalkenyl esters can be prepared by one of three ways, thus:

(i) dehydrohalogenation

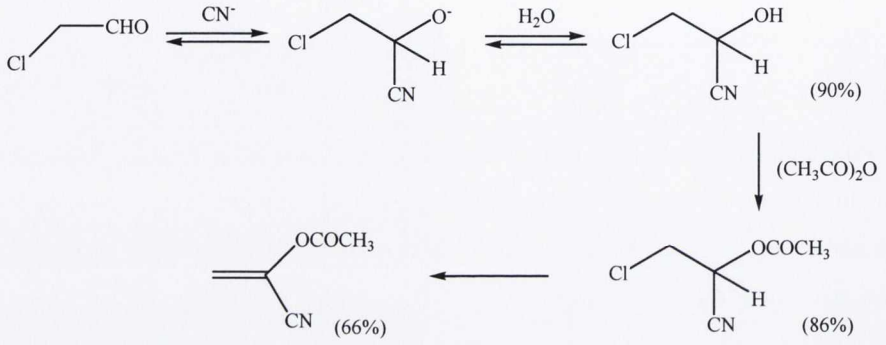


Figure 1.27 Dehydrohalogenation of 1-cyano-2-haloethyl acetate prepared from chloroacetaldehyde[82, 83]

(ii) base catalysed addition

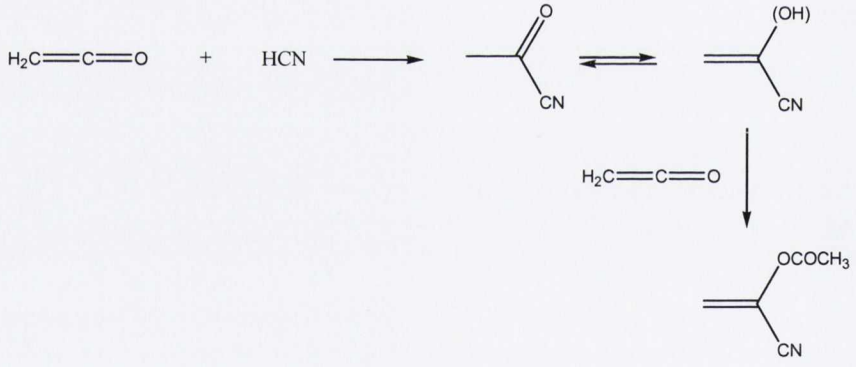


Figure 1.28 Base catalysed addition of hydrogen cyanide to ketene[85, 86]

(iii) reaction of acetic anhydride on acyl cyanide

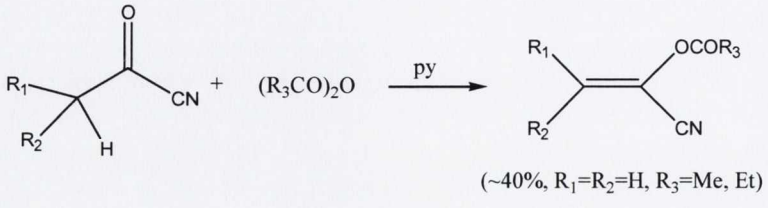


Figure 1.29 Reaction of anhydride on acyl cyanide[87] (for a review on acyl cyanides[88]).

Acetoxyacrylates were prepared by the acetylation and dehydrohalogenation of β-chlorolactic esters as shown in Figure 1.30[84].

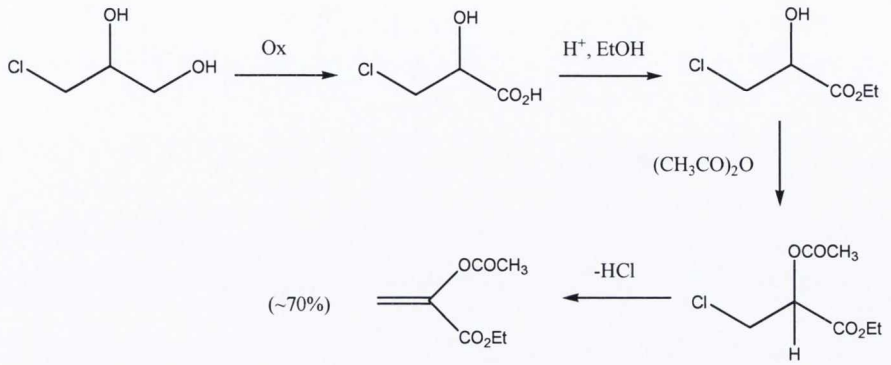


Figure 1.30 Preparation of acetoxyacrylates from chlorolactic ester[84]

Preparation of CVC essentially also used the dehydrohalogenation route similar to that described in Figure 1.30 above employing alkyl chloroformate in place of acetic anhydride[89].

These monomers, particularly AACN and AA give durable, hard polymers when radical polymerised[84]. In some cases copolymerisation, even with monofunctional monomers such as acrylonitrile, produce insoluble materials which seem to indicate crosslinking[90]. The carbonates and fluorinated versions show heat resistance and may be molded (unlike cyanoacrylates)[89,90,91]. It would be worth re-investigating these materials in a very pure form for anionic homo-polymerisation to study co-polymerisation with cyanoacrylates.

1.2.5 α- Nitroethylenes

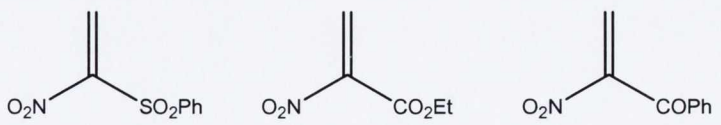
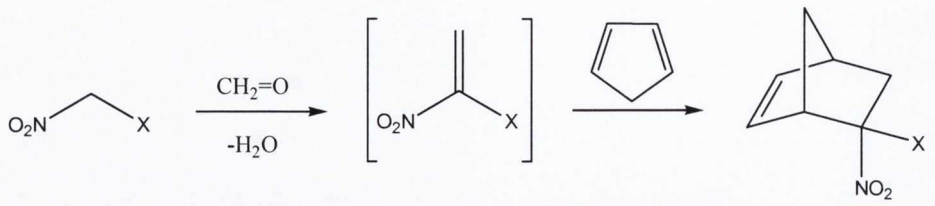


Figure 1.31 Activated nitroethylenes generated for *in situ* Diels-Alder reactions[91]



X = SO_2Ph (~98% yield), CO_2Et (~80%), COPh (~82%)

Figure 1.32 Synthesis of Nitronorbornene Derivatives[92]

Activated nitroethylenes such as those illustrated in Figure 1.31, have thus far never been isolated although their Diels-Alder adducts are readily prepared by condensing commercially available nitromethane derivatives with formalin in the presence of dienes and acetic acid as shown in Figure 1.32. Preparation of the parent nitronorbornene has been described by Ranganathan et al.[93] and alkyl substituted nitronorbornenes and anthracene Diels-Alder adducts have been described by Feuer et al.[94]. In a monomer context, Babievskii et al. attempted to prepare 2-nitroethacrylate by conventional Knöevenagel reaction[95]. These authors could isolate a nitrohydroxypropionate but not the monomer following dehydration. The succeeded in preparing Diels-Alder adducts directly from the propionate in the presence of various dienes by heating under pressure. The retro Diels-Alder reaction to liberate the monomer was not described. Dinitroethylene has not been isolated but its Diels-Alder adducts are also known.[96] Many useful references on the synthesis of nitroacetic acid, its salts and esters have appeared[97,98,99,100].

1.2.6 α-(Alkyl/Aryl sulfanyl/sulfinyl/sulfonyl) acrylates, acrylonitriles and related

Figure 1.33 Generalised structures of (Alkyl/Aryl sulfonyl) acrylonitriles and acrylates

There exists considerable discrepencies between the primary and patent literature regarding the syntheses of these electron deficient ethylenes. Shearer and Coover[101a] allude to a standard base catalysed Knöevenagel synthetic procedure from sulfonyl-type

methylene bases as a preferred method that requires thermal depolymerisation or thermal 'crack'. They also refer to an alternative procedure requiring no retrograde polymer thermal cracking as a route to monomer, but rather the extrusion of acetic acid from adducts such as those as shown in Figure 1.34. These authors refer to adhesive compositions derived from a wide variety of monomers summarised in Figure 1.35, but give little detail on characterisation. Hill[101b,c] provides some further details and limited characterisations (mpt, bpts) on similar materials derived form Knöevenagel reaction. As it is not uncommon for critical detail to be omitted in patent literature, it is not clear as to whether these procedures work or not.

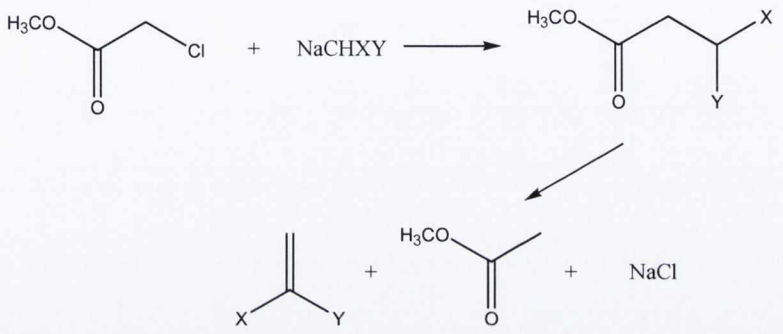


Figure 1.34 'Crackless' route to sulfonyl ethylenes posed by Shearer and Coover[101a]

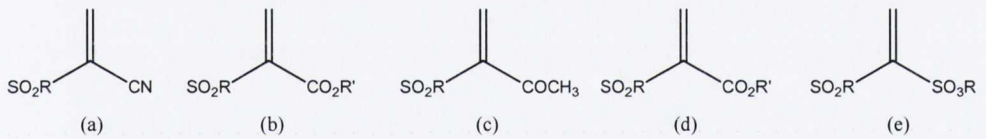


Figure 1.35 Sulfonyl ethylenes claimed by Shearer and Coover[101a]: for example, α-(methyl sulfonyl) acrylonitrile (a), α-(methyl sulfonyl) acrylate (b), 1-acetyl-(methyl sulfonyl) ethylene (c), 1,1-(bismethylene sulfonyl) ethylene (d), α-(methyl sulfonyl) vinyl sulfonate (e)

Gipstein et al.[102], in a detailed paper, commented on their lack of ability to repeat the synthesis described above[101]. These authors refer to the patent work as a Mannich reaction, rather than a Knöevenagel reaction and interestingly further employ Mannich reagents, such as Eschenmoser's salt, in an attempt to arrive at alkylsulfonyl acrylates from α-(alkysulfonyl) acetates but without success. In that regard they followed a generalised route described by Roberts et al.[103] for methylene carbonyl compounds via Mannich intermediates. The failed attempts should be repeated given findings of the present work and likely resulted from the presence of strong base. Gipstein et al. subsequently elected for the oxidation of α-(phenylselenium) propionates as a reliable

high yielding route to the target molecules. This is summarised in Figure 1.36. These authors also experimented with the deacylative methylenation method illustrated in Figure 1.37 to overcome some of the disadvantages of using selenium compunds (cost, waste disposal), but this only produced polymer (see also[104, 105]). It is interesting to note that the small alkyl esters of these monomers were highly reactive and produced insoluble polymers after spontaneous polymerisation. The di-t-Bu esters were inherently more stable[102].

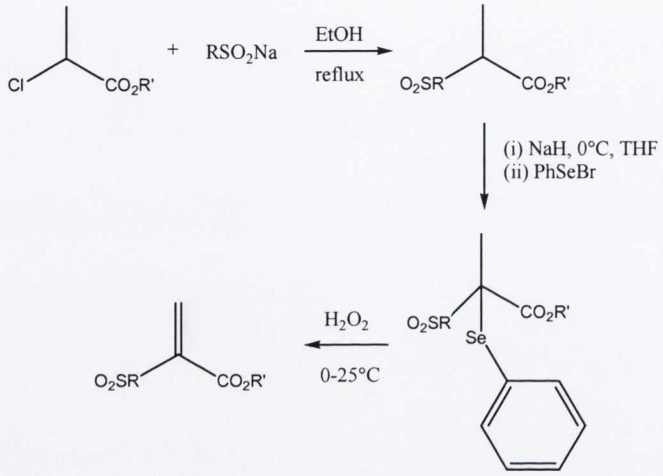


Figure 1.36 Activated olefin synthesis via elimination of alkyl phenyl selenoxide[102]

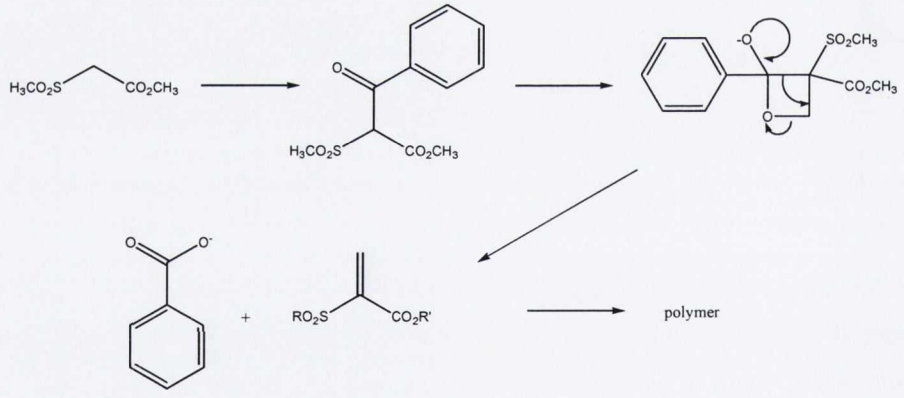


Figure 1.37 Attemptd deacylative methylenation reaction for methyl sulfonyl methacrylate [102]

Fotsing et al.[106] also encountered difficultly repeating claimed Mannich reactions for α-(phenylsulfonyl) acrylonitriles[107]. The methodology they employed to arrive at an analytical sample in low yield (~5%) is summarised in Figure 1.38. They could produce

the target in a 55% yield by a more exotic method requiring photolysis or thermolysis of allenyl azides[106].

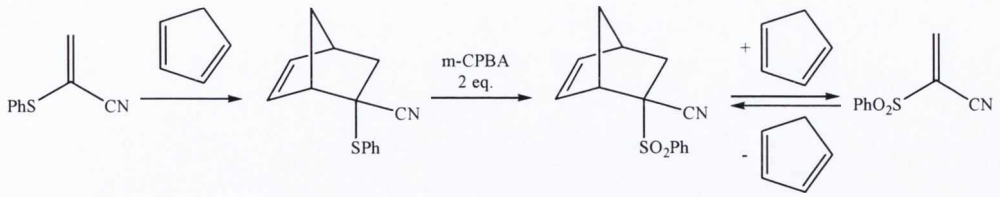


Figure 1.38. Route employed for analytical sample of α-(phenylsulfonyl) acrylonitrile; a moderately high yielding route is further described[106]

Bazaova et al. detailed the much simpler Mannich reaction to arrive at α-(phenylsulfonyl) acrylonitriles in an apparently satisfactory yield[107]. Their strategy is outlined in Figure 1.39 and involved careful isolation of the piperidine Mannich base, followed by its mild thermal decomposition (80 °C) under strong acid conditions. Fotsing et al. make the valid point, however, that the NMR assignments for the vinyl protons in paper of Bazaova et al. are not consistent with expectations (4.11 and 4.99 ppm, $(CD_3)_2CO$), and that they could not repeat the procedure to arrive at the target (finding CH_2= in $CDCl_3$: at 6.71 and 7.12 ppm by their alternative method). Nonetheless, the Mannich approach is of interest, particularly in the context of the present work.

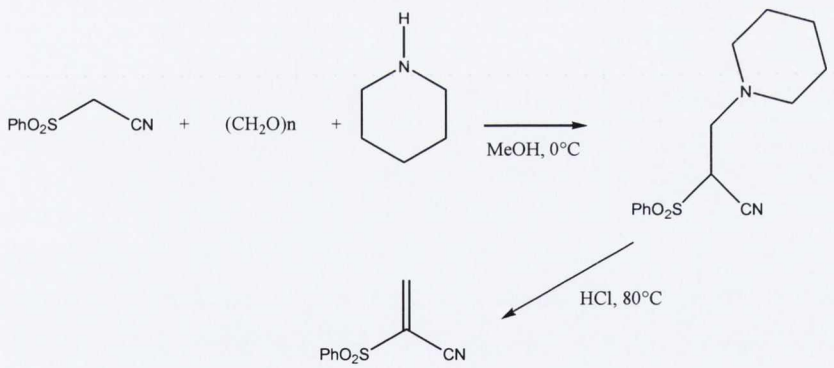


Figure 1.39 Mannich route to α-(phenylsulfonyl) acrylonitrile[107]

The starting α-(phenylsulphanyl) acrylic materials used in some of the preparative work described by Fotsing et al., are themselves interesting and have been described by Miller et al. (acrylonitrile, acrylates) and Leyendecker et al. (acrylates)[108],[109]. The former authors developed a high yielding eliminative deoxygenating procedure from readily available starting materials under mildly basic conditions as shown in Figure 1.40.

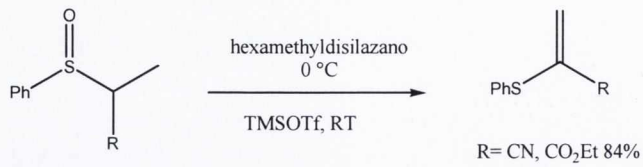


Figure 1.40 Eliminative deoxygenating of α-cyano or α-carboxyalkyl/ phenyl sulfoxide yielding equivalent vinyl sulphide[108]

Leyendecker et al. employed a thermal dehydrohalogenation of halothiophenoxy esters as a key step as outlined in Figure 1.41. Their ultimate targets were the interesting a-(phenylsulfinyl) acrylates, which are analogous to methylene malonates[109], however they indicated that the vinyl sulfides were subject to self polymerisation after 5 days at r.t. and Yang et al. chose not to isolate these unstable species in pure form before oxidation to sulfinyl acrylates. The sulfinyl equivalents were stable liquids or were crystalline (R=Me) [110].

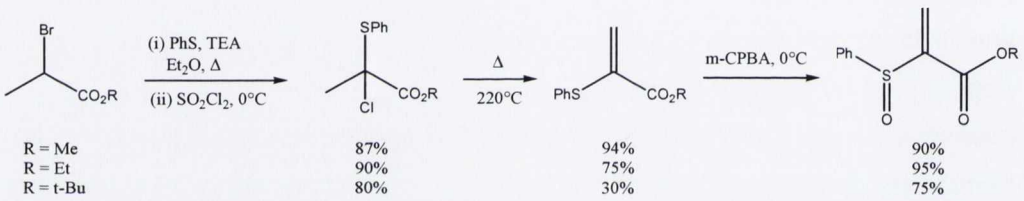


Figure 1.41 Leyendecker et al. route to a-(phenylsulfinyl) acrylates via a-(phenylsulfanyl) acrylates[109].

Yamazaki et al. provide detail on the seleneoxide elimination route to α-(phenylsulfonyl) acrylates. [111]

Sulfone sulfides and alkenyl bis-sulfoxides have been described by Hughes et all.[112] 1,1-Bismethylsulfonylethene is a reactive material isolatable as a crylstalline solid or as a crystalline ether adduct. The chemistry is shown in Figure 1.42.

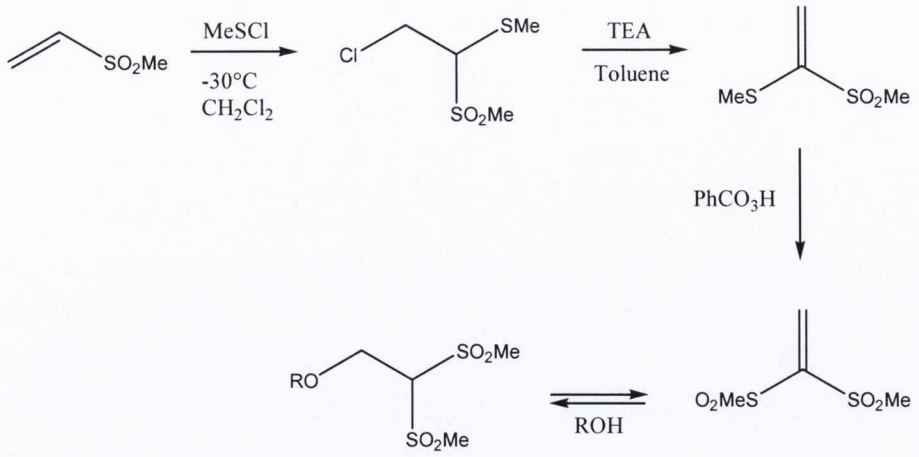


Figure 1.42 Route to 1,1-bismethylsulfonylethene[111]

Trifluromethylated vinyl sulfides, sulfinyls and sulfonyls have been decribed by Planqueret et al. according to the reaction scheme in Figure 1.43[113].

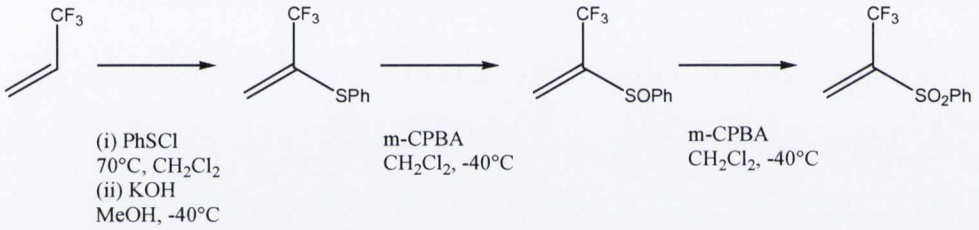


Figure 1.43 Trifluoro vinyl sulfides, sulfinyls and sulfonyls[113]

1.2.7 Methylene Dialkyl/aryl ketones

Interesting reference is made above to the deployment of the Mannich reaction in the synthesis of a-(phenylsulfonyl) acrylates and acrylonitriles that deserves further investigation. A similar approach was used by Moehrle and Schaltenbrandt [114] using the preformed Mannich reagent, dimethyl iminium chloride (Eschenmoser's Salt) to synthesise methylene diketones. In this case the Mannich base intermediate spontaneously decomposed on addition of water to release the olefin as indicated in Figure 1.44.

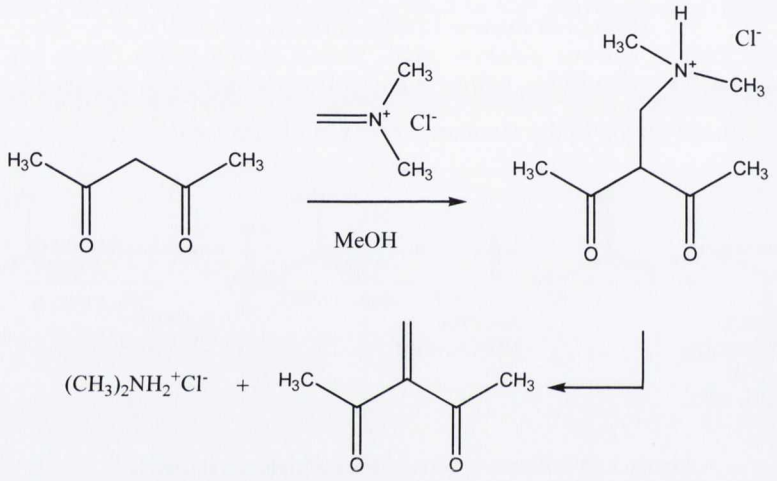


Figure 1.44 Mannich reaction for the production of Methylene dimethylketone[114]

These materials were studied as substrates for Michael reactions and the method was never developed for the isolation of pure, highly reactive monomers. Furthermore, this method relies on the relative ease of enolization of the methylene base and the 1,3-diketones are particularly suitable in this case whereas methylene bases with less acidic hydrogens may not.

1.2.8 Substituted Styrenes

Styrene derivatives with aryl systems heavily substituted by strong electron withdrawing groups (NO_2 [115, 116, 117], CF_3 [118, 119], and CN [120]) have also been reported as highly reactive electrophilic monomers that preferentially undergo anionic polymerisation. Many of these monomers are impractical to synthesise commercially due to the nature of the starting materials or low reaction yields. The synthesis described in Figure 1.45 via Mannich reaction, for tri-nitrostyrene is nonetheless interesting to note [115, 116, 117]

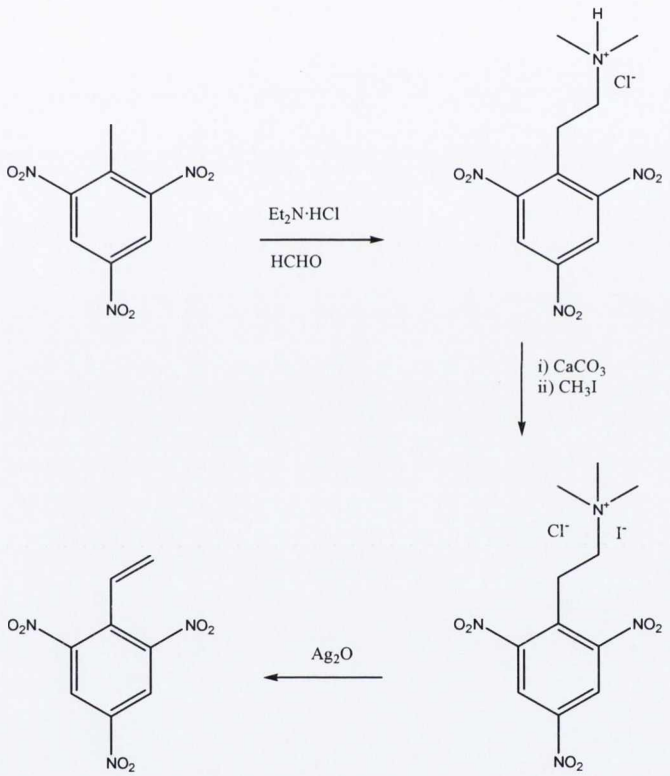


Figure 1.45 Synthesis of tri-nitrostyrene via Mannich reaction[115, 116, 117].

1.3 Imine and iminium salts

Imine is a very useful molecule as intermediate or as starting materials in organic reactions and their synthesis is reported to be really easy[121]. In the past the use of imines as synthetic intermediate has been limited to mainly two processes: reduction to amines, and precursors to azaallyl anions for reaction with a variety of electrophiles (Figure 1.46).

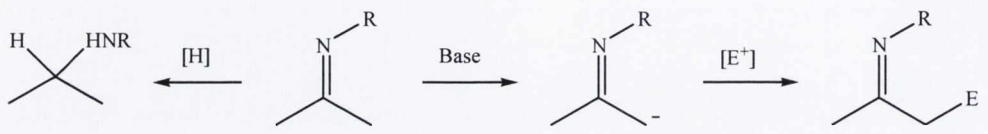
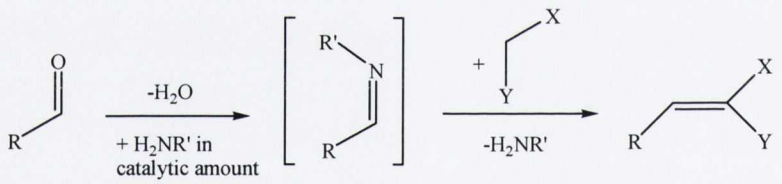


Figure 1.46 First use of imines as synthetic intermediate

Imine intermediates are also present in many organic reactions; for example in the synthesis of olephinic compound by:

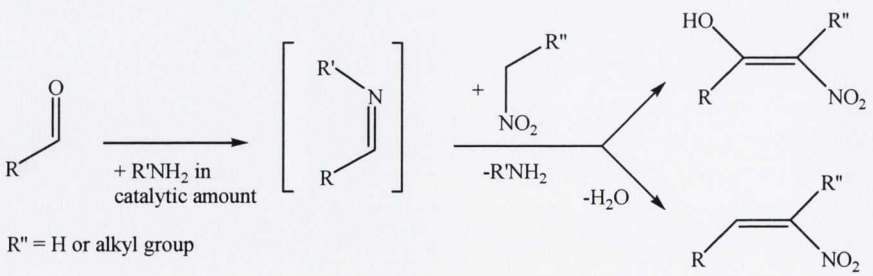
- Knöevenagel condensation



X = -COOH, COOR, -CN
Y = -COOH, COOR, -CN

Figure 1.47. Imine in Knöevenagel condensation

- Addition of "nitroalkyl" to carbonylic compound



R" = H or alkyl group

Figure 1.48 Imine in nitroalkyl addiction

- In the production of Mannich basis

Figure 1.49 Imine in Mannich basis synthesis

Besides it is possible to turn imine to iminium salt trough acid protonation; therefore the iminium salts are also derivatives of carbonilic compounds and they are very useful molecule in organic synthesis both catalytic as stoichiometric amount e.g.:

- In stochiometric amount for direct synthesis of α,β-unsaturated molecule (as in our method before reported).

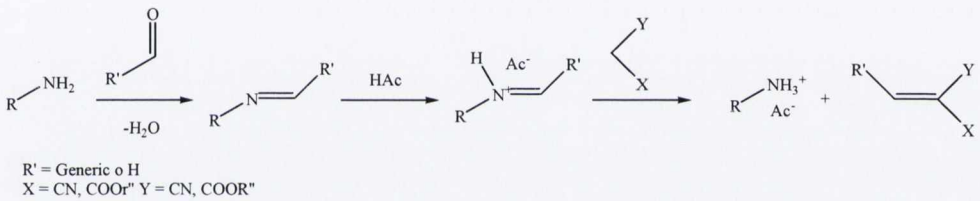


Figure 1.50 Use of imine as organic intermediate in organic synthesis

- Or for production of secondary amine

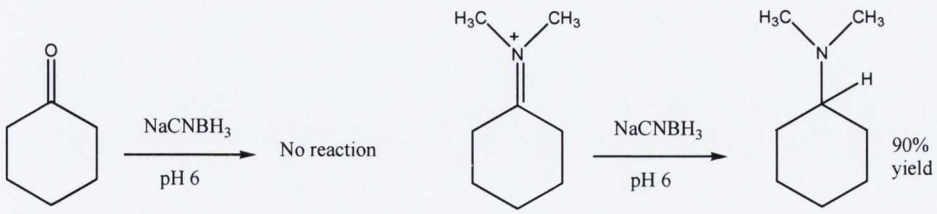
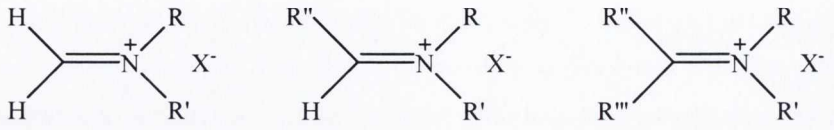


Figure 1.51 Use of imine in stoichiometric amount for synthesis of secondary amine

The methylene iminium salts can be divided into three different types: methylene iminium salts (**1**) derived from formaldehyde; ternary iminium salts (**2**), derived from aldehyde; and quaternary iminium salts (**3**), derived from ketones (see scheme below).



(**1**) (**2**) (**3**)

R, R' = H, alkyl, aryl R'' = R''' = alkyl, aryl
X = Cl, Br, I, BF_4, ClO_4, OTf, CH_3SO_3, CF_3CO_2, etc...

Figure 1.52 Different type of methylene iminium salt

Iminium salts are more electrophilic than the corresponding imines because of their highly polarized C=N bond. Iminium ions have found importance in the synthesis of heterocyclic ring systems[122]. They react as electrophiles in C-C bond-forming reactions, not only with organolithium, magnesium and copper reagents, but also with electron-rich systems such as eneamines, indoles, and hydroxyarenes[123].

The only iminium salts widely available commercially are Eschenmoser's salts[124] $[(Me_2N{=}CH_2)^+I^-]$ or $[(Me_2N{=}CH_2)^+Cl^-]$.

Pioneering investigation by Böhme *et all.*[Error! Bookmark not defined.] into the synthesis, properties and reactions of preformed iminium salts have provided much of the basis for their recent applications in organic synthesis. Important is that all the compound containing carbon-nitrogen double bonds can be hydrolyzed to the corresponding aldehyde or ketones. For imine of ammonia and primary amine the hydrolysis is easy and can be carried out with water, in particular imine of ammonia is seldom stable enough for isolation, and hydrolysis usually occurs *in situ*, without isolation; instead the hydrolysis of Schiff bases with aril substituent is more difficult and requires acid or basic catalysis[125].

1.4 Ionic Liquid

1.4.1 Introduction/History

Ionic liquids (ILs) are materials composed of cations and anions which melt at or below 100 °C. This is the current definition of IL that now day every chemist accepts. Nevertheless the first discovery on ILs is back in the 1914 when Paul Walden observed the liquid form (mp 13-14 °C) of ethylammonium nitrate[126]. After that in the 1934 a patent based on pyridinium chloride ionic liquids[127] was granted for the dissolution of cellulose; unfortunately only after many more years in the 1948 another patent first[128] and open literature later[129] spoke about this new class of solvents. In particular a new 1-ethylpyridinium bromide mix with aluminium chloride ionic liquid was produced. In the following years only a scarce interest was attributed to IL because always moisture sensitive (usually based on $AlCl_3$, See Seddon review[130] for further information) and "chemically complicated". Only in the 1992 appeared the first air and water stable ionic liquids based on imidazolium cation plus acetate, nitrate and tetrafluoroborate counterion[131]. The interest in these new materials was still moderate and only from the beginning of the new millennium more and more potentiality for industrial application and research development has been shown and therefore this topic has been deeply investigated by many research groups and companies.

Additionally, ionic liquids (ILs) were initially introduced as alternative green reaction media because of their unique chemical and physical properties of non volatility, non flammability, thermal stability, and controlled miscibility, today they have marched far beyond this boundary, showing their significant role in controlling reactions as solvent or catalysts[132,133]. Another feature of ionic liquids is their ability to be reused many times. Over the last few years, there have been several reviews published in which ionic liquids occupied a central theme. In these reviews, ionic liquids were considered in terms of (i) how ionic liquids might be useful in catalysis, not only for homogeneous and heterogeneous catalysis but for transition metal-mediated catalysis and organometallic reactions as well[134135] (ii) their use as solvents in organic and bio-organic reactions[136,137], and (iii) their reactivity[138]. However, there are few reviews available that deal with specific reactions in ionic liquids [137,139]. As previously

mentioned, there is a crescent industrial interest in IL and a recent review of K. R. Seddon well resume this particular topic[130].

In conclusion there is a great deal of material to be covered and the only scope of this work is to introduce the reader to this fascinating world of ionic liquid solvents.

1.4.2 Properties/Features

The great interest for such compounds relies on the fact that they posses several attractive properties such as negligible vapour pressure, chemical and thermal stability, nonflammability, high ionic conductivity, wide electrochemical potential window and moreover the ability to act as catalysts. In contrast to conventional solvents that are constituted of molecules, ionic liquids consist of ions and are liquid at room temperature (RTILs) or have a low melting point (generally below 100°C).

Usually the melting point of any inorganic salt is dictated by the electrostatic potential which exist between its cations and anions, and for salts like sodium chloride is very high (m.p. 800 °C). Therefore the melting point is a reflection of this electrostatic potential or better expressed as their lattice energy (Figure 1.53).

$$E = k\,(Q_1 * Q_2)/d$$

Figure 1.53 Lattice Energy equation

In the previous equation, k is the Madelung constant, Q_1 and Q_2 are the charges of the ions and d is the interionic separation. It is clear that the lattice energy increases with higher charge of the ions and decreases with bigger ions distance. It is even more interesting to observe that the lattice energy decreases with the mismatches in size and shape of ions, in other words ions with different sections produces a less efficient ion packing. Then the salts in which there is a consistent ion size and shape mismatch are expected to have lower lattice energy and lower melting point. Moreover the absence of vapour pressure can be justified by the addition of a global electrostatic potential of the sample.

The ionic character of ionic liquids allows them to potentially behave in a very different manner when used as solvents as compared to conventional molecular liquids. A huge

amount of different ionic liquids can be envisioned by the simple combination of different anions and cations. Despite their great potential, most are yet to be investigated and so far only a few types of cations and anions comprise most ionic liquids (Figure 1.54). ILs based on 1,3-dialkylimidazolium cations are by far the most used. In fact from the pure combination of known cations and anions, the types of ionic liquids can reach 10^8, while the most common used and study ILs are only 300-400 types. A so wide family of organic liquid salt definitely suggests a huge potential application.

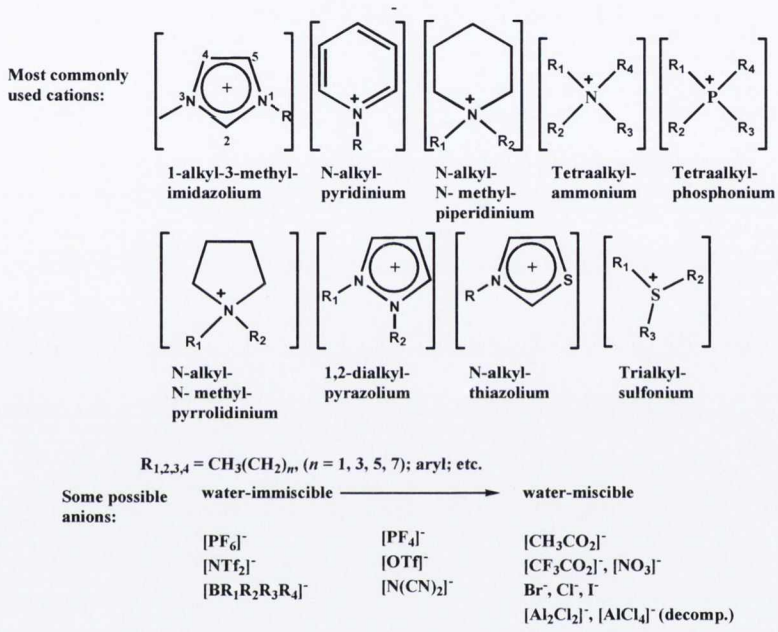


Figure 1.54 Some commonly used ionic liquid systems. The abbreviation [Cnmpyr]+ represents the 1-alkyl-1-methylpyrrolidinium cation, where the index n represents the number of carbon atoms in the linear alkyl chain. [Pwxyz]+, [Nwxyz]+ and [Sxyz]+ are normally used to represent tetraalkylphosphonium, tetraalkylammonium and trialkylsulfonium cations, respectively, where the indices w, x, y and z indicate the length of the corresponding linear alkyl chains, Seddon et al.[140]

By changing the anion or alkyl chain of the cation, one can vary physical properties such as the hydrophobicity, viscosity, density, and solvation of the ionic liquid system. For this reason they have been referred to as "designer solvents"[141]. ILs can be easily separated from the organic products of a reaction but this process usually requires extraction with a non polar organic solvent. Another more industrial suitable approach is based on the distillation of volatile organic products or just the phase separation (e.g.

The BASIL™ process by BASF)[142]. Many authors associate drawbacks to the use of ILs like high viscosities make stirring and homogenization of the reaction medium difficult, with slow dissolution of solids and higher costs as compared to most organic solvents. In fact these is not correct because many examples of not expensive and low viscosity room temperature ILs are known. Furthermore in some cases the ILs have found application just as performance additive[143].

Important seems to underline that ILs have been not only studied and used as simple substitutes to organic solvents for organic reactions but in many cases they acted as reagents or catalysts (task-specific ILs) and as media for immobilizing catalysts or inducing chirality.

Very often the ionic liquids produce an influence on organic reaction and the open question is why and how they produce an effect. Unfortunately there is not a clear answer yet but everybody agrees that "the data on properties, such as dielectric constant, polarity, etc. are not sufficient to explain the solvent/catalyst effect of ILs in organic transformations". Few authors have suggested that ionic liquids act as an organocatalyst[144] example by means of strong hydrogen bonding. On the other hand Welton [135,145] has postulated that the most important effect is from a combination of catalyst and solvent properties. Nevertheless many data are produced and many polarity data based on different methods are available[132,134,146,147].

At this point a short note must be dedicated to the synthesis of ionic liquids. In fact despite the simple structure that usually composes the IL cation, the preparation of the precursor and ILs themselves, they requires plenty of "non-green" chemical compounds and organic solvents. In other words, the preparation of IL is very often not green at all. Nevertheless in the literature are present examples of relatively cheap, easy and "green" to synthesise ionic liquid[130,167], usually obtained by simple neutralization reaction[148,170]. Moreover in the last years Kou and co-workers reported the first example of ionic liquids generated from biomass[149].

1.4.3 ILs as a medium for enantioselective catalysis

Recently J. Durand reported a global overview regarding the recent advances in the investigation of ILs as solvent in asymmetric catalysis[150]. Concerning the catalytic application of ILs a fact particularly interesting for asymmetric catalysis is the reusability and easy recovery of the IL as normally a chiral catalyst has an high-added value. A reported summary about the structures of ILs applied in asymmetric biocatalysis[151] showed the imidazolium alkyl derivates as the most commonly used followed by pyridinium, ammonium and pyrrolidinium salts. Different applications are reported in the field of : enzymatic resolution of alcohols[152] and 1,2-diol with important enhancement in enantioselectivity[153]; asymmetric aldol reaction (mainly proline as catalyst)[154], asymmetric addition of methyl vinyl ketone to aldehydes[155], asymmetric Mannich[156]. Many reactions metal catalyzed have been developed in ILs as well using P and N donor ligand as chiral source for hydrogenation, olefin oxidation, C-C bond formation and miscellaneous. The idea to immobilize the catalyst in the IL phase has been investigated in order to reduce the leaching problem even if in some cases a decrease in selectivity was detected.

1.4.4 ILs Physicochemical properties

The null volatility of ILs has been considered a key property responsible of their increased popularity so this behaviour needs to be understood as much possible at the molecular level. In particular recent experiments have underlined two important limits connected with thermodynamics studies: at room temperature the low vapour pressure are not measurable while at high temperatures the most might decompose. Surprising Earle et al[157] showed the possibility to distill ILs under reduced pressure (below 500 K) and to separate two ILs by distillation. Shortly different research groups worked about the prediction for boiling points[158], measurement for vapour pressures[159] and heat of vaporization of ILs.[160] These experiments showed enthalpies of vaporization between 120 and 200 $kJmol^{-1}$ opening new possibility for gas-phase processes involving IL. The combination of mass spectrometry with any other technique (thermogravimetric analysis) seems to be very promising to analyze vapour even if the routinely determination of ILs thermodynamic properties still very difficult and not always

possible[161] especially at high temperature . This aspect would be very important in order to design ionic liquid with specific properties in terms of vapour pressure and enthalpy of vaporization. However an increasing understanding[162] of ILs behaviour at high temperatures is one of the major safety issues faced by chemical industries. For example adiabatic calorimetric studies of imidazolium ionic liquids exhibited no exothermic activity for the [BF_4], [NTf_2] and [DEP] anions in high temperatures applications but [FSI], [TCM], B(CN)4 anions exhibited exothermic behaviour and pressure increasing as well. This detailed knowledge can favour some ILs applications for large battery packs for electric vehicle and it is necessary for safety reasons.

1.4.5 Task Specific Ionic Liquid (TSIL)

Task specific ionic liquids (TSILs) are a new exiting IL type that can be defined as ionic liquid in which a functional group is covalently tethered to the cation or anion (or both) of the IL[163]. Consequently those new ILs can be use as powerful catalyst, solvent or solvent and reagent of reaction. Even if this is a quite recent topic, the TSIL have already found important application in many fields.

Davis and co-workers first introduce the term "task specific ionic liquid" in 2000[164] when they outlined the concept of designed IL with functional groups able to impart them particular properties and reactivities. One of the first "designed" IL was done to interact in specific ways with a solute, in particular a novel thiazolium-ion based OIL (organic ionic liquid) was showed capable to promote the benzoin condensation[165] (Figure 1.55). The mechanism was suppose to go through an thiazolidene-carbene catalyst capable to condensate two molecules of benzaldehyde together.

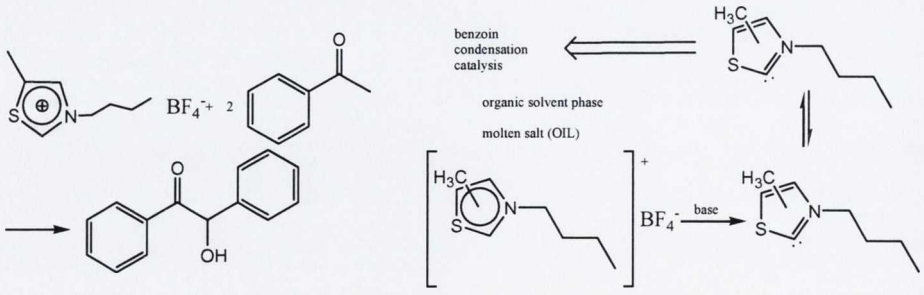


Figure 1.55 Benzoin condensation in ionic liquid

In conclusion the main rationale for the inclusion of functional groups in ILs are:

- Modify the solvent physical properties, H-bond acidity-basicity, polarity, solvatation, etc…
- Introduce functional groups able to covalently bond or catalytically activate a dissolved substrate
- IL as substrate in substitution of a reagent of reaction

1.4.5.1 TSIL synthesis

A consistent number of TSIL are already reported in literature, many of them have active functionalities supported on the cation side of the salt. The Figure 1.56 gives an overview of functionalized imidazolium cations that have been reported.

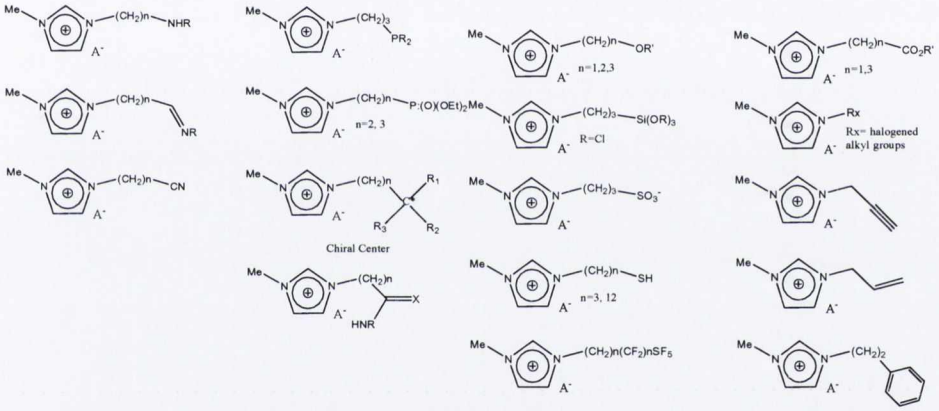


Figure 1.56 Funtionalized imidazolium cations, Xuehui et al.[166]

The most used approach for the synthesis of TSIL was performed by the grafting technique of pre-existing functional group onto the positive ionic part (Figure 1.57) [167]. In other words it was first use a tethering technique based on classic ILs synthesis.

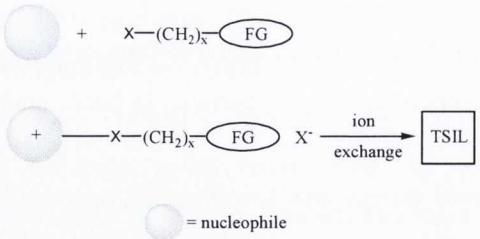


Figure 1.57 TSIL Synthesis by grafting technique

The functional group was usually present on an organic halide and the ionic liquid was generated by displacement from a base like imidazole, phosphine, pyridine, etc... The anion was therefore substituted by the desired one via metathesis reaction. Main disadvantage was the purification of the IL from halide salt usually precipitated as by-product. However complete precipitation of the halides by-product is very difficult and this is known to influence strongly the physical and chemical properties as well, for example, poising catalysts dissolved in ILs[168]; moreover the halide necessarily had to incorporate the desired functional group. A second approach was developed by Wasserscheid and co-workers based on a Michael reaction (Figure 1.58)[169]. In this way a consistent number of new ILs were generated simple reacting suitable ammonium salt with olefins.

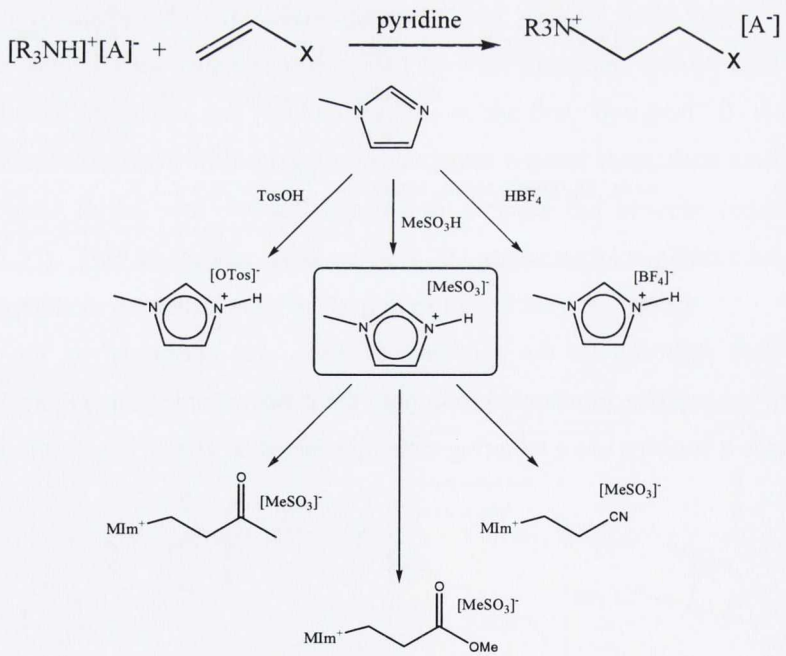


Figure 1.58 TSIL Synthesis by Michael reaction[169]

This approach gave good yields, the metathesis step was avoided and an IL free from halide was easily obtained.

A clever completely new approach for the synthesis of switterionic imidazolium ionic liquid was reported by Ohno and co-workers (Figure 1.59)[170]. In fact Ohno developed a new interesting area called ZIL (zwitterions ionic liquid).

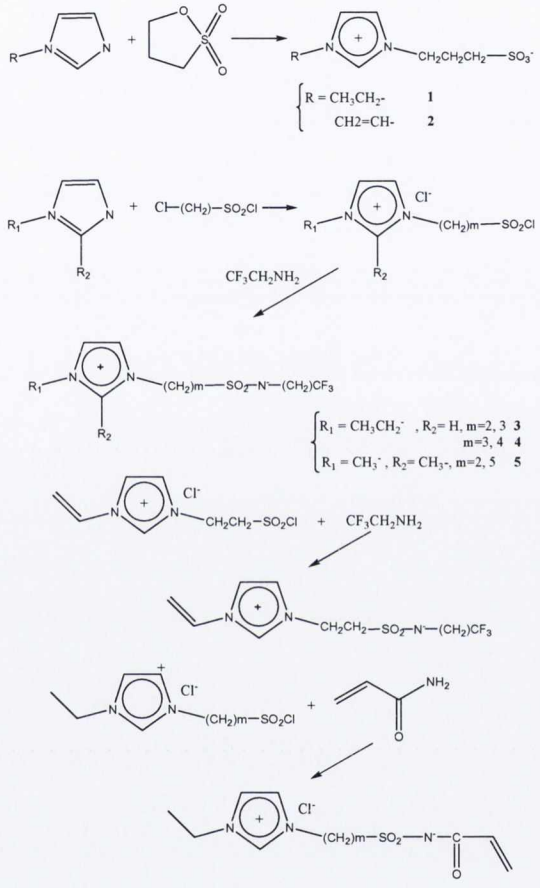


Figure 1.59 Synthesis of Switterionic Ionic Liquid (ZIL)[170]

The chemical opposite of acidic TSILs are those containing basic function, in this case Davis and co-workers[171] reported and imidazolium type ionic liquid containing a tethered primary amine function (Figure 1.60) In the same paper the use as trapping agent against carbon dioxide was showed as well as the intermediate involved in the reaction.

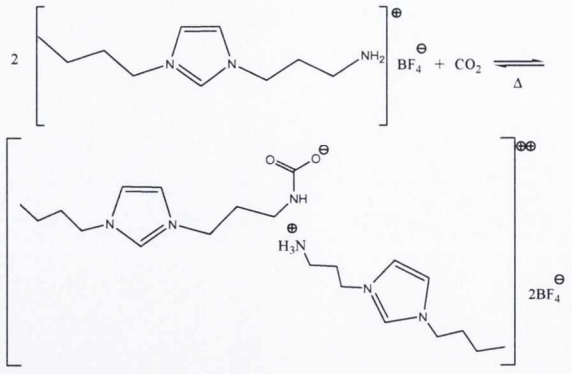


Figure 1.60 TSIL with amine function, Davis[171]

The stable carbamate double salt was observed by ^{13}CNMR and a possible application of basic TSIL was clearly noted. In fact the removal of CO_2 from crude natural gas is now day performed by volatile organic amines and the use of a basic TSIL could easily avoid loss in the gas stream.

In the literature functionalised ILs are generally recognised as ILs with functional groups in the cation. Generally the cation functionalization requires in most cases only a single reaction step, making them relatively easy to prepare. However the viscosity of ILs is a key property, especially in large-scale applications and electrochemical device application like solar cells, and usually ILs containing functionalised cations have higher viscosities compared to conventional ionic liquids with the same anions. Recent research in order to overcome this problem have showed that asymmetrical anions with higher content of fluorine atoms can reduce significantly the viscosity of the resulting ionic liquid. It is in fact commonly accepted that the anion structure controls the properties of the ionic liquid, however the develop of new ILs with functional anions has not attracted many interests so far. Compared to functionalized ILs with functional groups in the cations, only a very few dual-functional ILs are known, elucidating the functionalities of the anion-functionalised ionic liquids are even rarer to see in the literature. This trend might be explained considering that the functionalization of the anion requires multi-step reactions and skills in organic synthesis. However the most of the examples are based on readily available materials (Figure 1.61) as transition metal oxides[172], aminoacids and transition metal carbonyl[173]. Very recently there are some anions on triazole backbone reported; they have potential applications in energetic materials.[174]

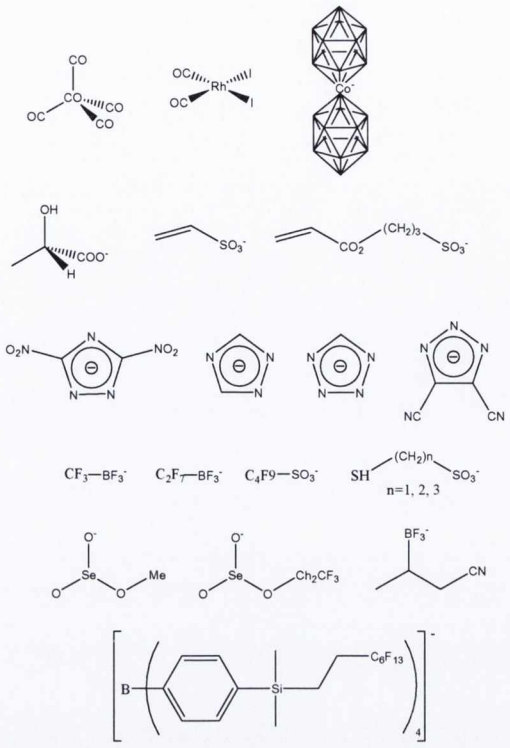


Figure 1.61 TSIL With functional Anions

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Chapter 2

2 THE IMINE APPROACH

2.1 Introduction

Cyanoacrylate adhesives have a number of ideal properties, such as their one-part solvent-free formulations and room-temperature curing but the physical performance of these adhesives limit their more widespread use As so-called "Instant Adhesive" cyanoacrylates are extremely reactive monomers, and are intolerant towards most nucleophiles. It is thus difficult to conduct chemistry on pure isolated materials. As a result, structural (hence property) modifications are difficult and the use of standard modification methods is limited. By developing cyanoacrylate monomers with enhanced performance that satisfy the demands of structural adhesive applications, and through the addition of useful new properties, new applications for cyanoacrylate adhesives may be possible. Therefore the need of new synthetic procedures to yield modified cyanoacrylate (CA) monomers by a truly pragmatic route suitable to industrial processing, represents an important technical challenge in need of a solution. The objective of this work is to consider completely new approaches to address this problem.

Herein an original mild synthetic approach is detailed. Potentially this mild approach allows the production of new multifunctional cyanoacrylates by a commercially viable route.

2.2 Benchmarking: Preparation of Ethyl Cyanoacrylate (EtCA) by Knöevenagel reaction and Thermal Depolymerization

The first work undertaken was to explore the classical route to cyanoacrylates via Knöevenagel reaction. This preliminary study was important to understand the real problem of this synthesis and in order to gain experience with reactive monomers. The Knöevenagel route for cyanoacrylate production consists of a two-step reaction. The first is the aldol condensations between alkyl cyanoacetates and formaldehyde under basic catalysis (usually secondary amine) for the production of a cyanoacrylic polymer (so-called "pre-polymer"). The second step consists ot the neutralization of the base then thermally cracking the polymer with cracking temperatures up to 200 °C and under vacuum. The cyanoacrylate monomer is isolated by distillation. The reaction was first performed on a small scale using 4.2 g of paraformaldehyde, 16.6 g of ethyl cyanoacetate (EtCAcet) and only the first step of reaction was performed.

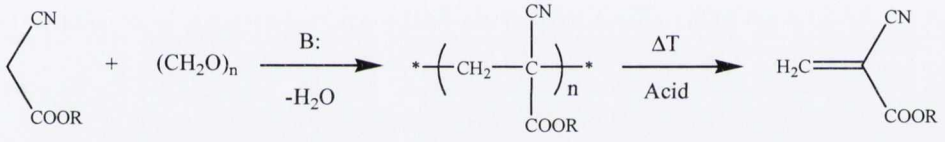


Figure 2.1. Knöevenagel reaction scheme

All the glassware employed was previously washed with acidic water (dip overnight in 5% aqueous sulfuric acid solution), carefully rinsed with tap water and dried in order passivate glass surfaces to prevent nucleophilic polymerization. A round bottom flask was equipment with a mechanical stirrer and Dean-Stark apparatus for azeotropic distillation. The mechanical stirring is important because the polymer obtained from the reaction of formaldehyde with EtCAcet was viscous and became more viscous when the solvent was removed. The polycyanoacrylate was produced with quantitative cyanoacetate conversion after 2h in refluxing heptane.

Subsequently the reaction scale was increased to 8.4 g of paraformaldehyde and the second stage polymer cracking was conducted. The EtCA monomer was obtained in good yield (60% weight yield) after the first distillation. A larger reaction was carried out with 42 g of paraformaldehyde and some problems were noted, mainly in the

distillation step. The thermal cracking was performed at 180-200 °C and 4 mbar vacuum but unfortunately after partial distillation of the monomer, some oligomer blocked the Liebig condenser (the ethylcyanoacrylate is a very reactive monomer and not stable even in acid washed glassware without additional stabilizer). The reaction was repeated in the presence of boron trifluoride diethyl etherate (0.5% by mole) as gas phase stabilizer to prevent nucleophilic polymerization. With this latter technique it was possible to obtain EtCA in 50% yield after distillation and without any polymerization inside the equipment. A further distillation was necessary to obtain high purity sample (b.p. 60 °C at 4 mmHg).

This initial work illustrated some practical problems associated with the Knöevenagel process for CA synthesis. It was noted that vapour phase stabilization during distillation and the use of acid washed glassware are important aspects of the preparation of reactive monomers.

2.3 Study on formaldehyde activation for crackless synthesis of monomeric EtCA

Some reactions (Table 2.1) were performed on a small scale in order to explore the reactivity of formaldehyde under different conditions. In general the aldehyde functional group is reactive towards nucleophilic species under basic or acid catalysis. Formaldehyde is the simplest aldehyde and its monomeric form is a gas with pungent smell. The more common commercial forms are paraformaldehyde and trioxane as polymers and formalin as an aqueous solution of the monomer (Figure 2.2). It is important to appreciate that formaldehyde has particular reactivity which is also influenced by its physical form. Some reaction tests or stability studies were performed directly in $CDCl_3$. This solvent was used in order directly check the reaction by high field NMR. Moreover all these preliminary tests were performed in small scale and only few milliliters of $CDCl_3$ were necessary. In order to optimise the reaction it was decided to use the NMR technique, as a fast method for looking the real composition of the crude. The reactivity results of formaldehyde with EtCAcet are shown in Table 2.1.

Table 2.1. First attempts on crackless synthesis of monomeric EtCA

Entry	Solvent	Catalist (g)	Temperature (°C)	Time (h)	Result
1	-	-	80-100	3	No reaction occurred
2[a]	-	-	80-100	3	No reaction occurred
3[b]	-	KSF (1)	100	3	Small monomer amount was observed and large amount of paraformaldehyde sublimed into the condenser
4[b, c]	-	KSF (0.5) + Na_2SO_4 (0.5)	100	2	Large amount of polymer was observed
5[d]	Ethyl acetate	Na_2SO_4 (1)	90	2	Small amount of free monomer was obtained
6[b]	Ethyl acetate	KSF (1)	90	2	No product was observed
7[c]	-	H_2SO_4 (0.5) + CH_3SO_3H (0.3)	100	0.5	Trace of monomer were observed but Production of gas occurred after longer reaction time
8	-	NaX[e] (1)	60	3	No product was obtained more large amount of aldehyde sublimed
9	$CDCl_3$	NaX[e] (1)	60	3	
10	CH_3NO_2	NaX[e] (1)	80	3	No reaction occurred

[a] 1,3,5-Trioxane was used instead of paraformaldehyde; [b]Zeolite type KSF, [c] Reaction performed in a closed flask employing screw capped test tube with rotational movement in order to mix tube contents; [d] Dean Stark apparatus was employed; [e] Zeolite type NaX;.

Observations:

Under these experimental conditions (Table 2.1, Entry 1, 2) no reaction seemed to occur. This behaviour probably shows that temperature alone is not sufficient to activate the aldehyde reagent (both 1,3,5-trioxane and paraformaldehyde).

1,3,5-Trioxane

CH_2O

(37 w % H_2O sol.)

Formalin

$(CH_2O)_n$

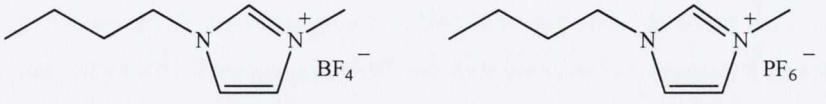
Paraformaldehyde

Figure 2.2. Commercial formaldehyde sources

Various catalysts were subsequently assessed to examine if the monomer could be produced under Knöevenagel conditions but without the formation of a pre-polymer.
Using catalyst (Table 2.1, Entry 3) some monomeric product was observed (^{1}H NMR). However, under these conditions, one problem was encountered because solid paraformaldehyde formed in the condenser; probably the KSF catalyst was able to depolymerise the paraformaldehyde giving the monomeric gas that re-polymerised inside the condenser. Using KSF + Na_2SO_4 (Table 2.1, Entry 4) only the formation of large amount of polymer was obtained. These results were important since they illustrate that KSF could depolymerise the paraformaldehyde and promote the reaction with the activated methylene base. However polymerisation of the monomer still occured.
Operating in solution and in the presence of a dehydrating agent (Table 2.1, Entry 5) it was possible to underlining the importance of water removal in order to avoid polymerisation of the monomer since water is nucleophilic enough to initiate polymerization.

2.3.1 Use of Ionic Liquids (ILs)

In order to explore the reactivity of non-classical solvents the potential use of some ionic liquids was studied. Previous work[175, 176, 177] reported the ability of ionic liquids (ILs) to promote nucleophilic attack on certain aldehyde compounds in the absence of base catalyst, following the classic Knöevenagel condensation. Therefore the two ILs shown in Figure 2.3 were chosen (1-butyl-3-methylimidazolium hexafluorophosphate = [bmim]PF_6; 1-butyl-3-methylimidazonium tetrafluoroborate = [bmim]BF_4) and some tests of reaction were performed.



[bmim]BF_4 [bmim]PF_6

Figure 2.3. Tested ionic liquids

The results are summarized in **Table 2.2**:

Table 2.2. Attempts in ILs

Entry	Solvent	Catalyst (g)	Temperature (°C)	Time (h)	Results
1	$[bmim]PF_6$	-	r.t.	24	No product was observed also at higher temperature or for longer reaction time
2	$[bmim]BF_4$	-	r.t.	24	
3	$[bmim]PF_6$	KSF (1)	80	3	Trace of monomer was observed
4	$[bmim]BF_4$	EDDA[a]	40	15	Some amount of polymer was observed

[a] EDDA = ethylenediaminediacetate

It may be concluded that the particular reactivity that these ionic liquids showed in previous work[175, 176, 177] it is not evident in the presence of paraformaldehyde.

2.3.2 Stability test of EtCA

2.3.2.1 Stability study of the monomer in the presence of molecular sieves, NaY zeolite, NaX zeolite and Na_2SO_4

Previous experiments reported some reactions with different dehydrating agents, or solid catalysts or ionic liquids. It was also important to check the compatibility and stability of target product against various reagents etc. Some of these were accomplished on the stability of monomeric EtCA on KSF, molecular sieves and Na_2SO_4 using $CDCl_3$ as solvent in order to examine directly and without any further "work-up". ^1H NMR was considered the best way to follow formation of the monomeric EtCA in a small scale without distilling the monomer. Non-stabilized pure EtCA (Henkel-Loctite) was used as reference. It was observed that the NaY zeolite causes the polymerisation of EtCA. On the contrary, NaX zeolite did not affect the stability nor did acid washed molecular sieves.

Further tests were carried out and the product (stabilized with sulphur dioxide) was stable for long time (1 week) in the presence of KSF and Na_2SO_4 but only for some hours in the presence of molecular sieves (not acid washed).

2.3.2.2 Stability study of the monomer in different IL_s

The stability of EtCA was studied by ^1H NMR in the presence of three different ionic liquids. Samples were prepared thus: IL (0.5 mmol), $CDCl_3$ (1 ml) and EtCA (0.5 mmol). The sample were examined by ^1H NMR immediately after reagent mixing, after a day at room temperature and after 2 days at r.t. plus 2 hours at 60 °C. The results were as follows:

a) With [bmim]BF_4 no formation of polymer occurred; the mixture was not altered after 2 days (even if heated);

b) With [bmim]PF_6 no polymer occurred after 1 day. After 2 days the amount of monomer slightly decreased in comparison with IL signals;

c) With [bmim]CH_3SO_3 there was no polymerisation after 1 day but the monomer almost quantitatively polymerised after 2 days.

Conclusion:

Many different approaches for the direct synthesis of ethyl cyanoacrylate were analysed but all of these had significant problem. Therefore it was possible to reaffirm the lack of probability of producing monomer directly without cracking prepolymer using the Knöevenagel reaction.

2.4 A New Synthetic Approach: "Imine Approach"

2.4.1 Why and How?

The aim of the present work was to find an inexpensive, green method to produce cyanoacrylate monomers under mild conditions, without stoichiometric production of water of condensation. A mild reaction infers one that need not revert to a thermal depolymerization of an oligomer. The main idea was to employ a derivative of paraformaldehyde in order to eliminate water (due to the dehydration step) by the environment of reaction. Intense study of different heteroatoms able to replace the oxygen atom was made. One possibility was to replace the oxygen with sulphur producing thioaldehyde. Therefore the derivative of formaldehyde with hydrogen sulphide (H_2S) was produced according to the literature[178, 179] by gentle bubbling of gas into aqueous solution of formalin and hydrochloric acid. In this way thioformaldehyde in trimeric cyclic form was produced. Subsequently different operative conditions were used (acid catalysts, basic catalysts, Lewis acids) but unfortunately no positive results were obtained. Another possibility was to substitute the oxygen with phosphorus but immediately it was rejected on the basis of cost. The last possibility was to replace the oxygen with nitrogen atom. In particular producing an imine (or Shiff base or aldimines). This intermediate immediately appeared attractive because it is easy to prepare, it is a stable compound, it has good reactivity and very good proprieties for acrylate synthesis. The imines are very stable[180] as compared to other Shiff bases known heretofore and this greater stability results from the particular structure of the aldimines. Because these compounds are so stable they can be readily purified, for example by distillation. One problem of using this intermediate in order to produce acrylate monomer is the fact that free amine (strongly nucleophilic) is liberated after reaction producing fast polymerization. To prevent this an acid was added. The acid addition was very important to catalyse the reaction (by additions of acid an iminium salt was produced by imine protonation[181] but also to create a favourable environment where cyanoacrylate monomer should be stable. It is known that the main acrylate polymerization mechanism is anionic polymerization and that it occurs in presence of both strong and weak nucleophile; therefore with amine compound there is fast polymerization, however protonation of the amine removes the its nucleophilicity.

2.4.2 The "Imine Approach" for EtCA Synthesis

In order to explore this new "Imine approach" that could avoid the elimination of water (detrimental for target EtCA monomer), N-methylidene-*tert*-butylamine (*tert*-butyl imine) was prepared in the presence of acidic catalyst. The rationale behind this approach is summarized in Figure 2.4.

The cyanoacrylates are highly reactive compounds so the choice of reaction solvent was limited. In particular it was important to use a solvent that could solubilize the reagents stabilizing the monomer product. It should have high boiling point and be deuterated in order to directly observe the crude reaction by ^{1}H NMR. After some preliminary tests it was decided to use the deuterated chloroform as reaction solvent for small scale preliminary reaction. Dimethylsulfoxide (DMSO) and dimethylformamide (DMF) were tested but they polymerized the cyanoacrylate monomer.

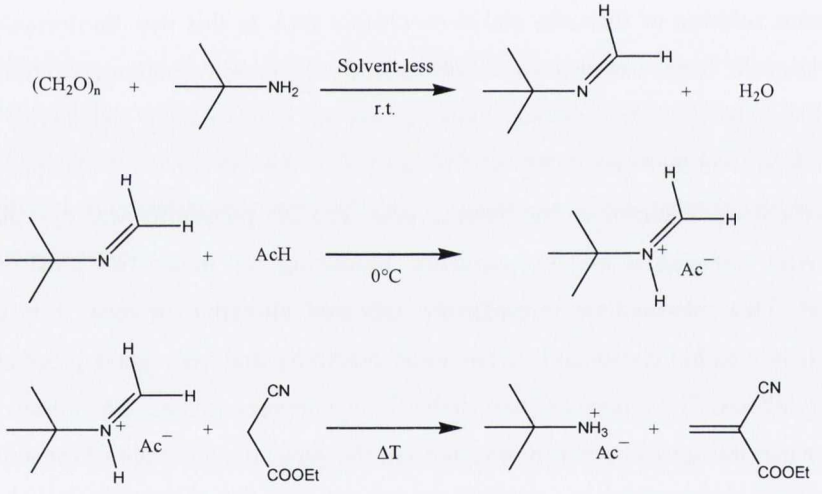


Figure 2.4. Overall scheme of the "Imine Approach"

In the new approach a simple imine is formed in a high yielding solventless reaction and water is removed in a separate step. In the second step the imine during neutralization with strong acid yielding an iminium salt in solution. In a final step the activated methylene compound is added directly to the solution of the iminium salt and target monomer is observed after mild heating.

2.4.3 Synthesis of N-methylideneamines (imines) and by-product analysis

Several references[182,183,184] describe the production of different formaldehyde imine intermediates. Initially it was decided to synthesize and to use the low cost material *tert*-butyl amine for synthesizing the corresponding imine. This was chosen because the *tert*-butyl imine intermediate had useful features for this research. They were the easy synthesis, the intermediate boiling point (85 °C) and the stability of the imine intermediate (in order to have the possibility to heat the reaction if necessary). The stability is connected with the molecule structure and in particular with the presence of a tertiary carbon atom in α position to amine group.

tert-Butylimine was obtained starting from both paraformaldehyde and formalin (37% aqueous solution).

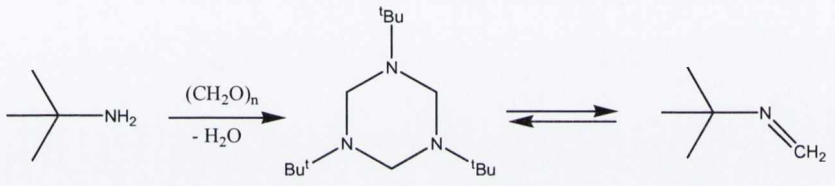


Figure 2.5. tert-Butylimine monomeric/trimeric equilibrium

As noted[182] the pure N-methylidene-*tert*-butylamine (slightly yellow oil) was in equilibrium with the respective trimer (1,3,5-tri-tert-butyl-l,3,5-triazacyclohexane). In particular by ^{1}H NMR and ^{13}C NMR studys of the neat imine the trimeric form is the only form detected. The corresponding monomer could be obtained either after dilution in polar solvent (e.g. chloroform) or by temperature effect (e.g. the distillation of the monomer occurs at 65 °C at atmospheric pressure but the trimer is immediately recombined after condensation).

2.4.3.1 Tert-butylimine (N-methylidene-tert-Butylamine) purification

It was observed that the synthesis of *tert*-butylimine gives a variable amount of side-product. The side-product was definitively identified as 5-*tert*-butyl-1,3,5-dioxinane (Figure 2.6, right):

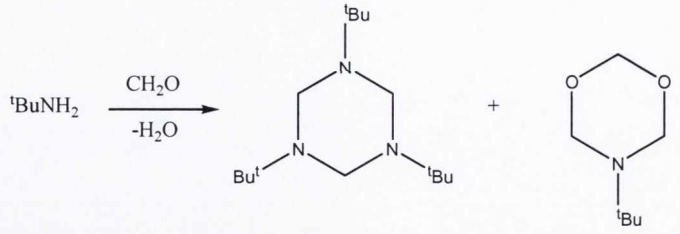


Figure 2.6. Preparation of 1,3,5-Tri-*tert*-butyl-1,3,5-triazacyclohexane

Partial purification of the imine was obtained by distillation using "bulb to bulb" (Kugelrohr apparatus) distillation under high vacuum. Indeed the side-products are more volatile than the trimeric imine. Subsequently, in order to proceed with the purification of larger amount of intermediate the purification of the imine reagent was performed by conventional distillation at atmospheric pressure. Different columns were employed, i.e. Hempel and Vigreux, without satisfactory results. However good results were obtained using Fischer distillation apparatus (with highly efficient column for fractional distillation). The fresh distilled imine appeared as a colourless oil with high mobility. An important observation was made during purification (Kugelrohr) under vacuum. The first fractions were side-products enriched by this method. On the contrary, heating (90-100 °C) at atmospheric pressure, the side-products were mainly left in the pot. A possible explanation was given considering that the imine reagent was basically in the trimeric form, by heating it was distilled in the monomeric form (thermal depolymerisation) and reverted to trimer after condensation (near 25 °C). Dilution in solvent (as observed by NMR) or heating produced the formation of the monomeric imine form. Therefore, under high vacuum distillation the operative temperature was lower ($\leq$ 50 °C) and so mostly the trimer was present with the side-product. The latter are more volatile than the trimer and distilled along with only a small amount of monomer.

2.4.3.2 Other imine synthesis

Some time was spent preparing other imine derivatives of formaldehyde[182, 183, 184 30, 31, 32] such as *n*-butylamine, *n*-propylamine, benzylamine, phenylamine and methylamine.

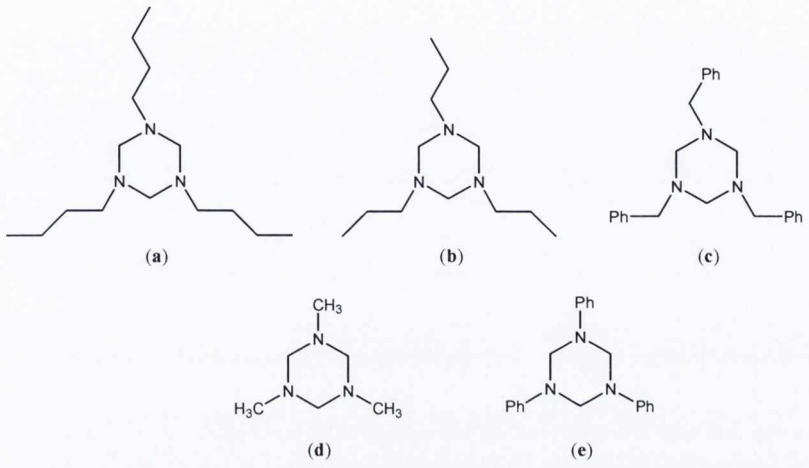


Figure 2.7. Various synthesized imine derivatives of formaldehyde; *n*-nutylimine (**a**), n-propylimine (**b**), benzylimine (**c**), methylimine (**d**), phenylimine (**e**)

Methylimine was prepared mixing paraformaldehyde and the aqueous solution of methylamine (40%) stirred at room temperature for 2 h. The product was extracted with dichloromethane and dried. It was identified to be the trimer of imine by ^{1}H NMR spectrum. N-propylimine and n-butylimine were prepared following the same procedure previously described for tert-butylimine (solventless reaction at r.t.). Benzylimine was prepared mixing the reagents in chloroform at r.t. in the presence of Na_2SO_4, phenylimine was prepared mixing aniline and paraformaldehyde in chloroform at r.t. then stirring 3 h at 50 °C.

In all these cases the imines were obtained in trimeric form while the monomer was not observed at equilibrium.

2.4.4 Study on catalyst, temperature and time reaction optimization

The first reactions were carried out directly in $CDCl_3$ on a small scale (5 mmol). A very interesting result was obtained, since the free monomer was easily observed. The yield was estimated by NMR (ratio to the EtCAcet and EtCA) was about 25-30%.
The imine derivative was reacted with EtCAcet also in two ionic liquids ([bmim]BF_4 and [bmim]PF_6) and gave the monomer EtCA but in lower yield. This approach seemed to be interesting and potentially optimizable by changing different reaction parameters (ratio acids, dilution, solvent, temperature and time of reaction). Use of an IL solvent is appealing because it could facilitate separation of the volatile monomer by distillation. After several tests the best result was obtained in $CDCl_3$ using a slight excess of acids (1:1 mixture of sulfuric acid and methane sulphonic acid), at 40 °C for 3 hours (40% yield).

2.4.4.1 Variation in ratio of strong acids (CH_3SO_3H/H_2SO_4)

Further studies were directed to optimize the amount and ratio of the acidic catalysts permitted to increase the yields previously obtained. The best (CH_3SO_3H/H_2SO_4) ratio was 1:1.4 employing the acids in slight molecular excess. Very particular behaviour was observed when the reactions were stopped at low monomer yield (< 20-30%): the reaction crude was clear, yellowish and a little opalescence was observed at the end of reaction, which disappeared after cooling to room temperature. Different behaviour was observed at higher conversion. When the reactions had about 50% yield it was possible to observe a phase separation in the reaction flask. The two different phases were analyzed. Immediately it was clear that the upper phase (yellow coloured) contained ammonium salts, acids plus a small amount of EtCAcet and EtCA. The lower phase was colourless and contained mostly EtCA, EtCAcet, chloroform plus a small amount of acids and ammonium salts. The analysis confirmed the proposed reaction route summarised in Figure 2.4 and the mechanism involving Mannich adducts was formulated to explain the reaction in detail (Figure 2.8). This approach is highly interesting as it shows the production of free (un-polymerised) monomer in a way not previously described.

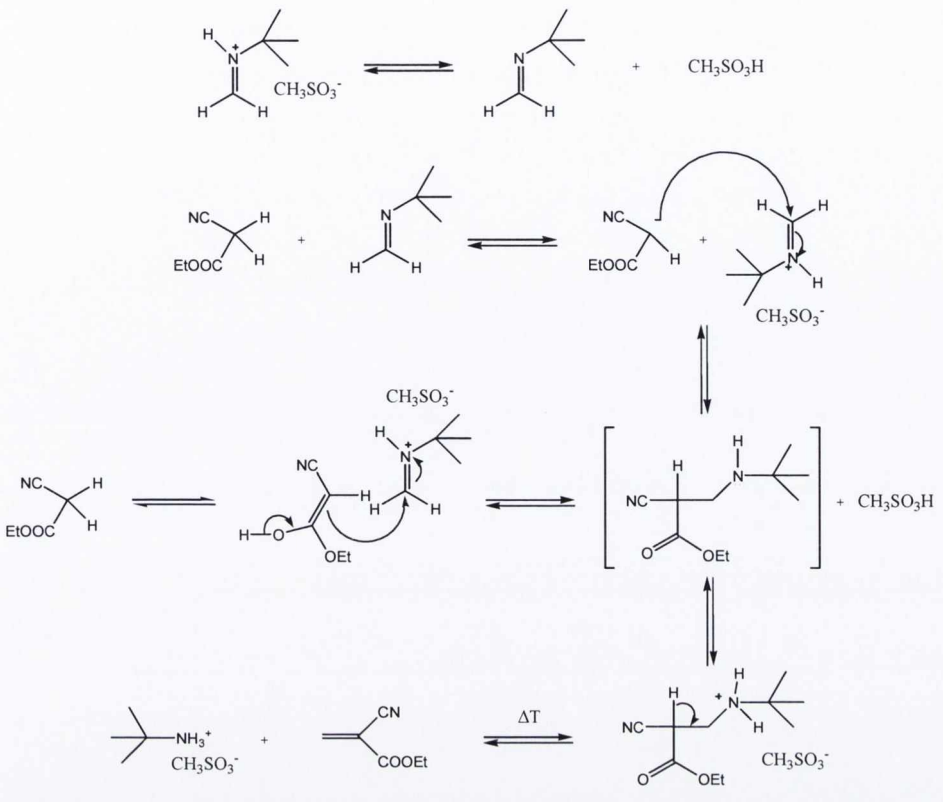


Figure 2.8. Proposed mechanism of Imine Reaction

2.4.4.2 Effect of the Acid nature

In order to explore the behaviour of the model reaction with different acid catalysts, various acids were used. A test was carried out using HCl as 'protonating' acid. For this reason dry gaseous HCl was bubbled into the solution of chloroform and imine. Unfortunately the iminium salt was not observed. Phosphoric acid, trifluoromethansulphonic acid, acetic acid and trifluoroacetic acid were also studied. The reaction carried out with H_3PO_4 at 40 °C seemed to produce polymer and in short time almost all the activated methylene base reagent disappeared. With acetic acid the reaction was fast, only polymer was produced and no monomeric EtCA was formed. Similar behaviour was observed with trifluoroacetic acid. Completely different behaviour was obtained using trifluoromethanesulfonic acid. After 30 minutes at 40 °C only little amount of product was observed. There was no change with prolonged reaction time. Moreover some amount of side-product was observed and at the end of

reaction the iminium salt was still present. No one of the tested acids gave phase separation, only the MSA/H_2SO_4 blend seem to have this peculiar property.

2.4.4.3 Use of a single acid as catalyst

Whereas good results were obtained with a mixture of methanesulfonic and sulfuric acid the use of a single acid as catalyst would be preferred.

It was verified that H_2SO_4 alone did not promote the reaction at all. Thus when sulfuric acid alone was added to imine in $CDCl_3$, it was not possible to observe the typical iminium signals by ^1H NMR. Tests made adding MSA produced a well resolved multiplet for iminium group.

The MSA was able to promote the reaction alone but gave low yield of monomeric EtCA plus polymer formation. Then the mixture of MSA and H_2SO_4 was important in order to generate a biphasic system and to prevent the product polymerization.

2.4.4.4 Importance of acid addition order

The addition order of acids was investigated in order to underline different roles played by each. The *tert*-Butylimine reagent was carefully purified by Kugelrohr distillation and reacted with acid. The results are summarised in the Table 2.3.

Table 2.3. Effect of acid neutralization on tert-Butylimine in the imine approach to CA synthesis

Entry	Addition order	Yield 1h (%)	Yield 3h (%)
1	a) H_2SO_4 b) $MeSO_3H$	38	41
2	pre-mixed	48	56
3	a) $MeSO_3H$ b) H_2SO_4	60	64

The addition order was found to be an important parameter. The best results were obtained (Table 2.3, Entry 3) adding first the methanesulfonic acid and then the sulfuric

acid. This method was deployed subsequently for the synthesis of EtCA. The reason for this behaviour does not find an easy explanation but it can be ascribed to a partial degradation of the reagent after direct addition of sulfuric acid.

2.4.4.5 Reverse addition and distillation of monomer

A further variable was reagent addition. Thus two reactions were performed with reverse addition of EtCAcet and iminium salt. The reactions conducted at a larger scale (from 5 mmol to 20 mmol) for the subsequent distillation of the monomer. The reaction in 20 mmol scale was carried out into a two neck round bottom flask already assembled with classic distillation equipment. The test was conducted at 65 °C (to avoid solvent evaporation). After two hours the distillation was carried out (heating under vacuum). NMR analysis of the crude showed 35-40% of yield monomer. In order to avoid polymerisation catalytic amount of $BF_3{\cdot}Et_2O$ was added time by time during the distillation step. The distilled fraction contained both EtCAcet and EtCA monomer (27% yield). This result showed the importance of complete conversion in order to avoid subsiquest difficult separation of reagent and product in the distilled fraction, as they have very close boiling points.

2.4.4.6 Exploration of solventless reaction

The model reaction (Figure 2.4) was explored in solventless conditions to see if further simplification was possible. The first tests were carried out at r.t. in the presence of $MeSO_3H$ or a mixture of H_2SO_4 and $MeSO_3H$, giving trace of product. This encouraging preliminary results prompted a more detailed study of solventless conditions.

Two reactions were investigated using (a) the mixture of $MeSO_3H$ and H_2SO_4 or (b) $MeSO_3H$ alone. In both cases after 15 min at 70 °C, the monomer was obtained in 25-30% yield, and after 30 min the monomer was accompanied by a large amount of polymer. The main conclusion here was the high reactivity under solvent free conditions. The problem was the need to stabilize the monomer once produced. Sulfuric acid was again examined as the sole acid under solvent free conditions.

The results are summarized in the Table 2.4.

Table 2.4. Effect of acid and solvent free condition on the imine reaction

n.	Catalyst	mmol[a]	Temperature (°C)	Time (h)	Monomer	Phase separation	Polymer
1	H_2SO_4	5.2	r.t. + 70	1 + 0.5	Trace after 1 h at r.t., possibly[b] 30% after 30 min	After 30 min at 70 °C	Some polymer produced
2	H_2SO_4	5.2	40	7	Trace after 1 h; small amount at 6 h	After 30 min	Small amount observed at 6 h
3	H_2SO_4	3.4	r.t. + 70	1 + 0.5	16% after 1h; after heating only prepolymer	Not observed	Large amount after 30 min at 70 °C
4	H_2SO_4	3.4	40	1	Small amount	Not observed	Small amount after 30 min, then increasing
5	H_2SO_4	5.8	r.t. + 70	1 + 0.5	Trace at 1h, small amount after heating	At r.t. but not observed at 70 °C	Small amount, but probably polymer not soluble in chloroform (hampered stirring)
6	$MeSO_3H$ H_2SO_4	2.4 3.44	r.t. + 70	1 + 0.5	Absent at r.t., about 25% at 70 °C	Not observed	Not observed

[a] Acid employed with 5 mmol of imine; [b] The evaluation is was made by internal normalization (i.e. referred to un-reacted EtCAcet) in the upper phase; but some amount of unreacted reagent was detected also in the viscous lower phase; all the yields of reaction were evaluated by NMR.

In all the reactions reported above the acid was added to a solution of imine and chloroform (using typical procedure), then EtCAcet was slowly added. Before starting the reaction the chloroform was removed under vacuum.

After these tests in solvent free conditions it was possible to say that both solventless and in chloroform solution, the presence of sulfuric acid alone was detrimental for acrylate production. The presence of methanesulfonic acid alone was useful to promote the reaction but it was not itself suitable to stabilize the monomer in high yield.

2.4.4.7 Two step reaction

It was previously reported that a biphasic system was observed at the end of the reaction when high yields were obtained. In details the chloroform phase (lower) contained monomeric EtCA and unreacted EtCAcet along with some $MeSO_3H$. In the upper phase (yellow) $MeSO_3H$, H_2SO_4, protonated *tert*-Butylamine with only a small amount of monomer and unreacted cyanoacetate were observed. A new two step procedure was designed to improve the previous results: the top organic layer was removed after 3 h of reaction at 70 °C and a second aliquot of iminium salt was added to the lower phase under magnetic stirring (1.5 h at 70 °C). After the second step a further phase separation was observed. The lower phase became enriched with monomer up to a 75% yield.

2.4.4.8 Used Eschenmoser's salt in the typical procedure of reaction

Eschenmoser's salt is the only iminium salt present as commercial reagent (N,N-dimethylmethylene ammonium iodide). Its reactivity was tested using EtCAcet as reagent. The salt had poor solubility in chloroform. The reaction performed with the iodide salt only gave large amount of polymer; the reactions with sulfuric acid only didn't occur. Thus the reactions with methanesulfonic acid only gave higher conversion but the product polymerized. When MSA and H_2SO_4 were added a colour change was noted and the solubility increased. After heating at 70 °C for 3h the reaction showed to be non-selective and gave the monomeric EtCA in low yield and a large amount of side-products.

2.4.4.9 Use of ILs

The Knöevenagel[185] condensation of various aldehydes with various active methylene compounds to give α,β-unsaturated compounds in ionic liquids had recently reported good results (never with formaldehyde and CAcet). Therefore the "imine approach" was studied using IL. The first tests were performed using [bmim]BF_4 (1-butyl-3-methylimidazolium tetrafluoroborate) with additional MSA or a mixture of H_2SO_4/MSA. Heating at 60-80 °C caused the formation of polymer, but the reaction carried out at r.t. gave monomeric EtCA in 20% yield. This result was lower than that

obtained in $CDCl_3$, but it was quite promising because it showed the high reactivity in ILs. When [bmim]PF_6 (1-butyl-3-methylimidazolium hexafluorophosphate) was used similar results were obtained. Further tests of reaction were made with iminium salt in [bmim]CH_3SO_3 (1-butyl-3-methylimidazolium methanesulfonate) but some problems emerged. Firstly this ionic liquid is solid at room temperature and only become liquid above 80 °C, therefore it was not possible to use the typical procedure for synthesis of EtCA monomer.

The crude reaction mixture was examined by ^{1}H NMR after 15 min and 1 hour. In both cases acrylic monomer did not result but only polymer and small amount of unreacted EtCAcet.

2.4.4.10 Model reaction behaviour with different imine reagents

In order to have a complete overview about the synthesis of EtCA monomers by direct routes identified in the current work, the effect of the imine structure on the reaction outcome was studied. In addition phenylimine, methylamine, propylimine and n-butylimine were prepared and tested. Only methylimine (obviously *tert*-butylimine) and EtCAcet under typical reaction conditions (70 °C for 3 h) gave 18% yield. It is clear that the structure of the carbon in α position to the nitrogen has a key role. Then any imine tested with an α primary carbon produced product and not polymer. The reason for this behaviour is not clear and the only hypothesis can be associated to isomerisation of the double bond.

2.4.5 Synthesis and stability study of iminium salts

As previously noted the new synthetic approach required protonation of the imine by acid. A study was made in order to explore the stability of iminium salts (always by ^{1}H NMR). Three samples were prepared, with the addition of 1,1,2,2-tetrachloroethane (s, δ 5.91 ppm) as internal standard.

a) *tert*-Butyl-imine (1 eq) + MSA (1 eq);
b) *tert*-Butyl-imine (1 eq) + MSA (2 eq);
c) *tert*-Butyl-imine (1 eq) + MSA (0.48 eq) + H_2SO_4 (0.68 eq).

The formation of protonated imine was observed through well resolved NMR signals only when MSA was added in excess (Figure 2.9, b).

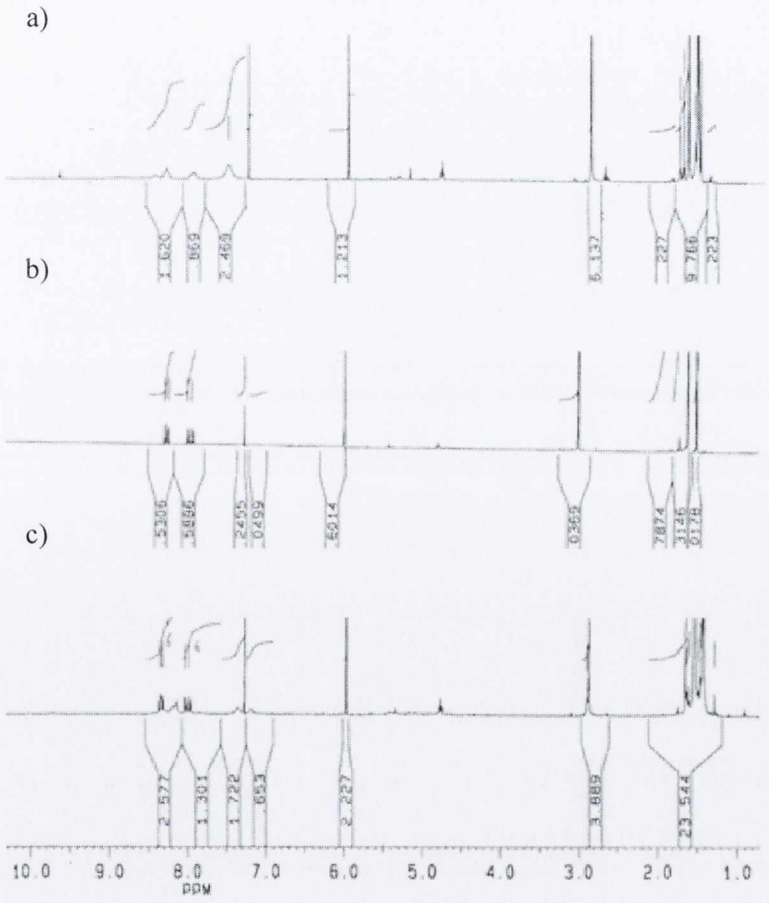


Figure 2.9. ^{1}H NMR (300 MHz, $CDCl_3$) of iminium salts; a) *tert*-Butyl-imine (1 eq) + MSA (1 eq), b) *tert*-Butyl-imine (1 eq) + MSA (2 eq), c) *tert*-Butyl-imine + MSA (0.48 eq) + H_2SO_4 (0.68 eq)

When the acid mixture was present (Sample c) an additional signal was observed at δ 8.15 ppm. The three samples were maintained at room temperature and analyzed again after 24 hours. The spectra of samples b) and c) recorded after one day showed no appreciable changes, instead the sample a) showed an increased signal at δ 7.4 ppm.

All these experiments were repeated employing fresh acids in order to control the water content but the same results were obtained.

Another study was performed in chloroform solution, then *tert*-butyl-imine (0.34 g, 1 eq) was diluted in 4 ml of $CDCl_3$ and MSA (0.38 g, 1 eq) slowly added dropwise. The

exothermicity was controlled by an ice bath. The mixture was then refluxed for 18 hours, the environment of reaction was maintained dry by means of a drying tube on the top of the condenser. The sample was analyzed before and after the thermal aging and the resulting spectra are reported in Figure 2.10.

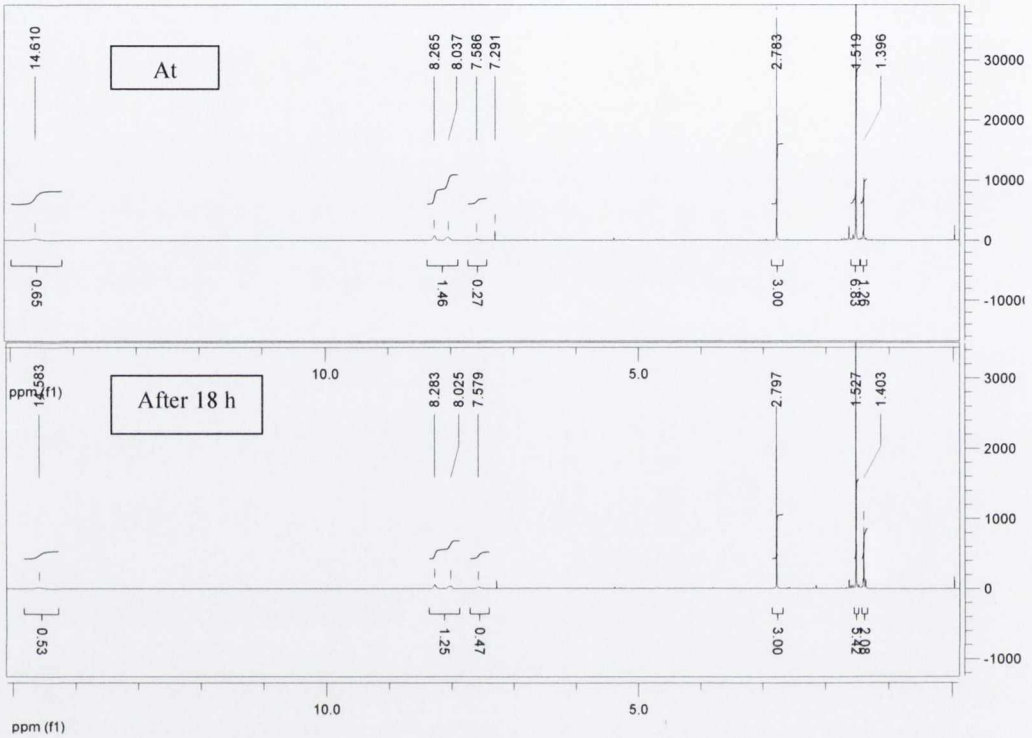


Figure 2.10. ^{1}H NMR (400 MHz, $CDCl_3$) of thermally aged *tert*-butyl-imine; At Start (top), After 18h (bottom)

A little change of the signal integration is observed. After thermal aging the iminium multiplet (δ 8.03 – 8.26 ppm) is slightly weaker and the broad singlet at δ 7.58 ppm is higher. At the same time the *tert*-butyl singlet at δ 1.52 ppm decreases and the one at 1.40 ppm increases. The signals at δ 7.58 and 1.40 ppm are in agreement with those of *tert*-butylamonium salt, nevertheless the solvent and reagent used were dry and the environment of reaction was kept dry. Thus the presence and increment of the ammonium signals is not fully understandable.

2.4.6 Effect of the solvent of reaction

Various solvents (instead of chloroform), more suited to industrial processes, were investigated under typical conditions, the results are summarized in the Table 2.5.

Table 2.5. Effect of the solvent under standard conditions for the new Imine Approach

No.	Solvent	Time (h)	Monomer Yield (%)	Phase separation	Polymer	Observations
1	$CDCl_3$-d	3	54	Yes after 30'	Little amount	Usual phase separation
2	Heptane	3	Trace of product	Yes	Large amount after 3h	Immediate phase separation
3	Toluene	3	30-35	Yes after 30'	Little amount	Reversed phase separation
4	THF	3	Small amount	Yes after 1 h	Large amount	Reversed phase separation
5	1,4-dioxane	2	55	Yes immediately	No	Reversed phase separation
		3	40		Some amount	
6	Chloroform	2	54	Yes after 30'	No	Usual phase separation
		3	40		Some amount	
7	Decahydro-naphthalene	2	52	Not observed	Little amount	Always homogeneous system
		3	small amount		Large amount	
8	Ethylene glycol dimethyl ether	2	53	Yes after 1 h	Small amount	Reversed phase separation [a]
		3			Large amount	
9	Chlorobenzene	3	55	Yes after 1 h	Little amount	Reversed phase separation
10	Tetrachloro-ethylene	2	36	Yes after 2h	Little mount	Usual phase separation
		3			Some amount	
11	Ethylene glycol dimetylether dry[b]	1	50	Yes after 1h	Little amount	Reversed phase separation[a]
		3			Some amount	
12	THF dry[b]	1	50	Yes	Trace	Reversed phase separation
		3	10		Large amount	
13	Dioxane dry[b]	1	52	Yes after 30 min	No	Reversed phase separation
		3	45		Some amount	
14	Ethyl acetate dry	1	40	Yes after 1 h	Trace	Reversed phase separation [c]
		3			Little amount	
15	Diethylene glycol dibutylether[b]	3	30[d]	Yes	Some amount	Reversed phase separation.[e]

Table 2.5 continue. [a] Addition of acid to imine gave a sticky solid that disappeared after 30' reaction; [b] Treated with molecular sieves after anhydrification procedure ($CaCl_2$ overnight and Na addition, in the presence of benzophenone as indicator and final distillation); [c] At the beginning formation of large amount of solid that disappeared after heating; [d] Roughly estimated observing the quartet signal of the reagent partially overlapped to the quartet signal of the product; [e] The lower phase is a very viscous oil.

Evaluation of the yield in solvent studies was only approximate since it was made by internal normalization (i.e. referred to un-reacted EtCAcet) evaluating the solvent phase composition (when phase separation is present). Some amount of product and unreacted reagent were detected also in the viscous phase containing the ammonium salt.

From these tests of reaction it was possible to gain important information. Chloroform gave better results relative to all others solvents tested, so this was a good choice for yield optimisation. The reaction carried out in chloroform produced 54% of monomer after 3h at 70 °C, no polymer was produced and the usual biphasic system was observed. Furthermore the interesting phase separation occurred in chloroform. This was considered important because it simplified separation and isolation of monomer. Normal chloroform gave the same results as deuterated chloroform.

Subsequent tests were carried out using two other chlorinated solvents; chlorobenzene and tetrachloroethylene. The first gave about 55% yield that was similar to the chloroform result but the second produced a lower yield (36%), moreover some amount of polymer was also observed . Neither the reactions produced phase separation but unfortunately large amount of ammonium salts dissolved into the organic layer. Subsequent tests were conducted using non-chlorinated solvent; e.g. toluene and ethyl acetate. Both produced reverse phase separation (non chlorinated solvent has lower density) and the final yield was lower. The reaction with toluene produced lower amount of product (about 30% yield) than ethyl acetate (40%). Both reactions gave some polymer. Given this trend of reactivity, it was decided to try oxygenated solvents, in particular only etherate solvents in order to avoid anionic polymerization. Thus 1,4-dioxane and tetrahydrofurane (THF) were tested. Interesting results were observed. Good yields were obtained after one hour (about 50%) for both. However, after 1 to 3 hours of reaction there was a fast increase in the amount of polymer.

Since positive results were obtained in ether solvents, ether glycol was selected to facilitate monomer separation. In particular ethylene glycol dimethyl ether and diethylene glycol dibutylether were selected. These are high boiling solvents which

would allow the monomer to distill before the solvent. The results were encouraging, about 50% yield just after one hour and the polymer formed after 3 hours.

2.4.7 Use of single acid (methanesulfonic acid) in high boiling solvent

The results obtained in glycol dialkylethers were encouraging with regard to a viable industrial process. So the MSA was studied in combination with this solvent. The solvents were dried using the procedure suggested for diethyl ether, *i.e.* treatment with $CaCl_2$, then distillation from metallic Na in the presence of benzophenone as indicator. The solvent was stored under dry atmosphere on molecular sieves.
The yields were evaluated by ^1H NMR diluting a sample in $CDCl_3$ and using internal normalisation and/or standard addition methods. Since the more intense signals were due to the polyether solvent, the integration of product and un-reacted cyanoacetate signals cannot be highly precise.

- *Use of diethylene glycol dibutyl ether (DEGBE)*

Using DEGBE (b.p. 256 °C, from Aldrich) a biphasic system was also observed. The lower phase became an orange sticky solid. The effect of reaction temperature was studied starting from 80, 85, 90 to 120 °C for 1 hour. The yield increased from 45% to 50%, but decreased at 120 °C due to polymerization even for shorter reaction time (10-20 min).

- *Use of tetraethylene glycol dimethyl ether (TEGME)*

TEGME (b.p. 275-276 °C from Aldrich) was employed in order to try the distillation of the monomer before the solvent.
No phase separation occurred, but a cloudy solution was formed at normal concentrations (2 ml of solvent) which gave a general precipitate on dilution (white powdered solid).

Thus the reaction was performed at higher dilution, 5 or 10 times, and good results were obtained. The yield values by internal normalization were between 70 to 75%. The white solid formed during the reaction at 85 °C for 1h was filtered off under nitrogen. It was examined by NMR and identified as the tert-butyl ammonium salt. The filtrate was collected in a round bottom flask and further reacted with 0.5 eq of iminium salt for 30 min at 85 °C. The yield of product was around 80-85%.

2.4.8 Effect of the reaction time (kinetic study)

A simple study was made on the kinetics of reaction. The reaction trend was evaluated in function of the time. The results are reported in Table 2.6.

Table 2.6. Effect of reaction time in the imine approach

Entry	Time (min)	Yield (%)	Observation
1	20	30	Large amount of residual iminium salt
2	40	43	Some residual iminium salt
3	60	50	Small amount of residual iminium salt
4	180	56	No residual iminium salt

In all the samples some amount of unreacted EtCAcet was observed. We obtained smaller yield than expected because of the interruptions during sampling.

A further test was performed to avoid sampling operation directly inside a NMR tube at 65 °C. The temperature was fixed at 65 °C (5 °C lower the standard procedure) to avoid overpressure and leakage of the chloroform. A gradual formation of monomeric product was observed. After 1.5 h the yield reached 50% and longer reaction time did not improve the result. After about 1 h the interaction and mixing of the two phases was difficult. In fact during the reaction the upper phase became viscous and the contact surface is very low inside a NMR tube.

2.4.9 Initial study on scale up

A Schlenk apparatus was modified with a rotaflow stopcock to tolerate low overpressure. The reaction was conducted at a scale of 25 mmol. The yield was not changed and the reaction is selective. However the yield was not good 40%. Similar scaling up was made also using tetraethylene glycol dimethyl ether. The reaction scale was increased to 50 mmol [4.3 g of imine reagent, 5.57 g (58 mmol) of methanesulfonic acid and 5.65 g of EtCAcet]. The reaction was carried out in a round-bottom flask of 250 ml. Using ^{1}H NMR technique it was possible to check the yield of the reaction. Indeed, after heating at 85 °C for 1 h, the reaction was filtered under nitrogen into a round bottom flask containing additional 0.5 equivalent of iminium salt and reacted for 30 min at 85 °C. For the filtration a dropping funnel with fritted septum was used, previously washed with an aqueous solution of H_2SO_4. The yield was the same obtained in smaller scale reaction, approximately 70% before solid filtration (first step) and about 80% after the second step.

Large scale reaction was repeated some times in order to isolate the monomeric EtCA by distillation. Previously it was verified that EtCAcet and TEGME were separable by distillation under vacuum at 4 mbar. Unfortunately the monomer isolation was complicated by premature polymerisation.

Considering that the monomer is stable in an acidic environment the distillation with additional sulfuric acid (0.2 eq) was attempted (repeated).

The reaction was carried out in 25 mmol scale (2.15 g of imine, and 2.83 g of EtCAcet) and was stopped after the first step. The filtered crude mixture was transferred into a round bottom flask fitted with distillation equipment and sulfuric acid (1.2 g) was added. The oil bath temperature was 100 °C and the vacuum was kept at 1 mbar. After 15 minutes, collection of distillate commenced, then ended after one hour. The temperature was increased at 120 °C and a third distillate fraction was collected. The first two fractions were distilled at 30 °C (distillation temperature), the third fraction at 90 °C. The ^{1}H NMR analysis of the three distilled fractions are described below:

- 1st fraction: EtCA (72%) with impurities of EtCAcet and polyether solvent.
- 2nd fraction: EtCA (61%) with small amount of EtCAcet (32%) and solvent (7%).
- 3rd fraction: EtCA (30%) and EtCAcet (30%) with a large amount (about 40%) of solvent.

The total yield of monomer by weight was 58%.

Some important observations were made:

1) The addition of sulfuric acid to the crude before starting the distillation strongly increased the monomer stability;
2) EtCA is the compound with the lowest boiling point, so the first fractions were richer in the monomer product;
3) Probably the use of a short column for fractioning distillation would allow a better separation of closely boiling point compounds;
4) The accomplishment of the two step reaction with higher yield could reduce the amount of unreacted reagent, thus facilitating the separation;
5) The addition of sulfuric acid represents a drawback of this procedure since it is in conflict with the advantage represented by the use of a single acid (only methanesulfonic acid) as reaction catalyst.

2.4.10 Some attempts for continuous flow reaction

A possibility of preventing the acrylate polymerisation could be the removal of the monomer from the crude when it is just formed. For this purpose some reactions were carried out using a new equipment simulating a continuous flow process. The new apparatus was obtained by assembling a Schlenk tube (reaction vessel) with a vacuum trap kept at low temperature (80 °C) and a second small Schlenk tube (EtCAcet reservoir). The two tubes were connected by a fused silica capillary. The reaction vessel, containing the mixture of imine and methanesulphonic acid in tetraethylene glycol dimethyl ether, was heated at 110 °C under vacuum (1 mbar). The EtCAcet was slowly added by means of the connecting capillary. This addition was carried out in about thirty minutes and the operating conditions (temperature and vacuum) were unchanged for additional 30 minutes. The distillation started in few minutes after following reagent addition and stopped one hour later. The liquid distillate was collected in the trap condenser. Unfortunately some distilled product polymerized inside the condenser, since no gas stabilizer was present. Examination of the distillate by ^{1}H NMR showed the presence of a large amount of solvent and a mixture 1:1 of monomer and reagent. Taking into account a partial polymerization of the monomer the yield was

approximately 50%. We can state that the study of a continuous flow reaction and isolation requires more sophisticated equipment and probably also a higher boiling solvent.

2.4.11 Conclusion

This preliminary work challenges the Knöevenagel reaction as the only convenient reaction for the preparation of cyanoacrylate monomers. In a relatively short study, an entirely new approach has clearly demonstrated an alternative route to the preparation and isolation of EtCA monomer in good yield. The outlook for developing this reaction looks very positive. Next step would be the study of the reaction mechanism, the optimization of the ionic structure of the iminium salt and further investigation with ionic liquids. In fact the latter appeared to have a solvent catalytic effect and they are also important for facilitating the separation of the target monomer as they do not distil (zero VOC, volatile organic compounds). This approach is quite feasible to achieve a high yielding crackless synthesis of cyanoacrylate. The more appealing facet of this new approach would be in the preparation of more esoteric cyanoacrylate esters that are difficult to prepare by the Knöevenagel reaction that must resort to aggressive thermal depolymerization of a pre-polymer.

2.5 Experimental

General experimental conditions.

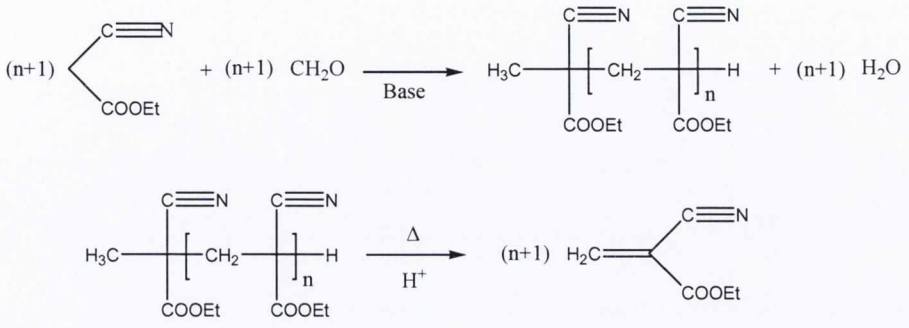
^{1}H NMR spectra (60 MHz) spectra were recorded in $CDCl_3$ using JNM-MY60 spectrometer.

^{1}H NMR spectra (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using a Bruker AM 300 spectrometer.

^{1}H NMR spectra (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Brucker Avance DPX 400 MHz spectrometer. Chemical shifts are measured in ppm. *J* values are given in Hz. IR spectra were recorded as thin films between sodium chloride plates using a Nicolet 380 FT-IR spectrometer, AT-IR were measured with the same equipment but with suited accessory for reflectance analysis. Mass spectra were recorded using a PE-GCMS Clarus 500, Perkin Elmer GCMS spectrometer. Melting points were measured in unsealed capillary tubes using an MEL-TEMP® melting point apparatus and are uncorrected. DSC analysis were recorded using a DSC Plus, Rheometric Scientific Inc. calorimeter. TGA analysis were recorded using a 1000M, Rheometric Scientific Inc. thermogravimetric analyser. X-Ray structures are obtained using a Rigaku Saturn-724 diffractometer.

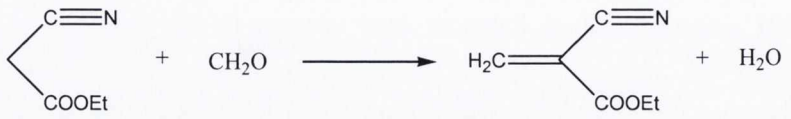
All reagents and solvents were used as received. PRIMENE amines were received from Rohm & Haas, all other reagents and solvents were supplied from Sigma-Aldrich.

Typical procedure for ethyl cyanoacrylate[186,187] synthesis by Knöevenagel reaction and thermal depolymerization.



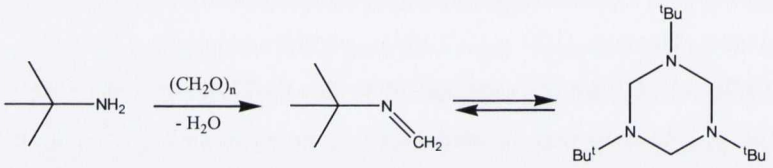
A three-necked round bottom flask (1 l) was equipped with a mechanical stirrer, a pressure equalizing dropping funnel (200 ml), a Dean-Stark water trap and an efficient reflux condenser. Heptane (120 g, 1.2 mol), paraformaldehyde (42 g, 1.4 mol) and piperidine (0.76 ml, 7.7 mmol) were added to the flask and stirred to form a slurry. EtCAcet (166 g, 1.47 mol) was inserted in the dropping funnel. The reaction flask was rapidly heated to reflux temperature and the cyanoacetate added at a constant rate over approximately 20-30 minutes. The final solution was refluxed until all the water formed during the reaction had been azeotropically removed and collected in the Dean-Stark trap. This occurred over a period of 1.5 hour and at 100 °C. Then the apparatus was reconfigured in order to removed the heptane by distillation. The residual solution was neutralized by slow addition of phosphoric acid (6.14 g, 0.06 mol) and methanesulphonic acid (0.220 g, 0.002 mol). Finally hydroquinone (1 g, 0.001mol) was added. The same distillation apparatus, but without the stirrer, was used for the thermal pyrolysis of the crude pre-polymer. The EtCA was collected in a flask containing catalytic hydroquinone and MSA. The pressure was gradually reduced until 1 mmHg and the temperature increased. Typically the product starts to distil (65-70 °C at 1 mmHg) when the crack temperature reaches 150 °C and the distillation is terminated when the pot temperature reaches 200 °C. The condensed product was finally redistilled at 60 °C and 4 mmHg.

General procedure for the synthesis of monomeric ethyl cyanoacrylate (preliminary test on formaldehyde activation for crackless synthesis)



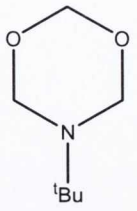
EtCAcet (1.06 ml, 10 mmol), paraformaldehyde (or 1,3,5-trioxane when specified) (0.3 g, 10 mmol), solvent (10 ml) and catalyst were introduced into a 25 ml round bottom flask, equipped with Liebig condenser and drying tube on the top. The reaction was stirring for a predetermined time at a defined temperature.

Synthesis of tert-Butylimine[183,188]



tert-Butylamine (146 g, 2 mol) was added portion wise (in 30 min) to paraformaldehyde (60 g, 2 mol) under stirring and cooling at room temperature. The resulting mixture was stirred for further 30 min at room temperature. The organic layer was separated and dried over anhydrous sodium sulfate. The slight yellow filtrate was distilled through a short packed column and the temperature of the vapor was kept above 65 °C. The pot temperature was 110–120 °C. The *tert*-butylamine (b.p. 64-65 °C) was collected in 70% yield as colorless oil. The pure monomer is not stable and after condensation it turns into trimer in several seconds. FT-IR spectra showed that the absorption band of C=N (monomer, 1596.4 cm^{-1}) significantly decrease in several seconds.

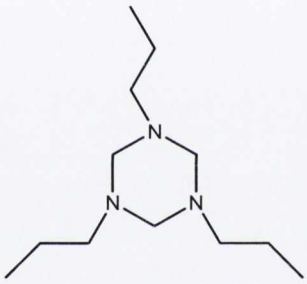
Side-product of *tert*-Butylimine synthesis: *tert*-Butyl-1,3,5-dioxinane[189]



Tert-Butyl-1,3,5-dioxinane has been characterized directly in mixture with *tert*-butylimine, the results are in agreement with the literature.

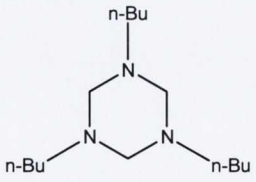
Synthesis of Propylimine[189]

Propylimine was synthesized using the same procedure described for *tert*-Butylimine.

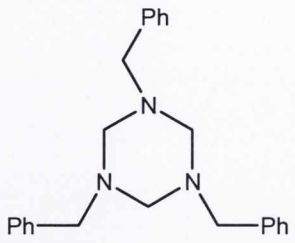


Synthesis of Butylimine[189]

Butylimine was synthesized using the same procedure described for *tert*-Butylimine.

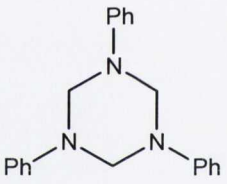


Synthesis of Benzylimine[189]



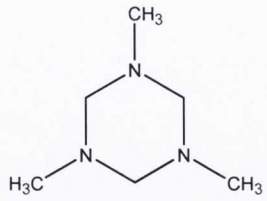
Benzylamine (21.4 g, 0.2 mol) was added to a dispersion of paraformaldehyde (6 g, 0.2 mol), sodium sulfate (7 g) and chloroform (15 ml). The resulting mixture was stirred at room temperature for 5 h. The final solution was filtered and the solvent evaporated. The product was a slightly yellow oil.

Synthesis of Phenylimine[189]



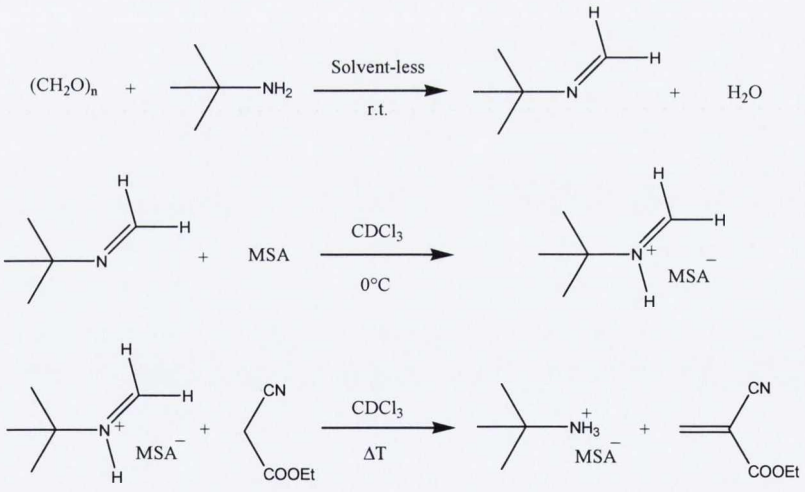
Aniline (18.6 g, 0.2 mol) was added to a dispersion of paraformaldehyde (6 g, 0.2 mol), sodium sulfate (7 g) and chloroform (15 ml). The resulting mixture was stirred and heated at reflux for 5 hours. The final solution was filtered and evaporated in a rotary evaporator. The product was recrystallized from chloroform to give white crystals.

Synthesis of Methylimine[189]



Methylamine 40 w % water solution (21.6 g, 0.2 mol) was added portion wise in 30 min to paraformaldehyde (6.0 g, 0.2 mol) under stirring and cooling at room temperature. The resulting mixture was stirred for further 1.5 h at room temperature. The final solution was extracted with dichloromethane (30 ml, three times), separated, dried over anhydrous sodium sulfate and the solvent evaporated in rotary evaporator. The product was purified by distillation (b.p. 32-35 °C at 20 mbar) and it was identified to be the trimer of methyl imine.

Optimized procedure for the synthesis of monomeric ethyl cyanoacrylate by imine approach



The reaction was carried out in a screw-capped test-tube previously acid washed. *Tert*-Butylimine (0.43 g, 5 mmol) was dissolved in $CDCl_3$ (2 ml) under stirring and cooled to 0 °C with an ice-bath. MSA (0.23g, 2.4 mmol) and sulfuric acid (0.33 g, 3.4 mmol)

were slowly added to this solution, since an exothermic reaction occurs. The EtCAcet (0.53 ml, 5 mmol) was added by dropping at room temperature and the reaction was stirred at 70 °C for 3 hours.

The crude was examined by ^{1}H NMR technique and the yield of EthylCA monomer was evaluated by internal normalization (*i.e.* referred to unreacted EtCAcet) and by internal standardization (*i.e.* referred to the amount of methane sulphonic acid introduced).

Procedure for the synthesis EtCA

(study on order of reagent addition)

The reaction was carried out in a screw-capped test-tube (for reaction in 5 mmol or in 25 ml round bottom flask for 20 mmol scale) previously acid washed.

Tert-Buthylimine (0.43 g, 5 mmol) was diluted in $CDCl_3$ (1 ml) and cooled under stirring to 0 °C with an ice-bath. MSA (0.23 g, 2.4 mmol) and sulfuric acid (0.33 g, 3.4 mmol) were slowly added to this solution, as an exothermic reaction occurs.

This mixture was transferred into a syringe and it was slowly added (in about 1.5 h) to a solution of EtCAcet (0.53 ml, 5 mmol) in $CDCl_3$ (1 ml) previously heated to 70 °C.

Then the reaction was stirred at 70 °C for 30 minutes.

The crude was examined by ^{1}H NMR technique and the yield of EtCA monomer was evaluated by internal normalization and internal standardization.

Procedure for the synthesis EtCA

(study on monomer distillation)

All the glassware was steeped in an aqueous sulfuric acid solution (5%) overnight. Then it was rinsed with distilled water, acetone and oven dry thoroughly.

The reaction was carried out in larger scale in a 25 ml two necked round bottom flask.

Methane sulphonic acid (0.92 g, 9.6 mmol) and sulfuric acid (1.33 g, 13.6 mmol) were slowly added under stirring to a solution of *tert*-butylimine (1.72 g, 20 mmol) in $CDCl_3$ (8 ml) cooled to 0 °C with an ice-bath.

The ethyl cyanoacetate (2.12 ml, 20 mmol) was added by dropping in five minutes at room temperature and the reaction was stirred at 65 °C for 2 hours.

The glassware was reconfigured for vacuum distillation with Liebig apparatus and the receiving flasks, in which some drops of the stabiliser (methane sulphonic acid) were added. Small amounts of $BF_3 \cdot Et_2O$ were sometimes added in order to avoid EtCA polymerisation.

After removal of the solvent, the distilled fraction (1.4 g) containing only ethyl cyanoacetate and ethyl CA monomer was examined by ^1H NMR spectroscopy. By the molar ratio of these two compounds, the yield of EthylCA monomer was evaluated to be about 28% (*i.e.* 5.6 mmol, 0.7 g) and 32% (*i.e.* 6.4 mmol, 0.72 g) of ethyl cyanoacetate unreacted.

Procedure for the synthesis of EtCA

(Study on the use of a single acid in high boiling solvent)

The reaction was carried out in a three necks round-bottom flask of 250 ml previously washed with acid (aqueous solution of sulfuric acid). *tert*-Butylimine (4.3 g, 50 mmol) was introduced into the flask and dissolved in 180 ml of tetraethylene glycol dimethyl ether (TEGME). Methanesulfonic acid (5.57 g, 58 mmol) was slowly added to this solution under stirring and cooled to room temperature with a water-bath because an exothermic reaction occurs. The ethyl cyanoacetate (5.65 g, 5.3 ml, 50 mmol) was added by dropping at room temperature and the reaction was heated at 85 °C under stirring for 1 hour.

Then, the reaction was filtered under nitrogen using a dropping funnel with fritted septum (the white solid was isolated and NMR spectrum revealed to be *t*-butylammonium salt) and the filtrate was collected into a round-bottom flask (250 ml) containing 0.5 equivalent of iminium salt (2.15 g of imine and 2.78 g of methanesulfonic acid in 10 ml of solvent). The mixture was reacted for 30 min at 85 °C. The yield evaluated by ^1H NMR (80-85%) confirm the result obtained in small scale reaction (about 80-85%).

Procedure for the synthesis and distillation of EtCA

(Initial study on scale up)

The reaction was carried out in a round-bottom flask of 250 ml previously washed with acid (aqueous solution of sulfuric acid). *tert*-Butylimine (2.15 g, 25 mmol) was introduced into the flask and dissolved in 100 ml of TEGME. MSA (5.57 g, 58 mmol) was slowly added to this solution under stirring and cooled to room temperature with a water-bath, because an exothermic reaction occurs. The ethyl cyanoacetate (2.65 ml, 25 mmol) was added by dropping at room temperature and the reaction was heated at 85 °C under stirring for 1 hour.

Then, the reaction was filtered under nitrogen, using a dropping funnel with fritted septum, into a round bottomed flask (250 ml). Sulfuric acid (12.5 mmol, 1.2 g) was added and the flask containing the crude was connected to the distillation apparatus. The temperature of the oil bath was 100 °C and the vacuum was 1.5 mbar. The distillation began after about 15 min and after 1 h it was finished. Then, the oil temperature was increased to 120 °C and the third fraction was collected. The first and second fractions were collected at a distillation temperature of 30 °C, while the third one at a temperature of 90 °C. Small amount of product was condensed into the liquid nitrogen trap.

Small amount of etherated BF_3 was introduced in the apparatus and MSA was added to the receiving flasks as stabilizer.

- 1st fraction (0.780 g): ethyl cyanoacrylate with impurities of ethyl cyanoacetate and polyether solvent.
- 2nd fraction (1.169 g): ethyl cyanoacrylate with small amount of unreacted reagent and solvent.
- 3rd fraction (1.204 g): ethyl cyanoacrylate and ethyl cyanoacetate (*ca.* 1:1) with a large amount of solvent (about the 40% of the total weight).

Taking into account the relative amount of monomer in these fractions it was possible to estimate that abt. 1.8 g of monomer was distilled (58% yield).

Procedure for the synthesis and distillation of EtCA in a continuous flow

The reaction was carried out in an apparatus obtained assembling a Schlenk tube (reaction vessel) with a vacuum trap kept at low temperature (-80 °C) and a small Schlenk tube, containing the ethyl cyanoacetate, connected to the reaction vessel by a fused silica capillary. To the reaction vessel containing N-methylidene-tert-butylamine (2.15 g, 25 mmol) in tetraethylene glycol dimethyl ether (10 ml) MSA (2.78 g, 29 mmol) was added. The reactor was heated at 110 °C under vacuum (1.5 mbar). After some minutes the ethyl cyanoacetate was slowly added by means of the connecting capillary. This addition was carried out in about 30 min and the operative conditions (temperature and vacuum) were unchanged for further 30 min. The distillation started just after few minutes of reagent addition and stopped only after one hour. The liquid distillate was collected in the trap-condenser. Unfortunately some distilled product polymerized on the walls of the condenser, since no stabilizer was present. The exam of the distillate by ^{1}H NMR evidenced a 1:1 mixture of monomer product and acetate reagent plus a large amount of solvent. The reaction yield of 50% could be assigned.

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Chapter 3

3 TSIL APPROACH

3.1 From "imine" to the TSIL approach

A logical consequence of the previous work, performed in common organic solvents, would be to investigate a new class of ionic liquid with active functionality (TSIL, task specific ionic liquid). In particular an IL, bearing an amine functional group, could be the key solution for the production of cyanoacrylic monomer without separation problems. As it is well known, the ILs are considered non-volatile, thermally stable solvents, indeed the separation of cyanoacrylate in ionic liquid solution could be obtained by simple distillation under vacuum. For this reason special attention was dedicated to this class of materials.

Whereas ILs have attracted properties on the one hand, a disadvantage of the better know materials is their high cost. The latter makes them unrealistic media for use in bulk industrial scale (100s of kilos). Thus it was important at the outset of this work, to evaluate ILs only if the prospect of low cost processing could be achieved.

The simplest TSIL is the one bearing either the active functionality (imminium group) and the "ionic site" at the same location-thus the simplest TSIL would be a liquid imminium salt. The physical proprieties of an IL are derived from the particular configuration of a cation and anion and even experts in the field have difficulty predicting the precise behaviour of a new ion combination. From a simplistic perspective, a combination of one hindered bulky ion with a smaller one usually leads to an ionic liquid. For this reason the physical form of imines and inorganic acids mixtures were investigated. A series of PRIMENE amines (Figure 3.1) were screened. These materials are low cost industrial raw materials produced in the kilo tonne scale. Furthermore they posess a primary amines function attached to a tertiary carbon (thus fulfil the primary criterium for the "imine approach") on a highly branched alkyl chain. Such materials appeared to be ideal with regard to potential low cost TSILs where task specificity in this case is specificity to the Mannich reaction for the production of CA.

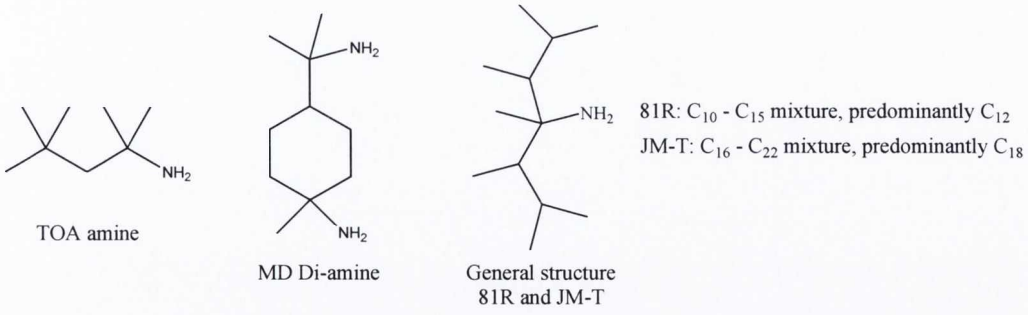


Figure 3.1. Molecular structure of Primene® amines

3.1.1 Synthesis of Primene® iminium salts

Primene® amines were reacted with paraformaldehyde overnight at r.t.. During imine formation a water phase was produced that was easily separated. The organic phase was finally purified by vacuum distillation. The immines per se are not charged and are obviously not IL in nature.

Imminium salts were prepared by slow drop-wise addition of acids (1 eq) to the freshly distilled imines (1 eq) and the exothermicity was controlled by means of cooling in an ice bath whilst stirring the reaction mixture. The blends thus formed were allowed to cool at room temperature and the final physical form was subsequently examined (Table 3.1).

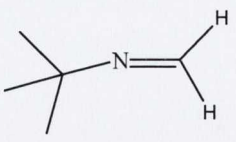
Table 3.1. Physical form screening of iminium salts

	tBu Imine	TOA Imine	81R Imine	JM-T Imine	MD di-imine[a]
H_2SO_4	s	s	L	L	s
H_3PO_4	s	s	L	L	s
MSA	s	s	L	L	s
BSA	s	s	L	L	L
OSA	L	s	L	L	s
NSA	s	s	L	L	s
LAS	L	L	L	L	L
SAS	L	L	L	L	s
AcOH	L	L	L	L	L
TFA	L	L	L	L	s
Stearic acid	s	s	L	L	s

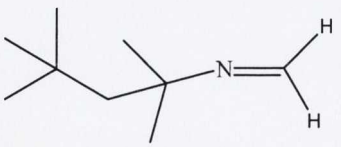
[a] Two equivalents of acid were used; Legend: s = solid; L = ionic liquid, MSA = Methanesulfonic acid; BSA = Benzenesulfonic acid; OSA = Octylsulfonic acid; LAS = Dodecylbenzene sulfonic acid, NSA = 2-Naphthalenesulfonic acid 70% pure, up to 15% of sulfuric acid), AcOH = Acetic acid, TFA = Trifluoroacetic acid, SAS = 2-Pentadecyl sulfonic acid;

Very interesting results were observed by mixing the above acids with hindered alkyl amines. Obviously only imines attached to tertiary carbons were tested (See Chapter "Imine Approach") and an interesting trend was observed.

The hindered, but not bulky *tert*-butyl imine, gave solid salts in combinations with many acids with the exception of LAS, OSA, SAS, AcOH, TFA (common anion in surfactant products). The same behavior was observed for the tert-octyl imine (TOA-imine) which has similar steric hindering to tert-butyl imine, but with a longer chain.



tert-butyl imine



TOA imine

Figure 3.2. Molecular structure of t-Bu and TOA imine

A completely different trend was observed for the 81R and JMT imines. In fact with these bulky bases only liquid salts (ILs) were observed. If we analyse their structure, we can image that the presence of such a large structure plays an important role. The 81R-Imine has a nitrogen group connected to a tertiary carbon which is substituted with a methyl group and two branched alkyl groups (Figure 3.3). Similar results were obtained reacting JM-T imine, which has the same chemical structure of 81R, but a higher MW.

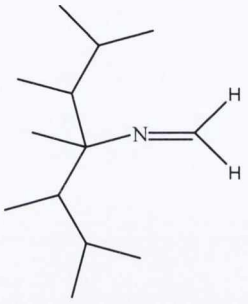


Figure 3.3. Molecular structure of 81R-imine

It must be noted that 81R and JM-T are not pure molecular compounds, but rather complex blends of isomers. Thus for example GC-MS chromatography of 81R-amine showed the presence of approximately twenty main isomers in a range between C_{10} and C_{14}. That the initial industrial raw material are mixture likely contributes to the easy with which the liquidus state results after acid neutralization. The dual functional primene MD (Figure 3.4) only gives an IL when used in combination with aryl sulfonic acids like BSA and LAS or AcOH.

3.1.2 Ionic Liquid Screening

Based on the aquired knowledge on Mannich chemistry applied to the synthesis of CAs and supported by the use of IL solvents, a new series of experiments was performed using a micro distillation equipment (mini-SPE, see paragraph 3.3, "Equipment").

Freshly prepared iminium ionic liquids (1eq Primene® imine plus 1.05 eq acid) were mixed at room temperature with EtCAcet (1 eq), the mixture was heated for 1 min at 100 °C, and finally a vacuum distillation was initiated (0.2 mbar) simultaneuosly as the temperature was allowed to rise to ~200 °C. The results obtained are summarized in Table 3.2.

Table 3.2. Screening reaction conditions for the synthesis of ethyl cyanoacrylate from TSIL

Entry	Imine	Acid	CA purity[a] (%)	CA Yield (%)
1	81R	MSA	95	73
2	81R	H_2SO_4	< 20	10
3	81R	MSA/H_2SO_4 (1:1)	77	46
4	81R	MSA/H_2SO_4 (1:4)	70	21
5	81R	BSA	79	64
6	81R	NSA	0	0
7	81R	LAS	79	50
8	81R	PTSA	36	16
9[b]	81R	H_3PO_4	0	0
10	TOA	MSA	82	44
11	MD	MSA	52	23
12	JM-T	MSA	40	26
13[b]	81R	AcOH	0	0
14	81R	TFA	0	0
15[b]	81R	Stearic acid	0	0

[a] The grade of purity was calculated on the basis of ^{1}H NMR analysis of unreacted acetate and yielded EtCA; [b] An exothermic event was observed after the addition of the cyanoacetate;

In order to guarantee an acidic environment and to avoid nucleophilic polymerization of freshly produced EtCA, a little excess of acid (5% mol) was used in the ionic liquid preparation. The results obtained are very interesting and they follow the same trend of those previously obtained in common organic solvents (See Chapter 2, "The Imine Approach").

The best result obtained was from the combination of 81R-Imine with MSA. The high purity and high yield clearly showed a key role played by the combination of acidity and hindrance. The same reaction performed with TOA instead 81R showed good purity but low yield. The latter usefully emphasises the role of a 'good TSIL' (in the current work this is both solvent and reagent for reaction) instead of a solid iminium salt (see Table 3.1). In other words higher hindering produces liquid imminium salts at room temperature which appears to promote a better Mannich reaction. Poor performance was observed also with JMT, in this case the reagent is a 'good TSIL', nevertheless it did not work very well and the result was surprising in consideration of its similar structure with 81R. MD di-imine gave poor resuls with regard to suitanbility of a TSIL for the Mannich reaction (Figure 3.4).

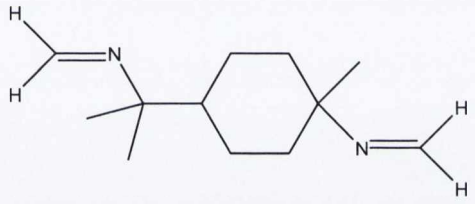


Figure 3.4. Primene MD® Di-imine structure

In the latter, the two imine groups have a little difference in sterical hindering and should form an intermediate situation between 81R and TOA. Unfortunately a very poor result was obtained even if a dual functional IL would be desiderable for a reduction of the reagent mass. Doubly charged ionic liquids are rare.

Interesting comparisons may be made between Entries 5, 6, 7 and 8; BSA (Table 3.2, Entry 5) produced a good reaction yield and purity for the monomer even if lower than for MSA (Table 3.2, Entry 1) highlighting lower iminium salt reactivity. A similar result was obtained using LAS (Table 3.2, Entry 7) and an even lower yield and purity was acheved using PTSA (Table 3.2, Entry 8). The main difference between the latter may be the water content. Both BSA and LAS are dry reagents whereas PTSA is a mono hydrated acid. The presence of water probably partially hydrolises the iminium salts with concomitant release of formaldehyde. The reaction was also tested with 81R and sulfuric acid (Table 3.2, Entry 2) and only a small amount of product was produced (10% yield). The selectivity was very low and a large amount of cyanoacetate was collected unreacted. The use of NSA (Table 3.2, Entry 6) did not yield any product, this

was likely due to its low purity since the technical grade (70%) contains up to 15% of sulfuric acid. For completeness the reaction was tested with a mixture of sulforic acid and MSA (Table 3.2, Entry 3, 4) and again the better result was observed when a lower amount of H_2SO_4 was empoyed.

From the previous studies some general conclusions may be drawn, thus:

- The best result was always obtained from a combination of 81R Imine and MSA which is the combination of a very hindered and bulky base with a strong sulfonic acid
- The reaction performed with 81R-Imine and only sulfuric acid produced fairly good results, like those from the combination of MSA with medium hindered amine.
- The use of sulfuric acid produced a very poor conversion, as did its use in mixtures with MSA.
- With ortho-phosphoric acid, acetic acid, trifluoroacetic acid and stearic acid only polymer was observed inside the distillation apparatus.

It seems that strong alkyl sulfonic acids have the ideal acidity strenght. Even slightly stronger aryl sulfonic acids do not perform so well and stronger sulfuric acid was even worse. In fact if we consider only the combination with 81R imine there was a reactivity trend that correlated directly with the acidity of the acids used. The strongest acids gave lower yield and more unreacted cyanoacetate. Using TSILs derived from the weakest acids, only polymer was produced. This behavior leds to the hypothesis of a lower IL reactivity, or, an IL degradation in the presence of stronger acids. On the other hand the imminium salts produced from TFA, orthophosphoric acid or weaker carboxylic acid did not have high thermal stability, some free base was liberated after heating under vacuum and all the freshly produced CA polymerised.

With the objective to better explain and rationalize these results, exhaustive ionic liquid reactivity and stability studies were undertaken.

The Mannich reaction for the production of cyanoacrylates was performed specifically in a task ionic liquid media for the remainder of this research (so-called "TSIL Approach").

3.2 Ionic Liquid reactivity and thermal stability study

The "TSIL Approach" is an entirely new method for cyanoacrylate synthesis and production. Study and optimization of this approach need to be conducted by considering the particular reactivity and chemistry of these highly reactive monomers. Commercial instant adhesive (super glues) give a practical demonstration about the extremely high reactivity of this class of compounds, which makes it easier to understand how difficult it is to handle these molecules, even by an experienced chemist.

Generally cyanoacrylates polymerize spontaneously in contact with any surface. This means that any reaction and subsequent purification involving cyanoacrylates must be performed with special attention in order to avoid unwanted polymerizations. Moreover the method under investigation is based on two consecutive steps of reaction, in particular the Mannich adduct intermediate cannot be isolated, which leads necessarily to new and original approaches for studying the reagents reactivity. The aim of the present discussion is to explain the difficulties encountered in this study and the solutions found to effect efficient monitoring of the reaction. The appeal of the TSIL process (or approach) is the combination of Mannich chemistry with an IL technology performed at relatively high temperature but for a very short time. It was critical to study reagents reactivity and thermal stability because this unique combination gives the TSIL process.

The criteria for a successful process require an understanding of four main areas, thus:

- *The physical form of the IL at room temperature*
- *TSIL/Cyanoacetate mixture Stability at r.t.*
- *TSIL Thermal Stability*
- *TSIL/Cyanoacetate mixture Reactivity*

3.2.1 Physical Form at room temperature

A general definition for ionic liquids is "*...materials that are composed of cations and anins which melt at or below 100 °C*"[190]. For the TSIL approach, this much to general. In fact the IL used in the reaction must be a liquid at room temperature. In some cases when a ionic liquid is fresly produced it takes some time before it starts to crystallize (or solidify). Even this situation is acceptable in the current work if there is enough time for the addition of the cyanoacetate reagent. This can be a good strategy if the cyanoacetate is a miscible with a liquid salt that may be prone to solidification and it may thus circumvent IL crystallization in certain instances. The possibility to avoid crystallization by using organic solvents it is another easy solution, but one that removes the benefit of solventless reaction. In the final analysis, the starting blend of reagent has to be liquid at room temperature and insoluble solid material should not be present. This is not a restrictive rule for reactions performed in small scale (e.g. by mini-SPE) but it is extremely important for large scale reaction. For technological reasons the reagent mixture has to be pumped into the reactor by means of a gear pump which is a high precision tool that does not tolerate particulates. On the other hand the addition of solid reagents to the IL is possible if the ionic liquid functions as a solvent. Heating to facilitate dissolution cannot be considered because the Mannich reaction between CAcet and iminium salts is thermal activated and premature reaction is undesirable.

3.2.2 TSIL / Cyanoacetate mixture Stability at room temperature

The TSIL Approach is a reaction triggered "on demand", that is, it is thermally activated but the mixture of IL and cyanoacetate has to be stable at room temperature. The blend has to be stable for a consistent period of time no shorter than a few hours at room temperature. When different combination of specific ionic liquid where first tested (Ionic Liquid Reactivity Screening) a very particular behavior was observed. In fact sometimes when the cyanoacetate was added to the ionic liquid an exothermic event was observed (Table 3.2, Entry 9, 13, 15). All the ionic liquid tested were obtained from the neutralization of the imines (1 eq) with a little excess of acid (1.05 eq) in order to guarantee the acidity of the system. In fact if the cyanoacetate was added to a slightely basic (defective of acid) an exothermic reaction (and increase of viscosity) would resulted with little or not product being produced on vacuum distillation.

A very strong exothermic event was observed from the addition of a cyanoacetate to neat imine, in this case high temperatures evolved and the viscosity was quickly increased ending with a very viscous gel. This thermal event was rationalized considering a Mannich, base catalyzed, reaction with production of cyanoacrylate that quickly polymerizes (Figure 3.5).

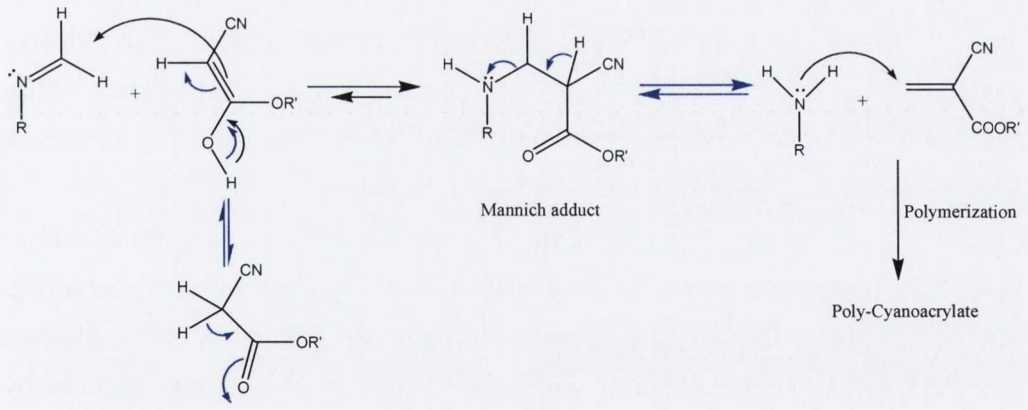


Figure 3.5. Cyanoacrylate formation by Mannich Reaction

Following this explanation we assert that the Mannich adduct between a primary amine and a cyanoacetate is not stable at room temperature. Klemarczyk et al[191] reported the synthesis and characterization of Mannich adduct between primary amine and EtCA. Nevertheless in the light of the current work we assert the instability of this particular adduct.

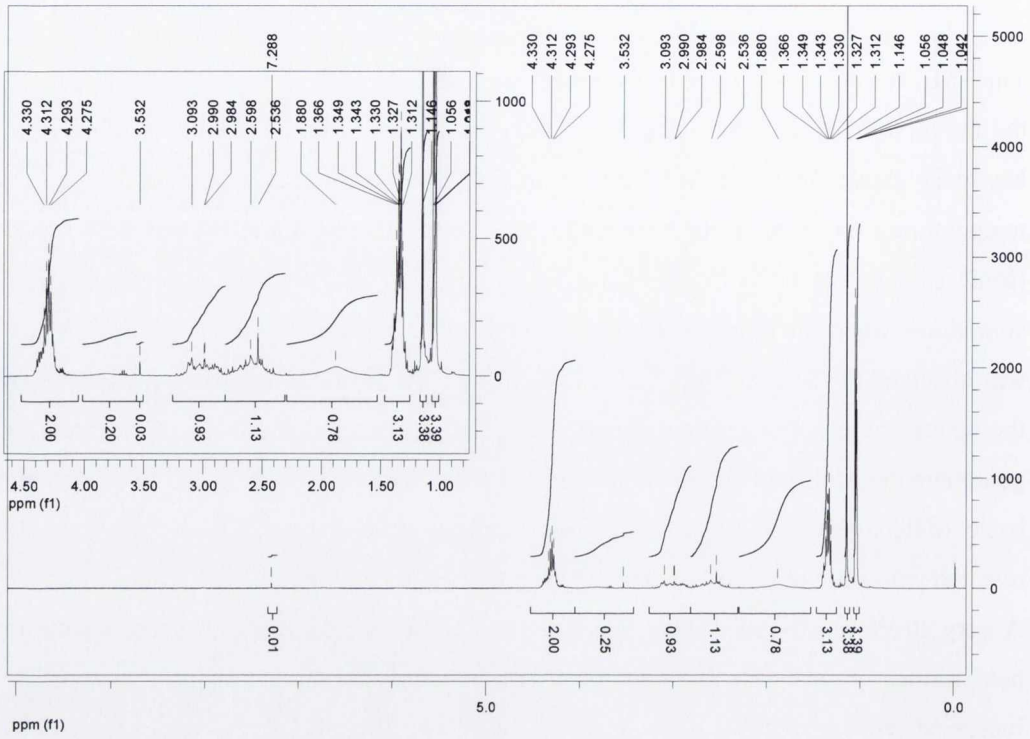


Figure 3.6. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) from the *tert*-butyl imine and EtCAcet reaction

The reaction between tert-Butyl imine (1 eq) and ethyl cyanoacetate (1eq) shows the total absence of the imine group ($N=CH_2$, d 7.40 ppm, d 7.26 ppm, J = 16 Hz) and of the cyanoacetate signal ($NCCH_2COO$, 3.53 ppm), which correspond to quantitative conversion (Figure 3.6). A complex blend of products was observed together with a consistent amount of polymer (broad signal centered at 2.60 ppm), as well as, a consistent amount of free amine (broad signal at 1.8 ppm).

Similar results were observed when 1 eq. of weak acid (e.g. orthophosphoric acid or acetic acid; respectively Entry 9 and 13, Table 3.2) or long chain carboxylic acid (e.g. Stearic acid, Entry 5 Table 3.2) were used to neutralize the 81R imine. In fact always a consistent increase of temperature was recognized after the cyanoacetate addition, by NMR analysis a quantitative conversion of the two reagents was observed as well as a large production of polymer. The tests were repeated several times and the same behavior was observed in every case. A rational explanation can be obtained from a simple acid-base neutralization equilibrium (Figure 3.7).

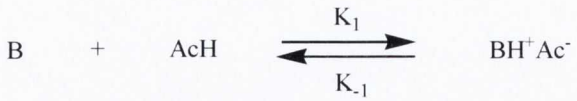


Figure 3.7. General acid-base equilibrium

The imines are considered weak bases then in order to have a full neutralization of the base it is necessary to use at least one equivalent of sufficiently strong acid. The acid strength of carboxylic acids (AcOH pKa = 4.73; Stearic acid = 4.35) is not sufficient for a complete base protonation, the same for orthophosphoric acid (pKa = 2.12). As previously observed the exothermicity probably corresponds to nucleophilic polymerization of the freshly produced CA. By ^{1}H-NMR of the mixture it was clear that the CAcet conversion (Figure 3.6, singlet at 3.5 ppm decreases) and the polymer production occurred (Figure 3.6, new broad signal at 2.6 ppm). Moreover if the TSIL reaction was attempted immediately (TSIL procedure by mini-SPE) a large production of polymer is obtained directly inside the distillation equipment (head and condenser). This was due to the fact that the completely neutralized imine is a non-volatile ionic liquid (zero VOC). Howeve,r if the neutralization is not complete the free base can distill together with the cyanoacrylate and produce a nucleophilic polymerization of the product.

3.2.3 TSIL Thermal Stability

The thermal stability of the IL is extremely important (See also paragraph 4.3.2 "Radical stabilizers investigation") for a number of important reasons. The most important one is to consider the evolution of the TSIL material during the reaction. In fact the ionic liquid is an iminium salt at the beginning and an ammonium salt at the end of reaction (Figure 3.8). Then the thermal stability of those two species must be studied independently.

1) TSIL Iminium salt stability
2) TSIL Ammonium salt stability

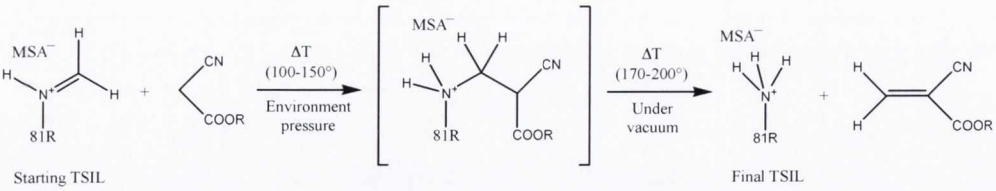


Figure 3.8. TSIL reaction scheme

The cyanoacetate reacts with the ionic liquid to produce a Mannich type adduct, this first step of reaction is performed by heating the IL/CAcet blend typically at 100-150 °C and no vacuum was applied (environmental pressure reaction). The second step was performed at higher temperatures, usually 170–200 °C under high vacuum (few millibars). The vacuum is applied only at the second step of reaction because only the cyanoacrylic product (and not the cyanoacetate reagent) has to distil. Ideally the cyanoacetate has to be fully consumed before the start of the second step of reaction. When the TSIL reaction is performed in the mini-SPE the vacuum was applied after a short heating time, otherwise when the TSIL reaction is performed in the SPE, wherein the vacuum is applied after the first reactor stage (Pre-Reactor or Pre-Heater section necessary).

Since both the reaction steps were performed at relatively high temperature the starting iminium IL and in particular the final ammonium IL have to be thermally stable. Thus a first explorative study was performed by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) of the ionic liquids used (Figure 3.9).

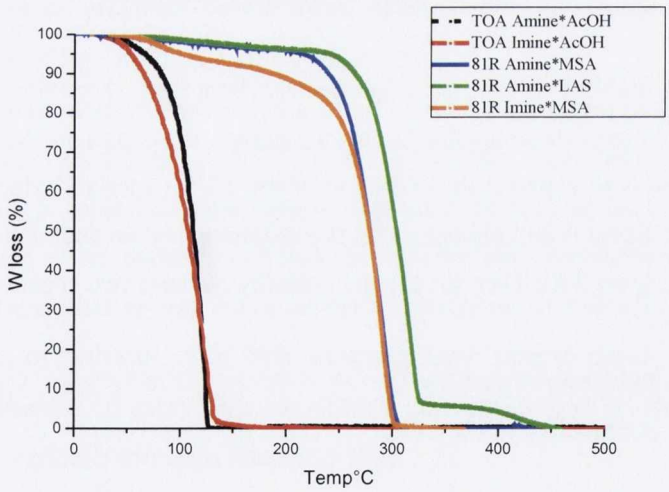


Figure 3.9. Thermogravimetric analysis of some Iminium-Amonium Ionic Liquid salts

The TGA analysis of TOA ammonium and iminium acetate salts (respectively TOA Amine*AcOH and TOA Imine*AcOH) showed that they start to decompose around 100 °C (Figure 3.9). Moreover a slightly lower thermal stability of the TOA iminium salt (TOA Imine*AcOH) is observed, this experimental data is in agreement with the lower basicity of imine species vs. amine species then faster release of free acetic acid.

The TGA analysis of sulfonic acid salts showed much higher thermal stability. In particular 81R ammonium methanesulfonate (81R amine*MSA) began to decompose at 250 °C and at 300 °C it loses 100% of the original mass. The situation is quite similar when LAS is used and only 20 °C higher thermal stability is observed. It was most interesting to observe the decomposition profile of 81R iminium methanesulfonate (81R Imine*MSA). The TGA profile shows a considerable weight lost (~10%) around 100 °C followed by a massive weight lost over 250 °C.

Prompted by the unusual behaviour of this iminium salt a DSC experiment was conducted (Figure 3.10).

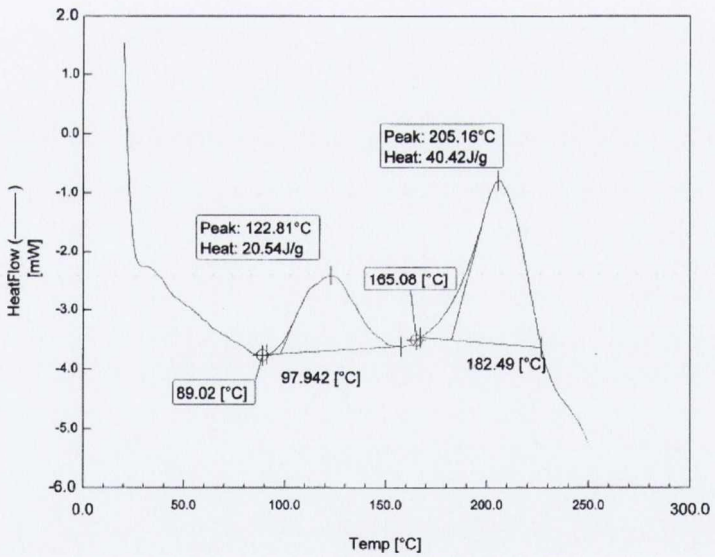


Figure 3.10. DSC analysis of 81R Imine*MSA (TSIL)

The DSC profile underlines two exothermic events, the first starts at 90 °C (maximum at 122 °C, heat 20 J/g), the second began at 165 °C (maximum at 205 °C, heat 40 J/g); both the two events happen below 200 °C in agreement with the first TGA slope of 81R Imine*MSA salt. At higher temperature a quick thermal decomposition is visible too.

These thermal events might be associated with the decomposition which could have negative impact on the ionic liquid reactivity so further analysis were performed. Besides the DSC profile of 81R Amine*MSA is recorded (Figure 3.11) and any thermal event is observed in the region between 50 and 250 °C.

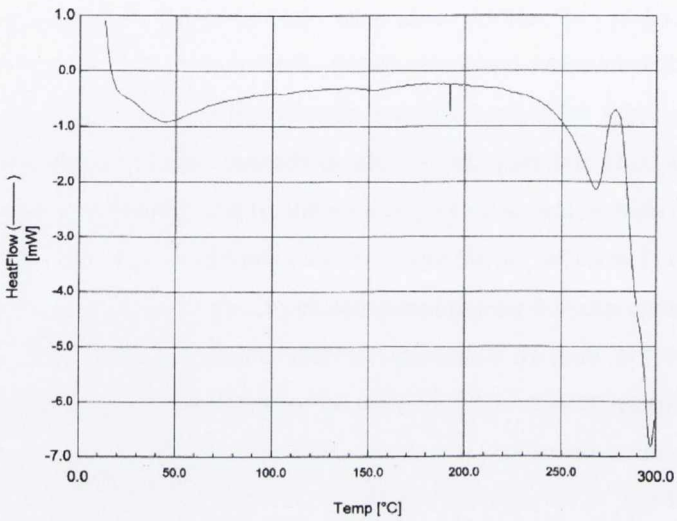


Figure 3.11. DSC analysis of 81R Amine*MSA (TSIL)

The behaviour of butyl cyanoacetate (1 equivalent) mixed with 81R Imine MSA (1 equivalent) is monitored by DSC (Figure 3.12).

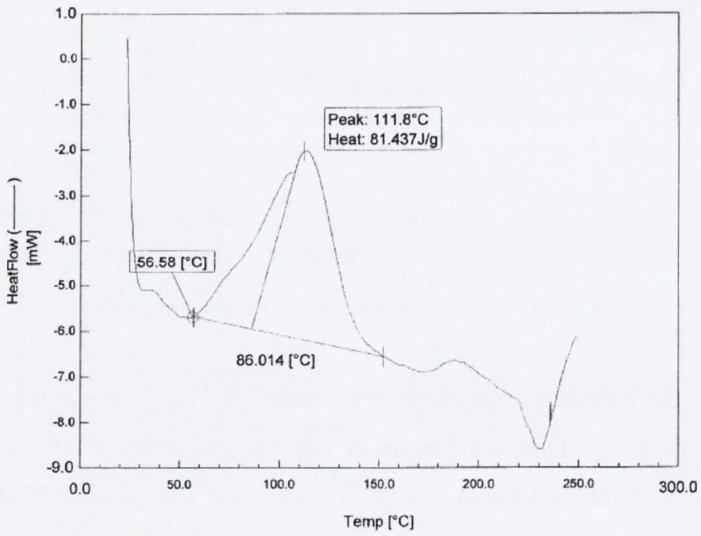


Figure 3.12. DSC analysis of 81R Imine*MSA (TSIL) plus butyl cyanoacetate

A new very strong exothermic event starts at 56 °C (maximum at 111 °C, heat 81 J/g) and a mild endothermic event is present over 200 °C. For comparison the DSC of pure butyl cyanoacetate was also performed (Figure 3.13).

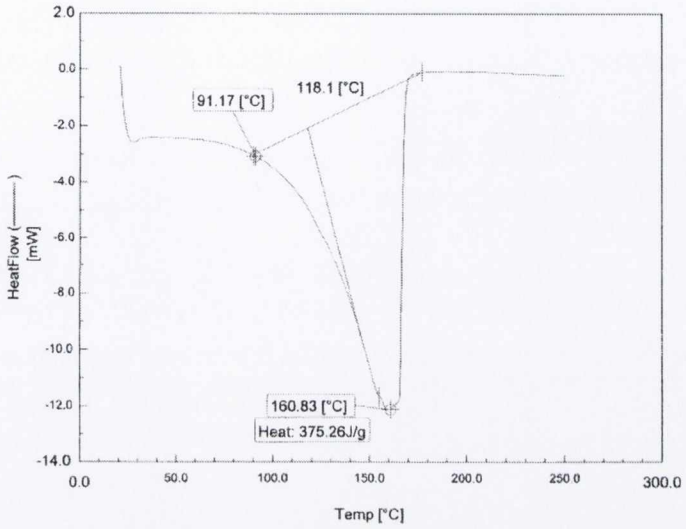


Figure 3.13. DSC analysis of butyl cyanoacetate

The DSC analysis of butyl cyanoacetate only, shows a consistent endothermic event (vaporization) below 200 °C, nevertheless in the presence of the IL the thermal profile is inverted (Figure 3.12) following a chemical conversion into a new non volatile compound (Mannich adduct).

A complete overview of the system has been achieved. It is clear that the iminium ionic liquid can be thermally modified and its chemical modification/degradation starts approximately at 100 °C. The reaction between the cyanoacetate and the imminium ionic liquid is thermal activated too, but it takes place at lower temperatures. In conclusion for a successful "TSIL Approach" it will be important to favour the cyanoacetate/IL interaction instead the IL degradation as competitive reaction path.

3.2.3.1 Further iminium salt stability study

The thermal modification of the iminium ionic liquid was studied deeply and the TOA imine was chosen as reference molecule for the study. TOA imine (14.10 g, 1.00 eq) was diluted in $CHCl_3$ (10 ml) and MSA (10.08 g, 1.05 eq) was drop by drop slowly added. The solvent was removed under reduced pressure (rotoevaporator). The resulting salt (solid at r.t. but clear colourless liquid above 100 °C) was heated 30 min @ 120 °C, analyzed by NMR, than heated additional 30 min @ 180 °C. The above temperatures were selected on the base of the thermal events previously observed by DSC (Figure 3.10).

Observation:

The IL was analysed by ^{1}H and ^{13}C NMR and it was substantially unchanged after thermal aging at 120 °C. After heating to 180 °C a consistent modification of its nature was observed. In fact either ^{1}H and ^{13}C NMR showed a consistent change.

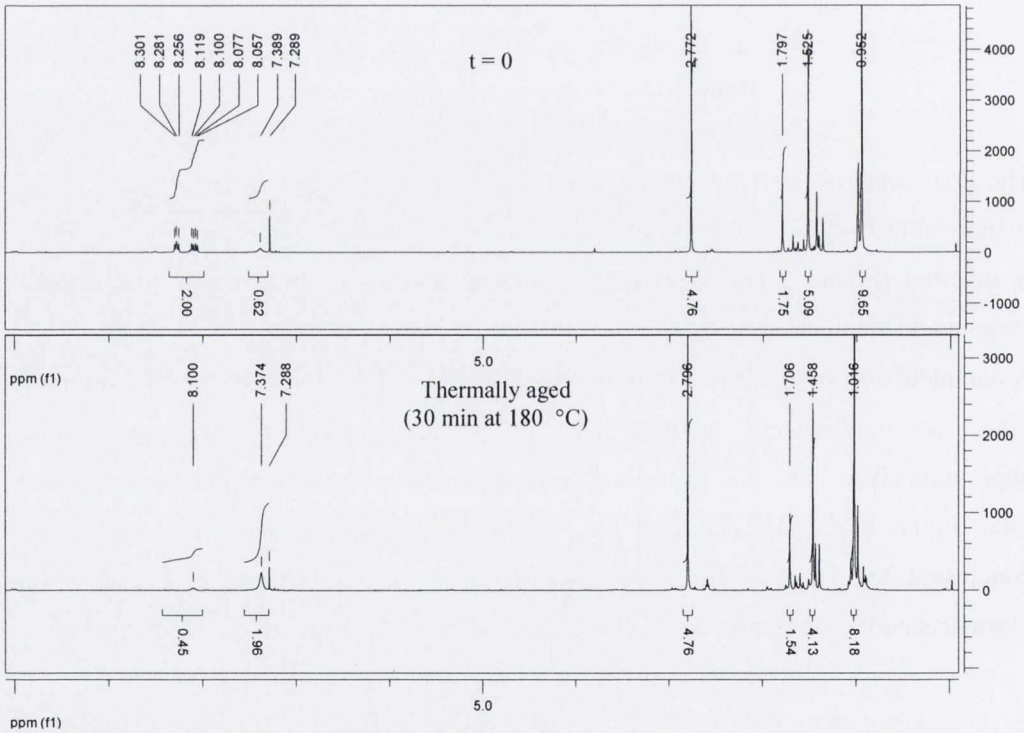


Figure 3.14. ^{1}HNMR spectrum (400 MHz, $CDCl_3$) of thermally aged TOA imine/MSA ionic liquid

Moreover the salt turned into a dark brown viscous material (soluble in common organic solvent and water), a large evolution of gas was observed (a bubble counter was connected to the system) and some material was distilled off (0.95 g).

From the NMR analysis of the thermally aged ionic liquid it is possible to observe a progressive degradation of the iminium functionality. In fact after 30 min at 180 °C almost the totality of the iminium multiplet (δ 8.1-8.3 ppm) is lost and at the same time the ammonium signal (δ 7.37 ppm) becomes higher. Moreover an acidic proton shifts to higher fields (from δ 14.41 to 13.44 ppm) and it becomes smaller. Also the three alkyl signals move to different fields (respectively from δ 1.97, 1.52, 0.95 ppm to 1.70, 1.45 and 1.01 ppm) and their relative integral ratio (2:6:11) is almost unchanged.

These observations show the disappearance of the imminium ionic liquid species and may be suggest the formation of a new ammonium salt compound. It has to be noted that the experiment is performed in the absence of water (dry environment) then a simple hydrolysis is not possible. Assuming that at high temperature a fast protonation-deprotonation equilibrium can be present, the imminium salt and the free basic imine could react together. The imine is a group that can react as an electrophile against nucleophiles or as a base in the presence of acids or as a nucleophile in the presence of strong electrophile. Then the reaction of TOA imine with TOA iminium salt could produce a dimeric – trimeric - polymeric structure. A confirmation of the new ammonium species is also detectable by FT-IR (Figure 3.15), in fact after thermal aging two new characteristic ammonium bands appear at 1630 and 1530 cm^{-1}.

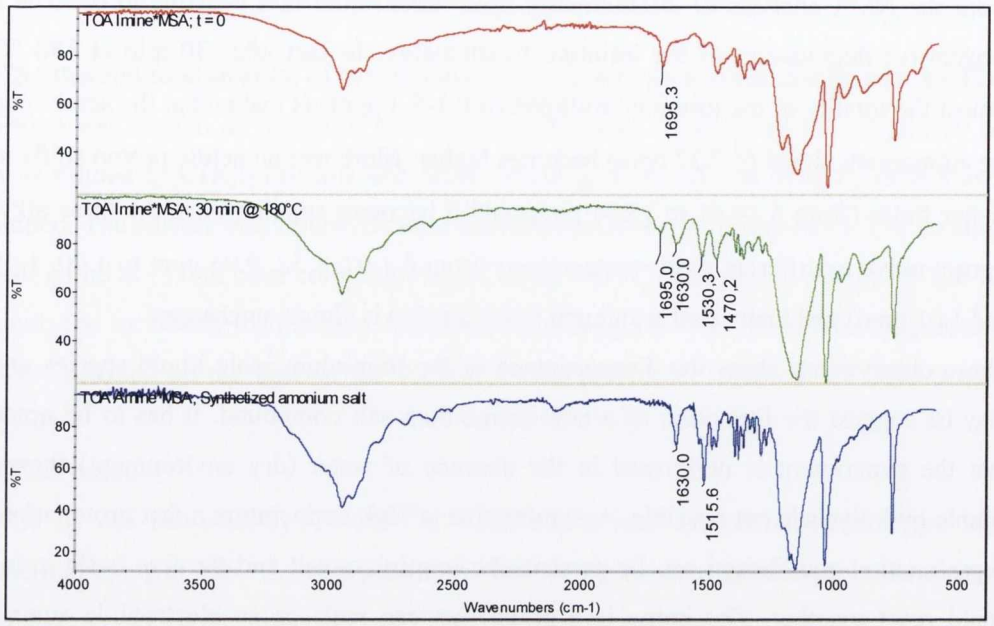


Figure 3.15. FT-IR spectra of thermal aged TOA imine*MSA salt and references

It is also interesting to observe the composition of the distilled fraction, either FT-IR (Figure 3.16) and ^{1}H NMR (Figure 3.17) underline the presence of olefin compounds.

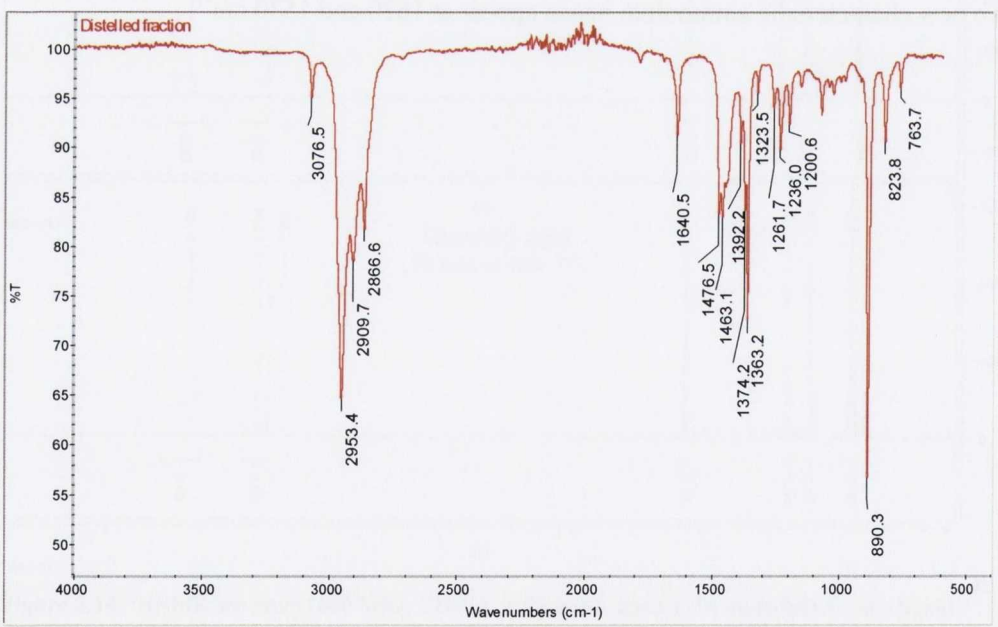
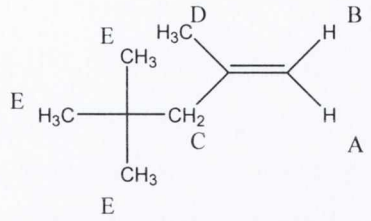
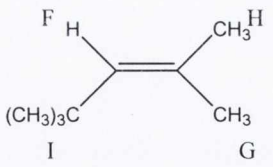


Figure 3.16. FT-IR of the distilled fraction from thermal aging test of TOA imine*MSA salt



2,4,4-trimethyl-1-pentene



2,4,4-trimethyl-2-pentene

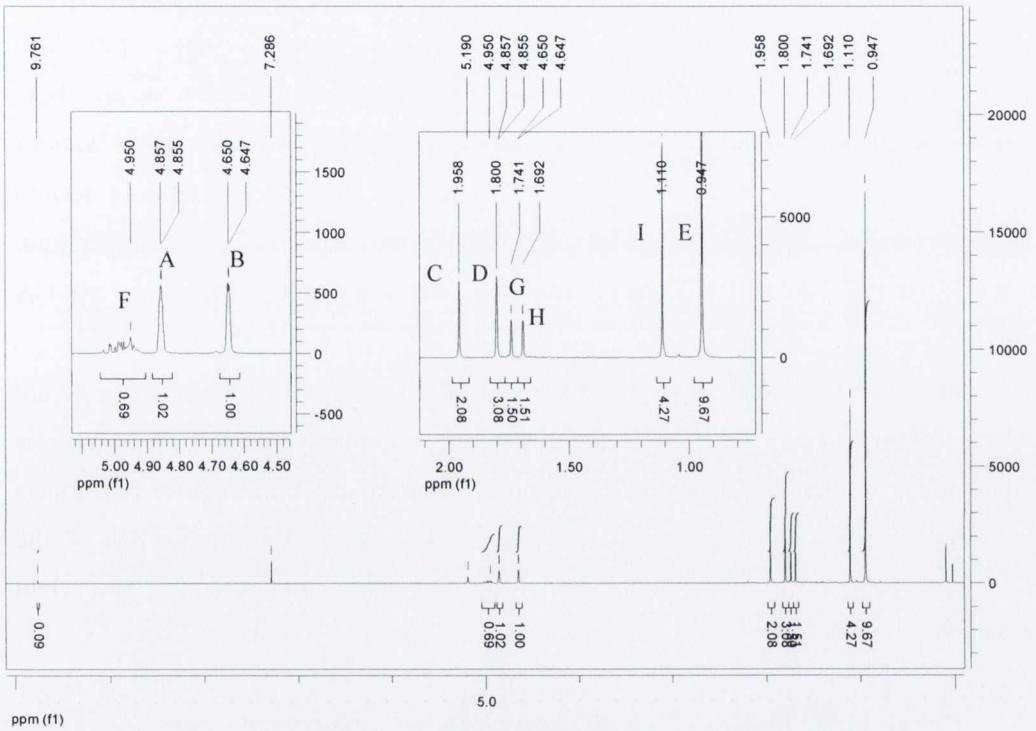


Figure 3.17. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the distilled fraction from thermal aging test of TOA imine*MSA salt

A mixture of two olefins, 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene, are identified (relative ratio 2 : 1).

In conclusion from the thermal aging of TOA Imine*MSA salt a new blend of ammonium specie is produces plus some olefins are distilled off.

3.2.4 TSIL / Cyanoacetate mixture reactivity

At this point of the discussion it is important to face the reaction monitoring. In fact so far only the physical form and thermal stability of the IL and IL/cyanoacetate blend have been faced. Nevertheless to have a precise control of the reaction parameters is extremely important in order to maximize the yield and selectivity of reaction. The TSIL process is formed by two main steps of reaction, the first corresponds to the reaction between the ionic liquid and the cyanoacetate, the second to the decomposition of the Mannich like adduct. The first step is typically performed in a range of 100 – 140 °C at environmental pressure; the target is to convert all the cyanoacetate and ionic liquid reagent in a Mannich adduct. This first stage of reaction is performed without vacuum because the cyanoacetate is a volatile compound and its boiling point is close to the correspondent cyanoacrylate. The second step is performed at higher temperature, usually between 170 and 190 °C and a strong vacuum is applied to achieve the fresh CA distillation.

The steps of reaction are closely dependent, in fact if residual amount of reagents are introduced under vacuum at higher temperature a contamination of the cyanoacrylate is produced with reduced selectivity. On the other hand, if the first stage or reaction is performed for too long or at too high temperature, an early decomposition of the Mannich adduct is promoted, then poly-cyanoacrylate is produced and low yield obtained.

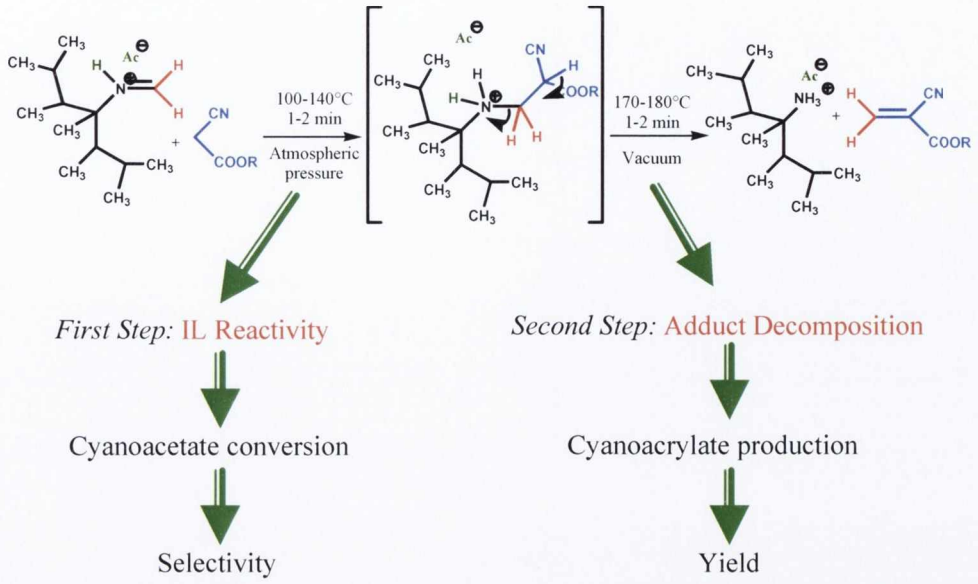
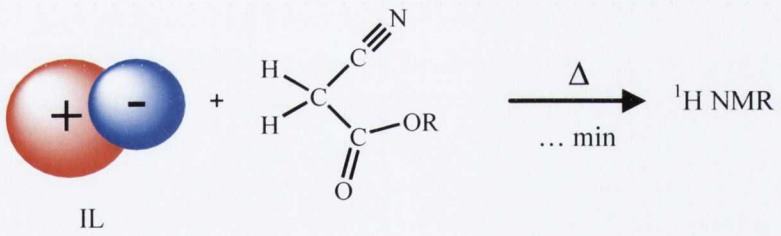


Figure 3.18. TSIL/cyanoacetate reaction.

In order to study independently these two steps, two different approaches are used, the first one examines the speed of the cyanoacetate conversion, the second analyses the speed of cyanoacrylate production.

3.2.4.1 Cyanoacetate conversion



Fresh produced imminium ionic liquid salt (1 eq) is mixed with a n-butyl cyanoacetate (1 eq), the obtained mixture is transferred into test tubes and heated at a pre-established temperature for a pre-determined time. The material is then quickly refrigerated to room temperature and the amount of cyanoacetate left is established by ^{1}H NMR analysis. Plotting the conversion in function of time it is possible to estimate the ionic liquid reactivity.

- 81R Imine(1.00 eq)*MSA(1.015 eq) and TBA Imine(1.00 eq)*SAS(1.10 eq)

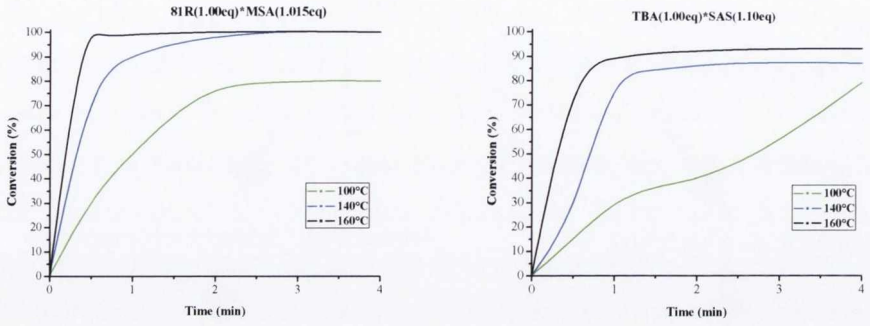


Figure 3.19. Conversion of cyanoacetate in function of time in the presence of 81R Imine (1 eq)*MSA(1.015 eq) (left graph) and TBA Imine(1 eq)*SAS(1.10 eq) (right graph)

A comparison between the ILs is reported. The first is obtained from a small hydrophilic anion (MSA in 1.5% of excess) plus a bulky cation (81R), the second from a big "lipophilic" anion (SAS) plus a small cation (TBA). The graphics show the conversion of the CAcet during 4 minutes of reaction. As predictable the difference in reactivity is more evident at lower temperature while at higher temperature the reactivity gap is reduced. The 81R*MSA is able to consume all the CAcet reagent in 3-4 minutes at 140 °C, instead TBA*SAS has a plateau and the conversion does not exceed 90% even after 4 min at 160 °C. This behaviour is very interesting and could be due to the reactivity nature of the two ionic liquids and to their internal stoichiometry. In fact the TBA*SAS ionic liquid has a large excess of acid (SAS is present in 10 mol % excess). Further investigations were made to full understand how the different reactivity emerged.

- 81R Imine (1 eq)*MSA (1.015 eq); 81R Imine (1eq)*MSA (1.05 eq) and 81R Imine (1 eq)*MSA (1.10 eq)

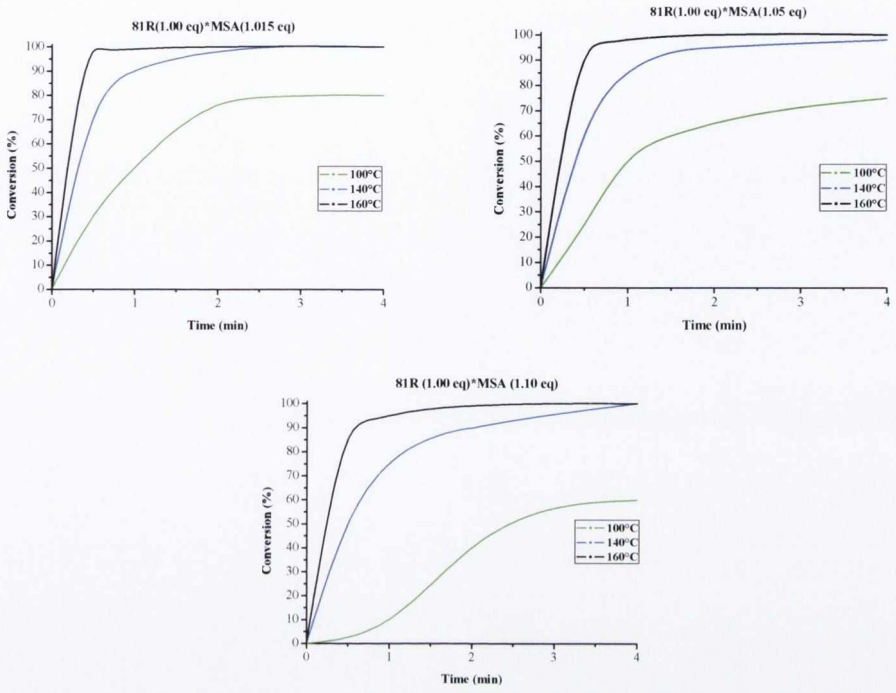


Figure 3.20. Conversion of cyanoacetate in function of time in the presence of 81R Imine(1eq)*MSA(1.015eq); 81R Imine(1eq)*MSA(1.05eq) and 81R Imine(1eq)*MSA(1.10eq)

By comparing the above results (Figure 3.20), the reactivity is greater when a smaller excess of MSA is used. This conclusion is in agreement with the base catalyzed nature of the first step of reaction. As previously observed the reaction between imines and cyanoacetate in basic environment proceeds quickly at room temperature and accomplishes exothermicity due to the cyanoacrylate polymerization. Instead lower reactivity is observed when an equivalent or larger amount of sulfonic acid is used to neutralize the ionic liquid; in this case the reaction proceeds only after heating.

- 81R Imine (1 eq)*MSA (1.015 eq) plus poly-phosphoric acid (5 and 10 w %)

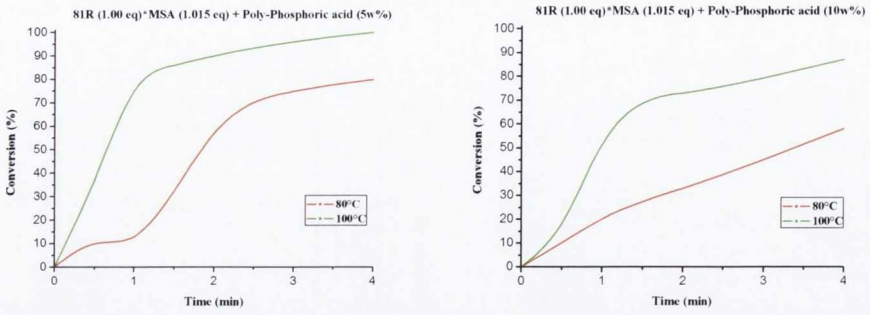


Figure 3.21. Conversion of CAcet in function of time in the presence of 81R Imine*MSA and poly-phosphoric acid 5 (left graph) and 10 w % (right graph)

In Figure 3.21 is reported the reactivity of the two systems based on 81R Imine*MSA (MSA 1.5 mol % in excess) ionic liquid. Poly-phosphoric acid is added to the reaction mixture in 5 or 10 w %. When 5 w % is added the increment of reactivity is significant, in fact the conversion reached after 1 min at 100 °C is 75% versus 50%. When 10 w % of poly-phosphoric acid is added the reactivity seems restored. This behaviour is apparently in contrast (for less than 5%) with what previously observed in the case of MSA. Moreover a rationale explanation is the peculiar reactivity of poly-phosphoric acid, which is able to produce phosphate from the reaction with weak nucleophiles, like water or alcohols[192] or to produce mixed anhydride in the presence of acid.[193] Therefore if the poly-phosphoric acid reacts with MSA there is a replacement of a strong sulfonic acid with a weaker phosphoric acid and the acidity strength of the system is reduced. Nevertheless when a larger excess of poly-phosphoric acid is present (10 w %) the original reactivity is recovered because of the abundant presence of phosphoric acid.

- 81R Imine (1.00 eq)*MSA (1.015 – 1.04 eq) plus P_2O_5 (4 w %)

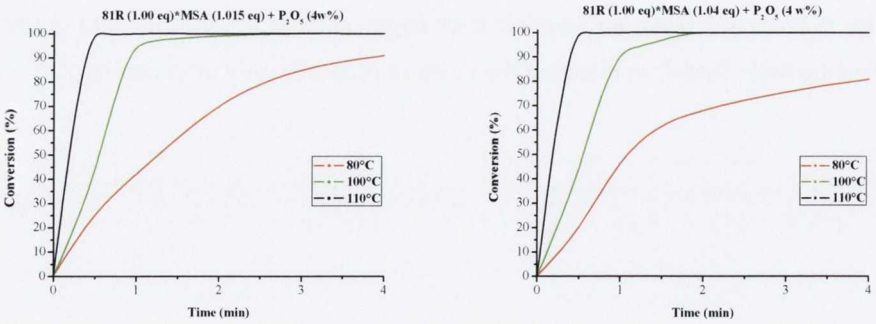


Figure 3.22. Conversion of CAcet in function of time in the presence of P_2O_5 and 81R Imine*MSA (1.5 mol% exc, left graph) and 81R Imine*MSA (4 mol% exc right graph)

The addition of small amount of phosphorus pentoxide produces an exceptional increment of reactivity. When 81R*MSA(1.5 mol % excess) plus P_2O_5 (4 w %) is tested almost quantitative conversion is reached after 1 min at 100 °C. This is twice the conversion obtained with only MSA (1.5 mol % exc.). The result can be explained by the high reactivity of phosphorus pentoxide toward weak nucleophile and acids. A chapter ("Acidity Investigation and Phosphate Solution") is dedicated to the P_2O_5 reactivity and to the P_2O_5/methanesulfonic acid solution (Eaton's reagent) properties. Briefly the great increment of reactivity can be associated to a partial exchange of MSA with phosphate functions, in fact high reactivity is maintained even in the presence of more methanesulfonic acid (4 mol % exc.).

3.2.4.2 Cyanoacrylate production

Freshly produced iminium ionic liquid (1 eq) was mixed with butyl cyanoacetate (1 eq); the obtained mixture was heated at 180 °C and after 30 seconds the reduced pressure was applied (2 mbar). After 10 minutes the temperature was increased at 200 °C and the test stopped after further 5 minutes. The tests were performed by means of a micro scale distillation apparatus (mini-SPE, See Chapter 3.3, "Equipment"). The amount of cyanoacrylate distilled was monitored and plotted as indication of the Mannich adduct decomposition.

- 81R Imine (1.00 eq)*MSA (1.03 – 1.10 eq)

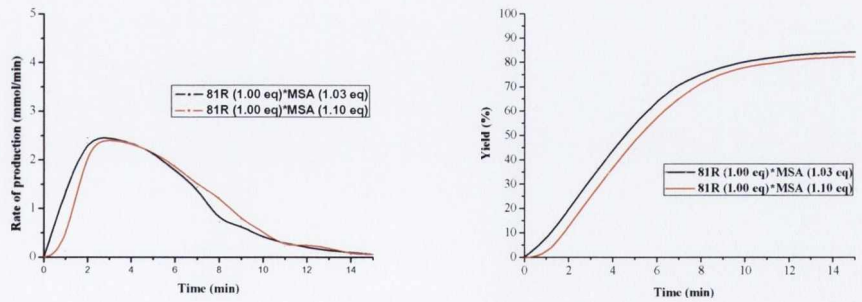


Figure 3.23. Cyanoacrylate production with 81R Imine (1.00 eq)*MSA (1.03 – 1.10 eq) ionic liquids; the plot on the left shows the mol of product in the unit time; the plot o the right shows the yield in function of time.

The cyanoacrylate distillation started very quickly, even after only 1 min it was already collected. The maximum rate of production (Figure 3.23) is observed after 2-3 min of reaction after which it slowly decreases. After 10 min the increment of temperature to 200 °C produces a little and not significant boost.

- 81R Imine (1.00 eq)*MSA (1.03 eq) and 81R Imine (1.00 eq)*SAS (1.10 eq)

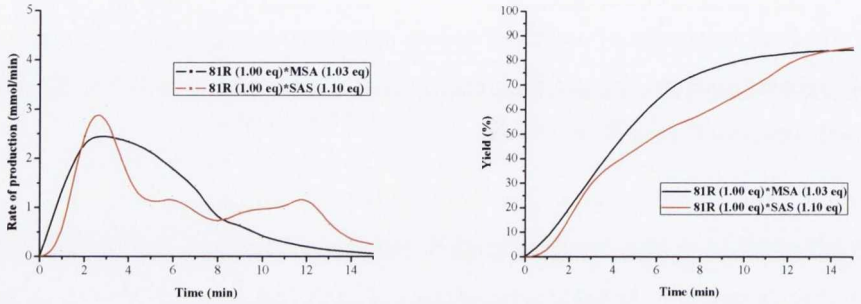


Figure 3.24. Cyanoacrylate production with 81R Imine (1.00 eq)*MSA (1.03 eq) and 81R Imine (1.00 eq)*SAS (1.10 eq) ionic liquids; the plot on the left shows the mol of product in the unit time; the plot on the right shows the yield in function of time.

The use of 81R Imine*SAS (10 mol % exc.) shows a consistent change in the rate of production profile. In fact the final yield of reaction is equal using both ionic liquids but in the case of SAS a consistent amount of product is even obtained after 8 minutes of reaction. Moreover the increase of temperature to 200 °C promoted a consistent increment of the production rate.

- 81R Imine (1.00 eq)*MSA (1.03 eq) and 81R Imine (1.00 eq)*SAS (1.25 eq)

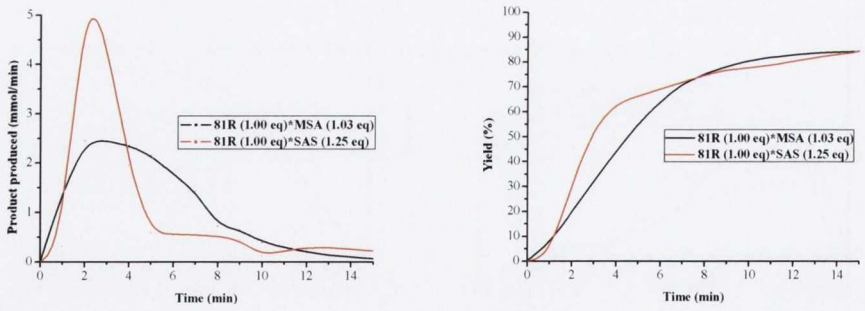


Figure 3.25. Cyanoacrylate production with 81R Imine (1.00 eq)*MSA (1.03 eq) and 81R Imine (1.00 eq)*SAS (1.25 eq) ionic liquids; the plot on the left shows the mol of product in the unit time; the plot on the right shows the yield in function of time.

A large excess of SAS produces a very quick distillation and impressive production rate values around 2-3 minutes, while the increase of temperature to 200 °C does not produce any consistent effect.

In conclusion the type (anion) and stoichiometry of the IL has an important influence on the product formation. In particular a large excess of acid promoted a quick product formation while a modest acid excess seemed do not produce any consistent effect. The increase of temperature, in order to increase the yield, worked only when the rate of production was low in the first minutes of reaction.

The rate of production in the time is extremely important and has to be carefully evaluated. In fact the reaction scale-up was performed in a SPE equipment (See Chapter 3.3, "Equipment") applying short residence time of typically few minutes. So a quick reaction is important in order to maximize the yield of reaction. In other words the produced Mannich adduct has only few minutes for undergoing total decomposition. So the reaction time of the second TSIL step of reaction, has to be comparable to the residence time in the SPE reactor. The rate of production in a SPE is anyway expected to be higher because of the higher distillation efficiency.

3.3 Equipment

3.3.1 Introduction

Commonly each reaction such as each workup operation is carried out in a suitable vessel. The small scale reactions are commonly performed in one or multiple neck round bottom flasks. In case of dehydration reactions the flask is equipped with chemical traps (e.g. molecular sieves) or physical traps (e.g. Dean-Stark apparatus). Gas-phase reactions are performed normally in pressurised reactors such as autoclaves.

The success of a chemical reaction requires the combination of chemical and process knowledge. This combination is even more important when applied to large industrial scale reactions since specilized process equipment can led to optimum performance.
This dissertation shows the evolution of a reaction from lab to industrial scale. The main steps are discussed in terms of reaction medium, scale of reaction and equipment used, thus:

1st Initial tests performed in chlorinated solvents and test tube

2nd subsequent tests in solvent free reaction in small scale and mini-distillation equipment

3rd scaled reactions in solventless conditions in large scale reaction and Short Path Evaporators (SPE)

3.3.2 Reaction performed in solution

The preliminary studies were carried out using glass test tubes (10 ml) screw capped as optimal solution for very small reaction scale.
The reactant solution was magnetically stirred and inserted in a thermostatted oil bath. For viscous material a different rotating system was used for the mixing. The reaction scale was increased about five times using a round bottom flask (100 ml) with a condenser while the heating and stirring system was unchanged. The technology applied at this early stage was adequate to study the reaction. The characterization of the

product was made by withdrawing small aliquots of reactant solution. In fact the solvent evaporation through distillation under vacuum caused the polymerization of the desired product.

3.3.3 Reaction performed in mini-SPE

Key in this research was the use of a solventless TSIL approach. A commercial "mini-SPE" (Figure 3.26) was selected as optimal technological solution for micro-distillation. In fact the product has to be removed quickly through high vacuum distillation and separated from the non-volatile ionic liquid.

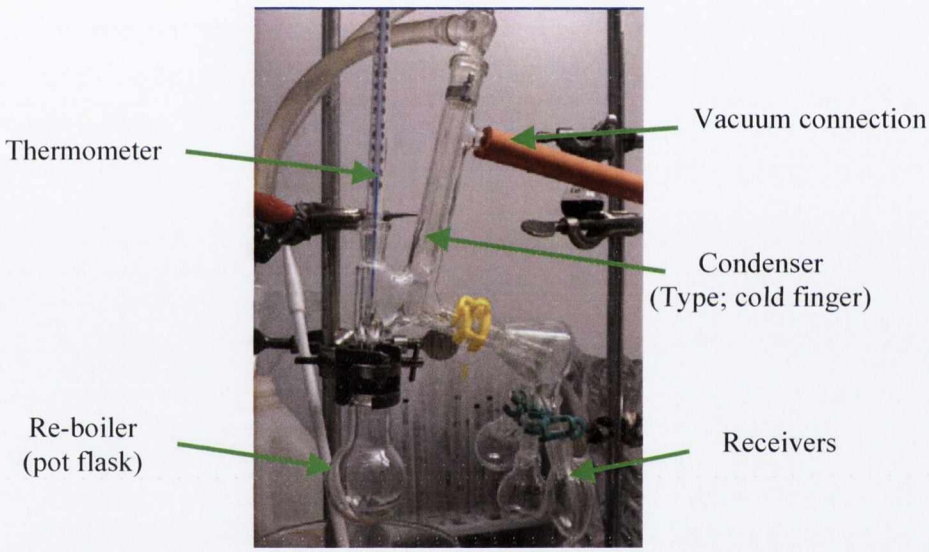


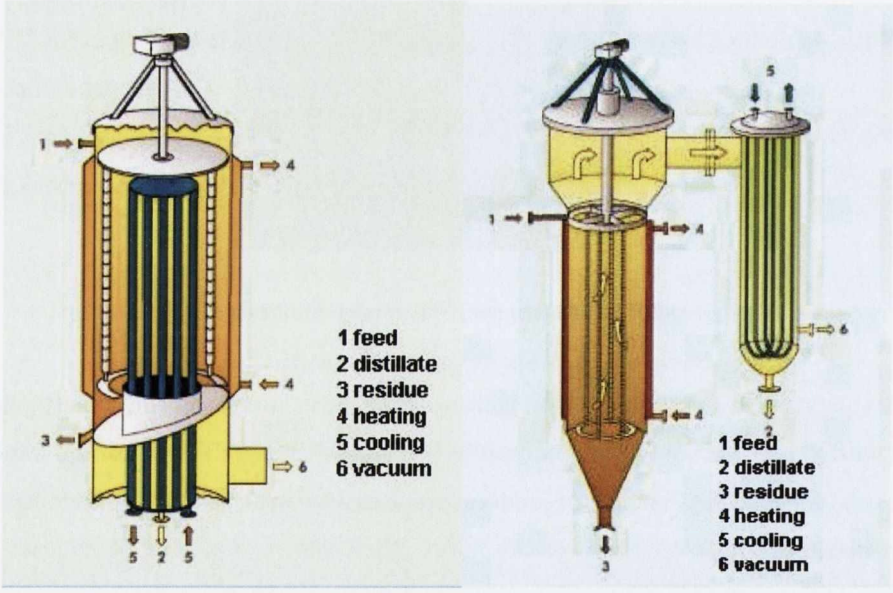
Figure 3.26. Commercial mini-SPE or mini-distillation equipment

This equipment was extremely useful in order to prove a concept and investigate this new reaction approach ("TSIL approach"). In a second stage of this work, the mini-SPE was used for reactivity studies of products and reagents and even for determining scale-up parameters.

3.3.4 Reaction in Short Path Evaporator (SPE)

Thin film evaporator equipment is commonly used for industrial flash distillations (or highly efficient distillation). The fundamental operating concept is that the thin film evaporator system is generated by a rotating wiper integrated in a heated cylinder. Two principal types of thin film evaporator systems can be distinguished: (I) the Short Path Evaporator (SPE) and, (II) the Wipe Film Evaporator (WFE). These reactors are usually built up in vertical direction, but the latter may also take a horizontal (conical shape) configuration.

The main difference between the two systems is where the condensation takes place. For the SPE, the condenser is central within the heating chamber and within the central rotor carring the wiper blades. A WFE system differs in that the condensation occurs on an external condenser located outside the reactor body (heating chamber). Schematics of this extremely useful evaporators are shown in Figure 3.27. In this work the SPE has been used as a reactor/evaporator.



SPE WFE

Figure 3.27. Schematic drawing of commercial SPE and WFE;
http://www.vtadeg.de/english/destillation.htm

The different configuration determines the maximum operateable vacuum which is in the range of 1-0.5 mbar for a WFE (physical limit named drop of vacuum). However, the SPE permits vacuum of less than 0.001 mbar and this type of equipment is often used for the isolation of volatile thermally sensitive materials.

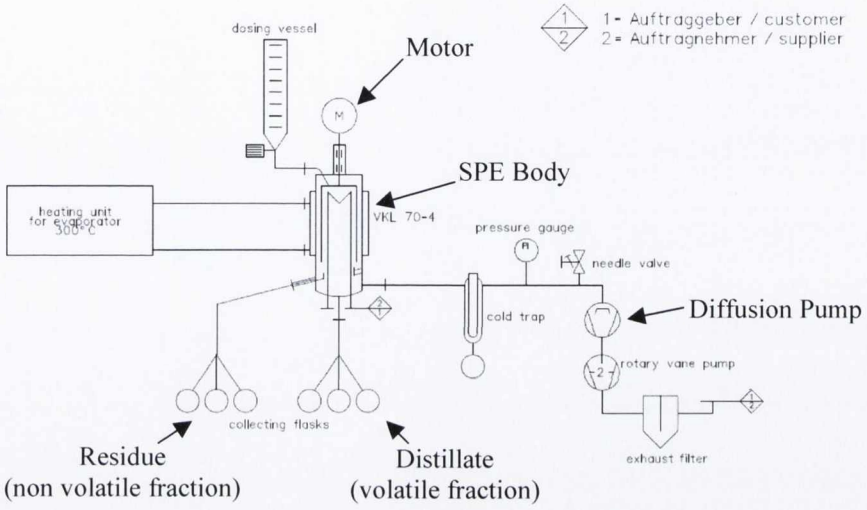


Figure 3.28. Schematic of SPE laboratory scale equipment

The SPE apparatus was selected for developing this work which is aimed to produce a class of thermosensitive and high-boiling molecules. The SPE was preferred for its higher potentialities and major flexibility in terms of application. Standard equipment was used initially as illustrated in Figure 3.28. Subsequent modification including the addition of an internal splash guard (metallic laminated structure) integrated with the rotor and interposed in between the surface evaporation area and the condenser. This additional component was very important in order to avoid contamination of the distilled product by splashing of viscous IL.

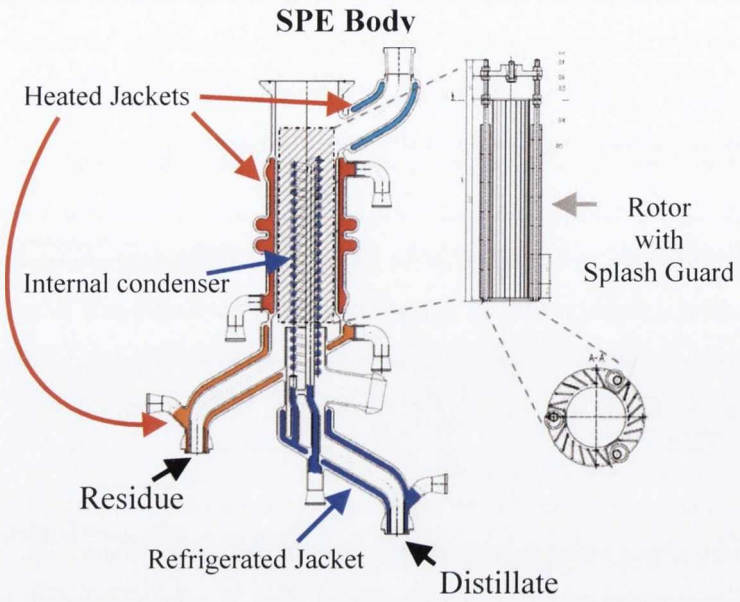


Figure 3.29. Schematic drawing of a section of SPE body; detail shows configuration of the splash guard around the wiper blades on the central rotor

3.3.4.1 SPE without pre-reactor

The first reaction tests were performed in a commercial and standard SPE. The reactant mixture [8IR imine (1.00 eq), MSA (1.05 eq), and butyl cyanoacetate (1 eq)] was added, using a dropping funnel, directly into the reactor. The operative conditions used are reported in Table 3.3.

Table 3.3. First TSIL attempts in SPE equipment

Entry	SPE Temperature (°C)	Vacuum (mbar)	Yield
1	120	0.001	0
2	120	0.2	0
3	150	10	0

The distillation process was very quick and efficient as the fractions collected had a weigh equivalent to 99% yield. Since the yield was suspect in such short time ^{1}H NMR analysis was undertaken for the distilled fractions, and only un-reacted starter butyl cyanoacetate with no trace of product.

The causes of the initial failed test were attributed to an over-efficient distillation and to a very short reaction time between the ionic liquid and the cyanoacetate. The residence time inside the reactor was much shorter than the requisite reaction time.

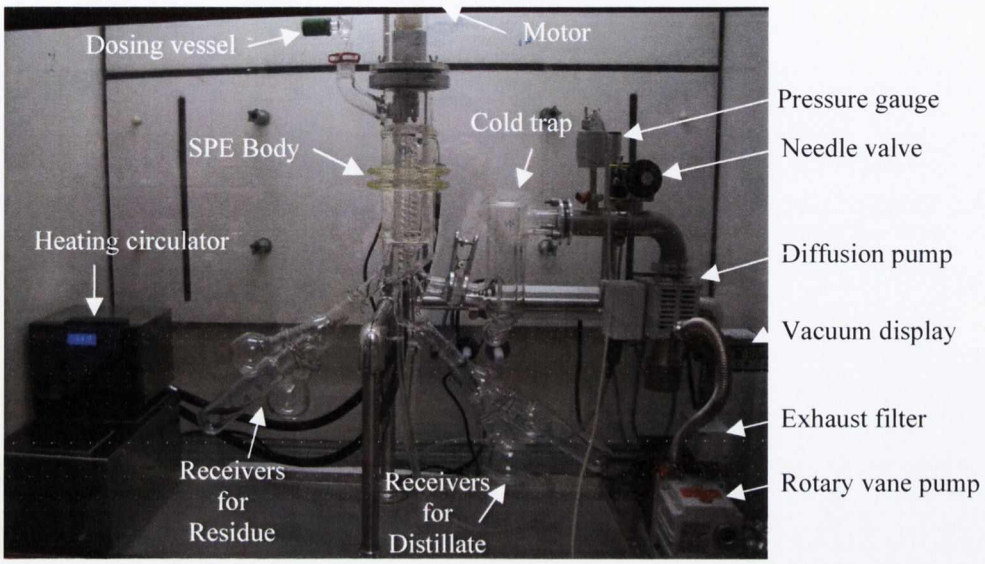


Figure 3.30. Photograph of a simple commercial SPE (VTA GmbH)

In the subsequent attempts, preheating of the reactant solution before the introduction in the SPE equipment was examined. In a subsequent modification, 20 ml of IL-butyl CAcet mixture were each time heated in a round bottom flask and heated (by dipping in a hot oil bath) for 4 min at 150 °C. The resulting viscous material was transferred into the dropping funnel (or dosing vessel) and slowly introduced in the SPE equipment (150 °C at 0.2 mbar). This approach led for the first time the formation and distillation of the desired product in a mixture of cyanoacetate/cyanoacrylate with a ratio of 1/6.

Further attempts were performed by pre-heating the reagent solution in a different way. Thus, 20 ml of reagent mixture was pre-heated 2-3 min at 150 °C directly inside the dropping funnel by means of a heating gun. The results are summarized in Table 3.4.

Table 3.4. TSIL attempts by first heating with an heating-gun (temperature approximately 150 °C)

Entry	SPE Temperature (°C)	Vacuum (mbar)	Yield (%)	Purity (%)
1	150	0.2	40	55
2	180	0.2	70	80

The results were very encouraging and the need to pre-heat the reagents before addition to the SPE apparatus (high vacuum and temperature) was evident. Subsequently different pre-reactors (or pre-heaters) were designed.

3.3.4.2 SPE with Glass pre-Reactor Coil

The first simple approach was realized with a jacketted glass-coil with various internal volumes as illustrated in Figure 3.31. The coil volume determined extend when the flow rate was roughly adjusted.

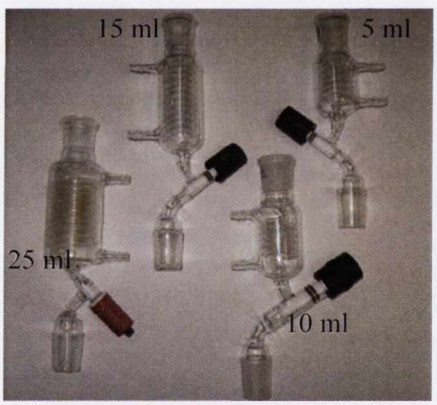


Figure 3.31. Jacket glass coil with different internal volume

This new apparatus component was integrated between the dropping funnel and the SPE reactor as shown in Figure 3.32, and it was named pre-reactor. The coils were equipped with a PTFE valve so the feed rate could be manually adjusted. Therefore by combining the pre-reactor volume (5, 10, 15, 25 ml) and the feed rate, it was possible to affect the reaction time (or residence time in the pre-reactor). The use of a second heating circulator bath made the temperature control of the pre-reactor independent from the temperature of the SPE.

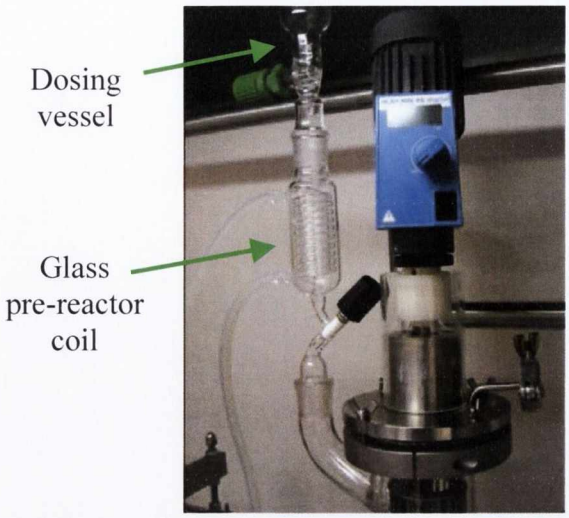


Figure 3.32. Picture of the top of the SPE equipment with integrated glass pre-reactor coil

Many experiments were performed using this equipment setting. Typical procedure was to heat the reagent mixture for 4-5 min at 140 °C by means of the 25 ml pre-heating coil; good yields (70 – 85%) and purity (60 – 90%) were always reported.

In conclusion the glass pre-reactor coil (Figure 3.31, Figure 3.32) showed great potentialities but also some drawbacks due to the crude manual control. The feed rate regulation was complex and not completely reproducible because the PTFE valve was a link between an high vacuum and an atmospheric pressure system. The feed rate and the residence time were strictly also connected with the viscosity of the reaction mixture. Superior design was thus required to properly control the chemistry.

3.3.4.3 SPE with Stainless Steel Five Stages pre-Reactor

The first reaction step had to be controlled completely through an automated system that allowed precision and accuracy. A new pre-reactor was thus designed following as illustrated in Figure 3.33

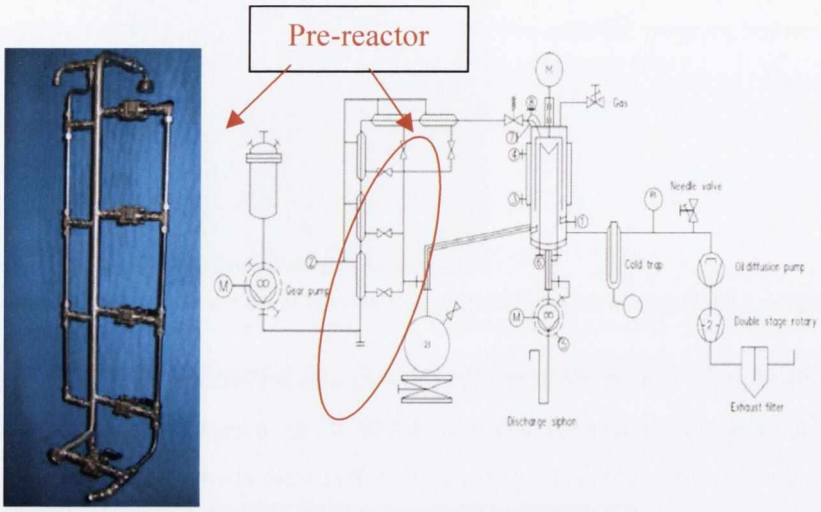


Figure 3.33. Schematic drawing of SPE laboratory scale plant and detail of a custom built 5-stages steel pre-reactor for the TSIL reaction

The pre-reactor apparatus was designed as a jacketted pipe divided into 5 zones (each 10 mls in volume) heated up independently from one another.
The technical problem to interface the pre-reactor (positive pressure) with the short path (negative pressure) was solved using a vacuum rated one-way overflow valve. The feed rate was precisely controlled by a precision gear pump furnished with a digital controller. Further customization included addition of inlets at the top of the SPE to permit the addition of stabilisers at various points in the process. This set up has been used for the study and optimization of the reaction, as well as for manifacturing-pilot plant scale production. The latter investment was made as a result of the success of this research and its process co-development.

Durign the course of the research the apparatus was also demonstrated to work in continuous production mode so long as the reactant reservoir was charged (see Figure 3.34). In this case a discharge gear pump replaced collection flasks. One experiment was conduced for 25 hrs uninterrupted production as a feasibility study.

Still further refinements can be made to this powerfull equipment and process by ganging a WFE at the output of the SPE and further refining the pre-reactor with a more efficient mini-heatexchanger at the input to the SPE.

The evolution of process design in concert with a detailed understanding of the chemistry has enabled this work to progress from a few gram scale reactions in tubes to bulk scale reactions wherein kilos of useful materials have been produced.

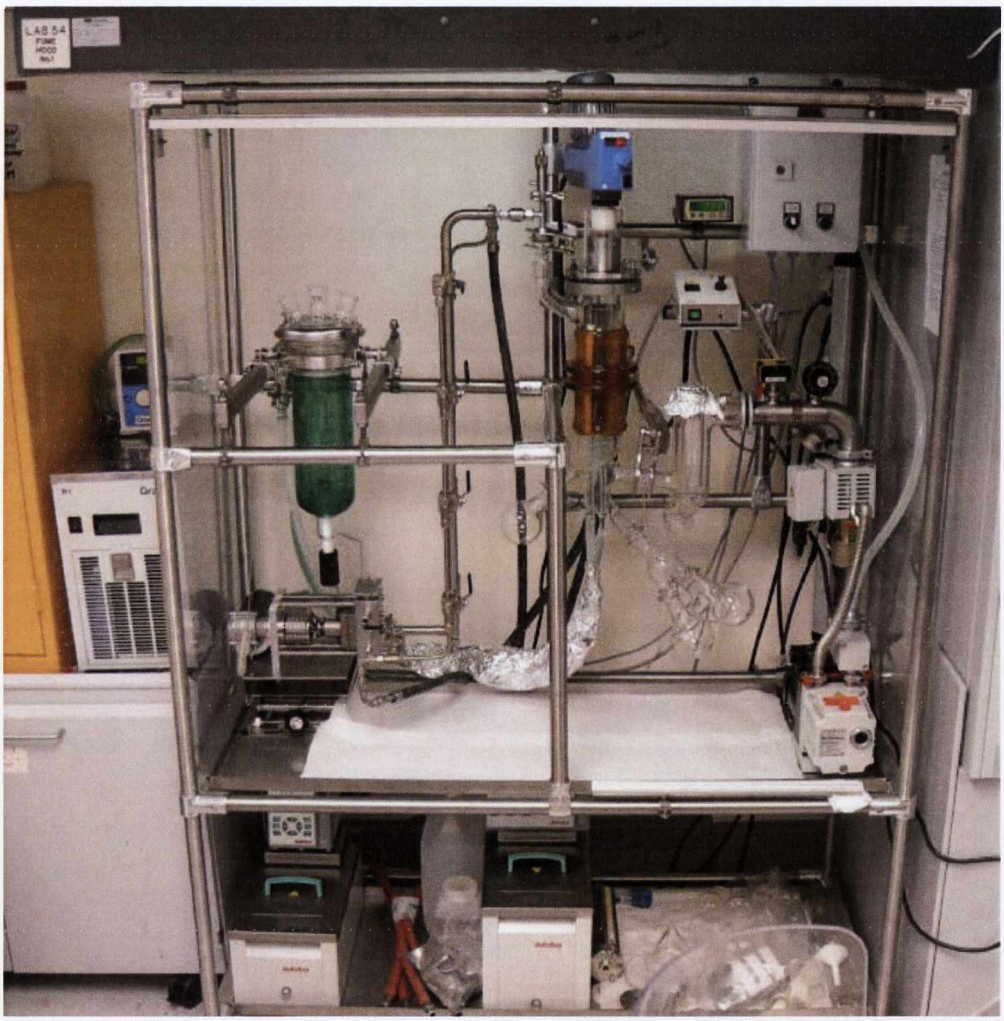


Figure 3.34. Picture of final SPE equipment set-up for TSIL approach

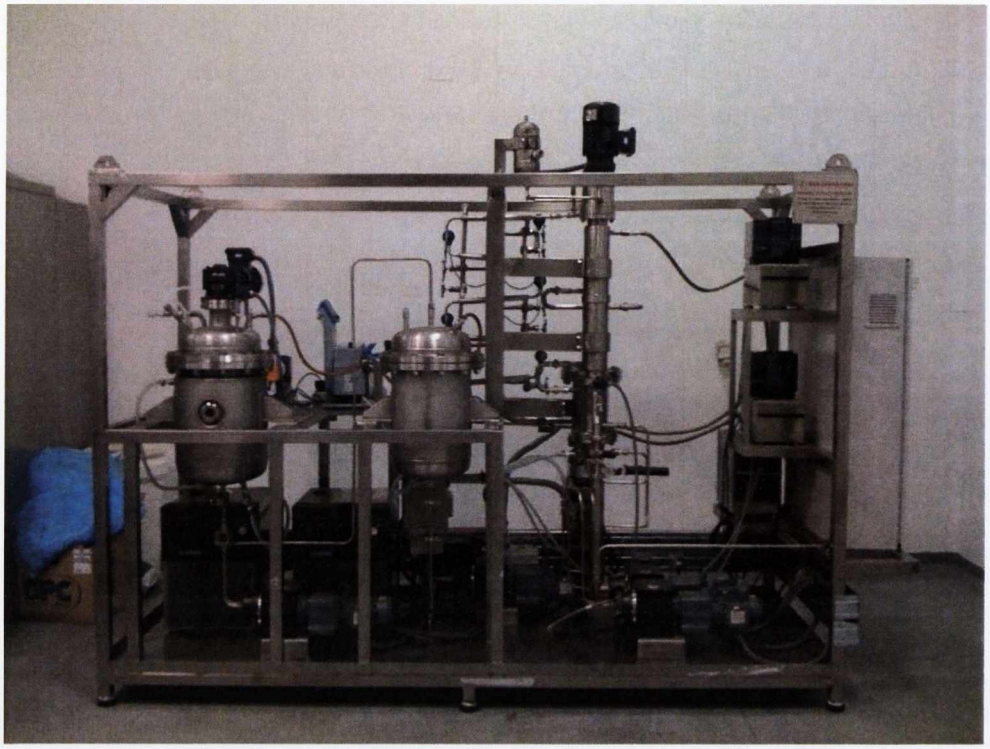


Figure 3.35. Picture of Pilot Plant SPE equipment for TSIL Approach

3.4 General applicability of TSIL method; CAcet evaluation

The robustness of the TSIL process was tested with different CAcets, in the mini-SPE equipment under the usual operative condition.

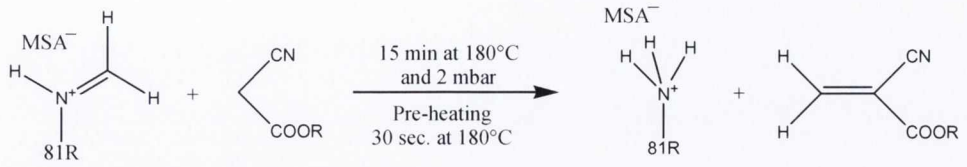


Table 3.5. CAs synthesis by TSIL method and mini-SPE

Entry	Cyanoacetate R	CA Yield (%)	CA Purity (%)
1	Ethyl CH_2CH_3	84	90
2	*n*-Butyl $CH_2(CH_2)_2CH_3$	86	95
3	*iso*-Propyl $CH(CH_3)_2$	72	92
4	2-Octyl $CH(CH_3)(CH_2)_5CH_3$	75	90
5	*neo*-Pentyl $CH_2C(CH_3)_3$	78	90
6	β-Methoxyethyl $(CH_2)_2OCH_3$	84	89
7	Propargyl $CH_2C{\equiv}CH$	80	90
8	Allyl $CH_2CH{=}CH_2$	84	92
9	Crotyl $CH_2CH{=}CHCH_3$	65	90
10	3-Ethyl-3-oxetanylmethy $CH_2C(CH_2OCH_2)CH_2CH_3$	0	-
11	Triethoxysilylpropyl $CH_2(CH_2)_2Si(OC_2H_5)_3$	0[a]	-

[a] Trace of product were detected

Most of the yields obtained are in agreement or superior to those reported in the literature[194,195]. Silicon-based cyanoacrylates gave modest yields probably because their low thermal/acidity resistance. The purity of reaction was high in the most of the cases. The oxetane CAcet did not produce any product and only hard solid material was obtained inside the distillation equipment.

Two different activated methylene compounds were tested too, the results are following reported.

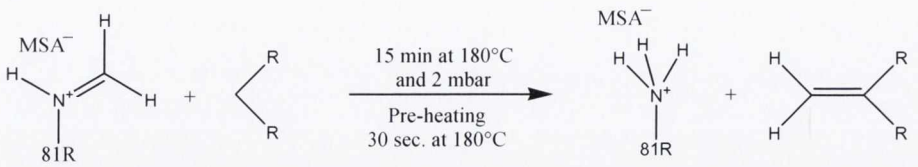


Table 3.6. Synthesis of reactive olefins by TSIL method

Entry	Activated methylene R	Yield %	Purity %
1	2-Methylene-malononitrile CN	50	90
2	2-Methylene-diethyl malonate $COOCH_2CH_3$	48	50

The most reactive compound is the malononitrile (Table 3.6, Entry 1), it produces the correspondent olefin in 50% yield and high purity. The less reactive diethyl malonate (Table 3.6, Entry 2) produces only 48% yield and 50% of the unreacted reagent was collected with the product. The reaction was repeated few times at higher temperature or for longer reaction time but always only 50% purity product was obtained.

The most successful cyanoacetate synthesis was performed by means of the SPE equipment (typical SPE procedure) and the results are following reported.

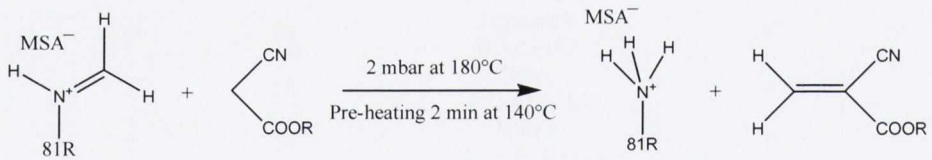


Table 3.7. CAs synthesis by TSIL method and SPE

Entry	Cyanoacetate R	CA Yield (%)	CA Purity (%)
1	*n*-Butyl $CH_2(CH_2)_2CH_3$	90[a]	95
2	*iso*-Propyl $CH(CH_3)_2$	70	91
3	2-Octyl $CH(CH_3)(CH_2)_5CH_3$	72	90
4	*neo*-Pentyl $CH_2C(CH_3)_3$	75	93
5	β-Methoxyethyl $(CH_2)_2OCH_3$	86	92
6	Propargyl $CH_2C{\equiv}CH$	78	93
7	Allyl $CH_2CH{=}CH_2$	80	95

[a] The residual IL was passed through the SPE a second time, the yield was boosted up to 97%

The reactivity trend was comparable to the which obtained by mini-SPE equipment. Moreover the yields and purity were observed to be always higher.
This behavior gives a confirmation about the high potentiality of this powerful distillation equipment.

3.5 Synthesis of Solid Cyanoacrylates

Up to now all commercial instant adhesives are based on liquid cyanoacrylates. Nevertheless a very interest new business opportunity could be generated by new forms of instant adhesives. In the literature few examples of solid cyanoacrylate have been reported. A class of solid cyanoacrylate is definitely represented by the Bis-Cyanoacrylates, those monomers have been extensively studied by Buck[196]. Those molecule are considered nondistillable and of interest to improve thermal performances; however their synthesis goes through the Diels-Alder approach and only small production of expensive material can be obtained. Another problem is the limited solubility of most bis-CAs in common alkyl cyanoacrylate, so that only small amount of dual functional monomer can be solubilised and only modest performance improvement can be reached.
In the TSIL reaction 1 eq of IL reacts with 1 eq of CAcet for the production of the correspondent cyanoacrylate. One equivalent of ammonium IL is generated that can be treated with base to regenerate the reagent amine. The production of bis-cyanoacrylate would require two equivalent of IL for each molecule of bis-CAcet reacted, so this approach could be considered non-economic for a large scale production. Moreover the bis-cyanoacrylate are high molecular weight molecules and their distillation could be considered extremely difficult even with a powerful distillation equipment like the SPE.

3.5.1 Propargyl Cyanoacrylate

Propargyl CA has been symthetized by TSIL Approach, the product resulted to be a crystalline solid. The structure has been studied by X-ray diffraction experiment and the crystal structure is reported in Figure 3.36.

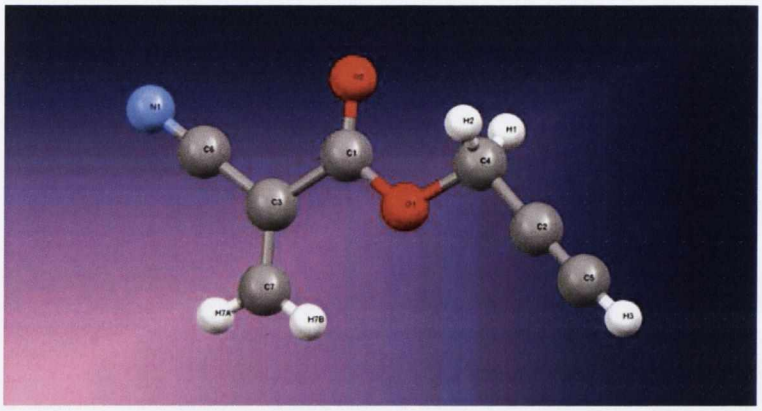


Figure 3.36. X-ray picture of propargyl CA

3.5.1.1 Polymerization attempts of propargyl cyanoacrylate in the solid state

An investigation was performed to investigate the possibility of performing a nucleophilic polymerization cyanoacrylate in the solid state. Then propargylCA was considered as solid monomer and butyl CA was used as reference.

Procedure:

The polymerisation attempts were performed by means of vapour phase initiation using of tert-butyl amine in a closed vessel. Some cyanoacrylate was homogeneously dispersed on the surface of microscope slide and a thin layer of active monomer was produced. The reference, butyl CA, was dispersed as described and tested in the liquid form instead propargyl CA undergone to identical test but after crystallization on the glass surfice.

The polymerization was performed after introducing the samples for 60 seconds in a closed vessel saturated with amines vapour. The container was made by a 1l beaker capped by a watch glass, few grams of TBA were dispersed on a layer of cotton.

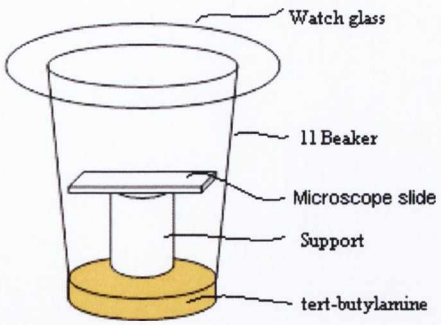


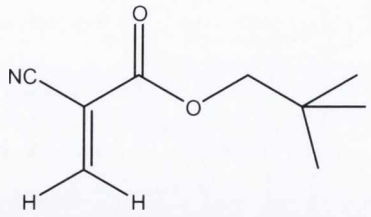
Figure 3.37. Drawing of the "reaction room"

The sample obtained after the polymerisation attemp was scraped from the glass surface by means of a steel spatula. The powder obtained was analyzed by FT-IR and ^{1}H NMR.

The polymerization of butyl CA proceed very quickly, in fact already few second after the introduction of the sample in the beaker, all the liquid active monomer turned into a white solid. Some milligrams of polymer produced were scraped off and dissolved in $CDCl_3$ and analysed by ^{1}H NMR. The latter solid sample was completely soluble in chloroform and from the NMR spectrum it was possible to observe only poly-cyanoacrylate. Diagnostic was the absence of the vinylic protons and the appearance of a new broad peak at δ 2.6 ppm (typical of CH_2 backbone polymer).

The same test performed with propargyl CA (crystallized on the surfice of the microscope slide) did not show any polymerization. The ^{1}H NMR of few milligrams of treated monomer clearly showed the presence of only monomeric cyanoacrylate.
It may be concluded that the crystalline form of propargyl CA did not polymerise in the solid state.

3.5.2 Neopentyl Cyanoacrylate

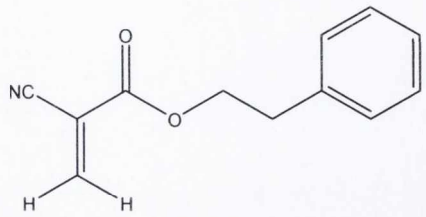


In the 1992 Hiroyuki Mikuni and Toshiyuki Chikusa[197] reported the synthesis and formulation of a new solid cyanoacrylate with superior adhesive properties using neopentyl cyanoacrylate monomer. They reported "*The novel compound, neopentyl a-cyanoacrylate exhibits excellent instantaneous adhesive properties. It has a melting point of 40 °C and is a solid at a room temperature It can be used itself as a hot-melt type instantaneous adhesive and also used as a liquid instantaneous adhesive in a mixture of conventional one or more cyanoacrylates in the same manner as conventional instantaneous adhesives*". The requisite CAcet was reported to be synthesised in 94%. This was used in a Knöevenagel reaction to produce crude monomer obtained in 43% yield. After redistillation the yield of pure material was 16%.

The synthesis of neopentyl CAcet was carried out by esterification. Thus 1.2 eq of Cyanoacetic acid were reacted with 1 eq of neopentyl alcohol in heptane by sulfuric acid catalysis (2 mol %), the reaction was refluxed for 1.5 hours until collection of theoretical amount of water into the Dean Stark trap. The product was purified by redistillation to yield pure neopentyl CAcet (colourless oil, 90% yield, 80 °C at 3 mmHg)

The synthesis of neopentyl cyanoacrylate was next conducted first by regular mini-SPE procedure, then repeated by SPE approach for larger scale production.

3.5.3 2-Phenyl-1-ethyl cyanoacrylate



A key criterion for successful commercialization of new materials is a low production cost. Thus inexpensive solid cyanoacrylate may considered an important target. The synthesis of two monofunctional solid cyanoacrylate (neopentyl and propargyl CAs) were successfully performed, however the formed material is quite expensive. The main factors that establish the cyanoacrylate cost is the yield of reaction and the cost of the CAcet reagent. Thus a literature search was conducted on known solid cyanoacrylate only adamantly was found but this is again exotic. Driven by the goal to produce a low cost solid monomer, the synthesis of 2-phenyl-1-ethyl CAcet and correspondent cyanoacrylate were performed. The 2-phenyl ethyl cyanoacrylate has been reported only twice in the literature[198] nevertheless characterization details have not appeared. The synthesis of 2-phenyl-1-ethyl CAcet was performed by regular Fischer esterification. A regular TSIL reaction by mini-SPE was performed, the product began to distil almost immediately and 1.23 g (65 % yield) of product were collected (117 °C at 0.5 mbar). The product was contaminated from approximately 10% of 2-phenyl ethanol and traces of methanesulfonic acid. Both contaminants were added to the same sample to confirm this. The ^{1}H NMR spectrum is reported in Figure 3.38.

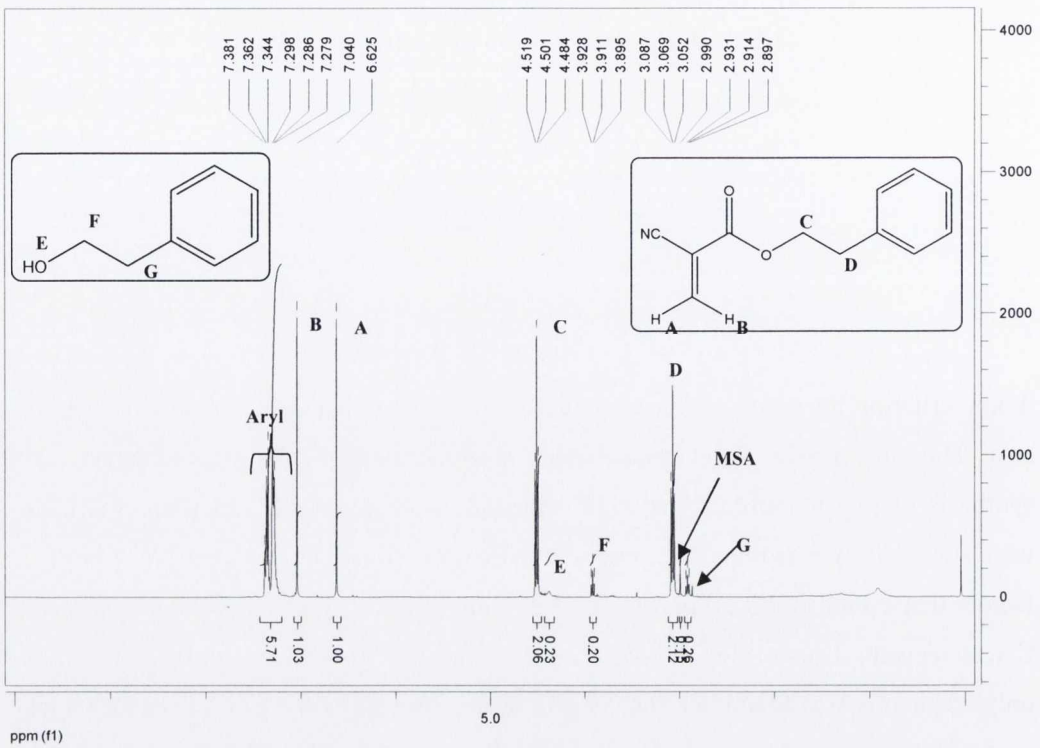


Figure 3.38. ^{1}H NMR (400 MHz, $CDCl_3$) of 2-Phenyl-1-Ethyl cyanoacrylate crude from TSIL reaction

This result was in agreement with what was observed previously with different CAcets. Therefore the same hypothesis postulated earlier (see chapter 4.5) can be use to explain this phenomena. The distilled product was stored overnight in the fridge crystallised to a solid material (mp 40 °C). A new solid cyanoacrylate was then successfully generated.

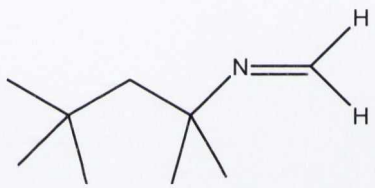
3.6 Experimental

General procedure for the synthesis of PRIMENE imine

The mixture of PRIMENE (2.43 mol) and paraformaldehyde (72.9 g, 2.43 mol) was stirred for 16 hours at room temperature. The water (low phase) was removed and the organic phase dried by sodium sulfate. The mixture was finally purified by vacuum distillation through a splash head (avoid bump over), the product obtained was a colorless oil.

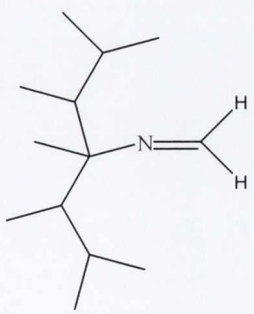
TOA imine [199]

(Methylene-(1,1,3,3-tetramethyl-butyl)-amine)



Colourless oil, bp 95-100 °C.

PRIMENE 81R imine



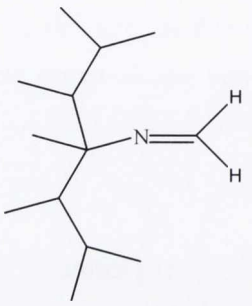
81R: C_{10} - C_{15} mixture, predominantly C_{12}

Colourless oil, bp 100-110 °C at 2 mbar;

δ_H (60 MHz, $CDCl_3$): 7.26 (br, s, 2H), 2.01-0.79 ppm (m, 26H);

AT-IR (Neat): 2949 s, 2925 s, 2876 s, 1650 w, 1462 m, 1372 m, 1217 w, 1021 m, 735 w (cm^{-1});

PRIMENE JMT imine



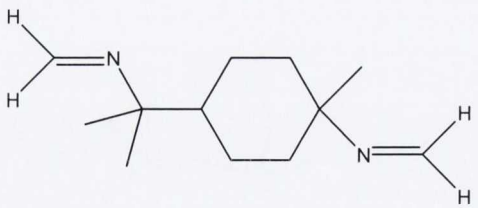
JM-T: C_{16} - C_{22} mixture, predominantly C_{18}

Colourless oil, bp 120-125 °C at 1 mbar;

δ_H (60 MHz, $CDCl_3$): 7.30 (s, 2H), 1.95 – 0.87 (m, 33H);

AT-IR (Neat): 2948 s, 2925 s, 2876 s , 1650 w, 1463 m, 1378 m, 1147 m, 1057 m, 1023 m, 1001 m, 965 w, 915 w (cm^{-1});

PRIMENE MD di-imine[199]

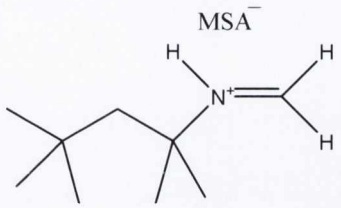


Colourless oil, bp 80-85 °C at 1 mbar;

General procedure for the synthesis of Ionic liquid from PRIMENE imine

Good quality ionic liquid is typically obtained by dropwise addition of the base into the acid or vice versa. 1 eq of fresh distilled PRIMENE was slowly added to 1 eq of acid. The reaction is cooled by means of an ice bath and the stirring is magnetic or mechanical respectively for small (20-30 mmol) and large reaction scale.

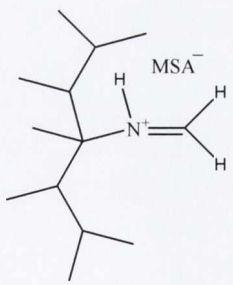
TOA imine * MSA



δ_H (60 MHz, $CDCl_3$): 8.50-7.30 (m, 2H), 2.79 (s, 3H), 1.80 (s, 2H), 1.52 (s, 6H), 0.95 (s, 9H);

AT-IR (Neat): 2952 m, 2904 m, 2866 w, 1695 w, 1527 w, 1473 w, 1210 s, 1156 s, 1037 s, 976 w, 767 m (cm^{-1});

81R imine * MSA



δ_H (60 MHz, $CDCl_3$): 9.00-7.50 (m, 2H), 2.80 (s, 3H), 2.00-0.70 ppm (m, 24H)

AT-IR (Neat): 2956 m, 2925 m, 2872 m, 1683 w, 1610 w, 1537 w, 1463 m, 1384 w, 1327 w, 1217 s, 1161 s, 1035 s, 960 w, 768 m (cm^{-1});

General procedure for micro scale TSIL reaction

(Study on ionic liquid)

To a mixture of PRIMENE imine (20 mmol) and acid (21 mmol), Ethyl CAcet (2.37 g, 20 mmol) was added at room temperature. The mixture was heated for 1 min at 100 °C, then a vacuum distillation started (0.2 mbar) simultaneously with an increment of temperature to 200 °C. The monomeric Ethyl CA was a colourless oil.

General procedure for the IL reactivity study

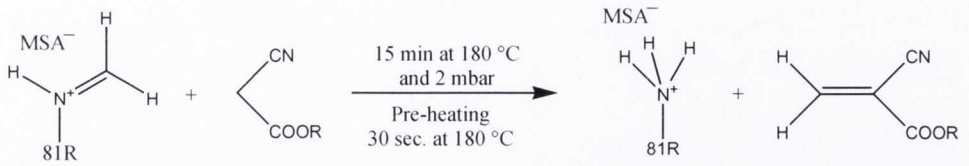
(Study of n-Butyl CAcet conversion as function of time)

To a mixture of imine (1 eq, 50 mmol) and acid (X eq, X = 1.015, 1.04, 1.05, 1.10), n-Butyl CAcet (1 eq, 7.05 g) was added at room temperature. The reaction mixture was divided into different aliquots (0.5 g) in test tubes and heated at the selected temperature for a pre-determined time. The samples were quickly cooled down at room temperature and the conversion established by ^{1}H NMR.

General procedure for the synthesis of n-Butyl CA by mini-SPE

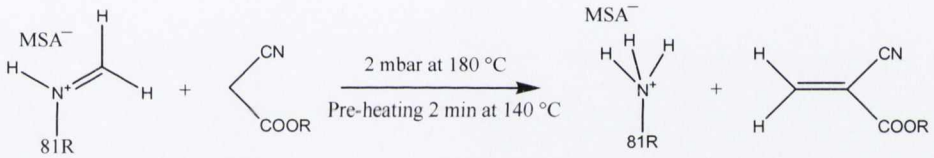
An acid (X eq, X = 1.03, 1.10, 1.25) was dropped slowly in 81R imine (1 eq, 20 mmol) and n-butyl CAcet (1 eq, 2.82 g) was finally added. The mixture was heated at 180 °C and after 30 sec the vacuum was applied (2 mbar). After 10 min the temperature was increased at 200 °C and the test stopped after further 10 min. The distilled CA was monitored as function of time.

Optimized procedure for the synthesis of CAs by mini-SPE



CAcet (1 eq, 20 mmol) was added to a mixture of 81R imine (1 eq, 20 mmol, 3.94 g) and MSA (1.05 eq, 21 mmol, 2.02 g). The reactant solution was heated at 180 °C and after 30 sec the vacuum was applied (2 mbar). After 15 min the distillation was stopped and the fractions were collected and analyzed by ^{1}H NMR.

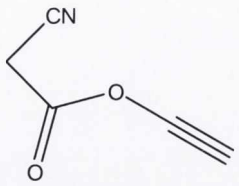
Optimized procedure for the synthesis of CAs by SPE equipment



MSA (60.48 g, 0.63 mol, 1.05 eq) was transferred in a three neck round bottom flask equipped with mechanical stirrer and dropping funnel. 81R imine (118.20 g, 0.60 mol, 1.00 eq) was dropwise added in 30 minutes time, the temperature was kept below 20 °C by means of an ice bath. CAcet (0.60 mol, 1.00 eq) was added and the solution was stirred few minutes to homogenise. The reagent mixture was transferred in the feeding vessel of the SPE equipment and the TSIL reaction started.

Pre-heater set-up: temperature 140 °C, reagent flow rate (feeding) 5 ml/min, 10 ml volume heated (only one stage of the pre-heater is heated).
SPE set-up: temperature 180 °C, vacuum 2 mbar, rotor rotation speed 300 rpm, condenser 5 °C.

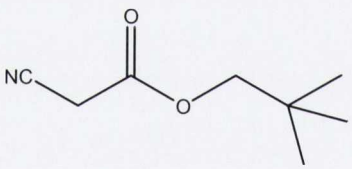
Propargyl CAcet[200]



Propargyl alcohol (78.4 g, 1.4 mol) and cyanoacetic acid (85 g, 1.0 mol) in toluene (200 ml) solution were refluxed for azeotropic removal of water in the presence of 2 or 3 drops of concentrated sulfuric acid. After stirring 8 h, about 17 ml of water were separated. After cooling, the reaction product was washed consecutively with 30% brine and water. The organic layer was dried by anhydrous sodium sulfate and filtered. The solvent was removed under vacuum and then purified by distillation. Propargyl CAcet (75 g, 0.61 mol) was isolated in 60% yield (95-97 °C at 0.8 mbar).

Neopentyl CAcet[200]

(Scale-up procedure)

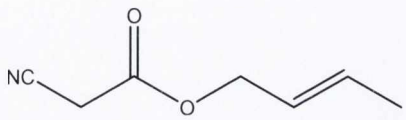


A 1L, three-neck, round-bottomed flask is fitted with a Dean-Stark apparatus for azeotropic distillation. Neopentyl alcohol (145.2 g, 1.65 mol, 1.0 eq.) and cyanoacetic acid (168 g, 1.98 mol, 1.2 eq.) were suspended in heptane (100 g) and heated at 90 °C under stirring until two clear phases were obtained. A catalytic amount of sulfuric acid (3.2 g, 2 mol %) was added and the biphasic solution was refluxed (oil bath at 125 °C) for 1.5 hours.

The reaction was checked by ^{1}H NMR and by the volume of water collected in the Dean-Stark trap. The heating was stopped when theoretical amount of water was collected in the Dean-Stark (~30 g). The mixture was allowed to reach room temperature, then the organic phase was extract first with 150 g of tap water, therefore

with 150 g of sodium chloride water solution (13% NaCl in water). The layers were vigorously shaken and separated; the organic layer was finally dry by azeotropic distillation of the heptane under reduced pressure. A light yellow oil was obtained, GC-MS analysis of the crude oil showed over 98% purity. The product was finally purified by vacuum distillation to yield 230 g (90 %) of neopentyl-CAcet.

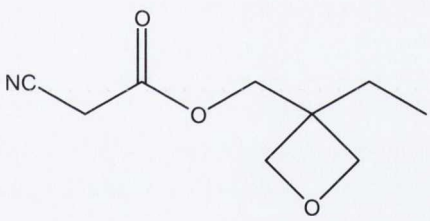
Crotyl CAcet[200]



Same synthetic procedure used for propargyl CAcet synthesis, 70% yield (62-64 °C at 0.15 mbar).

Oxetane CAcet

(3-Ethyl-3-oxetanylmethy CAcet)



In a 500 ml flask were placed 3- Ethyl-4-hydroxymethyl oxetane (116.2 g, 1 eq), methyl cyanoacetate (148.5 g, 1.5 eq), $Ti(O\text{-}Bu)_4$ (0.68 g). The reaction mixture was heated in the oil bath (160 °C) under N_2 atmosphere distilling the volatile fraction. The pressure was reduced gradually to 10 mbar in 4 h.

The reaction mixture was extract with water (200 ml), dried with sodium sulphate to yield 3-ethyl-3-oxetanylmethy cyanoacetate (87.1%).

δ_H (400 MHz, $CDCl_3$): 4.41 (dd, 4H, J_1 = 9.7, J_2 = 6.2 Hz, CH_2OCH_2), 4.34 (s, 2H, CH_2OOC), 3.53 (s, 2H, CH_2CN), 1.74 (q, 2H, J = 7.4, CH_2CH_3), 0.90 (t, 3H, J = 7.4, CH_3)

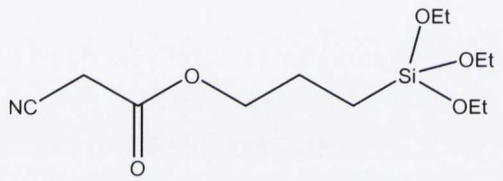
δ_C (100 MHz, $CDCl_3$): 8.08 (CH_3), 24.70 (CH_2CN), 26.53 (CH_2CH_3), 42.53 ($C(CH_2)_4$), 68.55 (CH_2OOC), 77.53 (CH_2OCH_2), 113.04 (CN), 163.26 ppm (CO);

AT-IR (Neat): 2965 m, 2933 m, 2876 m, 2264 w, 2162 w, 1744 s, 1460 w, 1387 m, 1336 m, 1259 m, 1178 s, 1004 m, 976 s, 826 m, 787 w, 668 w (cm^{-1});

GC-MS: (EI) m/z (%):$NCCH_2COOCH_2$ 98 (15), $NCCH_2COOH_2$ 86 (35), NCC^+H_2 40 (20).

Triethoxysilylpropyl CAcet

(3-Triethoxysilyl-propyl-CAcet)



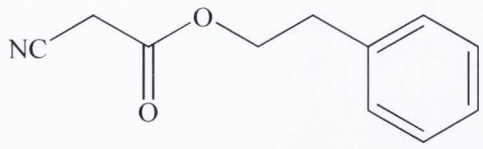
δ_H (400 MHz, $CDCl_3$): 4.19 (t, 2H, J = 5.60 Hz, CH_2OOC), 3.83 (q, 6H, J = 5.90 Hz, OCH_2CH_3), 3.48 (s, 2H, CH_2CN), 1.81 (m, 2H, $CH_2(CH_2)_2$), 1.22 (t, 9H, J = 5.90 Hz, CH_3), 0.66 ppm (t, 2H, J = 5.65 Hz, CH_2Si);

δ_C (100 MHz, $CDCl_3$): 163.80 (COO), 113.03 (CN), 68.10 (CH_2OOC), 59.00 (OCH_2), 24.30 (CH_2CN), 21.90 ($CH_2(CH_2)_2$), 17.80 (CH_3), 6,20 ppm (CH_2Si);

AT-IR (Neat): 2975 w, 2928 w, 2888 w, 2259 w, 1756 s, 1443 m, 1390 s, 1335 m, 1270 m, 1166 m, 1106 s, 1070 s, 953 s, 775 s, 460 m (cm^{-1});

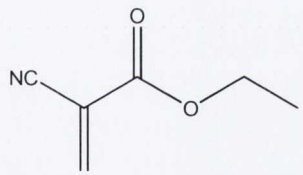
GC-MS: (EI) m/z (%), M+ 289 (2), M-EtO 244 (10), $NCCH_2COOCH_2$ 98 (15), $NCCH_2COOH_2$ 86 (35), NCC^+H_2 40 (20);

2-Phenyl-1-ethyl CAcet[201]



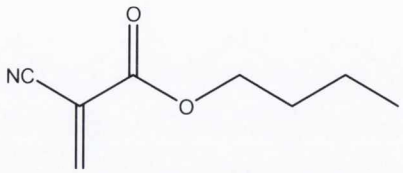
2-Phenyl-1-Ethanol (122.0 g, 1.0 mol) and cyanoacetic acid (85 g, 1.0 mol) in heptane (60 mL) solution were refluxed for azeotropic removal of water in the presence of para-toluensulfonic acid (3.8 g, 0.02 mol). After 4 h 16 mL of water were collected into the Dean-Stark trap. After cooling, the heptane was removed under low pressure, a solid precipitate (unidentified side product) was separated by filtration and the final crude washed twice (1 part crude, 0.5 part isopropyl acetate, 0.5 part brine, 0.5 part tap water). The product was dried by isopropyl acetate distillation. The product was then purified by vacuum distillation (117-120 °C/0.5 mbar); 2-phenyl-1-ethyl CAcet was isolated in 86% yield (162 g, 0.86 mol).

Ethyl CA[194, 200]



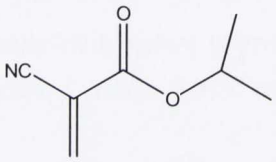
The synthesis was performed following the optimized procedure for CAs production by mini-SPE or SPE equipment.

Butyl CA[194, 200]



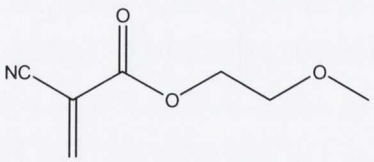
The synthesis was performed following the optimized procedure for CAs production by mini-SPE or SPE equipment.

iso-Propyl CA[194, 200]



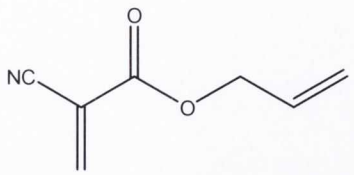
The synthesis was performed following the optimized procedure for CAs production by mini-SPE or SPE equipment.

β-Methoxyethyl CA[194, 200]



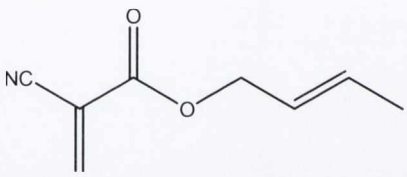
The synthesis was performed following the optimized procedure for CAs production by mini-SPE or SPE equipment.

Allyl CA[194, 200]



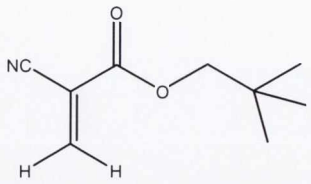
The synthesis was performed following the optimized procedure for CAs production by mini-SPE or SPE equipment.

Crotyl CA[194, 200]



The synthesis was performed following the optimized procedure for CAs production by mini-SPE

neo-Pentyl CA[194, 200]



The synthesis was performed following the optimized procedure for CAs production by mini-SPE or SPE equipment.

The DSC analysis confirmed a melting point of 40-41 °C

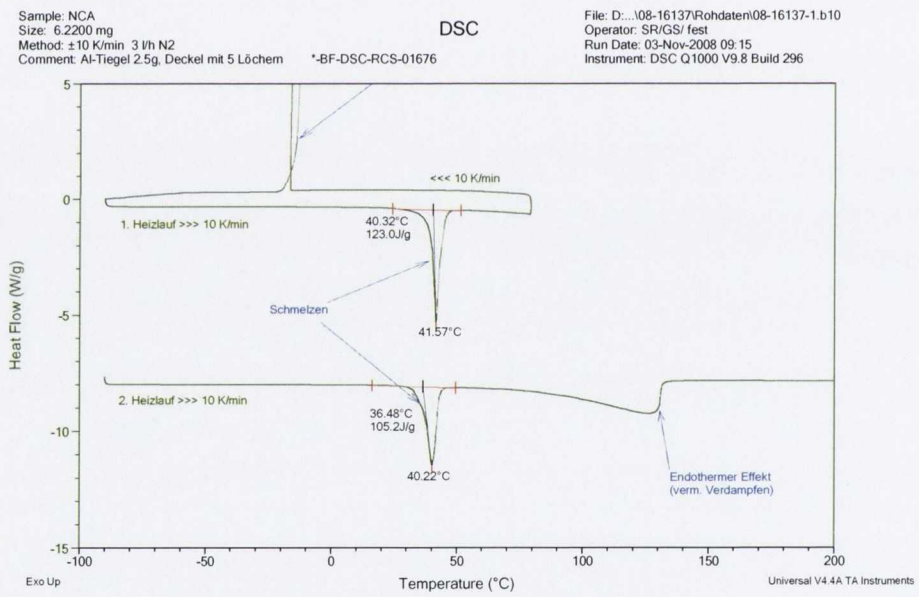
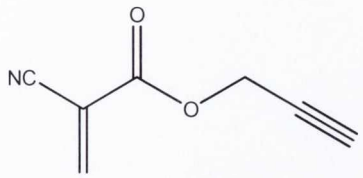


Figure 3.39. DSC analysis of neo-pentyl CA

Propargyl CA[194, 200]



The synthesis was performed following the optimized procedure for CAs production by mini-SPE or SPE equipment. The monomer is a colourless oil (90 °C at 2 mbar).

The DSC analysis confirmed a melting point of 43-44 °C

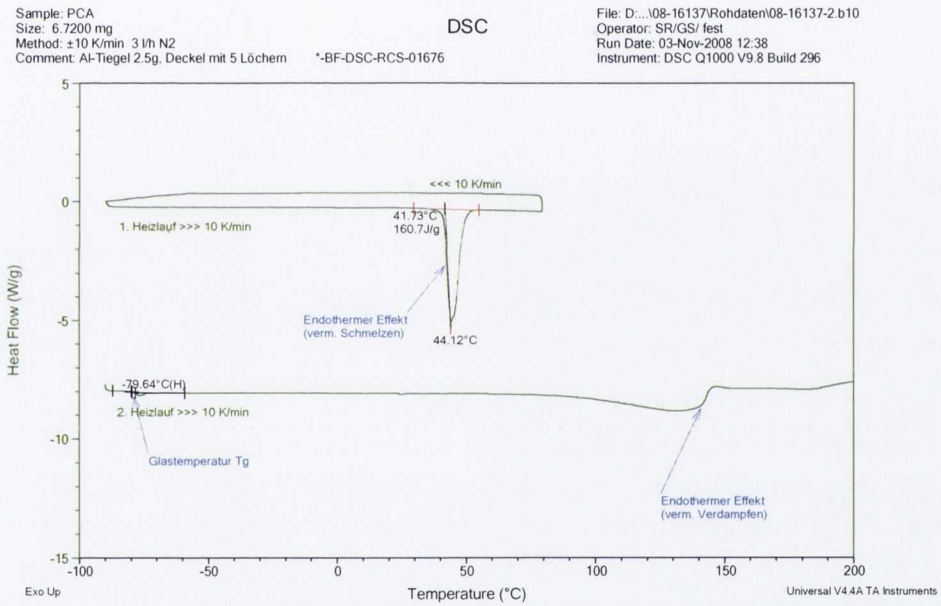
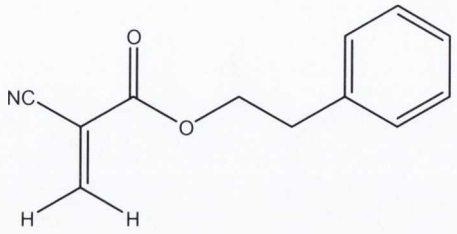


Figure 3.40. DSC analysis of propargyl CA

2-Phenyl-1-Ethyl CA



The monomer was collected in colorless oil (117 °C at 0.5 mbar, yield 65-70%), by cooling it became a crystalline solid (melting point 40 °C).

δ_H (400 MHz, $CDCl_3$): 7.23 (s, 5H, Ph), 6.94 (s, 1H, CH), 6.53 (s, 1H, CH), 4.44 (t, 2H, CH_2OOC), 3.00 ppm (t, 2H, CH_2Ph);

δ_C (100 MHz, $CDCl_3$): 159.95 (COO), 143.01 (CH_2=), 136.55 (C, Ar), 128.62 (CH, Ar), 128.25 (CH, Ar), 126.47 (CH, Ar), 116.11 (CNC), 113.96 (CN), 66.84 (CH_2COO), 34.45 ppm(CH_2Ph);

AT-IR (Neat): 3419 w, 3129 w, 2917 w, 2855 w, 2238 w, 1956 w, 1715 s, 1601 w, 1497 m, 1316 s, 1155 s, 973 s, 928 m, 793 m, 721 m, 695 s, 666 m, 462 m (cm^{-1}).

References:

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CHAPTER 4

4 FUNTIONAL CAs

4.1 Hybrid molecule synthesis

The TSIL method is a real alternative way for the CAs production; it is based on Mannich chemistry and offers higher reaction performance (higher yields, higher purities, etc...) in comparison to the traditional Knöevenagel process, which has been optimized in production over many decades.

The success of this new process is based on lower reaction temperature and, even more important a very short reaction time. The combination of these two parameters becomes the key factor for the production of new thermal sensitive molecules impossible to achieve by Knöevenagel.

The cyanoacrylates are usually not considered "structural adhesive", in the technical language used in the adhesives sector, because they are not thermally and hydrolytically resistant. This lack of performance is due to an easy thermal unzipping of the polycyanoacrylate chain that is furthermore favoured from the absence of cross-linking between polymer chains. Where the polymer chains are highly interconnected with each others, forming a network, cross-linking occurrs. So cross-links are bonds that link one polymer chain to another and this type of interaction can produce a consistent modification of the polymer's physical properties, because the polymer chains are linked together with a reduction of their ability to move. A low cross-linking degree can increase the viscosity of the polymer, an intermediate cross-linking degree can change a viscous polymer into a solid material with elastomeric properties and a highly cross-linking degree can produce a solid, very hard and glassy polymer. In conclusion the introduction of cross-linking in a cyanoacrylic polymer is strongly desired.

In the past many attempts at this goal and intense efforts were made for the synthesis of bis-cyanoacrylate[202, 203, 204] which can introduce cross-linking in a cyanoacrylic polymer. The effect of bis-CAs in mixture with alkylic CAs has been extensively studied and important limitations have been discovered. In fact the Bis-CAs generally have poor solubility in regular CAs (with alkylic esters), furthermore they did not substantially improve the thermal and hydrolytic resistance of the polymer. In addition no one industrial process is currently able to efficiently produce these chemicals in viable quantities for commercialization. Thus the necessity of a new approach is obvious.

The introduction of active functionalities in the CA polymer was a major goal of this work. Those active functionalities could be used to invoke a second polymerization for a crosslinked network generation. The only way to introduce functional pendants in a poly-cyanoacrylate is by polymerization of dual functional CA. The types of functional groups considered were acrylates, methacrylates, oxitanes, epoxides and siloxanes.

The first molecule faced by TSIL approach was an hybrid (dual functional, Figure 4.1) cyanoacrylate-methacrylate compound (2-methacryl ethyl cyanoacrylate or HEMA-cyanoacrylate, Figure 4.1).

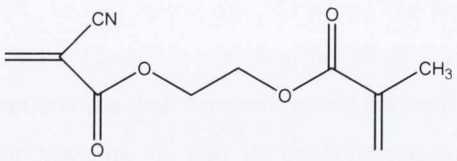

Figure 4.1. Structure of HEMA-cyanoacrylate

This cyanoacrylate monomer could be produced by TSIL reaction from the correspondent 2-methacryl ethyl CAcet (HEMA-CAcet, Figure 4.2).

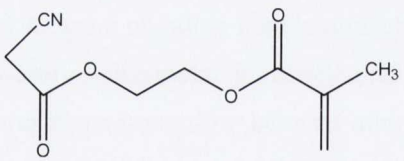

Figure 4.2. Structure of HEMA-CAcet

This molecule is consistent with our requirements (dual functional), plus the HEMA-CAcet was reported to be easily produced by esterification of cyanoacetic acid with 2-hydroxyethyl methacrylate (HEMA) (Figure 4.3).

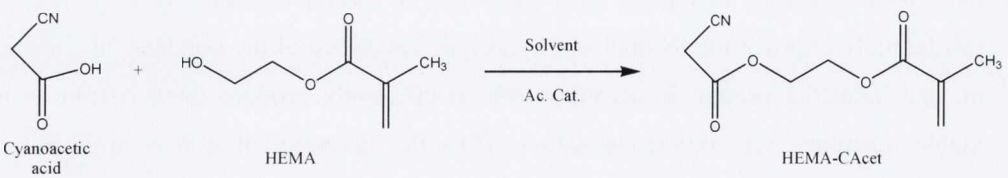

Figure 4.3. Esterification reaction between cyanoacetic acid and 2-Hydroxyethyl methacrylate.

4.2 First experimental TSIL attempts (Preliminary Studies)

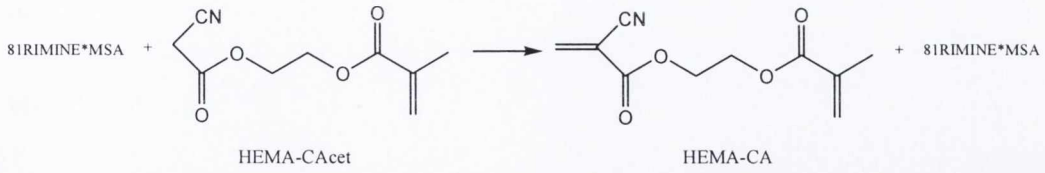

Figure 4.4. TSIL reaction for the synthesis HEMA-cyanoacrylate.

The first test concerning the synthesis of HEMA-cyanoacrylate (Figure 4.4) was performed following the usual TSIL procedure by mini-SPE equipment (1 eq 81RImine, 1.05 eq MSA, 1 eq CAcet; pre-heating 30 sec. at 180 °C; distillation 180 °C at 0.5 mbar). Hydroquinone (5% mol, stabilizer concentration) was added to the reaction mixture in order to avoid radical polymerization of the methacrylic group. The reaction was repeated several times under slightly different operative conditions, but the same results were always observed.

No product was obtained in the condensed phase and only trace of HEMA-CAcet un-reacted plus, some HEMA, and hydrocarbon side-product, were separated by distillation. Moreover, always after 10 min of reaction, the crude turned into a semi-solid material blocking the magnetic stirring, so a radical polymerization occurred.

In conclusion the selected CAcet/cyanoacrylate was definitely thermal sensitive and even under "mild" TSIL conditions was not obtained. Nevertheless by taking in account the synthetic problems, the reaction was transferred to the SPE. This decision was driven by the shorter reaction time applied in a reactor such as a SPE.

The reaction was performed upon above mentioned reagent mixture composition (1 eq 81RImine, 1.05 eq MSA, 1 eq CAcet), preheating 2 min. at 120 °C, distillation at 0.5 mbar and 170 °C.

Surprisingly a crude HEMA-cyanoacrylate (approximately 40% yield) was collected as volatile compound (product). The product was not pure and extra signals were observed by ^{1}H NMR (Figure 4.5).

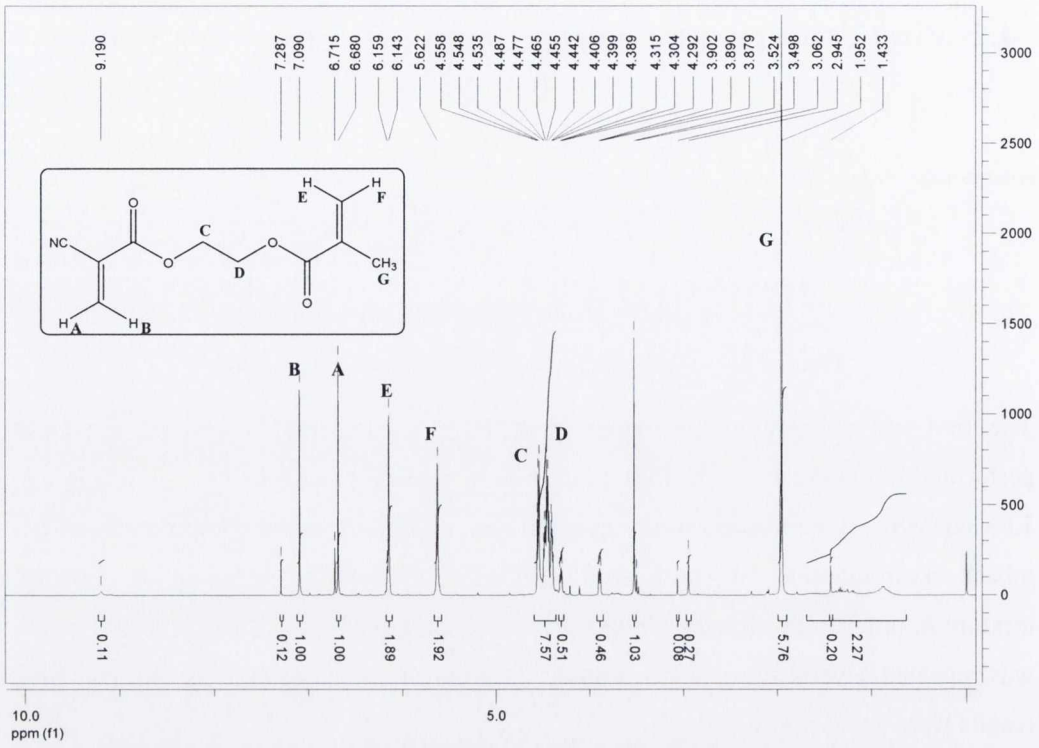

Figure 4.5. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of crude HEMA-cyanoacrylate (Inset)

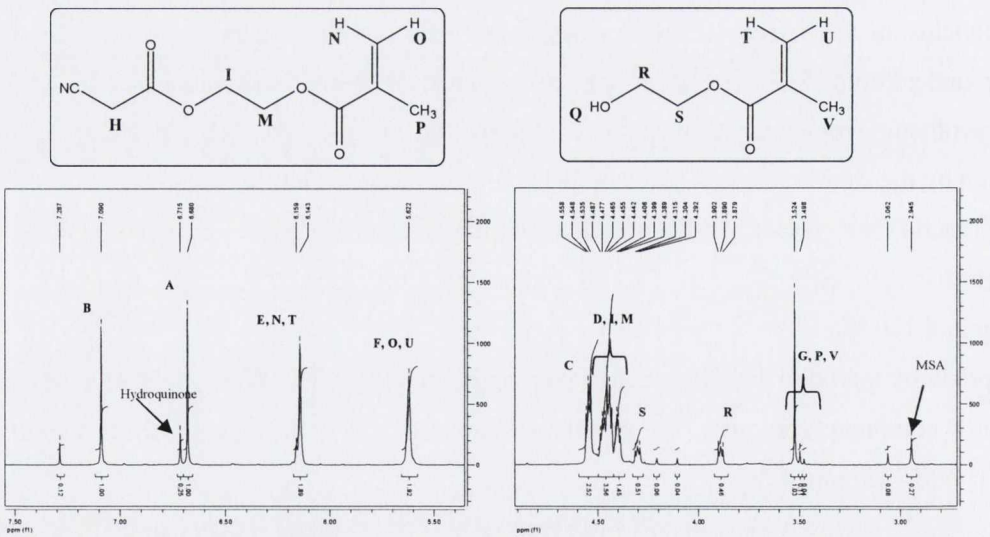

Figure 4.6. Enlargement of Figure 4.5 and assignment of reagent and side-product

The reaction selectivity was poor and many compounds were detected in a blend with the product among which HEMA CAcet (10-20%), HEMA free alcohol (10-20%),

methanesulfonic acid, hydroquinone, and hydrocarbon side products. The reaction was repeated several times, but the selectivity of reaction was clearly a problem. In conclusion the TSIL reaction combined with the SPE equipment showed the potential to produce HEMA-cyanoacrylate, however variations in temperature and reaction time did not produce any consistent improvement. A detailed study of each parameter was required to explore and improve this situation.

4.3 Radical stabilizers investigation

From the preliminary results a few problems were underlined; in particular high radical sensitivity toward radical polymerization as well as poor selectivity of reaction. A first investigation was performed on the radical stabilizer "additive". This study has been divided in two main sections, the first connected with the efficiency of the stabilization and the second with the compatibility of the stabilizer with the ionic liquid.

4.3.1 Radical Stabilizers Efficiency

A study was undertaken due to the need to have a stable system toward radical polymerization. Many stability tests were performed leading up to the target. The HEMA-CAcet tested was purified by redistillation, and stabilized for storage with 0.1 % of BHT (2,6-di-tert-butyl-4-methyl phenol).

The first set of experiment were conducted by mixing the CAcet with different radical stabilizers. The mixture was prepared directly inside glass test tubes, purged with nitrogen gas to avoid stabilizing oxygen contribution, and sealed (not hermetically in case of gas production). The blends were heated, by dipping the test tubes into a hot oil bath, until the magnetic stirring was stopped due to the polymerization occurred (Table 4.1).

Table 4.1. Evaluation of different radical stabilizers

Entry	Radical Stabilizer	w (%)	Temperature (°C)	Polymerization time (min)
1[a]	-	-	150	10
2[b]	DBHT	5	150	50
3[c]	Cu_2O	0.5	150	5
4[a]	-	-	160	3
5[d]	DBHT	5	160	8

[a] HEMA CAcet only, [b] 4,4'-methylene bis(2,6-di-tert-butyl phenol) DBHT is fully solubilised only after heating, [c] Cu_2O is not soluble even after heating, [d] Completely soluble only after heating

A stable system was observed in the presence of DBHT (4,4'-Methylene bis(2,6-di-tert-butyl phenol)) at 150 °C, nevertheless increasing the temperature up to 160 °C a dramatic reduction of stability was observed. Few tests were repeated after the addition of MSA (5% w) considering the general knowledge that radical systems are usually more stable in acidic environment (Table 4.2).

Table 4.2. Evaluation of different radical stabilizers in acidic environment after addition of MSA.

Entry	Radical Stabilizer	w (%)	Temperature (°C)	Polymerization time (min)
1[a]	-	-	160	50
2[b]	DBHT	5	160	45
3	Cu_2O	0.5	160	10
4[a]	-	-	170	40
5[b]	DBHT	5	170	20
6[c]	hydroquinone	5	170	20
7	PTZ	0.5	170	60

[a] HEMA CAcet only, [b] The radical stabilizer is completely soluble only after heating, [c] The radical stabilizer is completely soluble at room temperature; DBHT = 4,4'-Methylene bis(2,6-di-tert-butyl phenol), PTZ = Phenothiazine

Very impressive stability improvement was observed at 160 °C with the addition of MSA only. In fact the monomeric methacrylate polymerized after 50 min instead of only 3 min (Table 4.2, Entry 1). This result was surprising in consideration that the polymerization of HEMA-CAcet occurs in a pure radical path while the addition of DBHT did not give any further improvement (Table 4.2, Entry 2). In other words the acidic stabilization seemed more effective than the radical stabilization. The same tests were repeated at 170 °C (same temperature applied with the SPE reactor during the TSIL reaction) show a consistent reduction in stability when DBHT (Table 4.2, Entry 5) or hydroquinone (Table 4.2, Entry 6) were present; only PTZ (Phenothiazine) was able to promote a longer stability (Table 4.2, Entry 7). This, apparently unpredicted result, was explained if we accept the acidity stabilization effect and also that the weak basicity of hydroquinone or DBHT (5% w) could reduce the acidity of the system.

The HEMA-CAcet was furthermore studied under TSIL reaction condition without vacuum applied. In detail HEMA-CAcet (1 eq.) and 81RAmmonium methanesulfonate

(1 eq.) were mixed together and the stability monitored. The ammonium salt was freshly prepared by mixing 81RAmine (1 eq) with MSA (1.05 eq) in order to simulate the TSIL reaction blend except for the active imminium functional group. The ammonium salt was intentionally used instead of the imminium salt to eliminate a further complication due to the reactivity of the CAcet function with electrophilic species. The tests were performed at 170 °C under inert atmosphere and 5% MSA excess was maintained constant for comparison with the previous experiments; the results are summarized in Table 4.3.

Table 4.3. Screening of radical stabilizers in the cyanoacrylate synthesis at 170 °C.

Entry	Radical Stabilizer	w (%)	Polymerization time (min)
1[a]	-	-	50
2[b]	DBHT	1	5
3	PTZ	0.5	20
4[c]	DBHT + PTZ	1+1	> 60
5[c]	DBHT + PTZ	1+0.1	> 60
6[d]	Vitamin E	1	18
7	Vitamin E acetate	1	1 solid.
8	Vitamin E acetate	5	2 solid.
9	Vitamin E	0.5	8 solid.
10	Vitamin E + PTZ	0.5+0.5	6-7 solid.
11[e]	$Fe(II)SO_4 6H_2O$	5	5 sold.
12	1% $Fe(II)SO_4 6H_2O$ + 1% DBHT	1+1	5 solid.
13	$Fe(II)SO_4 6H_2O$ + Vitamin E	1+0.5	10 solid.
14	Uric acid	1	2 solid.
15	$FeCl_3$	1	10 solid.
16	$CuCl_2$	1	5 solid.
17	Vitamin E + $FeCl_3$	1+1	25 solid.
18	Vitamin E + $FeCl_3$	0.1+0.1	6 solid.
19	Hydroquinone	1	> 60

[a] HEMA CAcet only,[b] The addition of a further acid excess did not change the result,[c] After 15 min a little agglomerate was observed but even after 1 h there was not bulk polymerization, [d]Vitamin E is a viscous liquid but well soluble in IL/CAcet mixture, [e]Large gas bubbling is observed at the beginning

Many very different radical stabilizers were tested and all the experiments above were rationalized. The Vitamin E, PTZ, hydroquinone, combination of DBHT and PTZ or VitE and $FeCl_3$ showed the highest radical stabilization ability; instead BHT only (or his dimeric form DBHT) widely used as radical stabilizers of acrylate and methacrylate functions did not work. It is interesting also to underline the contrast between the high efficient Vitamin E and the ineffective Vitamin E acetate.

In conclusion the TSIL reaction for HEMA-cyanoacrylate production had to be performed in the presence of Vitamin E, or PTZ or hydroquinone or in a mixture of them.

4.3.2 Radical Stabilizers Compatibility

The selection of a radical stabilizer or of a radical stabilizing package, efficient against radical polymerization of methacrylic functions, is not sufficient alone. The stabilizers used must be compatible with the TSIL reaction.

4.3.2.1 First investigation; hydroquinone effect

Hydroquinone has been found to be a very good radical stabilizer in order to avoid radical polymerization of the HEMA CAcet/cyanoacrylate during the TSIL reaction; nevertheless an investigation was performed in order to understand a possible interaction with the CAcet/ionic liquid reagents.

For practical reasons (smaller reaction scale, faster experiments, etc...) the tests were performed with the support of the mini-SPE. Taking into account the previuos results using HEMA CAcet with this equipment (too long reaction time), the most representative CAcet seemed to be the 2-methoxy ethyl CAcet indeed its ester structure is very like the HEMA-CAcet except for the methacrylic group (Figure 4.7). The reactions were performed with the usual operative conditions and the results are summarized in Table 4.4.

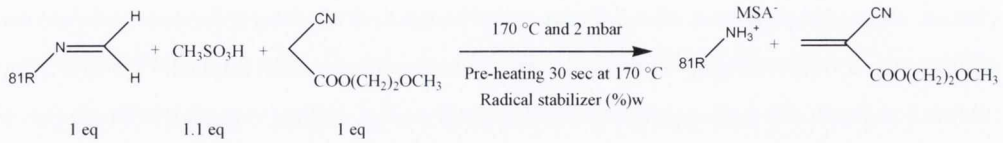

Figure 4.7. Model reaction of β-methoxyethyl CAcet in IL and in the presence of MSA.

Table 4.4. TSIL reaction results with different radical stabilizer and results

Entry	Radical stabilizer	w (%)	Yield (%)	Residual CAcet (%)	Observations
1	Hydroquinone	10	73	8.5.	Large gas bubbling and smoking, quick distillation, 3% methoxyethanol detected
2	-	-	74	4.5	Poor gas bubbling, very slow distillation, no methoxyethalol detected.
3	BHT	10	60	6	Slow distillation, no alcohol detected.
4	BHT	5	75	3.6	Very slow distillation, no alcohol detected.

From the previous experiments two different types of interactions were evident:

I) Interaction of hydroquinone with the ionic liquid

II) Interaction of hydroquinone with the CAcet

I) The interaction against the IL was made clear by the large gas bubbling and the reduced CAcet conversion, in fact a higher CAcet residue was collected in mixture (8.5% instead of the reference 4.5%) with the product. The hydroquinone is a phenol compound, therefore it could act like a weak nucleophile toward strong electrophiles like iminium salts, this reaction should be reversible and any real side product can be imagined (Figure 4.8).

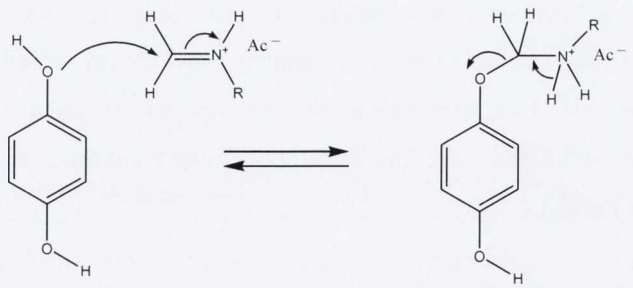

Figure 4.8. Proposed nucleophilic attack of hydroquinone towards imium salt

It is important to consider another aspect of phenols which they are reactive toward formaldehyde at the ortho and para position (allowing up to 3 units of formaldehyde to attach to the ring). This reaction can be acid or base catalysed and it is historically used for the production of phenol-formaldehyde resin.

Moreover even if mediated by metal halides under basic catalyst the *ortho*-formylation of phenols by formaldehyde treatment has been reported[205].

An interesting Mannich-type reaction between formaldehyde and phenols has been recently reported too[206]. The authors showed the possibility to produce functionalized phenols in orto position. A Mannich reaction was performed between an amine and formaldehyde and trifluoroacetic acid was used as catalyst of reaction (Figure 4.9). The product was isolated after 24 h of reaction at r.t. (very mild compared to the TSIL reaction).

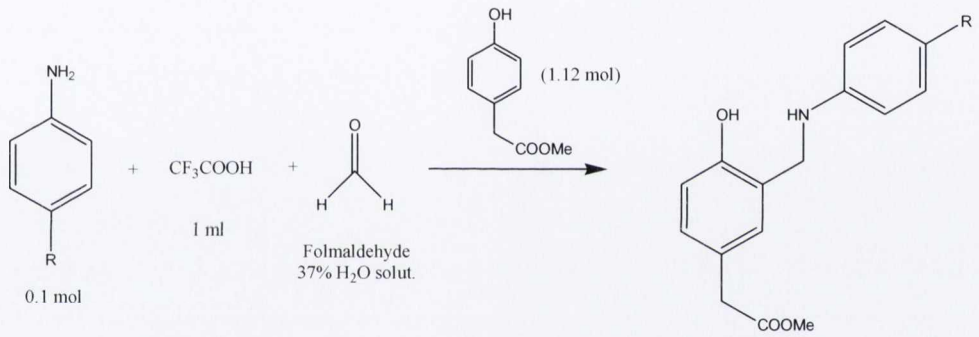

Figure 4.9. Mannich-type reaction between formaldehyde and phenols.

A similar reaction can be imagined also between the 81Riminium methanesulfonate salt and the hydroquinone, nevertheless the observed gas bubbling can not be explained yet. Hydroquinone is also well known for its reducing properties, in fact in the past it has been widely used as reducing agent in photographic printing. In the present work the hydroquinone was in mixture with an iminium salt which easily undergoes reduction. If the reduction happen a methylated ammonium salt should be produced. At the same time the hydroquinone should be transformed into benzoquinone and a deep-black solution should be observed (50/50 mixture hydroquinone/benzoquinone is a deep dark complex called Quinhydrone). In order to investigate this possibility few tests were performed and the results were following reported.

Hydroquinon/81Rimminium methanesulfonate tests

Thermal stability tests were performed by heating the TSIL (81Rimminium methanesulfonate) alone (*Test A*)or in blend with hydroquinone (*Test B*), in order to perform tests as much as possible close to the real TSIL operative conditions, at 180 °C and under vacuum. The results were quickly analysed by low field NMR, FT-IR and GC-MS (EI). The low field NMR 60 MHz was preferred to the high field NMR for the complexity of the sample as 81Rimine is a blend of many isomers..

- *Test A:* 81RIminium methanesulfonate (11.96 g, 0.04 mol) was heated at 180 °C and 1 mbar vacuum was applied, after 30 sec of reaction the ionic liquid turned from a clear colourless liquid into an orange material, no bubbling was observed and in few minutes the distillation of material began. After 15 min the distillation stopped, the IL was observed to be dark brown and two distilled fractions were separated; Fract.*A1*, 0.55 g (b.p. 75-80 °C); Fract.*A2*, 0.8 g (b.p. 80-90 °C).

- *Test B:* 81RIminium methanesulfonate (11.96 g) was mixed with 10 mol % hydroquinone (0.22 g, 0.002 mol) and heated at 180 °C under vacuum (1 mbar). From the start, violent bubbling was observed, the IL quickly turned into a dark brown liquid first and in a deep black later (like black ink) after few extra minutes. The heating was stopped after 15 min and two fraction were collected; Fract.*B1* 0.55 g (b.p. 60-70 °C), Fract.*B2* few drops only.

First qualitative information was obtained from the odour of the distillates, Fract.*A1* and Fract.*A2* had a strong unpleasant smell likely amine/imine compounds, instead Fract.*B1* and Fract.*B2* were associated with a pleasant persistent smell (like terpenes); their ^{1}H NMR were recorded (Figure 4.10).

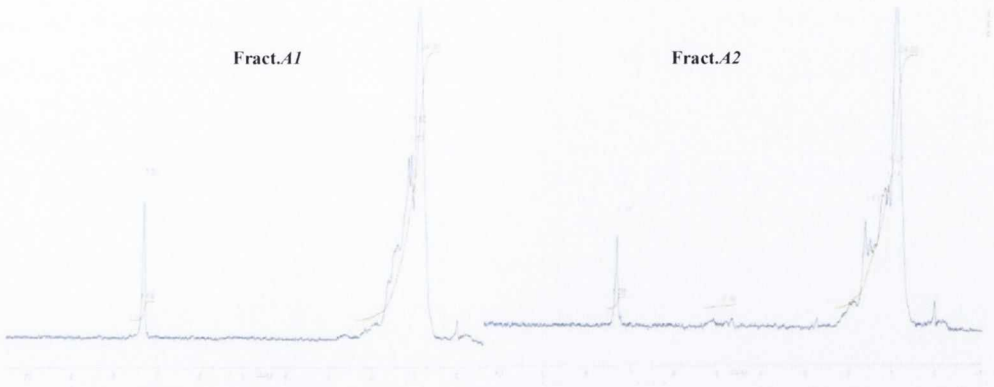

Figure 4.10. ^{1}H NMR spectra (60 MHz, $CDCl_3$) of Fract.*A1* and Fract.*A2* (60 MHz, $CDCl_3$)

Different molecular structure of Fract.*An* (n = 1,2) and Fract.*Bn* (n = 1,2). In fact only Fract.*A1* and Fract.*A2* show a clear imine singlet at δ 7.31 ppm (typical of imine compounds); additionally a new broad signal appears in Fract.*A2* in the region between δ 4.5-5.5 ppm (Figure 4.10).

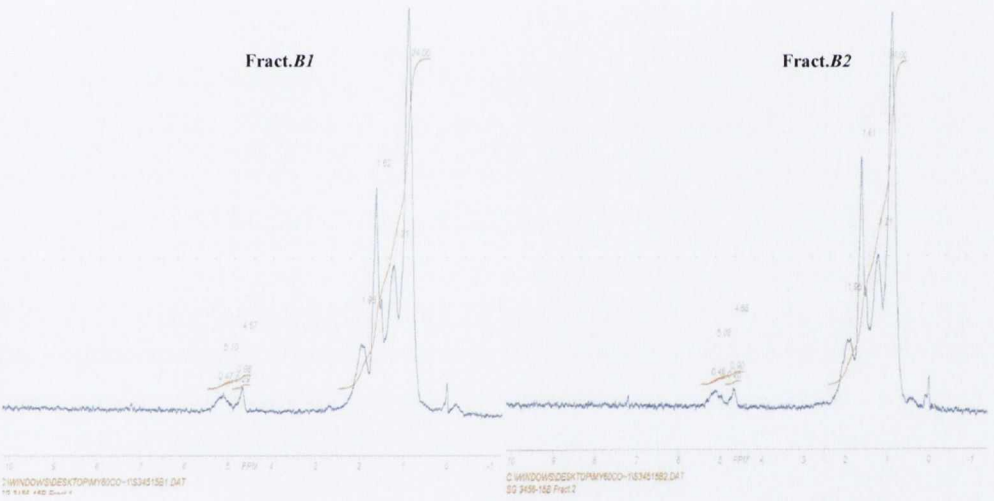

Figure 4.11. ^{1}H NMR spectra (60MHz, $CDCl_3$) of Fract.*B1* and Fract.*B2*

Fract.*B1* and Fract.*B2* (Figure 4.11) are free from the imine signal and clearly show two new broad peaks in the region of the olefin protons, δ 5.14 ppm and 4.67 ppm (typical for geminal olefinic protons). Other two new peaks were observed at δ 1.95 ppm (typical for vinyl methylenes) and 1.61 ppm (typical for vinyl methyls).

In agreement with the unpleasant smell, fraction *A1* and *A2* were identify to be formed mainly by thermally dissociation and recondensation of 81Rimine; fraction *B1* and *B2* were supposed to be mainly formed by olefins. Moreover in consideration of the chemical shift signals and olefinic protons integrals (integration for one proton) a blend of tetra substituted and terminal double substituted olefins were present.

Very interesting also was the comparison between the mixture of IL and hydroquinone before and after the heating (Respectively Test.*B* Start; Test.*B* End; Figure 4.12)

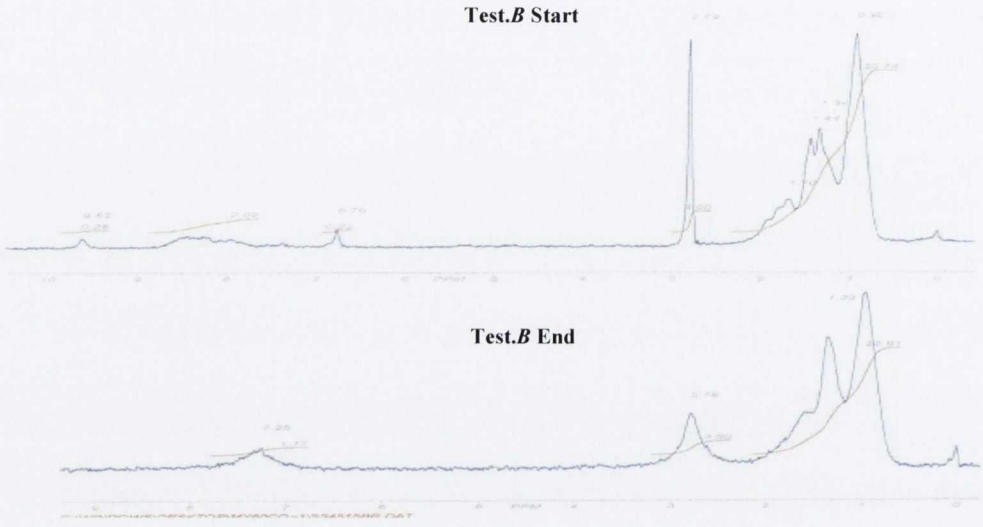

Figure 4.12. ^{1}H NMR spectra (60MHz, $CDCl_3$) of Test*B* Start and Test.*B* End

The hydroquinone signal at δ 6.76 ppm totally disappears after heating, the ionic liquid becomes black and partially insoluble in chloroform. Moreover the broad multiplet at δ 8.5 ppm (iminium protons) disappears and only a new broad signal appears at δ 7.2 ppm (like ammonium salt).

The comparison with FT-IR analysis gave a confirmation of those hypothesis (Figure 4.13).

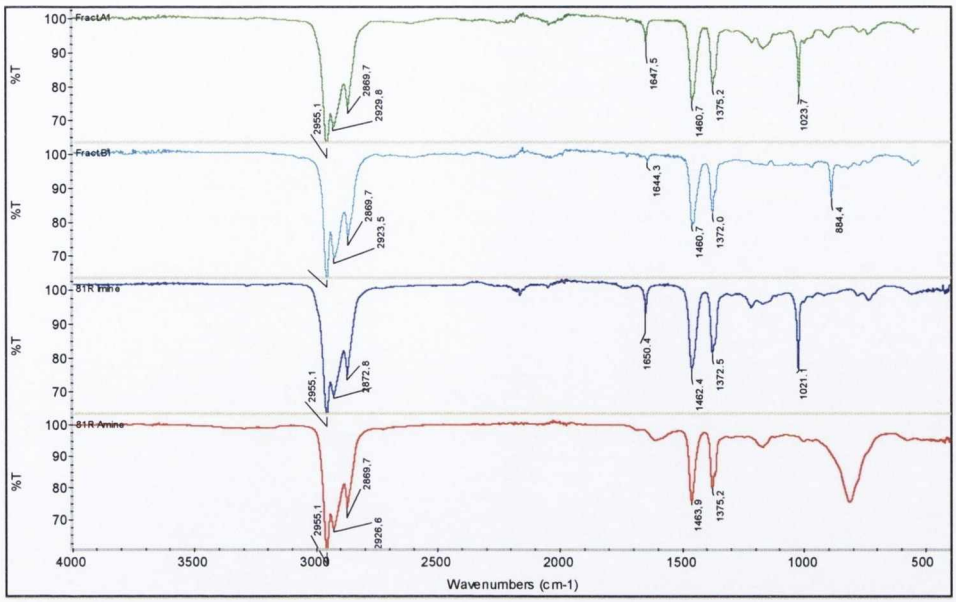

Figure 4.13. AT-IR spectra of Fract.*A1* (green line), Fract.*B1* (azure line), 81R imine (blue line) and 81R amine (red line).

Fract.*A1* showed a band at 1647 cm^{-1} corresponding to the stretching of N=C, the bending of the N=C is evident also at 1023 cm^{-1}. These two signals are absent in Fract.*B1* which shows a very small adsorption at 1641 cm^{-1} (ν C=C) and a strong new signals at 884 cm^{-1}. Mono-substituted alkenes have an adsorption near 1640 cm^{-1} (stretching), tri or tetra-substituted alkenes adsorb at or near 1670 cm^{-1}. Those signals are in agreement with the previous hypothesis.

GC-MS of Fract.*A1* and *B1* were conducted to confirm the molecular structure and the lost of molecular mass, the chromatograms are following reported (Figure 4.14).

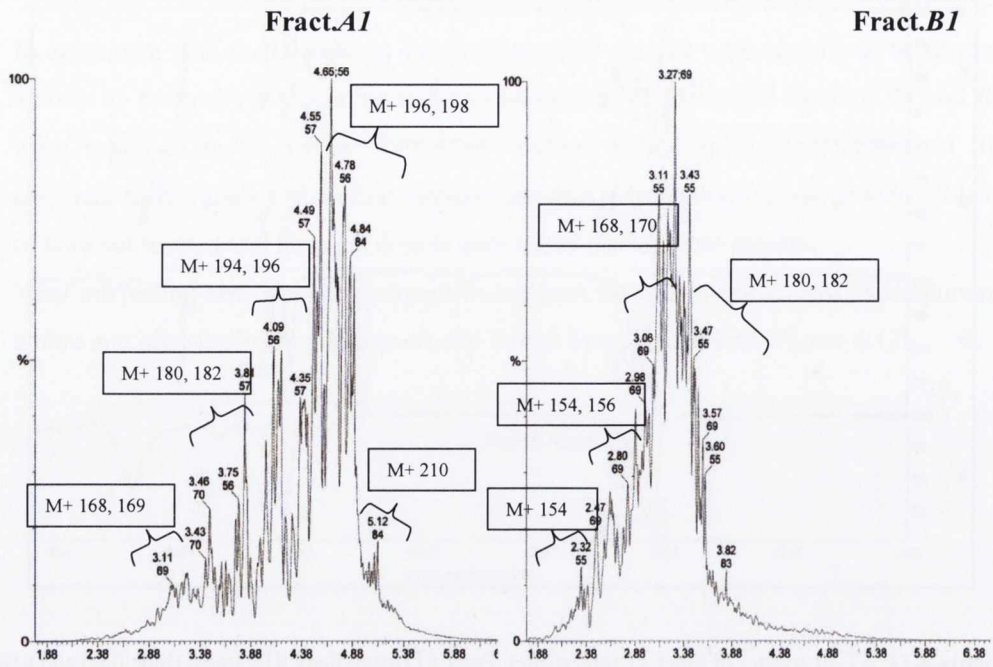

Figure 4.14. GC-MS of Fract.*A1* and *B1*

A very complex mixture of isomers is observed in both the distilled fractions, the average retention time of Fract.*B1* is two minutes shorter and the lower molecular weigh was in the range of 16-18 g/mol. This result is once more in agreement with the previous observation, that Fract.A1 has a molecular mass in agreement with the theoretical imine, it is less volatile and was also more polar (longer retention time).

In conclusion the TSIL ionic liquid undergoes thermal dissociation under vacuum at high temperature, and the starting imine was recovered first and a little decomposition started later. When hydroquinone was present the decomposition followed a different path and lighter material, probably unsaturated hydrocarbons were collected.

The low thermal stability of 81R Imminium methanesulfonate salt (starting TSIL ionic liquid) was no surprise and it has been already observed in separate studies. Moreover for the TSIL process it was not a problem because the IL reagent was reacted, at lower temperature and atmospheric pressure, with CAcets to yield cyanoacrylates plus ammonium salt. The thermal stability of 81R ammonium methanesulfonate was much higher. Moreover the hydroquinone interaction with the IL was clear even if the evolution of gas was not exhaustively explained.

II) The interaction could be between hydroquinone and CAcet ester side. We must remember that the TSIL reaction is performed at high temperature in an ionic liquid media and it is well know the ability of some IL to promote esterification/trans-esterification or elimination reactions. For this reasons if we consider the hydroquinone as a weak nucleophile it would not be surprise if there was an interaction with the CAcet with subsequent release of free alcohol. In this case a non distillable 4-hydroxyphenyl CAcet (very high b.p. material) should be produced as well (Figure 4.15).

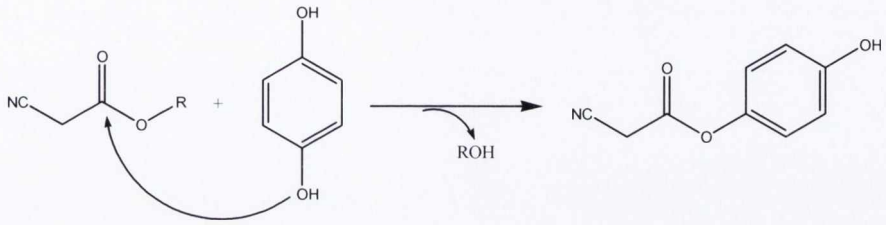

Figure 4.15. Esterification reaction for the production of 4-hydroxyphenyl CAcet

In a recent paper Romanelli[207] proposed a high yield reaction performed under mild operating conditions for the production of phenyl acetate. The synthesis were performed by mixing alcohols with acid anhydrides and catalyzed by Wells-Dawson heteropoly acid ($H_6P_2W_{18}O_{62}\cdot 24H_2O$). This reaction was performed with phenols, obviously acid catalyzed and performed with very active anhydrides. In our case an acidic ionic liquid is used as well as high reaction temperatures, then an unusual trans-esterification reaction could happen. The synthesis and use of phenyl-CAcet is reported in literature[208, 209]. On the other hand the hydroquinone-CAcet reaction was never been reported in literature, but a few similar structure were considered[210](Figure 4.16).

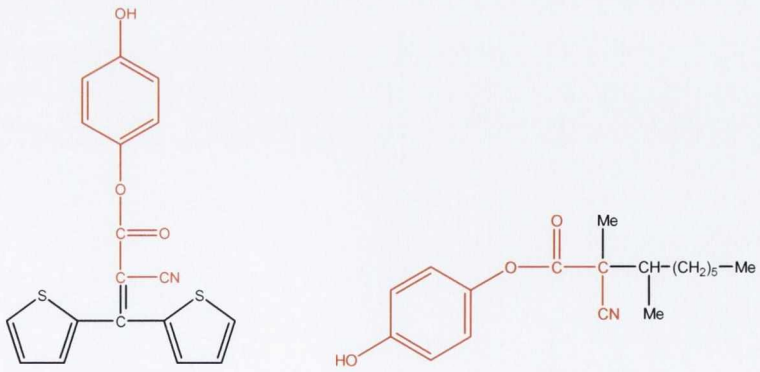

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Figure 4.16. Hydroquinone-CAcet derivatives reported in literature[198]

At this point already many fragments of information were available and a new hypothesis can be formulated. The previous results were in agreement with a multiple interaction of the hydroquinone with both the ionic liquid and the CAcet. Moreover a compound has to be produced in the gas phase which is non nucleophilic. Nevertheless no traces of cyanoacetic acid were detected but only alcohols were condensed. In conclusion it seemed that the cyanoacetic part was in somehow lost during the reaction (gas phase). It must be remembered that the cyanoacetic acid has a decomposition temperature of 160 °C and it produces carbon dioxide plus acetonitrile.

A possibility was that the freshly produced species 4-hydroxyphenyl CAcet reacts with the IL and decomposes in the Mannich intermediate state with the production of gaseous by-products (Figure 4.17).

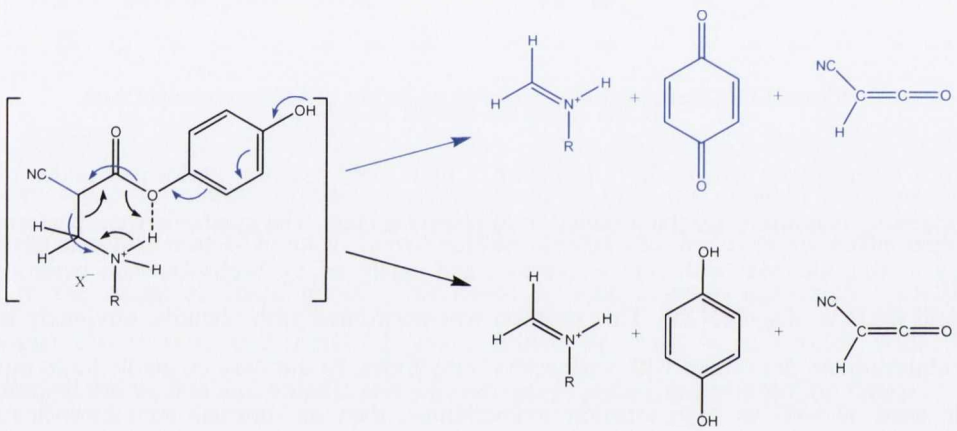


Figure 4.17. Proposed mechanism of Mannich adduct decomposition

If this Mannich adduct structure is carefully observed it is possible to recognize a possible six member ring intramolecular hydrogen bonding. This structure is quite unique and it could produce unique effect on the Mannich adduct decomposition.

The well accepted Mannich adduct decomposition path way is the one where the residual activated methylene proton gives elimination with release of ammonium salt and olefin.

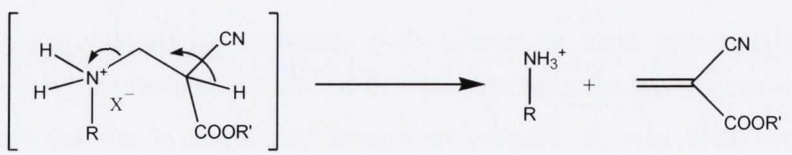


Figure 4.18. Common Mannich adduct decomposition

This decomposition path is the rational mechanistic decompositions that lead the production of cyanoacrylate during the TSIL reaction, it is in agreement with the reported literature as well as with the high reaction yields obtained in the TSIL reaction. Nevertheless if we consider the same structure and another decomposition pathway could be theorized. The simplest one is the reverse Mannich addition, this reaction should return the starting imminium salt plus the CAcet unmodified (Figure 4.19).

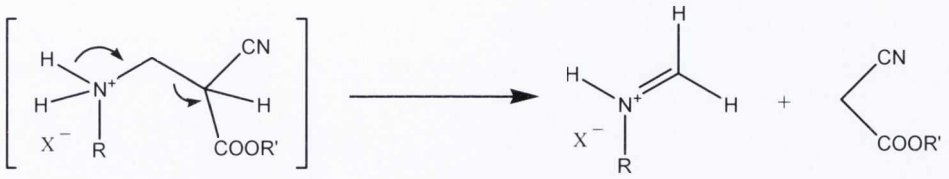


Figure 4.19. Alternative proposed decomposition mechanism.

This decomposition is definitely not favoured in comparison with the previous one mainly for two reasons: (1) the first is the acidity of the protons involved, the one in α position to the nitrile or ester group is the most acidic than the easiest to be removed, (2) second the carbon – nitrogen bond energy (308 KJ/mol) is lower that the carbon-carbon bonding (348 KJ/mol).

Nevertheless a very interesting intramolecular hydrogen bonding is possible and new hypothesis can be proposed (Figure 4.20).

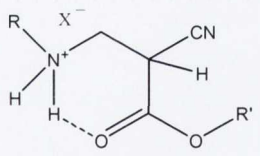


Figure 4.20. Schematization of the intramolecular bonding.

The intramolecular six membered ring interactions are very interesting because of their unique behaviour. For example, in our case, the ammonium proton should be able to create interesting hydrogen bonding with the oxygen of the carbonyl group, with increase of acidity of the ammonium salt, as well as, an increase of acidity of the ester group. Then the keto-enol tautomerism can be further favoured and a new intramolecular hydrogen bonding can be imagined (Figure 4.21).

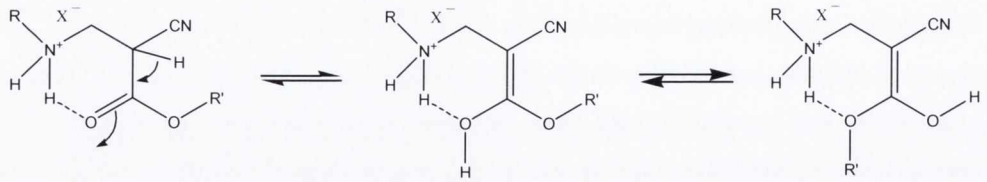


Figure 4.21. Representation of the keto-enol tautomerism and intramolecular hydrogen bonding.

In other words the intramolecular hydrogen bonding as well as high temperatures (like those used during the TSIL reaction; 170-190 °C) could promote the keto-enol tautomerism and favour an unusual hydrogen bond.

At this point a very exothermic degradation with release of imminium salt reagent, alcohol and some volatiles can be proposed (Figure 4.22).

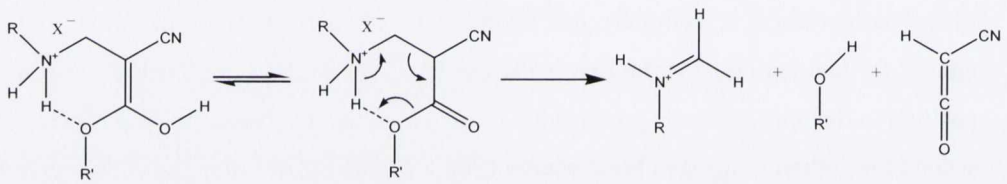


Figure 4.22. Mechanism of thermal degradation.

Following this route the imminium salt is regenerated as well as the hydroquinone plus two new volatile chemicals, the original alcohol (like β-methoxyethanol in this experiment) plus a ketene, as the 3-oxoacrylonitrile. Intuitively the ketene could be detected in the condensed phase together with the cyanoacrylate and traces of alcohol, unless it quickly reacts to yield the original CAcet (Figure 4.23).

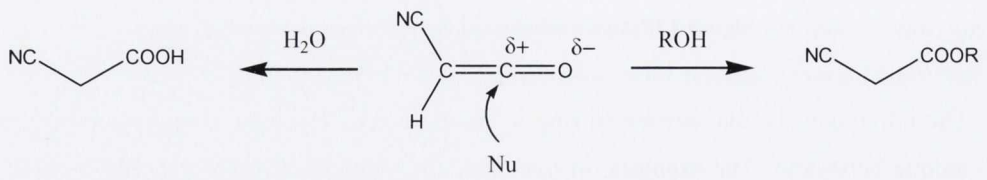


Figure 4.23. Possible ketene transformation

Chemists have long used ketenes as useful intermediates in the synthesis of organic molecules and a good number of exhaustive reviews are available[211]. The production of

a high energetic molecule like a ketene was unlikely but at the same time was in agreement with all the experimental observations gas production, alcohol condensation, apparent disappearance of the cyanoacetic part. Moreover the decomposition and alcohol release is acid promoted (larger excess of MSA produces larger alcohol production) that is in agreement with a higher enol formation in stronger acidic environment. The ketenes are molecules produced industrially from the pyrolysis of acetones,[212] by base catalyzed elimination of acyl chlorides (Figure 4.24) or from carbenes.

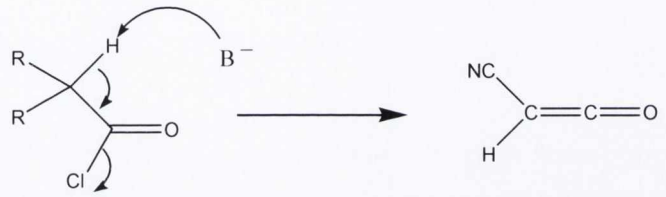


Figure 4.24. Ketenes synthesis by base catalyzed elimination of acyl chlorides.

The ketenes are highly energetic molecules and to confirm the current theory we should be able to trap it for its detection. However this is very difficult because ketene is highly volatile and extremely reactive towards nucleophiles. With water it would produce cyanoacetic acid, or CAcet in the presence of alcohols. Further thermal degradations are not excluded.

The thermolysis of the ester side will be discuss later and the possible mechanisms faced to explain the release of free alcohol.

Conclusion:

It has been showed the destructive interaction of hydroquinone with the ionic liquid (81R iminium methanesulfonate) and/or with the CAcet. The performed study gave good hypothesis to explain the poor results about the HEMA-cyanoacrylate synthesis. It should be borne in mind that the use of hydroquinone was in catalytic amount (5 mole %) and if a simple transesterification occurred it should produce at max only an equivalent amount of free alcohol. This was not in agreement with the large amount of HEMA free alcohol collected when HEMA-CAcet was used as CAcet reagent. This behaviour might suggest a catalytic degradation or a combination of effects. In other words the most reliable hypothesis seemed the one with regeneration of the hydroquinone and imminium salt. Moreover it has to be underlined that cyanoacetic

acid was never detected in the condensed fractions, this was quite strange and further studies will be dedicated to this topic.

In conclusion the hydroquinone worked in the current system as a very good radical stabilizer but because of its collateral effects it couldn't be used in the TSIL reaction.

4.3.2.2 Further investigation-stabiliser compatibility

In consideration of the necessity to have a good stable radical system a further investigation on radical stabilizers compatibility was performed. Again the mini-SPE was considered the best equipment for this study and once more the 2-methoxyethyl CAcet was chosen as model reagent (Figure 4.7).

The radical stabilizers under investigation were DBHT, PTZ and α-Tocopherol (Vitamin E). As for the hydroquinone investigation the distillation speed, the gas bubbling, CAcet conversion and product purity were monitored. The results are summarized in Table 5.

Table 4.5. Results on different radical stabilizators for the 2-methoxyethyl CAcet TSIL reaction

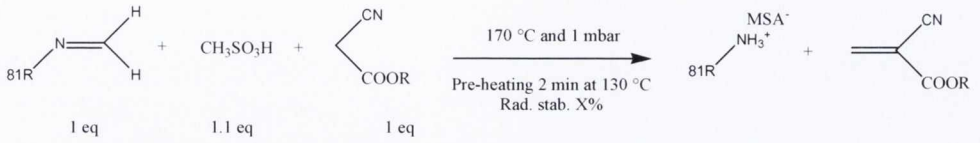
Entry	Radical Stabilizer w (%)	Yield (%)	Residual CAcet (%)	Observations
1	DBHT 2.5	73	5	Very slow distillation, regular bubbling
2	DBHT 2.5 + PTZ 0.5	44	20	Very quick distillation, large bubbling, change of IL colour
3[a]	PTZ 1	72	8	Low product purity
4	Vitamin E 1	76	5	Slow distillation, regular bubbling

[a] PTZ is added after the pre-heating stage

The previous experiments generated some conclusions. The trials performed with only DBHT (Entry 1) produces a good result and presumably no interaction with the starting materials is present. The reasons could be either that the tert-butyl groups hinderd or the ortho-para positions were already substituted. However just a catalytic amount of PTZ (0.5%, Entry 2) produces an evident negative interaction and gas bubbling was observed, the IL/CAcet mixture turned into an unusual dark-green colour and low conversion was observed. From the data so far obtained it was possible conclude that the PTZ has a pronounced destructive interaction with the ionic liquid reagent. Different behaviour was highlighted when the PTZ was added, after the pre-heating stage, in

other words, if added after the exhaustive reaction between IL and CAcet, its influence was definitely lower. In fact higher yield and modest bubbling were observed but a consistent amount of CAcet was still collected unreacted. Much better results were given by Vitamin E (Entry 4).

These reactions were last performed in large scale using the SPE equipment (Figure 4.25).



β-methoxyethyl cyanoacetate; $R = R^1 = (CH_2)_2OCH_3$
HEMA cyanoacetate; $R = R^2 = (CH_2)_2OC{=}OC(=CH_2)CH_3$

Figure 4.25. General TSIL reaction scheme

Table 4.6. TSIL reaction, in the presence of different radical stabilizer, performed using SPE equipment

Entry	Radical Stabilizer w (%)	R (CAcet)	Residual CAcet (%)	Observation
1	Vit.E 1	R^1	~ 15	No polymerization
2	Vit.E 1	R^2	~ 20	Consistent HEMA alcohol detected, polymerization [a]
3	DBHT 2 + PTZ 0.1	R^2	~ 30	Consistent HEMA alcohol detected, polymerization [b]
4	DBHT 5 + PTZ 0.1	R^2	~ 30	Consistent HEMA alcohol detected, polymerization [b]

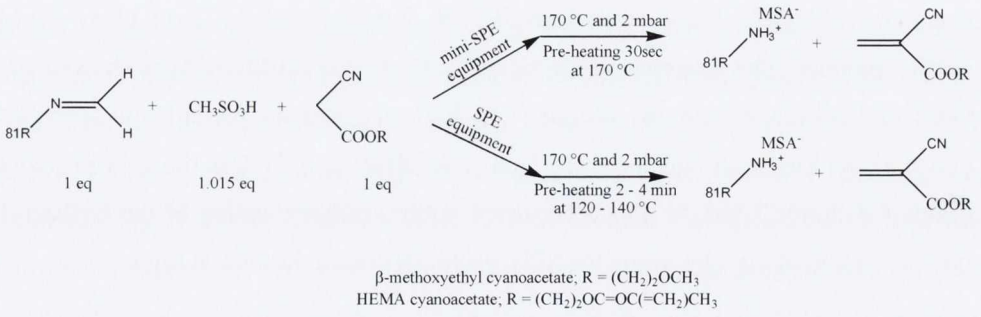
[a] The product was collected partially polymerized; [b] The product was collected partially polymerized and radical polymerization in the SPE reactor was present too.

The reactions performed into SPE still showed low performance, only the reference reaction (Table 4.6, Entry 1) performed with 2-methoxyethyl CAcet gives a good quality product. The attempts conduced with Vit.E and HEMA-CAcet showed once more low selectivity and the product was collected already partially nucleophilicly polymerized. Similar results were obtained with DBHT and PTZ, in those two reactions (Table 4.6, Entry 3 and 4), also a consistent radical polymerization of the methacrylic function occurred directly inside the SPE reactor, blocking the central rotor.

4.4 Acidity investigation and phosphate solution

The synthesis of HEMA-cyanoacrylate in an acidic ionic liquid environment was previously investigated. The TSIL ionic liquid was always produced with a little excess of MSA (typically 5%) in order to guarantee an acidic environment and to avoid nucleophilic polymerization of the fresh produced cyanoacrylate. This excess was modified in order to explore the influence of a strong sulfonic acid towards ester thermolysis. Thus the TSIL reaction for the HEMA-cyanoacrylate synthesis was performed with 3, 5 and 10 mol % MSA excess. In conclusion poor selectivity of reaction was observed, in particular larger acid concentration produced more free alcohol. The need to reduce or eliminate this strong acid environment for the production of this type of CA, was clear. For the reasons already described, the TSIL reaction would be performed at low temperatures and in a neutral (pH) environment. In order to explore this idea the identification and use of a reagent able to work as a medium strength acid (weaker than sulfonic acids) and eventually capture weak nucleophiles as well (e.g. to transform a volatile alcohol to a not distillable compound) would be desirable. Nevertheless this chemical has to be compatible with the TSIL reagents (IL/CAcet mixture) and simultaneously it has to promote/catalyze the reaction.

The TSIL reaction of β- methoxyethyl CAcet was chosen as model reaction (Figure 4.26). All the tests were performed in the presence of $BF_3{\cdot}Et_2O$ as gas-phase stabilizer (1 mol %). A screening of different phosphate additives was made. Generally they are powerful desiccant agent able to react quickly with alcohol and water, and so to work as a trap for weak nucleophiles (e.g. alcohols released from thermal hydrolysis/decomposition of esters).



β-methoxyethyl cyanoacetate; R = $(CH_2)_2OCH_3$
HEMA cyanoacetate; R = $(CH_2)_2OC{=}OC(=CH_2)CH_3$

Figure 4.26. General TSIL reaction scheme

The most important reaction conditions and considerations were derived and summarized in Table 4.7:

Table 4.7. β-Methoxyethyl cyanoacrylate synthesis using different additives

Entry	Additive 1 mol (%)	Cat. 2 mol (%)	Type equipment	Yield (%)
1[a]	P_2O_5 7	_	Mini SPE	70
2[a]	MPA 6	_	Mini SPE	-[b]
3	P_2O_5 3	_	Mini SPE	65
4	MPA 6	_	Mini SPE	18
5	MPA 6	SAS 5 after pre-heating	Mini SPE	78
6	MPA 7	SAS 5 from the second stream	SPE	70
7	PPA 10	_	Mini SPE	74
8	PPA 5	_	Mini SPE	68
9	PPA 10	_	SPE	75
10	PPA 5	_	SPE	80

[a] The reactions are performed without the addition of $BF_3{\cdot}Et_2O$ as gas-phase stabilize; [b] The monomer was not collected as it completely polymerized in the distillation apparatus; MPA = metaphosphoric acid; PPA = polyphosphoric acid

I) TSIL reaction with P_2O_5.

Two reactions were performed using mini-SPE equipment only (Table 4.7, Entry 1, 3) achieving promising results. The reactions occurred quickly with good yield and without any polymerization. Nevertheless the same reaction was not performed using the SPE because of the total insolubility of the phosphorus pentoxide in IL. An

important detail is that the P_2O_5 was added to the IL/CAcet blend just before the heating to avoid any consistent reaction/interaction with the reagents at room temperature.

II) TSIL reaction with meta-phosphoric acid.

The results unfortunately were not positive as the product distillation was slow and its polymerization was observed (Table 4.7, Entry 2, 4); only in the presence of a further excess of sulfonic acid the reaction worked regularly (Table 4.7, Entry 5). The acid was added to the crude after the pre-heating stage (30 sec at 180 °C) and before applying the vacuum. Modest result was observed transferring the reaction to the SPE equipment (Table 4.7, Entry 6), in fact a very slow distillation and poor reaction yield were obtained. The lack of performance was attributed to the poor solubility of metaphosphoric acid in the reagent mixture. For this reason the acid was settled on the bottom of the feeding vessel and was not inside the SPE reactor (body).

III) TSIL reaction using low molecular mass polyphosphoric acid.

The polyphosphoric acid (115% H_3PO_4 basis) is completely soluble in the reagent mixture at 5 and 10 w (%). The reaction performed using the mini-SPE equipment showed promising results (Table 4.7, Entry 7, 8). Finally the reaction was transferred to the SPE, both 5 and 10 mol % of poly-phosphoric acid were tested (Table 4.7, Entry 9, 10) and good results were obtained.

The subsequent target was to transfer the good preliminary results obtained using poly-phosphoric acid at 5 mol % for the HEMA-cyanoacrylate synthesis. The test was performed by means of the SPE equipment using the same operative conditions reported above (Figure 4.7).

Table 4.8. HEMA cyanoacrylate synthesis using best additives from Table 4.7.

Entry	Cat. mol (%)	SPE Pre-heater temperature (°C)	Yield (%)
1	TFA from the second stream	120-130	20-25
2	H_3PO_3 from the second stream	100	25-25

A considerable amount of HEMA (alcohol) was detected together with the product (Entry 1, Table 4.8). The temperature of the pre-reactor was reduced from 130 °C down

to 100 °C (Entry 2, Table 4.8) reducing the HEMA content but increasing the unreacted CAcet collected. In both tests the desired product was obtained in low yield and purity (< 50%).

Previous tests (See Paragraph 3.2.4 "TSIL/CAcet Mixture Reactivity") showed that the complete CAcet conversion occurs after 4 minutes at 100 °C. This means that the operative conditions of the pre-reactor can't be milder than those used here.

Two additional tests were performed using a different IL stoichiometry (Table 4.9), in order to reduce the acidity of the system only 1 eq MSA (IL anion) was used (Figure 4.26).

Table 4.9. β-Methoxyethyl cyanoacrylate synthesis using IL with 1 eq MSA and different additives.

Entry	PPA mol (%)	Type equipment	Yield (%)
1	5	mini-SPE	50
2	10	mini-SPE	67
3	5	SPE	43

Two attempts were performed by mini-SPE with 5 and 10 mole % of poly-phosphoric acid (Table 4.9, Entry 1, 2). The product was obtained in good purity but low yield, the reaction was transferred to SPE equipment (Table 4.9, Entry 3) and again a poor result was observed.

In conclusion all the reactions performed were not completely successful and the necessity for a different approach was evident.

After an extensive bibliographic search relating the properties of polyphosphoric acids (PPA) and phosphate in general, a different reactivity/interaction with weak nucleophiles like H_2O and alcohols was noted. In particular a review in 2002 summarizes the different interaction of alcohols with PPA and P_2O_5[213]

As described the PPA is a mixture of linear, oligomeric chains of phosphorous and oxygen atoms. The physical form is closely dependent to the length of polymer: a short oligomer is a liquid as the chain length grows the materials becomes progressively more viscous. What is most important is that the linear structure of the PPA makes it less reactive than the P_2O_5. This different reactivity is based on the higher energy of the tetrahedral phosphoric anhydride compared to the linear one. From the reaction of PPA

and water only phosphoric acid (ortho) is quickly produced, likely from a mixture of alcohol mono phosphate are rapidly produced. Therefore from the reactivity of alcohols with PPA a cleavage of the chain happens. At the end large amount of orthophosphoric acids are produced because each chain forms one molecule of acid (Figure 4.27).

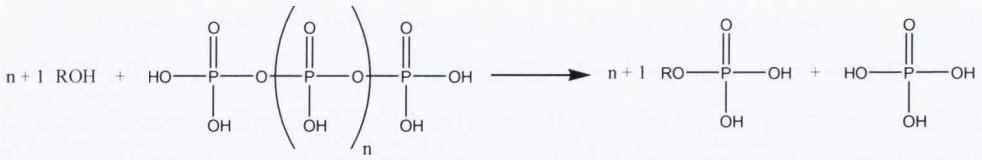


Figure 4.27. Reaction of alcohols with PPA

A mixture of phosphate (mono-phosphate in blend with bis-phosphate) can be obtained by appropriate temperature and alcohol/polyphosphoric acid ratio control.

As previously mentioned the phosphorous pentoxide shows a different and higher reactivity which is due on its tetrahedral structure. As described the overall reaction mechanism is quite complex, nevertheless it can be simplified as follows (Figure 4.28):

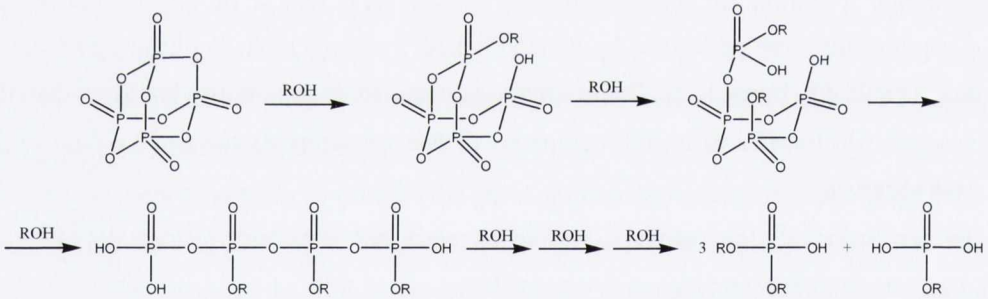


Figure 4.28. Schematic mechanism of phosphorus pentoxide reaction with alcohols.

First an alcohol molecule opens the tetrahedral structure and forms a bicyclic one, then a second alcohol molecule produces the monocyclic structure and finally the acyclic products.

A quick study was therefore performed in order to explore the interaction of those structures (PPA and P_2O_5) with free sulfonic acid. In particular 1 equivalent of MSA has been mixed with 1 equivalent of PPA (115% by Aldrich) and a very mild exothermicity was observed; even after heating up to 100 °C the mixture analyzed by ^1H NMR didn't show any reactivity. Only after heating at higher temperatures (180 °C) a mixture of phosphoric acid, methanesulfonic anhydride and traces of free methanesulfonic acid

could be collected by distillation. In conclusion a reaction between polyphosphoric acid and MSA could happen but only at high temperature.

The interaction of MSA with phosphorus pentoxide is well known, in fact a solution of P_2O_5 in MSA (7% w) is called Eaton's reagent[214] and it has been used to catalyse many chemical reactions. For example it has been used as a condensing agent and solvent for aromatic acylation, in Fischer indole synthesis[215] , in synthesis of aryl sulfones[216] and for the production of amides by Beckmann rearrangement.[217] The nature of the catalytic species is not certain but probably it is supposed to be a very active mixed anhydride. Few authors affirmed that the anhydride species were visible by NMR[218] but a deep analysis was performed for a better understanding of its composition and reactivity. The Eaton's reagent was used as received from Sigma-Aldrich. The mixture was analyzed by NMR. The MSA/P_2O_5 solution was only partially soluble in deuterated chloroform, a phase separation was observed directly inside the NMR tube. By ^{1}H NMR spectrum the splitting of the signals was observed; in particular three main signals were present at δ 3.19 (s, 1.4H), 3.32 (s, 3.00H), 3.46 (s, 0.91H) and 3.60 ppm (s, 0.19H), further two signals were present at δ 10.57 (s, 0.6H) and 11.18 ppm (s, 1.43H). Evident was the presence of new molecular species in consideration that the methanesulfonic acid has only one methyl group, moreover the presence of two different acidic protons drove the attention toward new acidic intermediates. Confirmation was given by the ^{13}C NMR where three carbon species were present, in fact three signals were observed respectively at δ 39.40, 39.50 and 41.43 ppm. Also the ^{31}P NMR underlined different phosphorus species, in this case four main signals were present respectively at δ 2.33 (6P), -13.21 (1P), -14.08 (2P) and -14.67 ppm (1P). In conclusion the presence of at least two-three different molecular compounds was evident and further studies were performed.

The analysis was repeated in deuterated acetone, the solution was homogeneous but the analysis showed an evident interaction between the reagent mixture and the solvent, in fact the solution rapidly turned to orange and black colour after few hours. Moreover the viscosity of the solution increased and by ^{1}H NMR only three signals were present δ 3.03 (s, 3H); 3.06 (s, 0.5H); 12.44 ppm (s,1.22H). The ^{13}C NMR showed two signals (δ 38.86, 40.58 ppm), and by ^{31}P NMR three main signals δ 4.06 (6P); -9.86 (2P); -10.69 ppm (5P) plus other three minor signals (δ -24.08, 0.2P; -24.49 ppm, 0.4P; -25.49 ppm,

0.7P). Then an interaction likely an aldolic poly-condensation of acetone and degradation of the MSA/P_2O_5 solution was evident.

A further study was performed in deuterated dichloromethane, surprisingly the MSA/P_2O_5 solution showed good solubility and few spectroscopic observation were performed. The solvent was first run alone (Figure 4.29, left) and as expected only two singlet at δ 5.36 (residual CH_2Cl_2) and 1.57 ppm (H_2O) were present. After small addition of MSA/P_2O_5 blend four new signals appeared, the dichloromethane residue was unchanged and the singlet at δ 1.57 ppm disappeared (Figure 4.29, right). After a further addition of MSA/P_2O_5 blend in the same NMR sample a new signal appeared at δ 3.31 ppm (Figure 4.30).

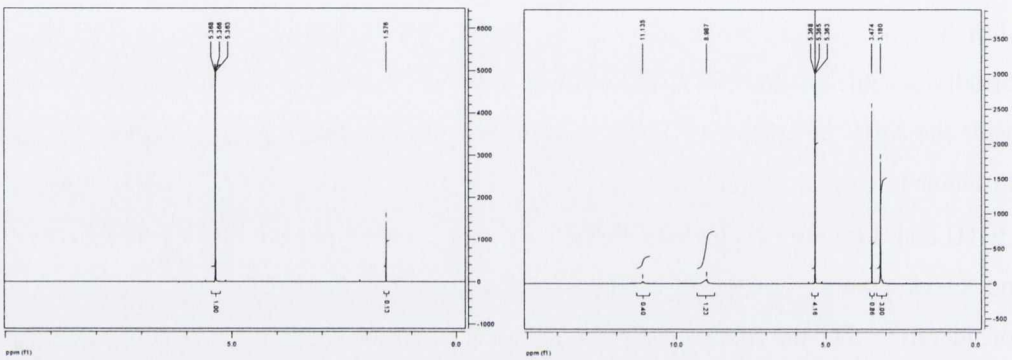


Figure 4.29. ^{1}H NMR (400 MHz) spectrum of CD_2Cl_2 (left) and ^{1}H NMR (400 MHz) spectrum of MSA/P_2O_5 blend in CD_2Cl_2 (right)

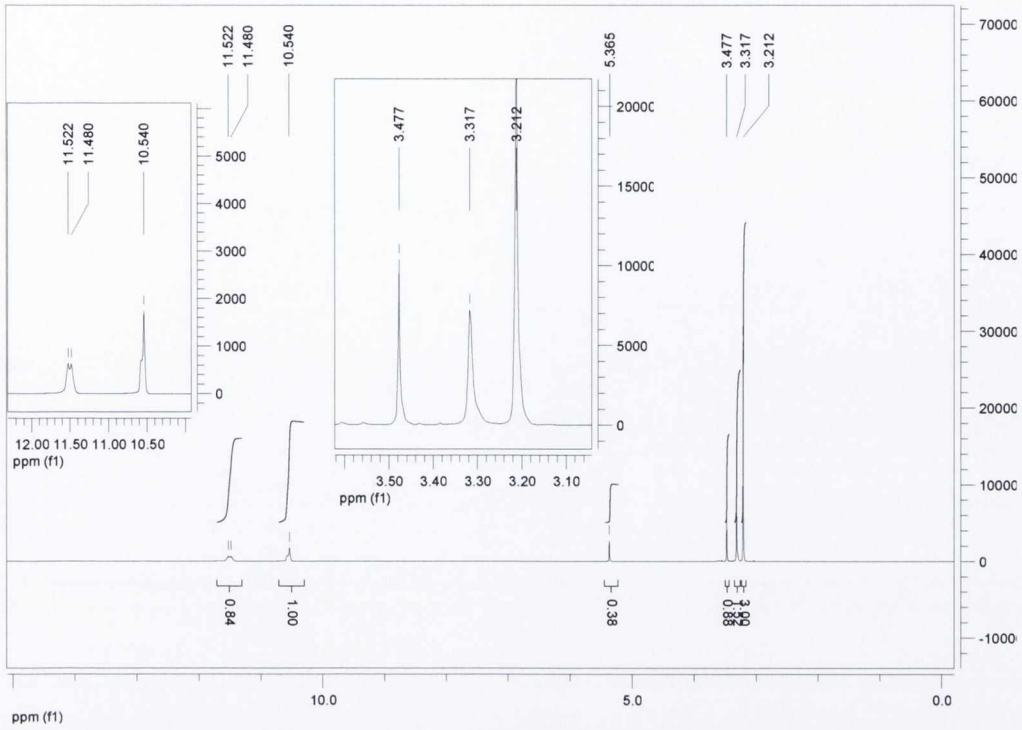


Figure 4.30. ^{1}H NMR spectrum (400 MHz) of MSA/P_2O_5 in CD_2Cl_2 at higher concentration

Very interesting was to observe that the new chemical present at δ 3.31 ppm (Figure 4.30, Inset) corresponded to the most active species, in fact at low concentration fully reacted with the traces of water left in solution, instead it was stable and visible when a well dried environment was present. Two different acid protons were present (δ 11.50 and 10.54 ppm) and three major resonances between δ 3.2–3.6 ppm that were consistent with the methyl groups of methanesulfonic acid.

The first methyl group at δ 3.21 ppm is in agreement with the literature and attributed to the methyl of free methanesulfonic acid. The signal at δ 3.47 ppm can be attributed to methanesulfonic anhydride, the singlet at δ 3.31 ppm probably belongs to a new mixed compound. Methanesulfonic acid was by far the most abundant methyl containing compound. The ^{13}C NMR was performed and three different carbons were observed (Figure 4.31).

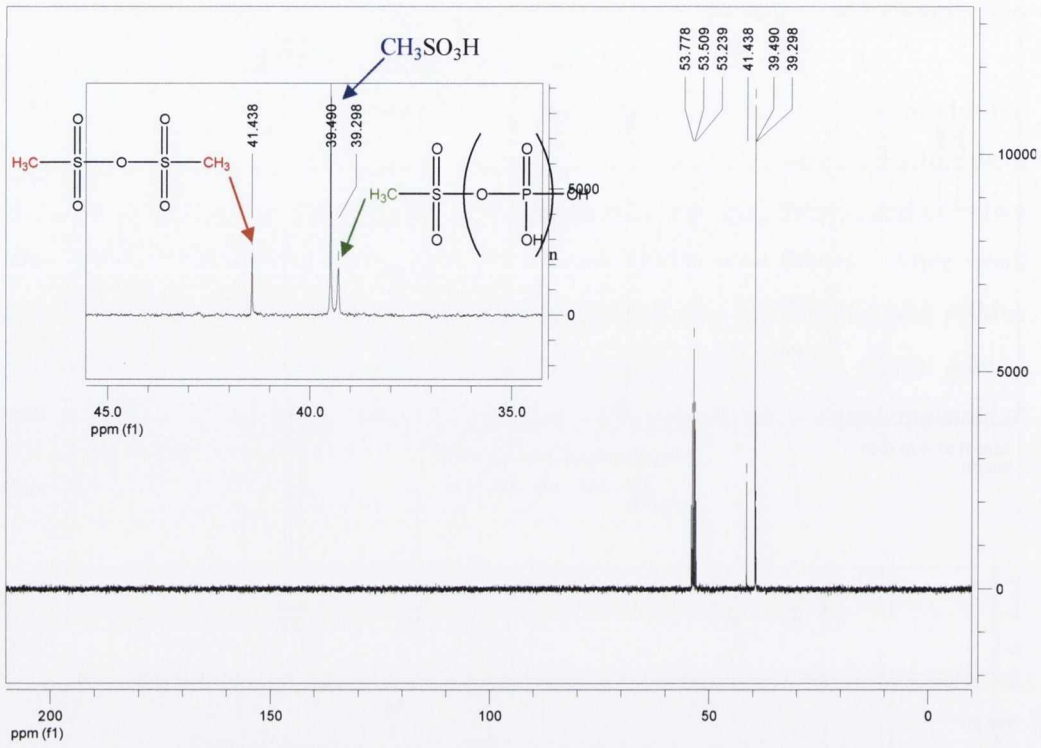


Figure 4.31. ^{13}C NMR spectrum (100 MHz) of MSA/P_2O_5 in CD_2Cl_2

The signal at δ 41.43 ppm is in agreement with the known methanesulfonic anhydride as well as the methanesulfonic acid signal at δ 39.49 ppm, again a new carbon species is present at δ 39.29 ppm, then the presence of a sulfonic-phosphonic mixed anhydride was supposed.

The ^{31}P NMR was recorded and few interesting new signals were present in region between δ -30 and 3 ppm (Figure 4.32).

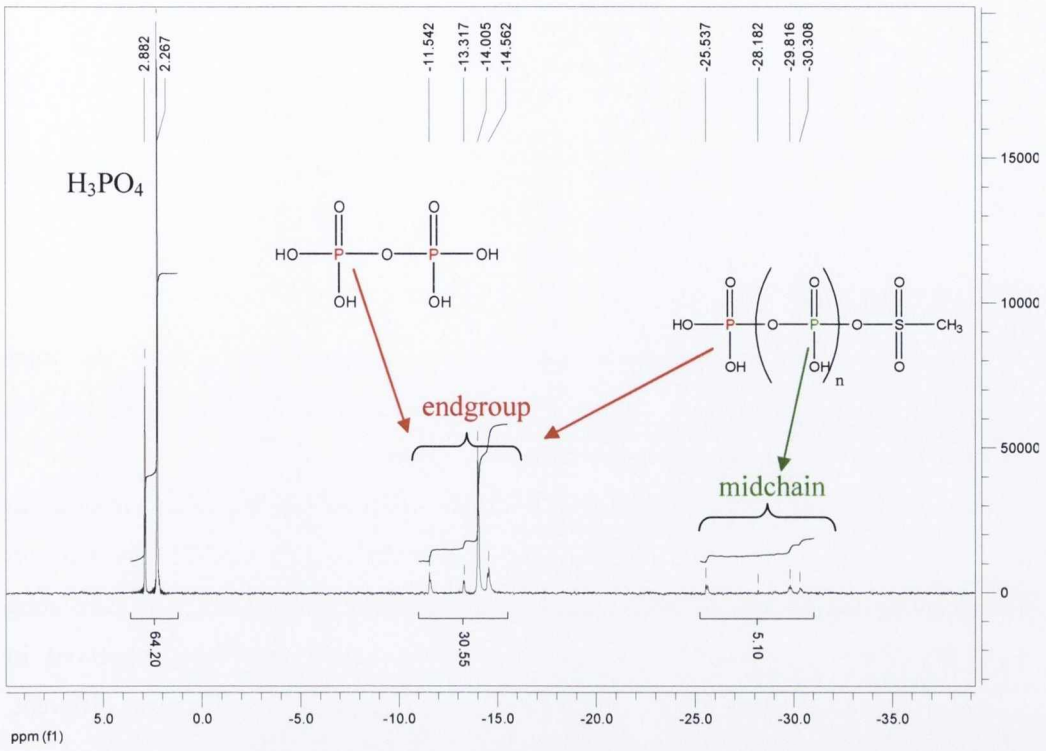


Figure 4.32. ^{31}P NMR Spectra of MSA/P_2O_5 in CD_2Cl_2

The ^{31}P-NMR spectrum suggested that, an average, a relative small number of phosphorus repeated units were present in the mixed anhydrides. The resonances were assigned according to Y-H. So et al.[218] Due to the complexity of the spectrum, individual phosphorus resonances were not assigned to the individual chemical structures.

Phosphoric acid was detected at a chemical shift of approximately +3 ppm and it was the most abundant phosphorus-containing species in the mixture. The midchain phosphorus region (δ -30 to -25 ppm) and the endgroup phosphorus region (δ -15 to -10 ppm) indicated a complex mixture of polyphosphoric acid oligomers (mixed anhydrides). By comparison, the ^{31}P NMR spectrum of polyphosphoric acid (as shown in Y-H. So et al.) is extremely simple, exhibiting very few spectral lines.

The approximate molar composition of the phosphorus species were calculated from the ^{31}P NMR spectrum and can be found in Table 4.10. These data should be read as "mole percent endgroup phosphorous", etc. and does not take into account the number of phosphorus atoms contained in the molecule (i.e., pyrophosphate has two identical phosphorus atoms per molecule). No branched phosphorus species (chemical shift of δ -45 ppm) were detected in the sample.

Table 4.10. Molar composition of phosphorus species in CD_2Cl_2 solution

Phosphorus species	Percent of phosphorus
Phosphoric acid (H_3PO_4)	64
Endgroups	31
Midchain	5

The level of midchain phosphorus groups were approximately 5% of the total phosphorus-containing species in the Eaton's Reagent sample. This suggested, on average, a small "n" repeat unit in the mixed anhydrides.

The study was repeated for "neat" Eaton's reagent (Sigma-Aldrich product) in order to avoid any solvent effect. Then Eaton's reagent was placed into a NMR tube with no solvent and ^{1}H, ^{13}C and ^{31}P NMR spectra were acquired. The results were consistent with phosphorous pentoxide-methanesulfonic acid mixture previously observed in CD_2Cl_2 solution. Only the molar composition of the phosphorous species was different, the result is reported in Table 4.11.

Table 4.11. Molar composition of phosphorus species in "neat" Eaton's reagent

Phosphorus species	Percent of phosphorus
Phosphoric acid (H_3PO_4)	40
Endgroups	48
Midchain	12

It seems that the residual water present in the deuterated solvent can consume part of the active mixed anhydride (lower midchain composition) or that the reaction between MSA and P_2O_5 can furthermore proceed in solution.

For completeness a fresh sample of Eaton's reagent was prepared and analyzed. Then 7 w % of P_2O_5 was added to MSA and a clear solution was obtained after 2 hours stirring at 40 °C. The spectroscopic study was once more repeated, identical signals were observed by ^{1}H, ^{13}C and ^{31}P NMR, only the phosphorus species composition was slightly different (Table 4.12).

Table 4.12. Molar composition of phosphorus species in "neat" freshly made Eaton's reagent

Phosphorus species	Percent of phosphorus
Phosphoric acid (H3PO4)	45
Endgroups	45
Midchain	10

Interesting work was published by Dan Farcasiu and Huisu Cao[219] in with the acidity of the Eaton's reagent is compared to the acidity of methanesulfonic acid only. They analysed the strength of the acids, by ^{13}C NMR spectroscopy, using mesityl oxide as indicator, and correlating the difference between the signals for C-β and C-α in mesityl oxide (Figure 4.33).

$$\Delta\delta = \delta(\text{C-}\beta) - \delta(\text{C-}\alpha)$$

Mesityl oxide

Figure 4.33. Protonation equilibrium of mesityl oxide

The authors observed that the acidity of MSA decreased slightly when P_2O_5 was added and continued to decrease as the weight percentage of P_2O_5 increased. Then the effect of water addition to pure methanesulfonic acid or to MSA/P_2O_5 mixture was explored also. The authors observed that, as expected, the water behaves like a base. Moreover for weight percentage lower than 3%, the water had a less acidity reduction effect with MSA/P_2O_5 mixture than on MSA alone. This is rationalized because small amount of water can hydrolyse the anhydride present in MSA/P_2O_5 acid mixture to the corresponding acids. Thus the water is converted to methanesulfonic acid and phosphoric acid. They observed a very little change in acidity after water addition at the beginning, only after all the anhydrides were consumed the water was able to reduce the acidity of the system. The addition of water to pure methanesulfonic acid produces from the beginning a rather steep decrease in acidity. For large amount of water the acidity of pure MSA and MSA/P_2O_5 blend decreased in parallel but the strength of the mixture was always higher than the strength of the methanesulfonic acid alone.

This work seems to be in agreement with what is observed in our spectroscopic study. In fact the water present in the CD_2Cl_2 quickly reacted with a very active species then totally consumed, only with higher concentration of Eaton's reagent it become visible and stable in solution. It seemed correct to assert that a very active mixed anhydride was present, probably its structure was not unique but present in a blend in different forms. It is then reasonable to accept the presence of a short chain mixed anhydride as shown in Figure 4.31, Figure 4.32. Moreover for higher P_2O_5 concentration solution the presence of branched phosphorous species is proposed[219], then it is possible to think that if one molecule of phosphorus pentoxide reacts with two or more molecules of methanesulfonic acid an asymmetric new mixed anhydride species can be produced (Figure 4.34).

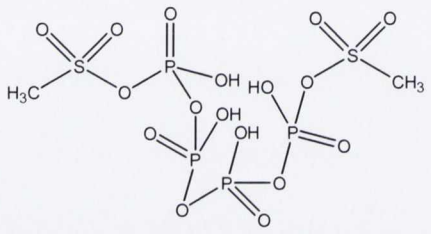


Figure 4.34. Proposed new asymmetric mixed anhydride species formed in higher P_2O_5 concentration.

At this point of the study it is important to underline that, theoretically, from the reaction of MSA with P_2O_5, the equivalents of free acid groups are kept constant. Obviously the acid nature changes and a weaker phosphoric acid (first pKa~2) is produced instead of the strong sulfonic acid (pKa~-2.5). The high boiling point methane sulfonic acid can be transformed into MSA anhydride or in a non volatile compound such as shown in Figure 4.34.

The following experiment was performed in order to investigate the ability of the P_2O_5 to react with MSA in diluted solution. Thus 1 mol % of MSA was added to highly pure, highly reactive Ethyl Cyanoacrylate, the reactivity against nucleophilic polymerization obviously suppressed (strong sulfonic acids are well known to be good stabilizers for CAs). After a few minutes a typical light yellow colour appeared. Then 5 mol % of solid P_2O_5 were added, and the solution was stirred overnight. The P_2O_5 did not dissolved as surprisingly, ^1H NMR (60 MHz) indicated the total disappearance of the MSA signal (singlet at δ 2.9 ppm) and the solution had returned to a clear colourless

liquid. A quick adhesion check ("Finger Test") indicated reactivity towards nucleophilic polymerization had improved supporting the thesis of anhydride production. This time no one new signal was observed at δ 3.4 ppm because, as assumed, the MSA reacted with the large excess of solid P_2O_5 producing a non soluble molecule like mono-phosphoric anhydride. The CA was still well stabilized in agreement with the theory of constant equivalents of free acid groups (at this stage in heterogeneous-solid phase or in the form of phosphoric acid).

4.5 New idea: TANDEM TSIL

(A new low temperature, low acidity TSIL reaction)

The acid strength of many acids and basis is well known and summarized in many pKa compilation tables[220].

Therefore it is easy to learn that the conjugate acids of regular aliphatic amines usually have pKa value around 10 and the correspondent imines have pKa values around 9. In conclusion the imines are weaker bases by one order magnitude. The comparison the pKa trend of some common acids that have already been tested in the TSIL method can be summarized as follow (Table 4.13):

Table 4.13. pKa Values of different acids

Acid representative of each category	pKa
Sulfuric acid	- 3.00
Methanesulfonic acid	- 2.60
Orthophosphoric acid	2.10
Acetic acid	4.76

A simple way to predict the TSIL ionic liquid reactivity against CAcet it is to follow the acidity scale (See also chapter "TSIL approach"). This is the reason why 81R imminium methanesulfonate salt does not react with CAcet at room temperature but only "on-demand" after heating (very important from a technological point of view). Instead a 81R imminium phosphate or carboxylate salts quickly react at room temperature with CAcet producing exothermicity and fast polymerization of the freshly produced cyanoacrylate (uncontrolled reaction). In a similar way 81R iminium sulfate is too stable and only at higher temperatures can produce reaction. This is the reason why the TSIL reaction can be best preformed with alkyl-sulfonic acids (and not any sulfonic acids).

Moreover the thermal stability of the correspondent 81R ammonium salt (IL by product after TSIL reaction) changes with the type of counteranion (See Paragraph 3.2). Then it is important to have an ammonium salt that does not decompose during the

cyanoacrylate distillation inside the short path equipment and only sulfonate anion (or stronger acid) have this propriety.

These learnings have lead to a new idea based on a so-called "tandem mechanism", which is summarized in Figure 4.35 and Figure 4.36:

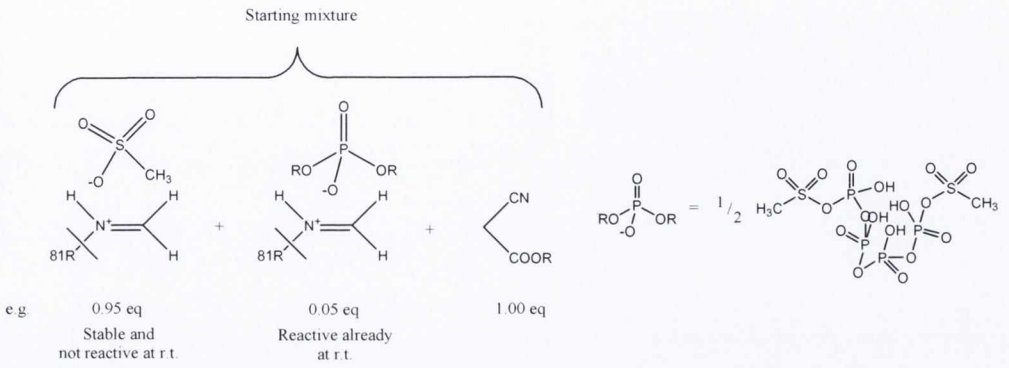


Figure 4.35. Schematic representation of the starting mixture of reagent

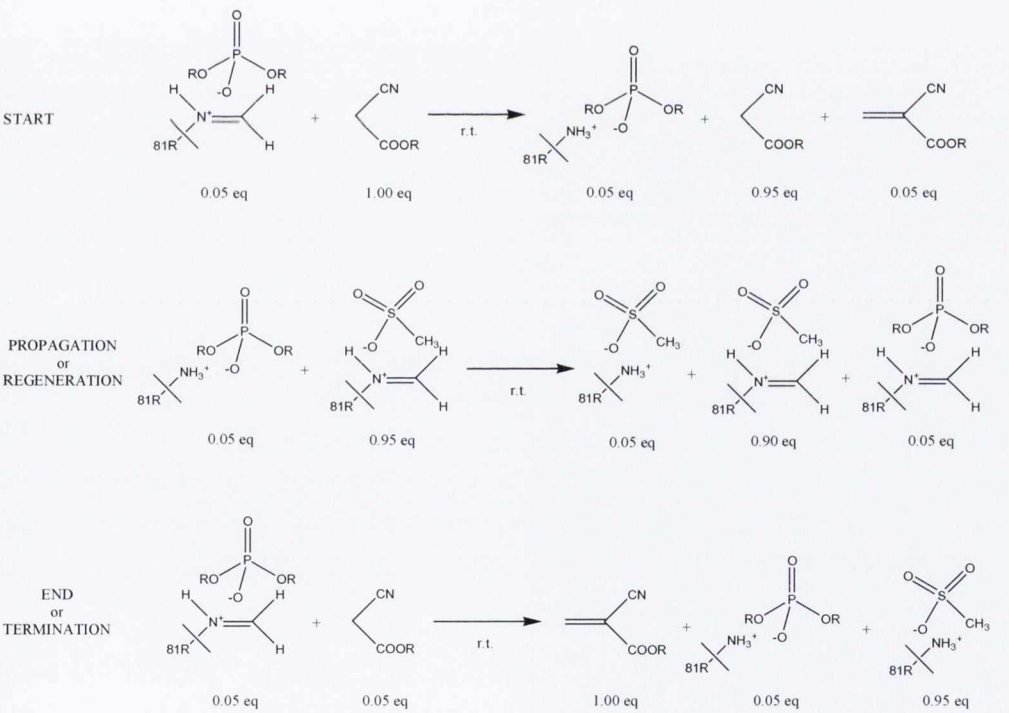


Figure 4.36. Proposed TSIL reaction by Tandem Mechanism divided in three steps: start, propagation and termination

The mechanism above was based on the synergic effect combining weaker/stronger acids and weaker/stronger bases. In the first step (Start) the most reactive 81R imminium phosphate (catalytic amount) can react with CAcet and produce some acrylate plus 81R ammonium phosphate. At this stage (Propagation or Regeneration) the phosphate anion can be replaced by the stronger methanesulfonic acid (the exchange is also favourite from the most basic amine produced) and a new catalytic amount of 81R imminium phosphate can be produced. The reaction finally terminates (End or Termination) with quantitative production of cyanoacrylate (1 equivalent) plus 0.95 equivalent of 81R ammonium methanesulfonate and just 0.05 equivalent of 81R ammonium phosphate.

4.5.1 Preliminary results

First experiment was performed using 81R imine (1 equivalent) plus phosphorous pentoxide 5 mol % solution in MSA (1.015 equivalents of MSA) and β-methoxy ethyl CAcet. The reaction was performed in mini-SPE equipment with the usual operative conditions (mini-SPE procedure; pre-heating 30 sec. at 170 °C following by 170 °C at 2 mbar). Immediately after the CAcet addition to the IL a consistent exothermic event was observed. The distillation of the product began very slowly and only after ten minutes some distillate was collected and three fractions were obtained. The first fraction (just few drops) was already totally polymerized before the end of the reaction. The second and the third were stable. By ^{1}H NMR analyses some important trends were observed. In the first fraction (the part soluble in $CDCl_3$) contained only some volatile hydrocarbon side-products but no trace of CAcet. This result was in agreement with higher reactivity of the IL, substantially no CAcet was left unreacted when the high vacuum started (30 seconds at 170 °C). The second fraction was pure monomer, the third one had a new small impurity peak at δ 3.04 ppm (0.2H).

Even more promising results were obtained from the following experiment which was performed with the same conditions as the previous one except for the percentage of P_2O_5 in MSA which was 2.5 mol % instead of 5 mol %. This time only a very mild exothermicity was observed after the CAcet addition (just few degrees) and monitored by means of a digital thermometer. The reaction was then performed as usual, the

distillation began slowly and three fractions were collected. The overall purity was improved with lower content of hydrocarbon side-product. The first fraction did not polymerise and did not show any trace of unreacted CAcet. The second fraction had a good purity, whereas the third fraction still contained the new impurity at δ 3.04ppm. This time the integral was equivalent to 0.11 protons, almost half of the previous attempt and in agreement with the lower P_2O_5 content.

The reaction was scaled-up using the SPE equipment. The stoichiometry of the previous experiment was used and similar result was optained. The product had a good purity, no CAcet reagent was traced in the distilled fraction but only product with a little impurity having a singlet at 3.00ppm that was temporarly ignored .

A new attempt was performed using the HEMA-CAcet (1 eq) as reagent of reaction, then 1.03 eq of MSA containing 2.5 mol % of P_2O_5 where mixed with 1 eq of 81Rimine, the CAcet was added and the reaction performed following the typical procedure by SPE equipment. The reagent mixture was reacted in the pre-heater for 2 min at 120 °C and the distillation was performed with 1mmbar vacuum at 170 °C. Few drops of $BF_3{\cdot}Et_2O$ were added as gas stabilizer and 1 mol % of vitamin E as radical stabilizer. The product was collected in good yield even if it partially polymerise close to the end of the reaction. In order to increase the stability of the freshly produced cyanoacrylate and in order to remove the polymerized monomer, a second distillation by regular glassware (Oil bath 160 °C, product b.p. 100 °C at 0.4 mbar) was made. The distilled product was analyzed by GC-MS and high field NMR. The product had very good purity, that was vastly superior to any previously obtained by TSIL reaction, the spectrum is following reported (Figure 4.37).

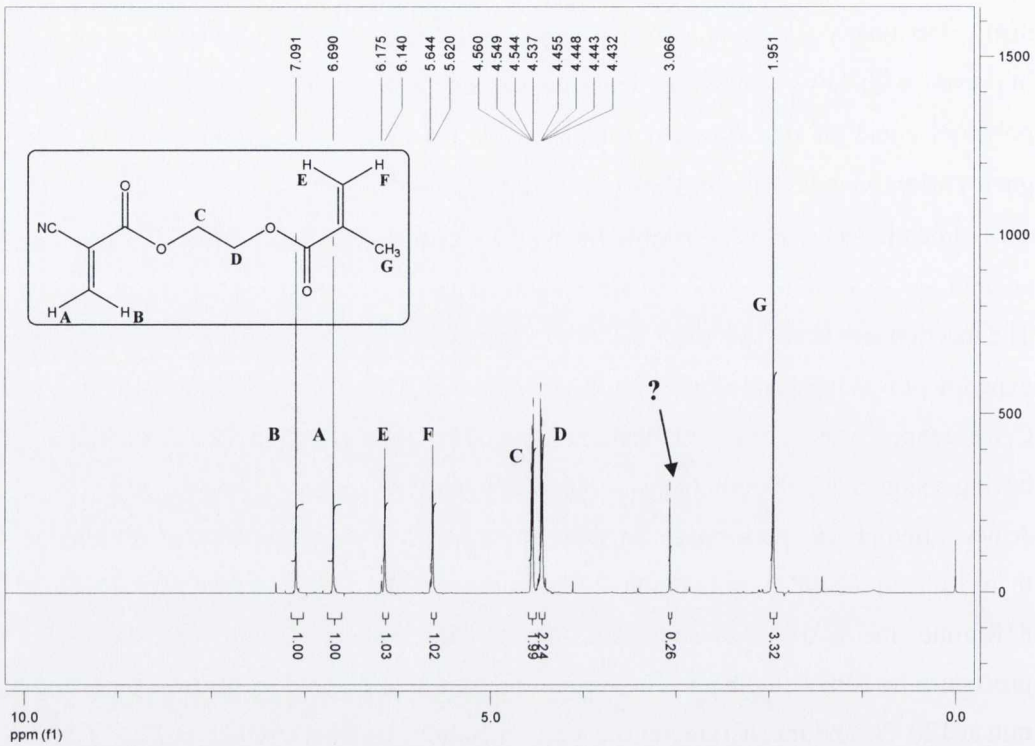


Figure 4.37. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of distillated HEMA-cyanoacrylate by TSIL method

Integration was correct and all the signals were successfully attributed, only the singlet at δ 3.06 ppm was unexpected as well two very small peaks just beside the methacrylic protons of the product.

An hypothesis was proposed to explain the new singlet that was assumed to be methane sulfonamide which could be produced at high temperature from the following reaction (Figure 4.38).

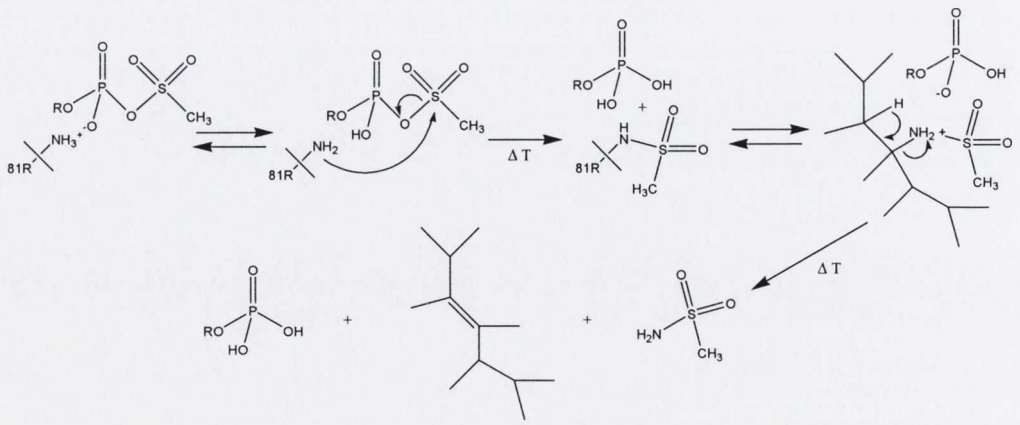


Figure 4.38. Proposed mechanism about the formation of methane sulfonamide at high temperature

To prove or to disprove this theory a small amount of methanesulfonamide (Aldrich 99% pure) was directly added to the sample and the ^{1}H NMR spectrum was recorded again. Unfortunately a new singlet appeared at δ 3.10 ppm, indicates it was not the impurity The spectrum (Figure 4.37) was reinvestigated in depth and it was noted that this new peak had an integration value of 0.26 protons, moreover just beside the methacrylic signals of the product two very small signals were observed. Those two singlets had one third of the area of the peak at δ 3.06 ppm, and no extra signals were observed; only the integrals of the multiplet at δ 4.4 ppm was a little higher than expected, as well as, the integral of the methyl group at δ 1.95 ppm (Figure 4.39).

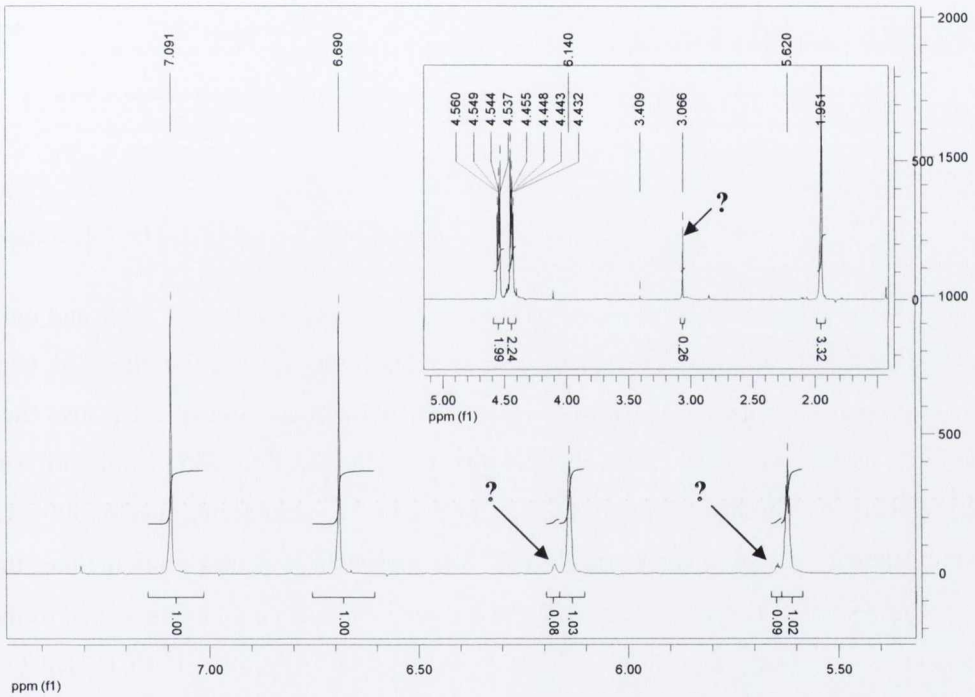


Figure 4.39. Enlargement between δ 7.5-5.5 and 5.00-1.5 ppm (Inset) of ^{1}H NMR (400 MHz, $CDCl_3$) spectra of distillated HEMA-cyanoacrylate (Figure 4.37).

These observations were curious and quite interesting at the same time, since the extra signals correlated. The sample was investigated by ^{13}C NMR, DEPT 135 the results are following reported (Figure 4.40).

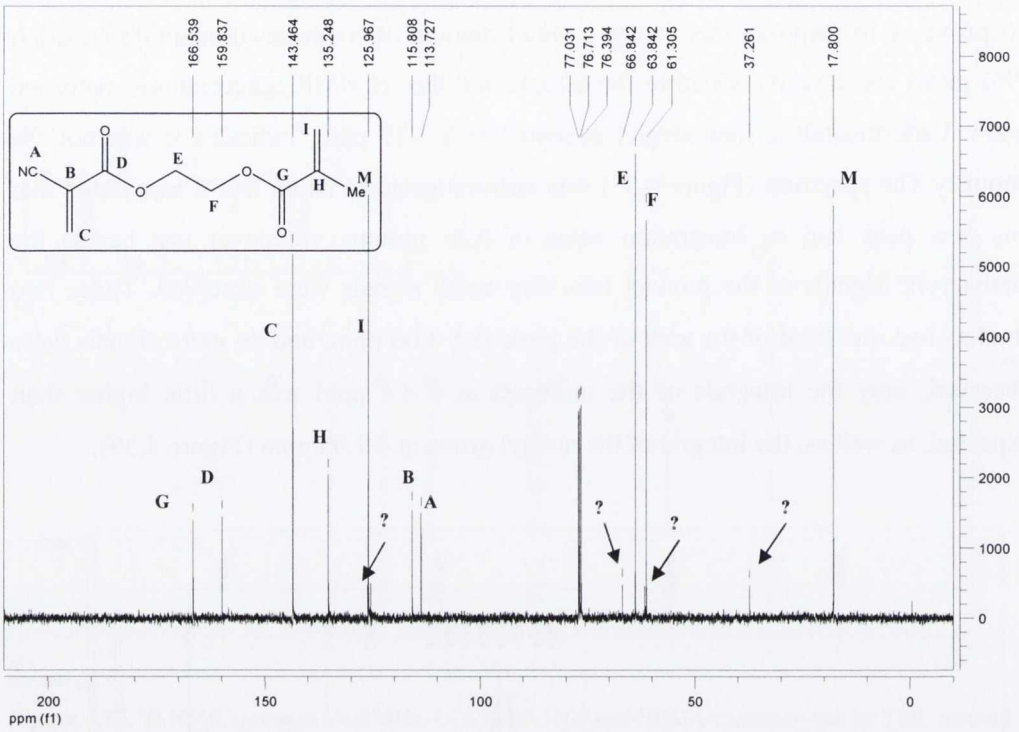


Figure 4.40. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of distillated HEMA-cyanoacrylate by TSIL method

Finally H-H COSY spectra was recorded but any new attribution was possible and only the predicted correlations were present; probably the impurity concentration was very low. The cyanoacrylates are usually not analysed by mass spectrometer because they tend to coat the mass detector, nevertheless this was done one time and the mixture was analysed (Initial temp 80 °C, ramp 20 °C/min to 280 °C, hold 5min, injector 300 °C, column 30.0 m x 250 μm). A broad peak was present at 5.8 min elution time, the product molecular ion was not visible but few fragmentations could be attributed to the cyanoacrylic-methacrylic product (m/z 68 = $NCCH_2CO^+$; m/z 69 = $H_2CC(CH_3)CO^+$; m/z 112 = $H_2CC(CH_3)COOCHCH_2$; m/z 124 = $NCC(CH_2)COOCH_2CH_2$), at 4.8 min was present a sharp peak partially overlapped to the previous one and with similar ion fragments; only the ion with m/z 124 was evidently not present.

The side product might have:

- At least two methacrylic protons
- Probably a CH_2-CH_2 ester chain similar to which of the desired product
- At least a CH_3 group attach to the methacrylic function as like as the product
- A methyl signal, likely a sulfonic $ROSO_2CH_3$ group is present

- No acidic protons are observed a low fields
- By dilution of the sample in ethyl cyanoacrylate no reduction of nucleophilic polymerization reactivity was observed (confirmation about the absence of acidic compounds)

Assembling all this data leads to postulate molecule-structure (Figure 4.41):

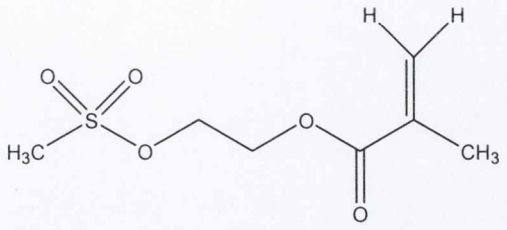


Figure 4.41. Proposed structure of the side product

An independent synthesis of the methanesulfonyl HEMA ester was performed following a modified literature procedure[221] . The product NMR spectrum is reported (Figure 4.42, Figure 4.43).

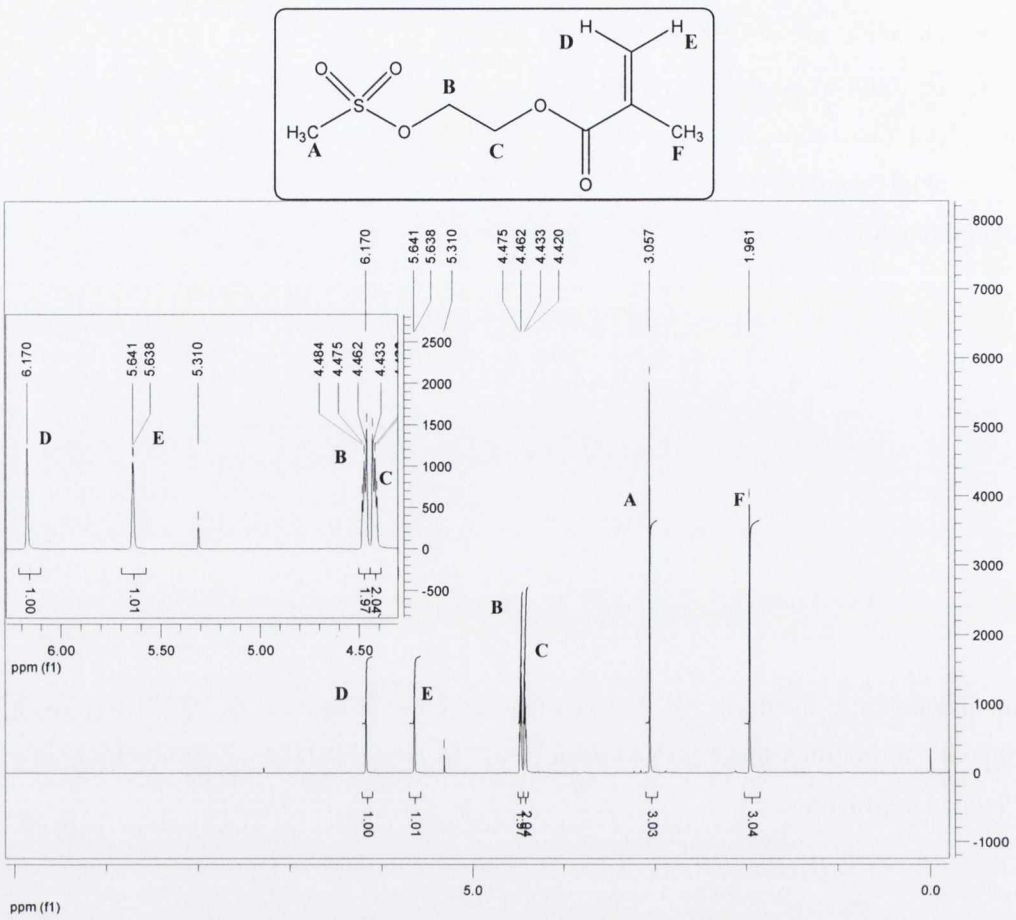


Figure 4.42. ^{1}H NMR spectrum (400 MHz, d_6-DMSO) of Methanesulfonyl HEMA ester

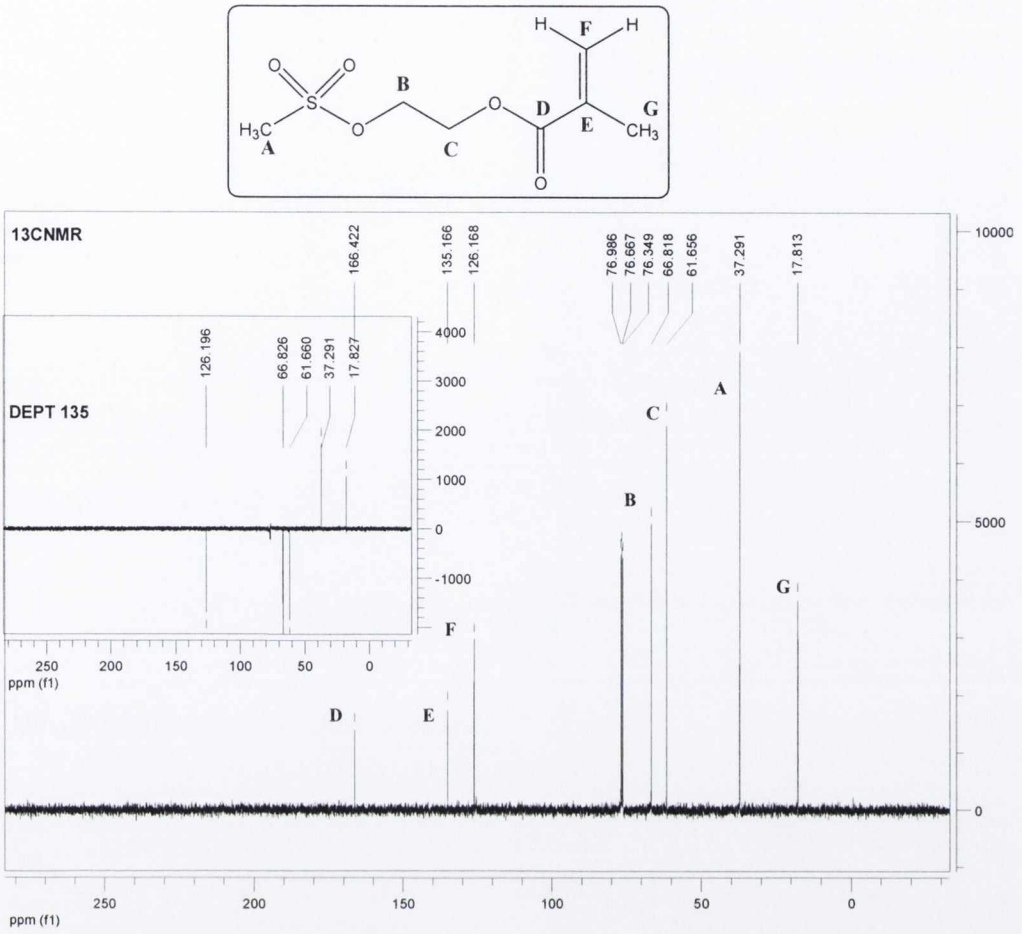


Figure 4.43. ^{13}C NMR spectrum (100MHz, d_6-DMSO) of methanesulfonyl HEMA ester

All the signals assigned could be attributed to the unknown product previously observed.

Then the sulfonyl HEMA ester was clearly identified as the side product produced in the Tandem TSIL reaction when the Eaton's reagent was used. This discovery raised questions about how, such a product could be produced. Various hypothesis were formulated.

FIRST Hypothesis:

Methanesulfonic acid is a strong Bronsted acid but in particular situations it could act as a weak nucleophile, in our case the Tandem-TSIL reaction was performed at high temperature and in a IL media which is relatively strong acidic environment. The unusual reaction can be favoured in the IL used as solvent, and the intermediate of

reaction (Mannich adduct) shows a very peculiar intramolecular hydrogen bond. A reaction with production of sulfonyl ester can be imagined (Figure 4.44):

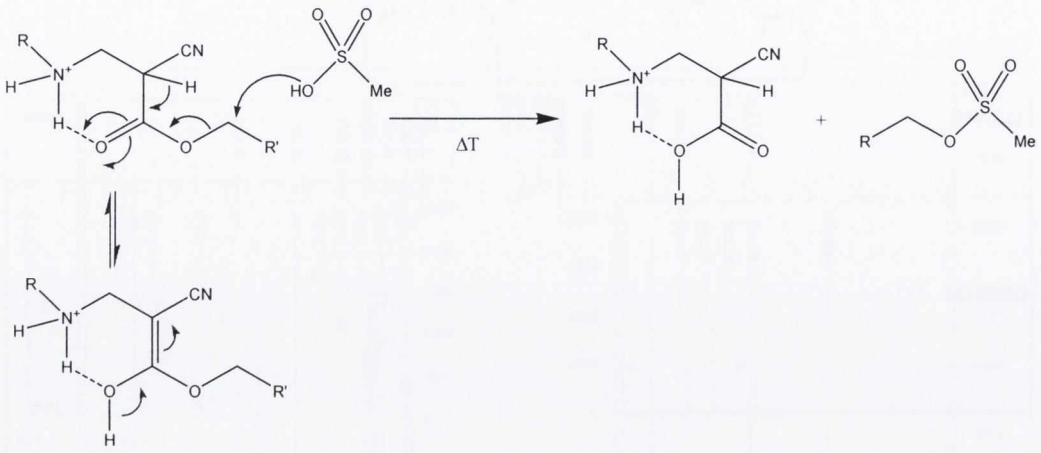


Figure 4.44. Proposed mechanism of sulfonyl HEMA ester formation

Following this hypothesis a sulfonyl ester and Mannich adduct were produced, the adduct in particular can furthermore decompose by two different paths:

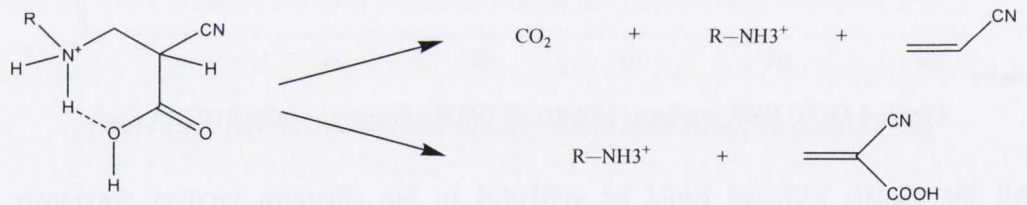


Figure 4.45. Proposed mechanisms of Mannich adduct decomposition.

In this first case a very volatile compound is produced (acrylonitrile); following the second pathway a heavy, extremely reactive cyanoacrylic acid is produced. As a consequence it would not be surprising that those hypothetic side-products have never been observed in mixture with the condensed product (cyanoacrylates).

SECOND Hypothesis:

The MSA behaves as a weak nuclophyle on the carbonyl group (Figure 4.46).

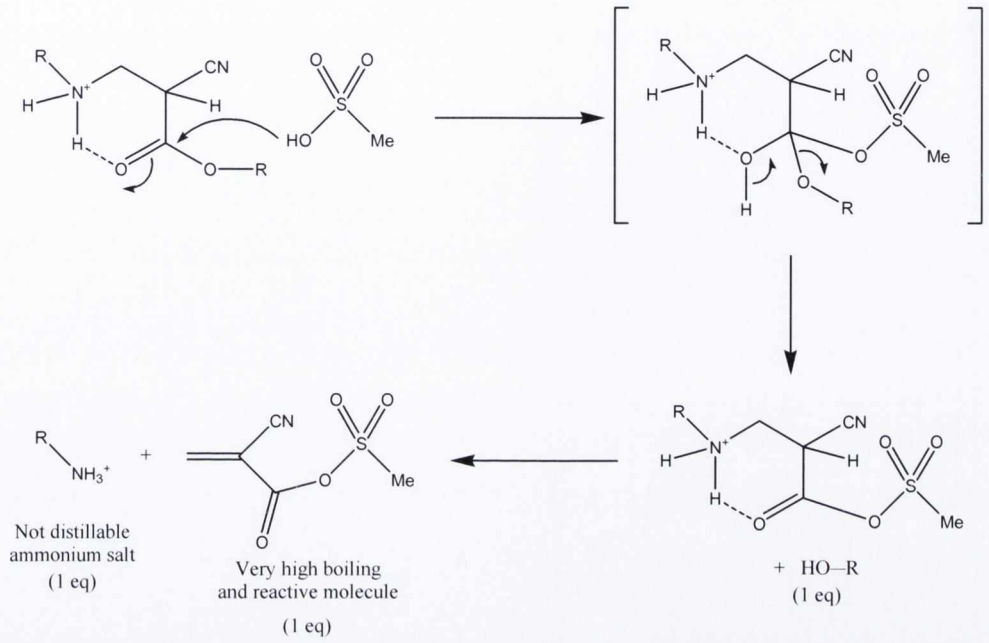


Figure 4.46. Proposed reaction mechanism based on MSA nucleophylic reagent

The proposed reaction above would not follow the conventional mechanism, but at high temperature and under acid catalysis, the energetically unfavoured decomposition might be justified. The side-product generated are ammonium salt, a volatile alcohol plus a very high boiling, very reactive mixed anhydride (it can undergo to further degradation).

THIRD Hypothesis:

The driving force of last proposed mechanism is the high temperature and the strong acidic environment of reaction (Figure 4.47).

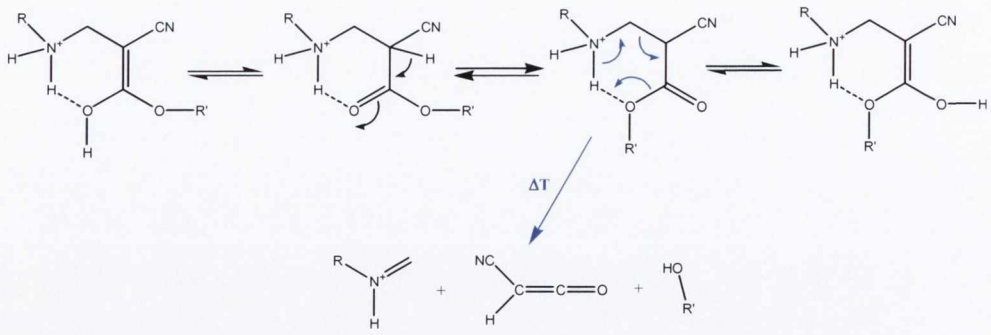


Figure 4.47. Proposed mechanism based on a promoted enolic equilibrium

In this case the acid only promoted the enolic equilibrium as well as the intramolecular hydrogen bond with the O—R oxygen instead of the carbonyl oxygen. A subsequent decomposition of the Mannich adduct could happen with the production of ketene, the reaction mechanism seemed to follow faithfully the base catalysed elimination reaction of acyl chlorides for the production of ketenes (Figure 4.48).

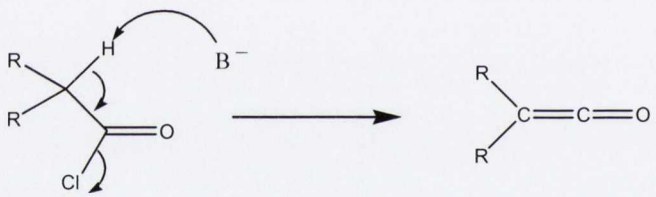


Figure 4.48. Based catalyzed elimination reaction of acyl chlorides

Following this decomposition pathway a very volatile and highly reactive ketene was produced, a species like that has never been detected in the condensed phase together with the cyanoacrylate but this no surprise.

At this point of the discussion very important is to observe that only the first hypothesis lead to the production of a methanesulfonyl ester, the other two paths produce a free alcohol instead. Then only the first hypothesis was in agreement with the side product methanesulfonyl HEMA discussed above. However when the TSIL reaction was performed with only MSA, without the Eaton's reagent (tandem approach), only free HEMA alcohol was detected. In other words the production of sulfonyl ester was subsequent to the release of alcohol and particular property of the Eaton's reagent. If

this argument is correct the methanesulfonyl HEMA ester had to be produced subsequent to the Mannich adduct decomposition and before the HEMA alcohol distillation. Then in consideration of the very active and non volatile sulfonyl-phosphonic anhydride present in the Eaton's reagent a very fast reaction in between the anhydride and the free alcohol can happen with the production of the sulfonyl ester (Figure 4.49).

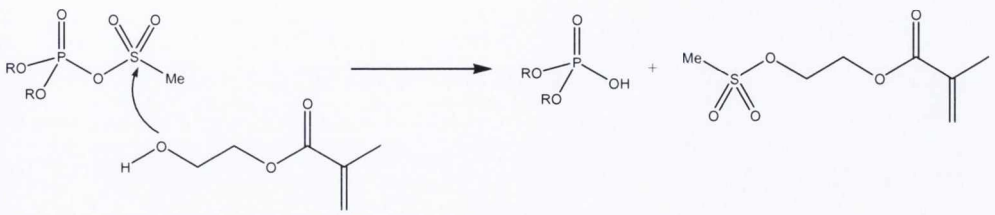


Figure 4.49. Proposed mechanism of sulfonyl ester formation from sulfonyl-phosphonic anhydride and free alcohol.

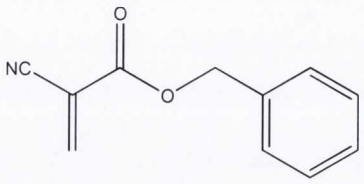
The production of free alcohol is a "pure" acid catalyzed reaction, when an excess of MSA is used a large production of free alcohol was observed, instead when the Eaton's reagent is used, only some sulfonyl ester was observed.

Furthermore it must be stressd that the three decomposition hypothesis are acid promoted and when a MSA/P_2O_5 blend was used the acidity strength of the system was lower. Moreover when the Eaton's reagent was used to neutralize the ionic liquid (for the TSIL reaction) no free MSA was present in the environment of reaction but only a weaker phosphoric acid was left.

A logic conclusion is that the decomposition of the Mannich adduct with production of free alcohol can happen also when the acidity of the system is lower and the alcohol produced is fully converted into the sulfonyl ester before his distillation.

This study thus highlights an intrinsic limitation of the TSIL approach for the production of cyanaocrylates. It is a weakness of the process and no one easy solution seems available, probably only a major change in the reaction/process approach could avoid this partial ester cleavage.

4.6 Synthesis of Benzyl Cyanoacrylate



The synthesis of a new very interesting monomer is faced by TSIL method. The literature[222, 223] reports the synthesis of the benzyl CAcet ester and its utilization in the Knöevenagel process for the production of the corresponding cyanoacrylate. This monomer could be very interesting industrially for its high refractive index (1.5078 n_D^{30}). Thus its reactivity can be useful to better understand the mechanism of the ester cleavage in the TSIL reaction. The synthesis of the benzyl cyanoacrylate monomer by Knöevenagel process is reported to give the product in 30% yield, it is furthermore interesting to see the potential of the TSIL method to improve this parameter also.

The synthesis of the CAcet reagent was performed, according with the literature,[222,223] by simple Fischer esterification of the cyanoacetic acid with benzyl alcohol catalysed by p-TSA. The CAcet was purified by regular vacuum distillation (b.p. 110 °C at 0.5mbar) and a colourless highly pure product (70% yield, 98% pure by GC) was obtained.

A regular TSIL reaction by mini-SPE equipment was performed (1st TSIL attempt) and a blend of products was collected (60% yield, b.p. 105 °C at 0.5 mbar). This preliminary result (Figure 4.50) was very promising, already twice the yield reported in literature was obtained and the experience indicates that large SPE equipment pushes yields higher still.

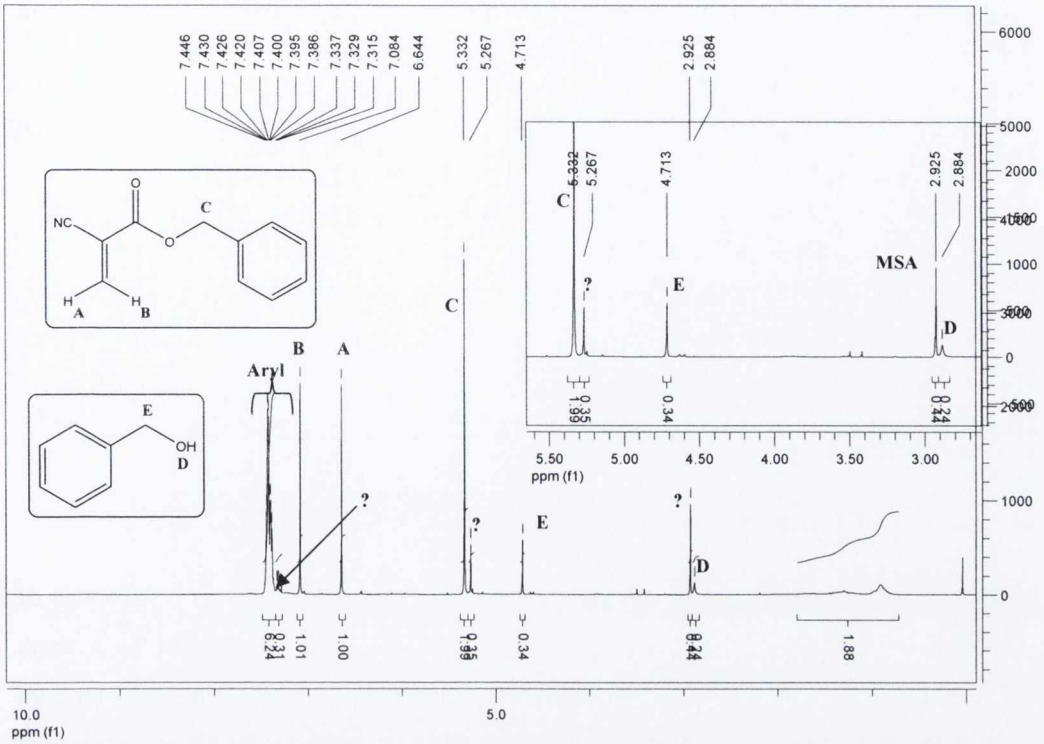


Figure 4.50. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of benzyl CA crude from 1st TSIL reaction attempt

The benzyl cyanoacrylate was clearly identified but extra signals were also observed. A small amount of benzyl alcohol (~15-20 mol %) was clearly present (δ_H CH_2, 4.71 ppm, also δ_C CH_2, 64.83 ppm) together with some hydrocarbon side-product (δ 0.8–2 ppm region from high temperature decomposition of the IL) and two unknown new signals at δ 2.92 and 5.26 ppm. Also the peak integrations were interesting. In fact the signal at δ 2.92 ppm was almost one third bigger than the one at δ 5.26 ppm. These lead to consider the hypothesis of new methanesulfonyl ester production. Moreover the broad signal at δ 2.88 ppm might be correlated to the proton of benzyl alcohol. The consistent release of benzyl alcohol is strange because no water is present in the environment of reaction so that hydrolysis is not possible.

Nevertheless the CAcet under account has a unique structure because of the benzyl ester group. The basic hydrolysis of ester groups is universally recognized to undergo through an Acyl-Oxygen Fission, this reaction is base catalyzed and the mechanism has been proven from many authors[224] .

The studies performed show that the base first forms a covalent bond with the esters resulting in the formation of a tetrahedral intermediate. The elimination of the alkoxide

group and the proton transfer from the carboxylic acid drives the equilibrium completely to the right.

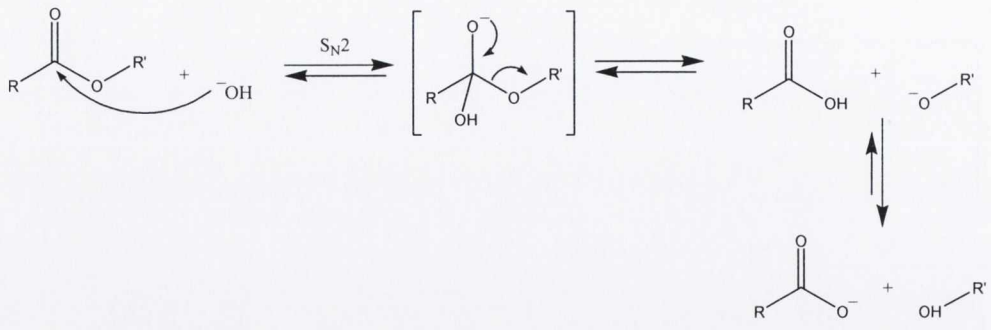


Figure 4.51. Ester hydrolysis mechanism by Acyl-Oxygen Fission

Nevertheless, as previously mentioned, in the "TSIL Approach" we are in absence of nucleophilic species, or only methanesulfonic acid could be considered as a weak nucleophile at very high temperature. Moreover the production of a consistent amount of free alcohol (e.g. 15-20 %, observed in the previous attempt) needs an equivalent amount of nucleophile, instead just 0.03 eq of free MSA are present in the TSIL environment of reaction. The only possibility to justify this approach it would be a catalytic reaction with regeneration of the sulfonic acid.

In the light of the peculiar benzylCAcet chemistry also another cleavage mechanism is possible. In fact the Alkyl-Oxygen Fission hydrolysis (Figure 4.52) is possible under acidic catalysis when esters, which lead to the formation of stable carbocation, are used[225] .

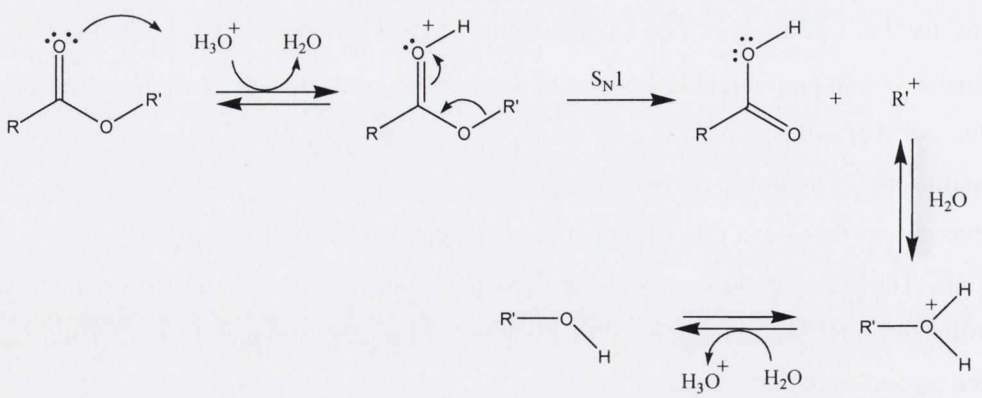


Figure 4.52. Ester hydrolysis mechanism by Alkyl-Oxygen Fission

Only tert-butyl esters or benzyl esters can undergo this reaction, the production of benzyl methanesulfonic ester could be obtained following this route in consideration of MSA as catalyst and nucleophile of reaction.

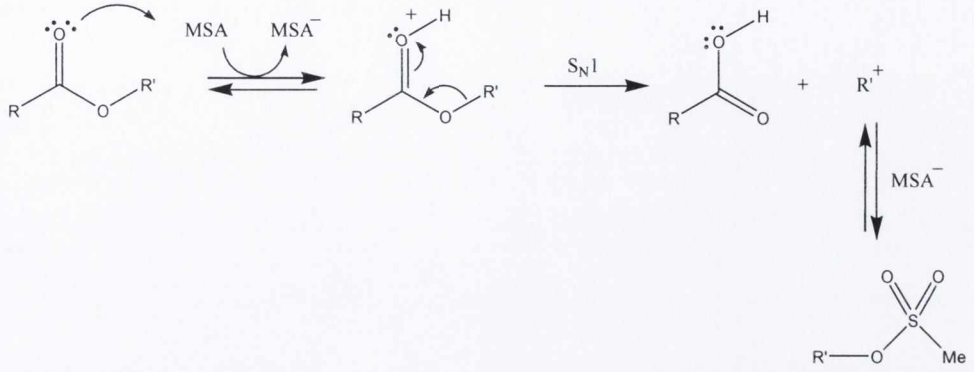


Figure 4.53. Methanesulfonyl ester production by Alkyl-Oxygen Fission mechanism

If the reaction described happens during the TSIL reaction, a methanesulfonyl ester could be produced, nevertheless the final sulfonic ester has to be present only in smaller percentages than stoichiometric with the "free" MSA of reaction.

The need of a full understanding of the side product lead us to an independent synthesis and characterization of methanesulfonyl benzyl ester. A modified literature procedure[221] was followed.

From the direct comparison of the side product present in the crude of 1st TSIL attempt' with the independently synthesized compound it is evident that methanesulfonyl benzyl ester is present in consistent amount. In particular both ^{1}H NMR and ^{13}C NMR spectra give an unequivocal confirmation.

The TSIL reaction was repeated (2nd TSIL attempt) using the Eaton's reagent (Tandem TSIL). The reaction was performed by regular operative conditions and by means of a mini-SPE equipment. The product began to distil more slowly than before (1st TSIL attempt), lower amount of product was collected (~ 40% yield only) and the collected product was richer in side-products; the proton spectrum is reported in Figure 4.54.

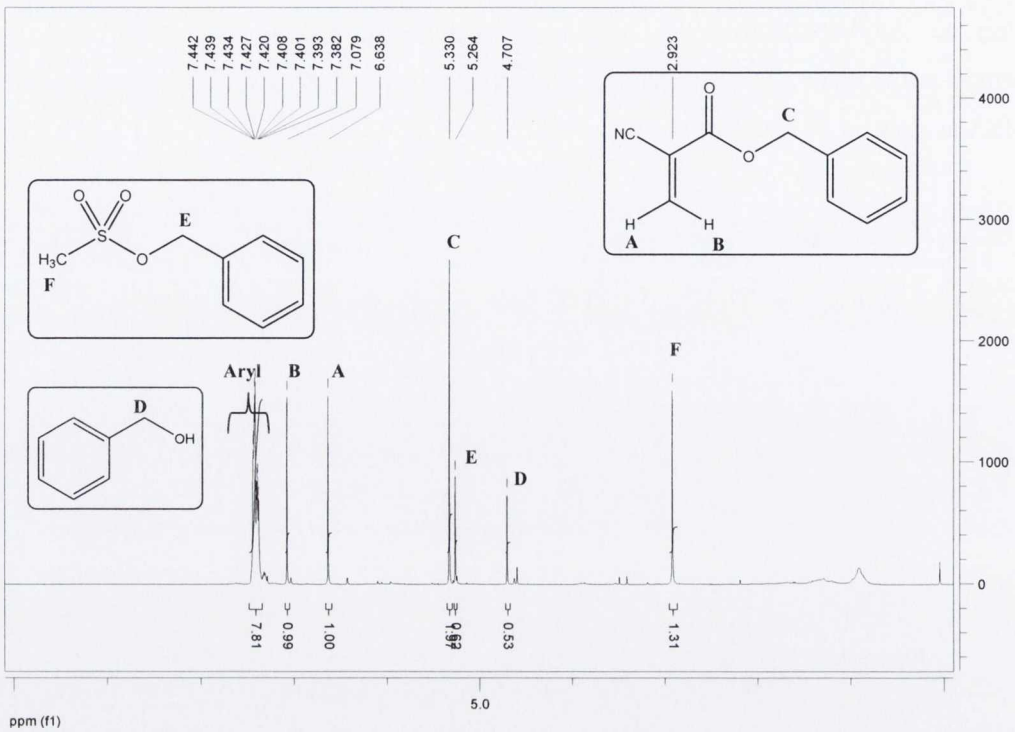


Figure 4.54. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of benzyl cyanoacrylate crude from 2nd TSIL reaction attempt

Benzyl cyanoacrylate is clearly visible (δ 5.33, s, 2H; 6.64, s, 1H; 7.08 ppm, s, 1H), the benzyl alcohol is still present and in slightly larger amount (δ_H 4.71 ppm; δ_C 64.83 ppm), again the methanesulfonyl benzyl ester was identified to be present too and in larger amounts than before.

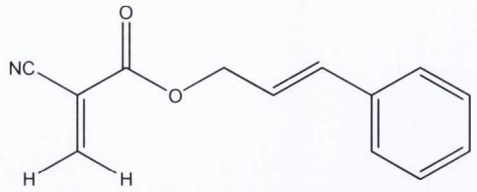
GC-MS analysis was performed also and three main peaks where observed; 2.24 min elution time was identified the benzyl alcohol, 5.04 min elution time the methanesulfonyl benzyl ester and 5.80 min elution time the Benzyl cyanoacrylate.

Conclusion

The methanesulfonyl ester derivative is for the first time observed in mixture with the cyanoacrylate (1st TSIL attempt) even without the use of Eaton's reagent. This result is unique and probably it is due to a specific property of the benzyl ester. Larger amount of sulfonyl ester are present when Eaton's reagent is used, than the final concentration of this side-product is probably result of two different contributions (two distinct reaction pathways), the first can be from an alkyl-oxygen fission mechanism, the second from an alcohol-trap effect of the Eaton's reagent (as previously discuss).

4.7 Synthesis of Cinnamyl cyanoacrylate

(3-Phenyl-2-allyl CA)



The synthesis of cinnamyl cyanoacrylate has never been reported in the open literature before. The synthesis of cinnamyl CAcet has been reported a few times instead[226]. The structure of this cyanoacrylate is of interest because of the possibility to perform various secondary polymerizations for example nucleophilic cure of the cyanoacrylic function plus radical/cationic polymerization of the styrene function.

The synthesis of cinnamyl CAcet was first attempted by Fischer esterification procedure. Thus cyanoacetic acid (1 eq) and cinnamyl alcohol (1.2 eq) were mixed together with 0.01 eq of sulphuric acid, 0.01 eq of DBHT and heptane. The water was removed by azeotropic distillation and the collection of water began almost immediately, unfortunately after 1h it suddenly stopped. Moreover the reaction mixture showed an increase of viscosity than a cationic polymerization of the styrene function was supposed. In order to overcome this problem the reaction was repeated without the sulphuric acid addition. The cyanoacetic acid is a carboxylic acid with an unusual high acidity strength (pKa = 2.43), then the esterification reaction could be self catalyzed, obviously the rate of reaction is expected to be lower but a considerable production of product should be obtained after longer reaction time. Then 1 eq of cyanoacetic acid was mixed with 1.2 eq of cinnamyl alcohol, 0.01 eq of DBHT and the reaction was refluxed overnight in heptane. After 12 hours only a small amount of water was condensed into the Dean Stark trap and the viscosity of the crude of reaction was definitely higher (like in the previous attempt), in conclusion the Fischer esterification approach was left behind.

A new attempt was performed by trans-esterification, than ethyl CAcet (1.1 eq) was mixed with cinnamyl alcohol (1 eq), 0.001 eq of DBHT and toluene; the solvent was distilled off and the Titanium tetrabutoxide added (0.0002 eq). The reaction was stirred

for 5 h at 110 °C and the ethanol removed by distillation. The product was obtained pure after vacuum distillation (50% yield).

This CAcet was subjected to a regular TSIL reaction performed by mini-SPE equipment, only one parameter was modified, the vacuum was applied immediately in consideration of the very high boiling point of the target molecule.
Unfortunately no product was collected in the distilled fraction, the crude quickly changed colour, at high temperature was still liquid and easily mixable by magnetic stirring but nothing was distilling even heating at 190 °C and applying 0.4 mbar vacuum.

Conclusions

In a relatively short study, an entirely new approach has clearly demonstrated an alternative route to the preparation and isolation of reactive monomers.

A proof of concept was demonstrated studying a Mannich reaction in solution which was transferred to a task specific ionic liquid technology. Thus a new very promising method (TSIL Approach) was defined. The reactivity and the thermal stability of a new class of inexpensive ionic liquid was studied and applied to the successful synthesis of known cyanoacrylates (CAs).

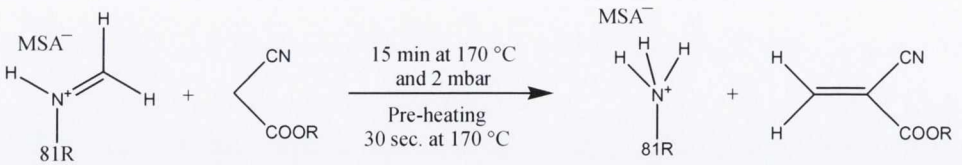
Thus the focus of the research was centered on the synthesis of CAs bearing specific functional groups such as CA-methacrylate molecular hybrids.

The scale-up of the reaction was realized, in particular the continuous flow process highlighted the great potentiality of the current work. The chemical process gave high yield and purity in kilos scale production and showed a broad applicability.

For the next it would be important to adjust the IL reactivity and to tune the ionic structure of the iminium salt to obtained an optimal process.
A further study of the side products will be important for a better understanding of the reaction mechanism.

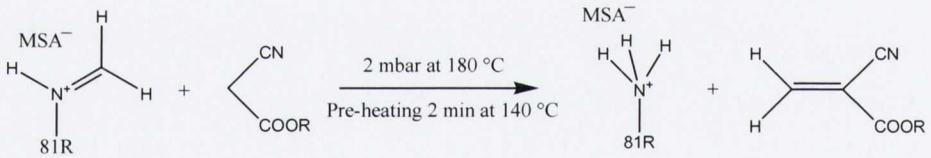
4.8 Experimental

General procedure for CAs production by mini-SPE



CAcet (1 eq, 20 mmol) was added to a mixture of 81R imine (1 eq, 20 mmol, 3.94 g) and MSA (1.05 eq, 21 mmol, 2.02 g). The reactant solution was heated at 170 °C and after 30 sec the vacuum was applied (2 mbar). After 15 min the distillation was stopped and the fractions were collected and analyzed by ^{1}H NMR.

General procedure for CAs production by SPE equipment

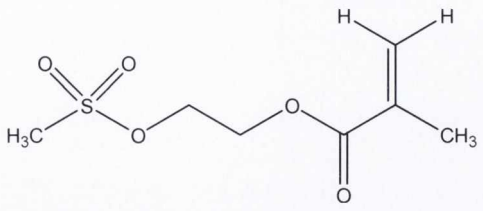


MSA (60.48 g, 0.63 mol, 1.05 eq) was transferred in a three neck round bottom flask equipped with mechanical stirrer and dropping funnel. 81R imine (118.20 g, 0.60 mol, 1.00 eq) was dropwise added in 30 min, the temperature was kept below 20 °C by means of an ice bath. CAcet (0.60 mol, 1.00 eq) was added and the solution stirred few minutes to homogeneous. The reagent mixture was transferred in the feeding vessel of the SPE equipment and the TSIL reaction started.

Pre-heater set-up: 140 °C, reagent mixture flow rate 5 ml/min, 10 ml volume heated (only one stage of the pre-heater was heated).
SPE set-up: 180 °C, 2 mbar vacuum, rotor rotation speed 300 rpm, condenser 5 °C.

Synthesis of HEMA methanesulfonate

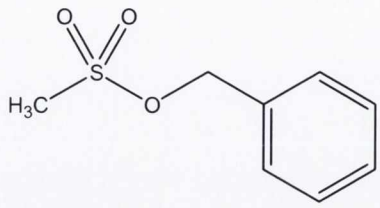
(2-methacryl-ethyl-methanesulfonate)



HEMA (1 eq, 2.6 g) was diluted in dry dichloromethane (30 ml), the solution was refrigerated at 0 °C by means of an ice bath, and triethyl amine (1.2 eq, 2,43 g) was drop-wise added. The methanesulfonyl chloride (1.1eq, 2.51 g) was then slowly drop-wise added. The reaction was performed for 30 min at 0 °C then left to reach 25 °C, after 1h of total reaction time the organic phase was washed three times with water, dried by sodium sulphate and the solvent removed under reduced pressure. The crude product was collect as a light yellow oil (3.7 g, 89% yield);

δ_H (400 MHz, $CDCl_3$): 6.17 (s, 1H, CH); 5.64 (s, 1H, CH); 4.46 (d.d., 2H, CH2OOC), 4.42 (d.d., 2H, CH_2OSO_2), 3.06 (s, 2H, CH_3SO_3), 1.96 ppm (s, 3H, CH_3CCH_2);
δ_C (100 MHz, $CDCl_3$): 17.81 (CH_3CCH_2), 37.29 (CH_3SO_3), 61.65 (CH_2OOC), 66.82 (CH_2OSO_2), 126.17 (CH_2=), 135.16 (C=), 116.42 ppm (COO);
AT-IR (Neat): 3023 w, 2962 w, 2937 w, 1716 s, 1642 m, 1450 m, 1409 w, 1350 s, 1319 s, 1296 s, 1157 s, 1058 m, 1020 m, 953 s, 917 s, 794 s, 731 m, 653 m, 526 s, 446 m (cm^{-1});
GC-MS; (EI) m/z (%) 39 (25), 41 (60), 68 (45), 69 (100), 79 (30), 112 (70), 113 (10).

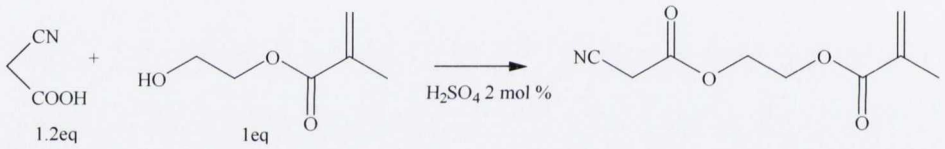
Synthesis of benzyl methanesulfonate[227]



Benzyl methanesulfonate was produced in agreement with the procedure of HEMA methanesulfonate synthesis. The crude product was a light yellow oil (3.0 g, 74% yield).

Synthesis of "HEMA" CAcet

(2-methacryl-ethyl-CAcet)



A 1L, three-neck round-bottomed flask is fitted with a Dean-Stark apparatus and with a capillary tube. The HEMA (214.6 g, 1.65 mol, 1.0 eq.), the cyanoacetic acid (168 g, 1.98 mol, 1.2 eq.), Vitamin E (7.3 g, 1 mol %), and 2,6-ditertbutyl-4-methylphenol (1.65 g, 0.5 mol %) were suspended in heptane (130 g) and heated at 90 °C under stirring until an homogeneous solution was obtained. A catalytic amount of sulfuric acid (3.2 g, 2 mol %) was added and the solution was refluxed (oil bath at 125 °C) for 3 h; in the meantime air was bubbled (10-15 ml/min) in the crude trough the capillary.

The heating was stopped when the reaction was complete and the theoretical amount of water was collected in the Dean-Stark trap (~30 g). The mixture was allowed to reach room temperature, then the heptane was removed by reduced pressure and the organic phase extract with 130 g of deionised water. The layers were vigorously shaken and separated; the organic layer was washed a second time with brine (130 g) and finally dry by Na_2SO_4. The product obtained was a yellow oil (280 g , ~85 % yield).

No polymer was detected during the work-up, either FT-IR and NMR spectrum of the crude oil showed over 95% purity.

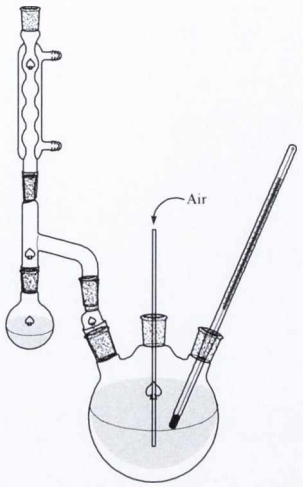


Figure 4.55. Set-up of the equipment of reaction

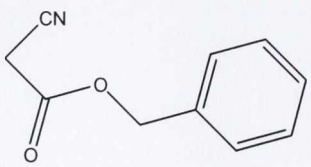
δ_H (400 MHz, $CDCl_3$):6.14 (s, 1H, CH), 5.63 (s, 1H, CH), 4.47 (t, 2H, CH_2OOCCH_2), 4.40 (t, 2H, $CH_2OOCCCH_3$), 3,52 (s, 2H, CH_2CN), 1.95 ppm (s, 3H, CH_3);

δ_C (100 MHz, $CDCl_3$): 17.80 (CH_3), 24.69 (CH_2CN), 61.03 (CH_2OOCC=), 68.54 ($CH2COOCH_2$), 112.97 (CN), 125.97 (CH_2=), 135.25 (C=), 162.90 (COO), 166.54 ppm (=CCOO);

AT-IR (Neat): 2970 w, 2938 w, 2267 w, 1760 m, 1716 s, 1634 w, 1511 w, 1454 w, 1401 w, 1368 w, 1323 m, 1299 m, 1156 s, 1033 m, 947 m, 820 w, 735 w (cm^{-1});

GC-MS; (EI) m/z (%): 113 (10), 112 (90), 110 (5), 87 (5), 96 (4), 70 (8), 69 (85), 68 (100), 45 (10), 41 (70), 80 (20), 39 (30).

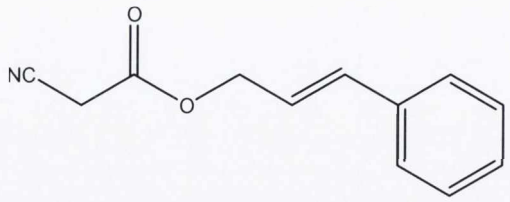
Synthesis of benzyl CAcet[228]



The CAcet was synthesized following the general acid esterification procedure in heptane solution (See Experimental section Chapter 3).

Synthesis of cinnamyl CAcet[229]

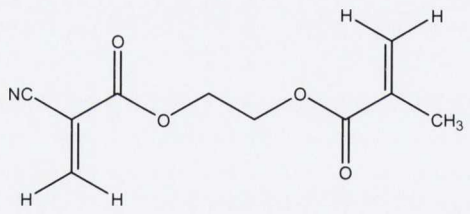
(3-Phenyl-2-allyl CAcet)



In a 100 ml flask were placed cinnamyl alcohol (26.8 g, 98% purity), ethyl CAcet (24.86 g) and toluene (20 g), the reaction was heated at 130 °C and the solvent removed. Than the $Ti(O\text{-}Bu)_4$ (0.14 g) and DBHT (0.43 g). The reaction mixture was heated in the oil bath (110 °C) and the volatile methanol was removed by distillation. After 5 hours of reaction, to the reaction mixture was added ethyl acetate (40 ml), water (40 ml) and extracted three times, dried by sodium sulphate and the solvent removed under reduced pressure. The product was distilled under vacuum to yield cinnamyl CAcet (b.p.140 °C at 0.3 mbar, 20 g, 50 % yield, 98% pure by GC).

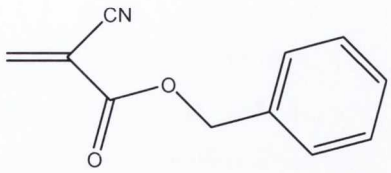
HEMA-CA[203]

(2-methacryl-ethyl-CA)



Colourless oil, bp 115 °C at 0.5 mbar.

Benzyl CA[222,223]



Colourless oil, bp 120 °C at 0.5 mbar.