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# Synthesis of 6-nitro-1,2,3,4-tetrahydroquinoline: an experimental and theoretical study of regioselective nitration

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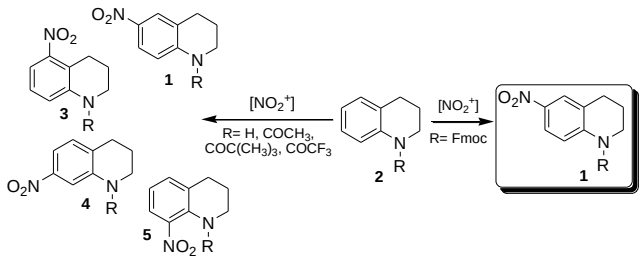


**ABSTRACT**

A revision of the literature on the nitration of tetrahydroquinolines yielded a number of inconsistencies. Thus, we have carried out a thorough study on the nitration of tetrahydroquinoline and some of its *N*-protected derivatives both experimentally and at theoretical level. The favoured position for nitration of tetrahydroquinoline depends on the protonation state of the ring amine group. In general, nitration is carried out in acidic conditions and, thus, tetrahydroquinoline would be *N*-protonated. However, if the tetrahydroquinoline amino group is protected, the neutral system will be the one undergoing nitration. Different protecting groups were explored varying, not only electronic and steric effects, but also deprotection conditions. Additionally, different reaction reagents and conditions were investigated. From this study we were able to achieve total regioselectivity for nitration at the 6-position. A very detailed NMR study was required to unequivocally characterise the four nitro isomers and, hence, mono and bi-dimensional $^{1}H$ and $^{13}C$ NMR studies were carried out. In parallel, a computational study has been performed that is in agreement with the experimental results obtained. With this purpose, all the σ-complexes of the four nitro isomers neutral and *N*-protonated were optimized both in gas phase and in water condensed phase by using the B3LYP/6-31++G** level of computation.

## INTRODUCTION

In the context of our recent research in medicinal chemistry we were interested to find an efficient method for preparing 6-nitro-1,2,3,4-tetrahydroquinoline (**1a**, Figure 1). The most obvious procedure for obtaining **1a** is the direct nitration of tetrahydroquinoline (THQ, **2a** in Figure 1). Moreover, the mechanism of nitration of aryl compounds by means of the electrophilic aromatic substitution (EAS) has been one of the most widely studied organic reactions.[1] The EAS reactivity and selectivity have been discussed in depth for a number of aromatic compounds. However, when we considered the synthesis of **1a**, we found very few examples of the direct nitration of **2** in a systematic way.

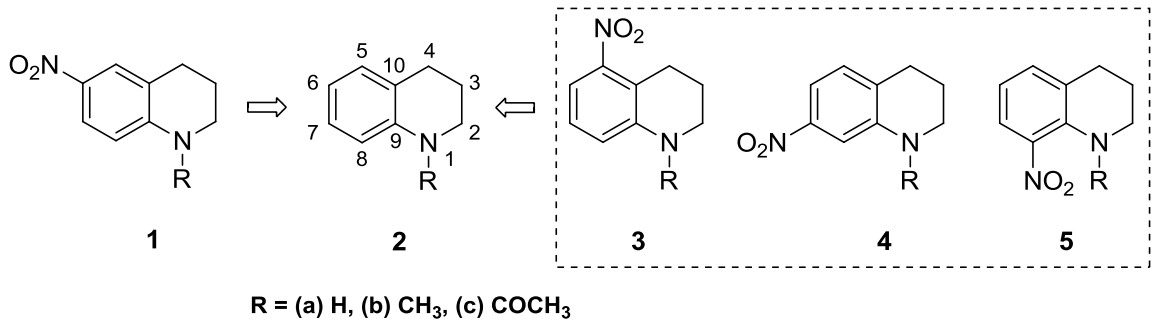



**FIGURE 1.** Structure of THQ (**2**) and THQ-nitro (**1**, **3**, **4** and **5**) derivatives.

Taking into account the relatively small number of articles dealing with this reaction we have summarized in Table 1 the most relevant references found in the literature concerning to the nitration of compound **2**. Thus, the first references to THQ-nitro derivatives are found in the late twentieth century, with the work of Hoffman and Königs[2] and subsequently Stoermer.[3] Few years later v. Braun, Grabowski and Rawicz,[4] reported that ring substitution in **2a**, in the presence of nitric acid, occurs exclusively at the position 7 of the THQ ring yielding the 7-nitro derivative (**4a**, Figure 1).

**TABLE 1.** Relevant literature concerning to nitration of THQ derivatives. Conditions, products' yields and melting points are shown for each publication.

| Entry | Authors | Year | R | Conditions | Products of Nitration[a] |
|---|---|---|---|---|---|
| **1** | Braun, *et al.*[4] | 1913 | H | $HNO_3$; $H_2SO_4$; 0ºC | 7-Nitro-THQ (mp 90 °C)[b] |
| **2** | Kulka, *et al.*[5] | 1952 | H | $HNO_3$; $H_2SO_4$; 0ºC | 7-Nitro-THQ 65% (mp 63 °C) |
| **3** | Utley, *et al.*[8] | 1972 | H | $HNO_3$; $H_2SO_4$; 0ºC; 3h | 7-Nitro-THQ 58% (mp 61 °C)<br>5-NitroTHQ 1.1% (mp 83 °C)[c] |
| **4** | Amit, *et al.*[9] | 1976 | H | $HNO_3$; $H_2SO_4$; 0ºC; 3h | 7-Nitro-THQ 51% (mp 63°C)<br>5-Nitro-THQ 7.5% (mp 81 °C) |
| **5** | Utley, *et al.*[8] | 1972 | $CH_3$ | $KNO_3$; $H_2SO_4$; 0ºC | *N*-Methyl-6-nitro-THQ 23% (mp 89°C)<br>*N*-Methyl-7-nitro-THQ 71% (mp 92°C) |
| **6** | Kulka, *et al.*[5] | 1952 | $COCH_3$ | $KNO_3$; $H_2SO_4$; 0ºC; 2h 30m | 6-Nitro-THQ 37% (mp 164 °C)<br>7-Nitro-THQ 20% (mp 63 °C) |
| **7** | Richardson, *et al.*[6] | 1960 | $COCH_3$ | $HNO_3$; $Ac_2O$; ice bath; 30m | 5-Nitro-THQ 89% (mp 83 °C)[c] |
| **8** | Mndzhoyan, *et al.*[10] | 1964 | $COCH_3$ | $HNO_3$; $Ac_2O$; 0ºC | 6-Nitro-THQ 50% (mp 162 °C) |
| **9** | Utley, *et al.*[8] | 1972 | $COCH_3$ | HAc; $HNO_3$; $H_2SO_4$; 10ºC/rt; 1h | 6-Nitro-THQ 45% (mp 162 °C)<br>8-Nitro-THQ 2.5% (mp 72 °C)[d] |
| **10** | Amit, *et al.*[9] | 1976 | $COCH_3$ | $HNO_3$; $Ac_2O$; 0ºC; 1h | 6-Nitro-THQ 80% (mp 162 °C)<br>8-Nitro-THQ 16% (mp 71 °C) |

a) In the case of acetyl derivatives, products obtained after hydrolysis step.
b) A correction on the melting point previously described for this compound was performed (entrie 2).
c) This compound was incorrectly referred in this paper as 8-nitro-THQ
d) This compound was incorrectly referred in this paper as 5-nitro-THQ

In 1952, Kulka and Manske[5] reproduced the nitration of **2a** as described by Braun *et al.* ($HNO_3/H_2SO_4$ at 0 ºC ) yielding 65% of 7-nitro-THQ (**4a**) and introducing a correction on the melting point previously described for this compound (from 90 ºC to 63 ºC). They also studied the nitration of the *N*-acetyl-THQ (**2c**, Figure 1) with potassium nitrate in concentrated sulphuric acid obtaining, after hydrolysis, a mixture of 6-nitro-THQ (**3a**) and 7-nitro-THQ (**4a**) approximately in a 2:1 ratio. The authors were surprised to obtain the

7-nitro derivative as one of the nitration products of 1-acteyl-1,2,3,4-tetrahydroquinoline since it had been reported that the treatment of this 1-acteyl-THQ with excess nitrous acid followed by hydrolysis produced a mixture of 6- and 8-nitro-1,2,3,4-tetrahydroquinoline.[3] Nitration of the acetyl derivative **2c**, was performed again by Richardson and Amstutz in 1960,[6] using a mixture of nitric acid in acetic anhydride, and getting, surprisingly, a completely different result. They reported obtaining, after hydrolysis, the 8-nitro-THQ (**5a**) in 89% yield, without any evidence of 6- or 7-nitro-THQ as it had been previously stated. However, this result was refuted later.

Between 1970 and 1973, Levkoeva and co. published a series of four articles about *Quinoline Derivatives* including the preparation of some of the nitro compounds.[7] In 1972, Utley and Vaughan studied the nitration of **2** in a more systematic way.[8] In their work, entitled *Substituent Effects in the EAS of Deactivated Systems*, they specifically studied the nitration of some *N*-methyl-THQ derivatives. They observed that by using $KNO_3/H_2SO_4$ 82%, the tertiary amino group, even though in an equilibrium between the *free base* (neutral or unprotonated form) and the *conjugated acid* (protonated form), was clearly shifted to the second one (see Figure 2). Under these conditions, *N*-methyl-THQ (**2b**) was nitrated on position 7 obtaining *N*-methyl-7-nitro-THQ (**4b**) in 71% yield and a small but significant fraction of *N*-methyl-6-nitro-THQ (**1b**) (23%). In this article, it is also reported the nitration of the unsubstituted THQ (**2a**) in standard conditions ($HNO_3/H_2SO_4$) giving, as expected, **4a** (58%) and a second product in a very low yield identified by the authors as "*8-nitro-THQ"* (1.1%). In addition, Utley and Vaughan also reported the nitration of the *N*-acetyl-THQ (**2c**) in a solution of glacial acetic acid in $H_2SO_4$ (70%) by addition of a mixture of $HNO_3/H_2SO_4$ (98%) obtaining after hydrolysis the expected 6-nitro-THQ (**1a**) (45%) and a small fraction of

a secondary product identified as "*5-nitro-THQ"* (2.5%). As shown below, the structures of these two minority fractions ("*8-nitro-THQ"* and "*5-nitro-THQ"*) were assigned incorrectly.

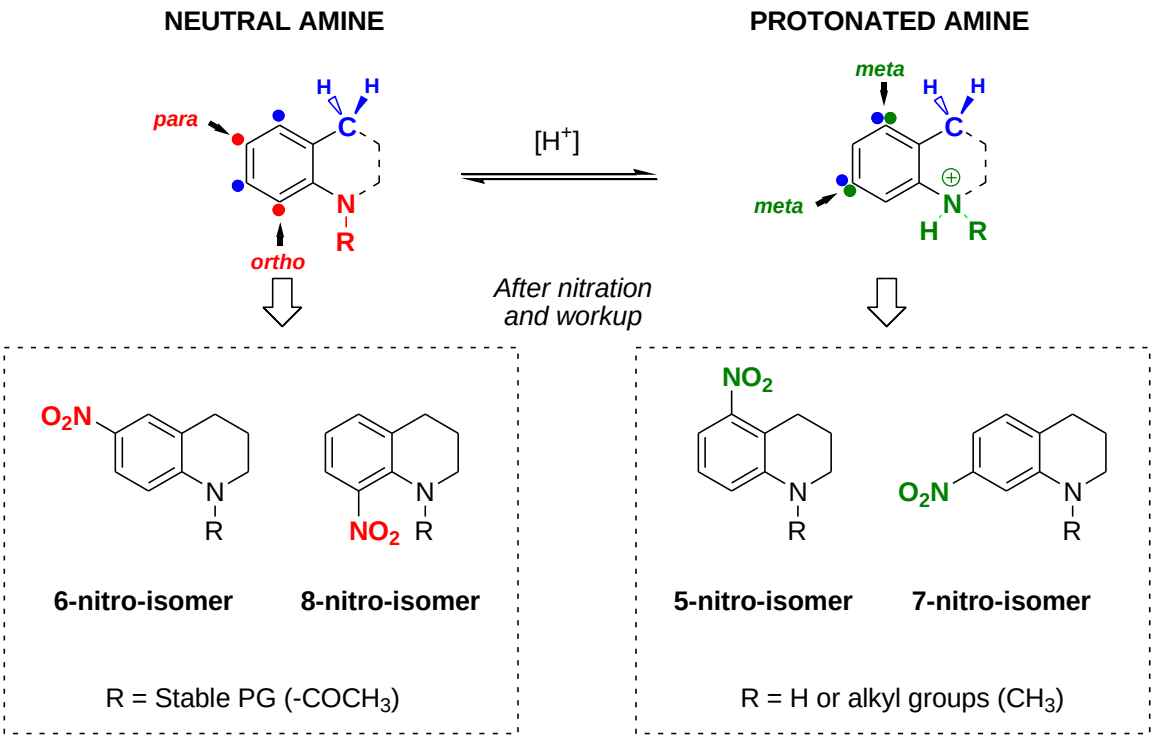



**FIGURE 2.** Selectivity criteria for THQ nitration depending on the *N*-protonation. Blue, red and green points indicate the orientation exerted by alkyl, neutral amine and protonated amine respectively.

In 1976, Amit, Ben-Efrein and Patchornick,[9] realizing the discrepancies reported on the nitration of THQ, stated in their article that: "*There has been confusion in the literature for a long time with respect to the correct structural assignments of 8-nitro-THQ and its 5-nitro-isomer*". To clarify this, they prepared the four nitro isomers (5-, 6-, 7- and 8-nitro-THQs) and reported their identification by spectroscopic properties ($^1$H NMR –90 MHz- chemical shifts experimental and calculated from substituent contribution and coupling constants). Firstly, they repeated the procedure described by Richardson and Amstutz in order to prepare 8-nitro-THQ (**5a**) from *N*-acetyl-THQ and they noted that: "*However, on applying this procedure*

*only 6-nitro-isomer was isolated, as also reported by other workers*[10] *who used the same method. Closer examination of the reaction mixture, however showed that it consisted of two compounds, which after acidic hydrolysis were separated ... to afford 6-nitro-isomer (80%) and a second nitro-THQ, m. p. 71 ºC, in 16% yield ...*". Then, they performed the nitration of the unsubstituted THQ in concentrated sulphuric acid obtaining **4a** (51%), as well as a second isomer melting at 83 ºC (7.5%). They characterised all isomers obtained by $^{1}$H NMR (90 MHz) confirming that the secondary product of the nitration of THQ and melting point 83 ºC was the 5-nitro-THQ (**3a**), while the secondary product of nitration of *N*-acetyl-THQ and melting point 71 ºC (after hydrolysis) corresponded to the 8-nitro-THQ (**5a**); therefore, the structural assignments previously reported by Utley and Vaughan were reversed.

Since 1980´s, we have not found more significant documentation about the preparation of our target compound **1a** by nitration. However, other methodologies using more specific conditions, as catalyzed regio- and chemoselective transfer hydrogenation of quinolines, have been employed for the preparation of this compound.[11]

As it has been just discussed, among the reviewed publications there have been contradictions concerning the regioselectivity in the nitration of the THQ (**2a**) or its *N*-acetyl-derivative (**2c**), as well as a lack of discussion of other relevant aspects as the poly-nitration problem or the use of general amino protecting groups. In view of this, we decided not only to attempt the selective synthesis of 6-nitro-THQ (**1a**), but also to carry out a systematic study of the nitration of THQ and some *N*-protected-THQ derivatives followed by a careful NMR characterization of the nitro compounds obtained. Thus, the nitration reaction was studied in function of: properties of protecting groups, time, temperature and concentration of the reactants. A thorough NMR study was carried out to provide with new insights and to

complete previous descriptions of the spectroscopic properties of the nitro-THQ series. In parallel, theoretical calculations at the DFT/B3LYP/6–31++G** level were performed to provide a better understanding of the selectivity of the process.

## Results and Discussion

### *Experimental study of nitration of THQ*

Figure 2 presents a general scheme of the selectivity in the nitration of THQ and its *N*-substituted derivatives (based on the CIP criteria, from now on we are going to refer the orientation –*ortho*, *meta* or *para*– with respect to the carbon substituted by the amine group). In an initial approach, the 1,2 position of the two substituents in THQ, alkyl chain (blue) and amino group (red), produce an antagonistic or non-cooperative effect on the orientation. Both groups are *ortho*-/*para*- activating and direct the nitration to alternate positions, though the amine effect will normally exert the determining influence (Figure 2). However, nitration reactions require acidic media and then, protonation of the amine plays a definitive roll in the final selectivity, since, as already discussed, the amine, when protonated, reverses its orientation effect resulting in a *meta* director group (green).

Thus, two main aspects must be considered: *(i)* the basicity of the amine group as a function of the *N*-substituent determining the ratio of protonated/unprotonated forms, and *(ii)* the stability of the *N*-substituting group. Hence, in acidic conditions, THQ or its *N*-alkylated derivatives shift the equilibrium to the protonated form,[8] and, as mentioned, the expected selectivity should be on the *meta*- positions producing the 5- and/or 7-nitro derivatives (**3** and **4**, respectively). Moreover, the *N*-substitution by a CO linked protective group reduces the basicity of the amine avoiding protonation, and thus, in the nitration of *N*-protected-THQ, the

original effect of the amine towards the *ortho*- and *para*- positions is kept and, after hydrolysis, the 6- and/or 8-nitro-derivatives will be obtained. However, it should be considered that, in case of instability of the protective group in acid media, the selectivity would be very low due to the coexistence of several species: protected, non-protected (neutral) and non-protected (protonated), which would probably lead to a mixture of the four nitro isomers.

First, direct nitration of the deprotected THQ using $KNO_3$ and $H_2SO_4$ standard conditions was carried out (Table 2, entries 1 and 2). In our hands, this nitration yielded the 7-nitro-THQ (**4a**) in 73%, as well as the 5-nitro-THQ (**3a**) in 18% in good agreement with the literature (Table 1, entries: 2-5). Only when the reaction was carried out in larger scale, traces of the 6-nitro-THQ (**1a**) were detected by NMR and mass spectral analysis, possibly corresponding to the nitration of a small fraction of unprotonated THQ present in the equilibrium.

As explained before, the synthesis of our target compound (6-nitro-THQ, **1a**) by direct nitration of THQ, requires the protection of the amino group. Nitration of *N*-acetyl-THQ (**2c**) had been previously performed and the best conditions in terms of selectivity consisted in the treatment of *N*-acetyl-THQ with nitric acid (1.48 equiv.) in acetic anhydride obtaining a mixture of 6- and 8-nitro-derivative in a 80:20 ratio.[9] Using strictly the same conditions, protection with acetyl group and then reaction with $HNO_3/Ac_2O$, the nitration yielded a mixture of 6- and 8-nitro isomers (**1a** and **5a**) in a 50:50 ratio, being the 6-nitro isomer selectivity well below that described by Amit *et al.* The procedure was repeated four times (Table 2, entries 3-6) with slight modifications in the reaction time and proportion of the reactants, but the isomeric ratio kept unchanged. Hence, different protecting groups (pivaloyl, trifuoroacetyl and Fmoc) were considered to improve the selectivity of the reaction (Scheme

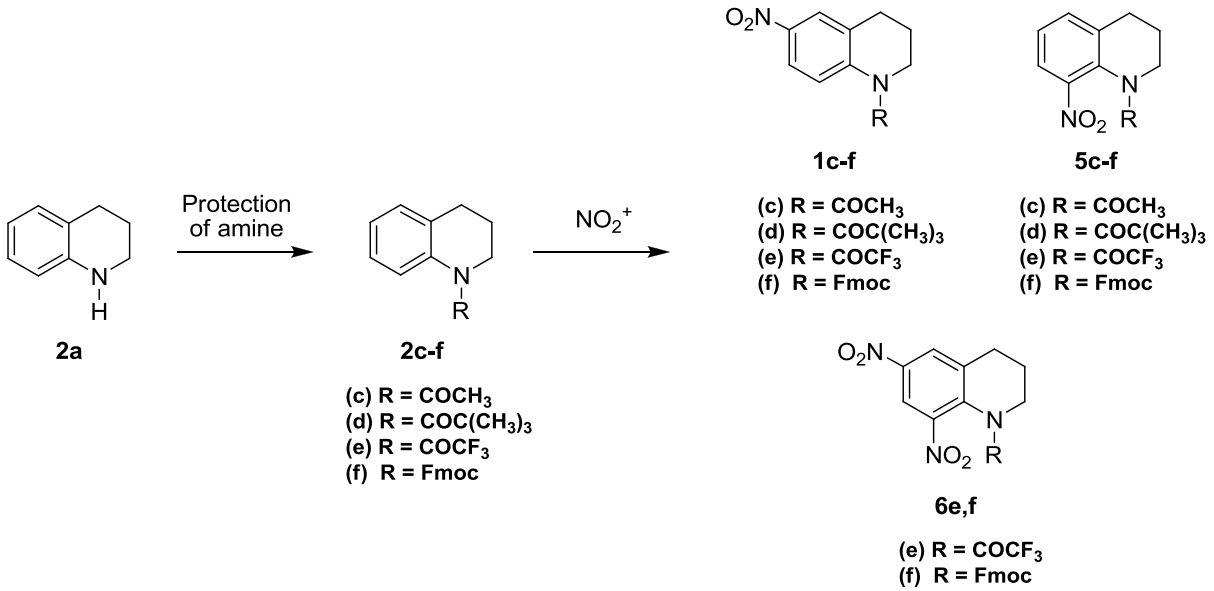
1). The use of other common protecting group such as Boc was discarded due to its low stability in acidic conditions.

**TABLE 2.** Selectivity obtained in different nitration reactions of THQ and *N*-protected-THQ. The ratio of products was determined by $^1$H NMR analysis.

| Entry | R | Reagents | Temp. | t | SM[a] | 5-nitro | 6-nitro | 7-nitro | 8-nitro | 6,8-dinitro |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | H | $KNO_3/H_2SO_4$ | 0ºC, rt | 1h | 9%[b] | 18%[b] | – | 73%[b] | – | – |
| **2** | H | $KNO_3/H_2SO_4$ | 0ºC, rt | 1h | 36%[b] | 11%[b] | 5%[b] | 48%[b] | – | – |
| **3** | $COCH_3$ | 1.5 eq $HNO_3/Ac_2O$ | –10ºC, rt | 24h | – | – | 50% | – | 50% | – |
| **4** | $COCH_3$ | 1.5 eq $HNO_3/Ac_2O$ | –10ºC | 4h | – | – | 50% | – | 50% | – |
| **5** | $COCH_3$ | 1.2 eq $HNO_3/Ac_2O$ | –10ºC, rt | 24h | – | – | 50% | – | 50% | – |
| **6** | $COCH_3$ | 1.2 eq $HNO_3/Ac_2O$ | –10ºC | 4h | – | – | 50% | – | 50% | – |
| **7** | $COC(CH_3)_3$ | 1.5 eq $HNO_3/Ac_2O$ | –10ºC | 4h | – | – | 80% | – | 20% | – |
| **8** | $COCF_3$ | 1.0 eq $KNO_3/H_2SO_4$ | 0ºC | 10m | 40% | – | 30% | – | 20% | 10% |
| **9** | $COCF_3$ | 1.0 eq $KNO_3/H_2SO_4$ | 0ºC | 30m | – | – | 40% | – | – | 60% |
| **10** | $COCF_3$ | 1.0 eq $KNO_3/H_2SO_4$/DCM[c] | 0ºC | 30m | 10% | – | 30% | – | 20% | 40% |
| **11** | $COCF_3$ | 1.0 eq $KNO_3/H_2SO_4$/DCM[c] | –25ºC | 30m | – | – | 75% | – | 25% | – |
| **12** | Fmoc | 1.0 eq $KNO_3/H_2SO_4$/DCM[c] | –25ºC | 8h | 60% | – | 20% | – | 20% | – |
| **13** | Fmoc | 1.0 eq $KNO_3/H_2SO_4$/DCM[c] | 0 ºC | 8h | 40% | – | 40% | – | 10% | 10% |
| **14** | Fmoc | 1.0 eq $KNO_3/H_2SO_4$/DCM[c] | rt | 2h 30m | – | – | 100% | – | – | – |

[a] SM= starting material
[b] Total yield of isolated products.
[c] Reaction diluted with dichloromethane (DCM)

**SCHEME 1.** Nitration of *N*-protected-THQ derivatives performed in this work.




Given the THQ structure, the increase of the steric hindrance on position 8 using a bulkier amino protecting group could lead to an improvement on the selectivity towards position 6. Thus, the replacement of the small acetyl group by a larger one as pivaloyl (trimethylacetyl) was explored. Reaction of **2a** with pivaloyl chloride in pyridine at room temperature afforded the protected compound **2d**, in 80% yield. Next, the treatment of **2d** with nitric acid (1.48 eq.) in acetic anhydride, 4h at –10 ºC was carried out and, as postulated, a considerable increase in the selectivity was observed and the 6-nitro-derivative **1d** was obtained in a 80:20 ratio *vs.* the 8-nitro-derivative **5d**.

Although the increase obtained with *N*-pivaloyl protection was significant, other protecting groups were studied in an effort to reach total selectivity. Trifluoroacetyl (-$COCF_3$) is a small protecting group (low steric effect) as acetyl, but with very different electronic properties. Furthermore, the presence of three electronegative F atoms near the amino group could act as an electronic shield protecting position 8 from nitration. Moreover, this protecting group presents the advantage that, after nitration, it can be easily removed by hydrolysis in a weak

base such as $NaHCO_3$. Hence, *N*-trifluoroacetyl-THQ, **2e**, was prepared by reaction of THQ with trifluoroacetic anhydride in DCM at room temperature in 80% yield. Then, nitration was performed following Amit *et al.* mild conditions,[8] using $KNO_3$ and $H_2SO_4$ in acetic anhydride. As shown in Table 2 (entry 8-10) the first attempts carried out at 0 °C yielded 6,8-dinitro derivative **6e** as major product. We found very little information about dinitration of THQ in the revised literature.[7d] A careful follow-up of the reaction by TLC and NMR (Figure 3) showed the presence of the 6-nitro and 6,8-dinitro isomers immediately, indicating that the introduction of the second nitro group in position 8 occurs very quickly. Thus, even though the use of $KNO_3$ could be considered as limiting reactant to avoid dinitration this was not the case since the dinitro compound appears from the beginning of the reaction.

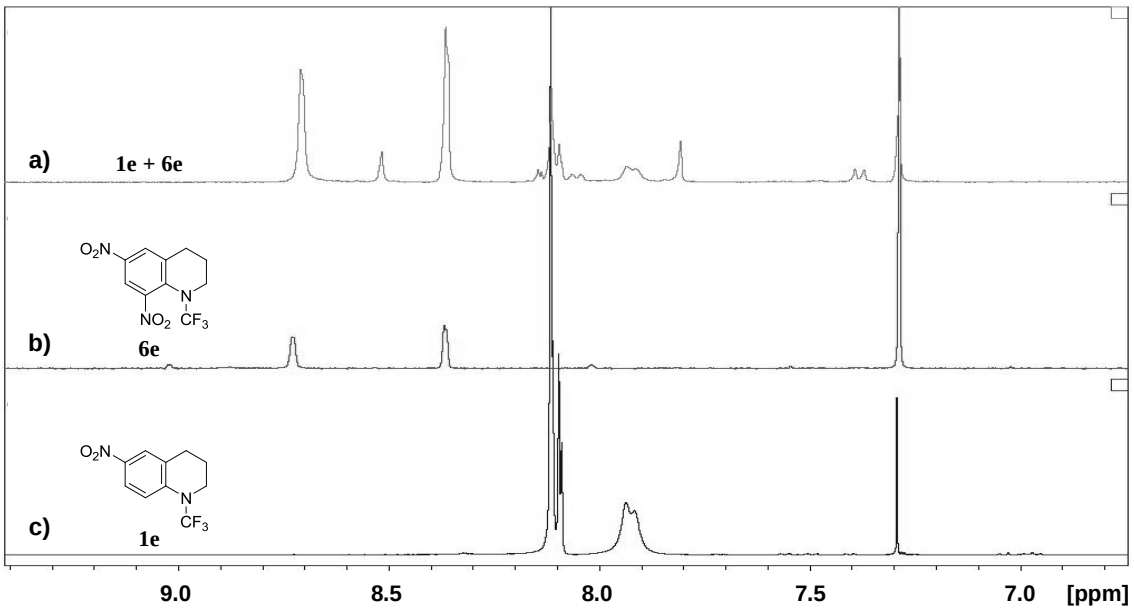



**FIGURE 3.** $^1H$ NMR ($CDCl_3$) spectrum of the aromatic region of: a) crude of nitration reaction of *N*-trifluoroacetyl-THQ (**2e**) at 0 ºC [*mostly dinitration*]*;* b) isolated 6,8-dinitro-*N*-trifuoroacetyl-THQ (**6e**); c) isolated 6-nitro-*N*-trifuoroacetyl-THQ (**1e**).

Attempts to optimize the reaction conditions to avoid the dinitration and favour the selectivity towards the 6-nitro derivative were made, and thus, the influence of temperature was evaluated. Considering that the presence of a $NO_2$ group produces a deactivating effect in the EAS increasing the energetic transition barrier required for the incorporation of a second nitro group, a temperature decrease could minimize the effect of dinitration. In fact, and as shown in Table 2 (entry 11), an experiment conducted at –25 ºC yielded only the 6- and 8-nitro isomers (**1e** and **5e** respectively) in an acceptable ratio of selectivity (75:25) with no evidence of the dinitro derivative. NMR experiments (Figure 4) evidenced the influence of temperature in the mononitration of *N*-trifluoroacetamide-THQ, showing that a temperature decrease results in the lack of formation of the dinitro compound.

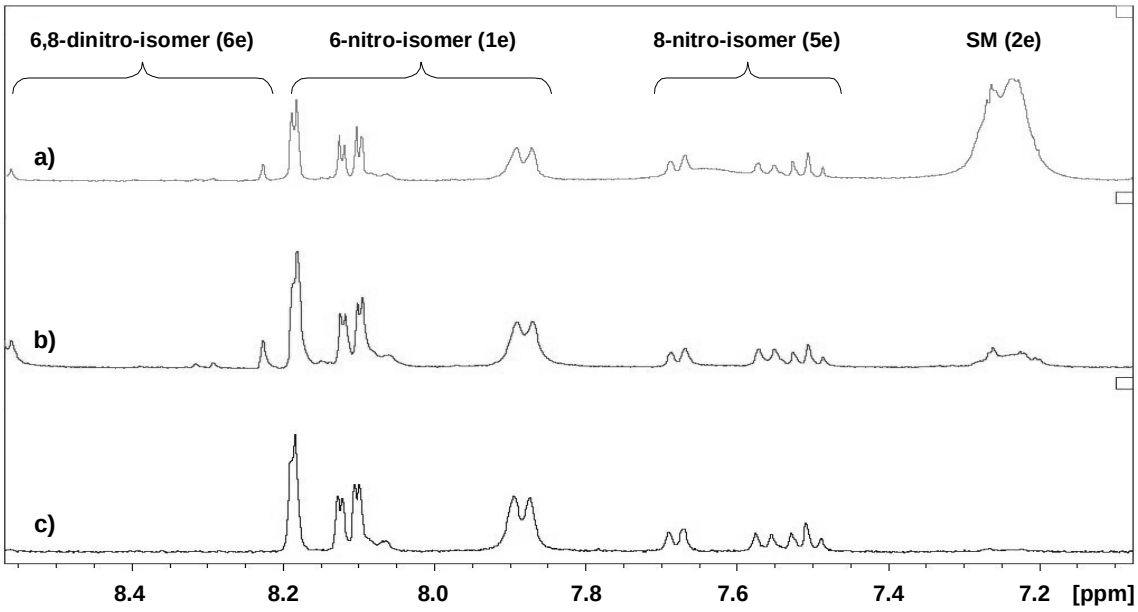



**FIGURE 4.** $^1$H NMR spectrum of nitration of *N*-trifluoroacetyl-THQ (**2e**) at: a) 0 ºC and 10 min, b) 0 ºC and 30 min, and c) –25 ºC and 30 min. (SM = starting material).

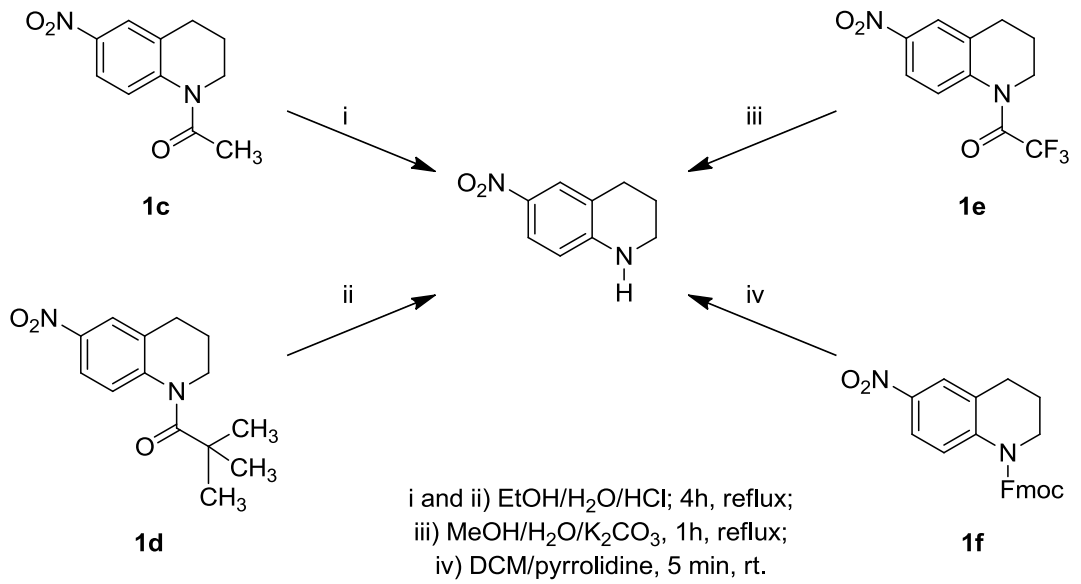
Later attempts to change the order of addition of reagents (generating the nitronium ion in advance instead of generating it *in situ*) and other experimental aspects (*i.e.* fractionated

addition of $KNO_3$), using similar low temperature produced lower yields of the 6-nitro isomer. We found that this method was very sensitive to small experimental changes.

Finally, continuing with the hypothesis of introducing a bulky group as an amine protection, fluorenylmethyloxycarbonyl (Fmoc) was used to force the selectivity induced by steric effects considering that is stable in acidic conditions and quickly removed with organic base. Protection with Fmoc was carried out by reaction of **2a** in DCM with Fmoc-Cl, yelding compound **2f** in 70%. Nitration of Fmoc-protected THQ was explored at three different temperatures (see Table 2, entries 12-14). At –25ºC (our best conditions using $COCF_3$ as protecting group) the reaction is relatively slow and non-selective recovering, after 8h, 30% of the starting material and a significant fraction of the dinitro compound (**6f**). When the reaction was performed at 0 ºC a considerable increase of the selectivity and the ratio of mononitrated compounds were observed. However, the best result with Fmoc was obtained when the reaction was carried out at room temperature, reaching 100% selectivity and yielding exclusively the 6-nitro derivative **1f** as confirmed by NMR experiments. Therefore, this methodology can be considered as the most efficient when searching the selective synthesis of the 6-nitro derivative.

For each case, isolation of the 6-nitro derivative **1a**, was carried out by a last step of deprotection (see Scheme 2) using acid or basic hydrolysis according to the corresponding *N*-protecting group ($COCH_3$, $COC(CH_3)_3$, $COCF_3$, or Fmoc). Yields were almost quantitative as reported in the experimental section. Similar deprotecting procedures were carried out with some of the *N*-protected-8-nitro derivatives obtained as secondary products yielding **5a**.

**SCHEME 2.** *N*-Protected-THQ derivatives and deprotection conditions used in each case.




***NMR Structural Analysis of 5-, 6-, 7- and 8-Nitrotetrahydroquinoline Derivatives***

Table 3 reports the δ and *J* values ($^{1}$H and $^{13}$C NMR) of the four 5-, 6-, 7- and 8-nitro-THQs (**3a**, **1a**, **4a** and **5a**) obtained in this work, proving that they have a monosubstituted tetrahydroquinoline structure. The unambiguous assignation of each isomer has been carried out through a careful analysis of NMR using mono- and bi-dimensional techniques such as $^{1}$H and $^{13}$C NMR, HMBC,[12] HSQC[13] and ROESY.[14] These techniques corroborate the assignment previously made by Amit and co.[9] and complete the characterization of this family of compounds with relevant spectroscopic information.

Compounds **1a** and **4a** (6- and 7-nitro-THQ) are ABX systems [d/dd/d] with the coupling constant pattern: $J_{A,B}$ = 8.0-8.9 and $J_{A,X}$ = 2.5-2.7 Hz. On the contrary, compounds **3a** and **5a** (5- and 8-nitro-THQ) are ABC systems [dd/dd/dd] with coupling constant patterns: $J_{A,B}$ = 8.3-8.5; $J_{A,C}$ = 7.0-7.9 and $J_{B,C}$ = 1.2-1.5 Hz. The assignation of the H1 and all the

correspondences of C-H pairs of **1a**, **3a**, **4a** and **5a** were established by $^{15}$N-H HSQC and $^{13}$C-H HSQC experiments respectively.

**TABLE 3.** $^{1}$H and $^{13}$C NMR (400 and 600 MHz respectively) spectroscopic data (δ in ppm, *J* in Hz) for 5-, 6-, 7- and 8-nitro-THQs (**3a**, **1a**, **4a** and **5a**) in DMSO.

| **$^{1}$H NMR** | **δH1** | **δH2** | **δH3** | **δH4** | **δH5** | **δH6** | **δH7** | **δH8** |
|---|---|---|---|---|---|---|---|---|
| **3a** | 6.41 s | 3.02 q | 1.77 q | 2.75 t | | 6.94 dd<br>$J_{6,7}$ = 7.9<br>$J_{6,8}$ = 1.1 | 7.05 dd<br>$J_{7,8}$ = 8.3<br>$J_{7,9}$ = 7.9 | 6.73 dd<br>$J_{7,8}$ = 8.3<br>$J_{6,8}$ = 1.1 |
| **1a** | 7.43 s | 3.29 q | 1.79 q | 2.72 t | 7.76d<br>$J_{5,7}$ = 2.7 | | 7.78 dd<br>$J_{5,7}$ = 8.9<br>$J_{7,8}$ = 2.7 | 6.48 d<br>$J_{7,8}$ = 8.9 |
| **4a** | 6.42 s | 3.22 q | 1.81 q | 2.75 t | 7.07d<br>$J_{5,6}$ = 8.0 | 7.22 dd<br>$J_{5,6}$ = 8.0<br>$J_{6,8}$ = 2.5 | | 7.27 d<br>$J_{6,8}$ = 2.5 |
| **5a** | 8.46 s | 3.46 q | 1.83 q | 2.79 t | 7.21dd[a]<br>$J_{5,6}$ = 6.8<br>$J_{5,6}$ = 1.5 | 6.51 dd<br>$J_{5,6}$ = 6.8<br>$J_{6,7}$ = 8.5 | 7.85 dd[a]<br>$J_{6,7}$ = 8.5<br>$J_{5,6}$ = 1.5 | |

| **$^{13}$C NMR** | **δC2** | **δC3** | **δC4** | **δC5** | **δC6** | **δC7** | **δC8** | **δC9** | **δC10** |
|---|---|---|---|---|---|---|---|---|---|
| **3a** | 39.8 | 20.3 | 23.8 | **147.7** | 109.9 | 126.8 | 117.6 | 146.0 | 110.1 |
| **1a** | 40.5 | 20 | 26.3 | 125.2 | **134.7** | 124.1 | 111.7 | 151.6 | 119.1 |
| **4a** | 40.2 | 20.3 | 26.8 | 129.5 | 108.9 | **146.7** | 106.2 | 146.5 | 127.6 |
| **5a** | 41.4 | 19.8 | 27.6 | 135.3 | 114.3 | 124.2 | **125.6** | 143.3 | 130.1 |

[a] $J_{5,7}$ = 1.5 Hz in $CDCl_3$

Selective 1D ROESY experiments (Figure 5) were employed to discern between the isomers **1a/4a** (ABX) and **3a/5a** (ABC) respectively. The irradiation of H1 (NH) proton at 6.42 ppm in the sample corresponding to one of the ABX systems identified the signal at 7.27 ppm with a small *J* = 2.5 Hz which was consistent with the structure of 7-nitro-THQ (**4a**). Similarly, the irradiation of the H4 proton at 2.79 ppm in the sample corresponding to one of the ABC systems identified the signal at 7.21 ppm with *J* values (6.8 and 1.5 Hz) consistent with the structure of 8-nitro-THQ (**5a)**. This allowed the definitive characterization of the four isomers

since the other two samples ABX and ABC should belong unequivocally to the compounds **1a** and **3a** respectively. The validity of the assignments was confirmed by HSQC and HMBC experiments (Figure 5) which showed a coherent C-H correlation pattern for each of the nitro derivatives (**3a**, **1a**, **4a** and **5a**). It was significant to note that the correlation between the hydrogen H5 and the carbon C4 was only present in the compounds **1a**, **4a** and **5a**. This correlation is not possible in compound **3a** because it has position 5 substituted.

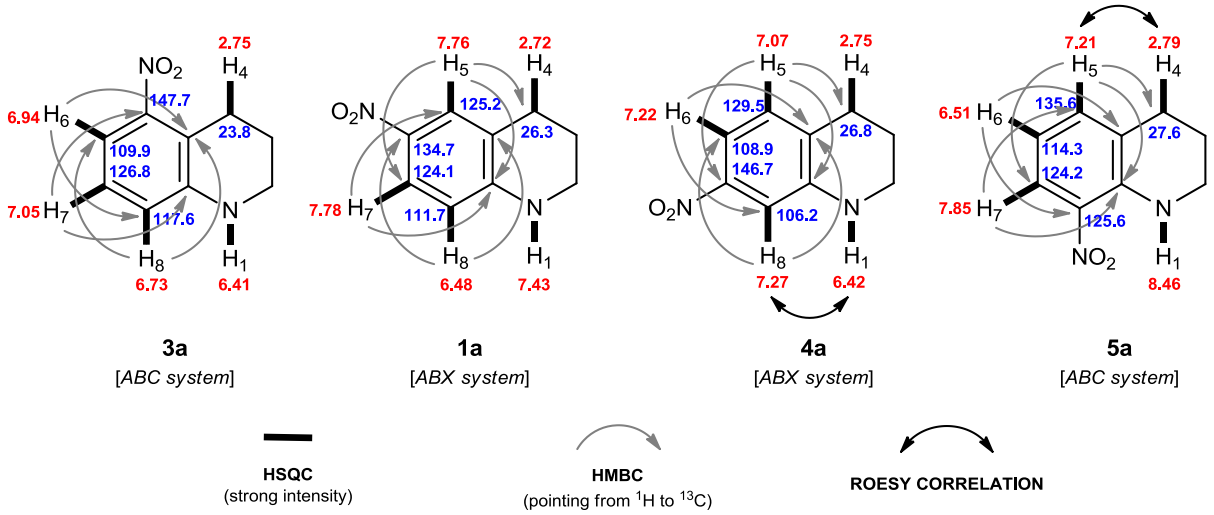



**FIGURE 5.** NMR structural elucidation of compounds **1a**, **4a**, **3a** and **5a**.

The $^{1}$H-NMR of compounds **3a**, **1a**, **4a** and **5a** are gathered in Figure 6. As can be expected the presence of the $NO_2$ group exerts significant influence. For each isomer, protons located in *ortho* to the nitro group suffer a considerable downfield shift as a consequence of the deshielding effect. With the exception of **3a**, the general pattern described for nitrobenzene analogues[15] is followed, where chemical shifts of the aromatic hydrogens are in the order *ortho* > *para* > *meta*. This influence is similarly manifested in the amine hydrogens. The H1 hydrogen shows a relative low value of chemical shift in compounds **3a** and **4a** where the nitro and amine groups are in *meta* orientation, (6.41 and 6.42 ppm respectively), a larger value (7.43 ppm) is observed in compound **1a** with *para* orientation and the largest value

(8.46 ppm) is shown for compound **5a** where the nitro group is located in *ortho* to the amine substituent. The electronic influence of the nitro groups is equally evident in $^{13}C$ NMR analysis where, for each of the four nitro derivatives, a larger displacement of the signal of the C in *ipso* to the nitro substituent compared with the rest of the aromatic carbons is observed (Table 3).

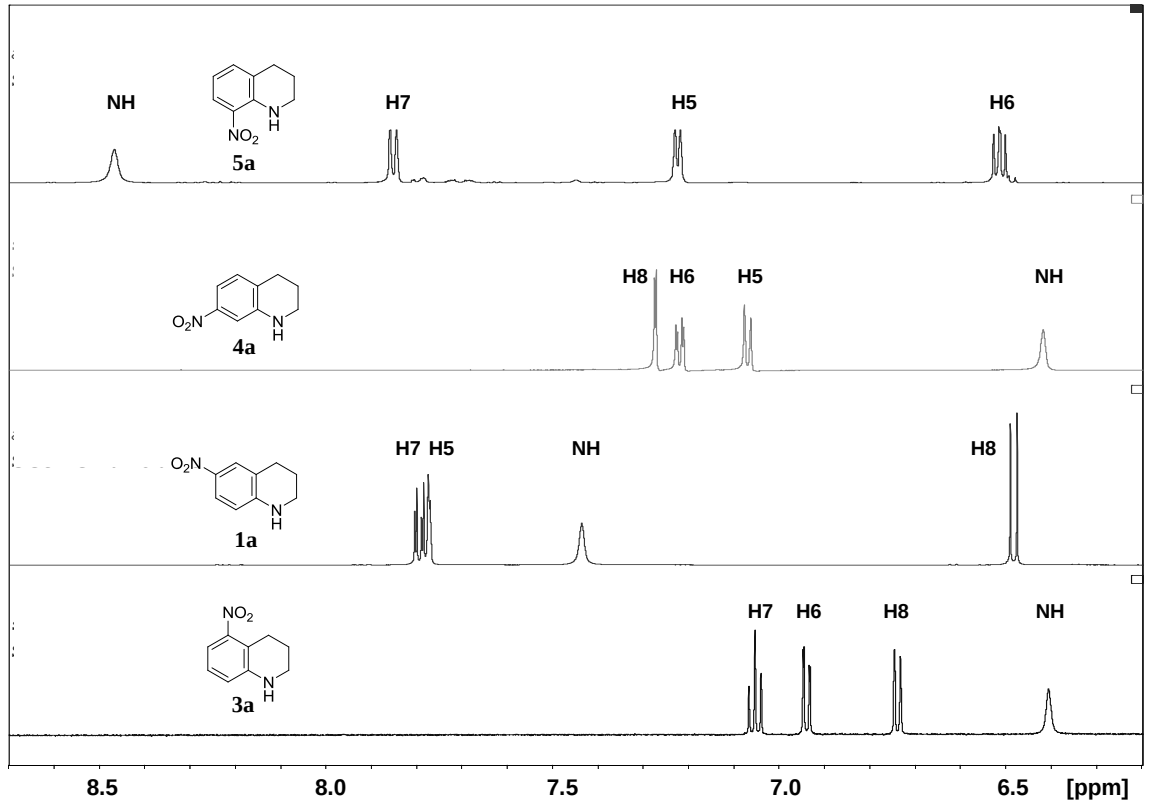



**FIGURE 6.** Aromatic region of the $^{1}H$ NMR spectra of compounds **1a**, **4a**, **3a** and **5a**.

On the contrary, it is known that the interaction by hydrogen bond produces a deshielding of the hydrogen involved.[16] Thus, the large chemical shift observed for H1 in compound **5a** could be simultaneously influenced by the existence of an intramolecular hydrogen bond interaction (**IMHB**) between this amine hydrogen and the lone pair of one of the oxygen atoms of the nitro group. Computations performed at DFT level (B3LYP/6-31++G**

level[17,18]) and the analysis of the electron density (AIM approach[19]) strongly support this hypothesis (Figure 7).

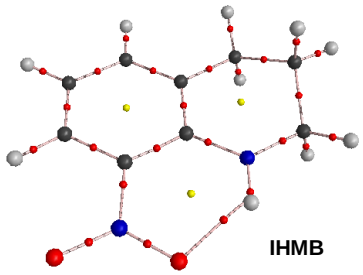



**FIGURE 7.** Molecular graph (according to AIM theory) of the compound **5a** at the B3LYP/6-31++G** computational level. Red and yellow balls indicate the bond and ring critical points respectively. The **IMHB** is indicated.

***Computational study***

In a parallel theoretical study we attempt the rationalization of the selectivity on the nitration of THQ. From a theoretical point of view, aromatic nitration is one of the most widely studied organic reactions and some of the references found in the literature reflect the long-debated controversy regarding the two postulated mechanistic approaches: the classical "Ingold-Hughe" interpretation or polar two-electron mechanism[20] and the subsequently proposed single-electron transfer (SET) mechanism.[21] One of the most thorough studies about theoretical understanding of aromatic nitration was carried out by Olah and co. in 2003.[22] In this work, there is an extensive description of the reaction path of benzene nitration including: *(i)* the approximation of $NO_2^+$ to the aromatic ring, *(ii)* the formation of the key arenium ion or Wheland intermediate (σ-complex), and *(iii)* the proton elimination to yield the nitro derivative. They conclude that: "*The initial interaction of benzene with a nitronium cation could either involve an initial single-electron transfer or a polar conventionally two-electron-transfer electrophilic mechanism, depending on the system and experimental conditions.*"

According to the authors, from a total of 37 geometries calculated to be involved in the process (including 16 minima and 21 transition states), four of them are of particular relevance in the description of the substitution mechanism (Figure 8): (A) non-oriented π-complex; (B) oriented π-complex; (C) σ-complex and (D) the final nitro-derivative. More recent studies have continued to deepen into the theoretical description of the mechanism of this reaction and the substituent effects.[23]

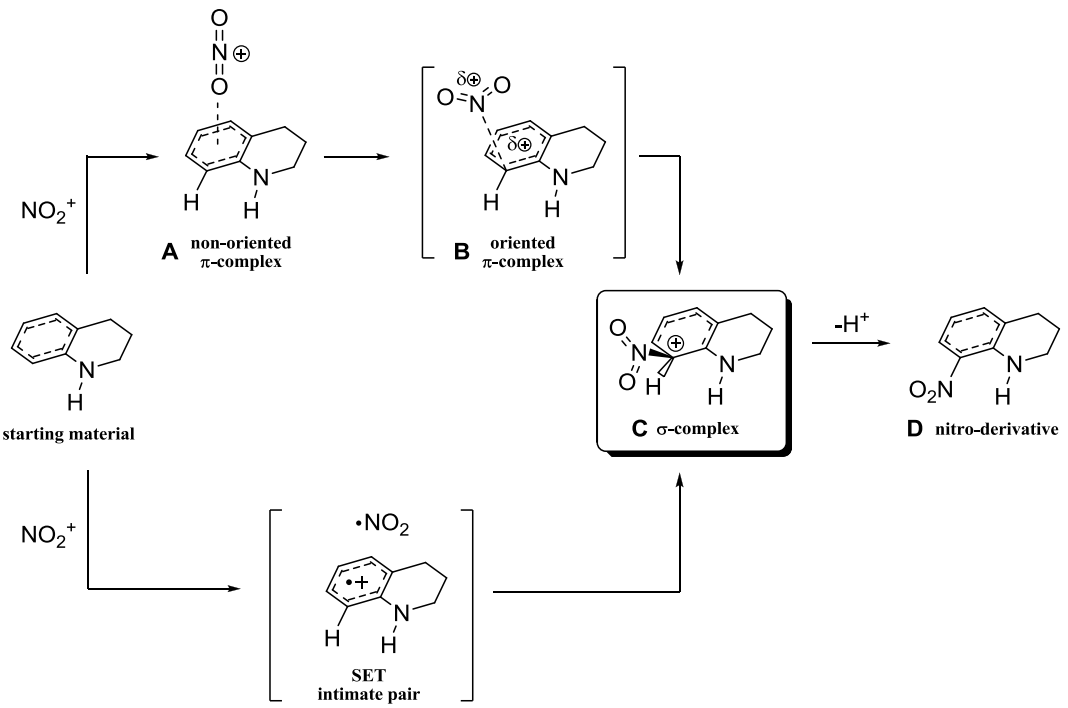



**FIGURE 8.** Different complexes and transition states involved in one of the four possible nitration processes of THQ.

The formation of the σ-complex is the rate-determining step of the reaction, and the subsequent step of proton elimination occurs comparatively faster. The relative stability of the arenium ion intermediated (σ-complex), and/or the oriented π-complex (usually in a narrow energy range), determines the positional selectivity of the process (regioselectivity). Based on the literature found, we have focused on the relative stability of the σ-complexes as a criterion

of selectivity. Thus, we have calculated the four possible Wheland complexes corresponding to the *ortho*- (8-nitro-sc), *meta*$_1$- (7-nitro-sc), *para*- (6-nitro-sc) and *meta*$_2$- (5-nitro-sc) selective THQ nitration in both its unprotonated and protonated forms (Figure 9) at the B3LYP/6-31++G** computational level. Incorporation of the nitro group in the aromatic system produces the movement of the corresponding H atoms forcing the $sp^3$ hybridation of the substituted carbon, showing NCH angles of ~100º in all the complexes. The corresponding C–H distances increase from 1.08-1.09 Å in the normal state to 1.10-1.12 Å in the intermediates. The N···C distances found between the nitro group and the substituted carbon in these intermediates are in the range of 1.50-1.60 Å, which shows the strength of the interaction since these values are very close to a standard covalent bond.

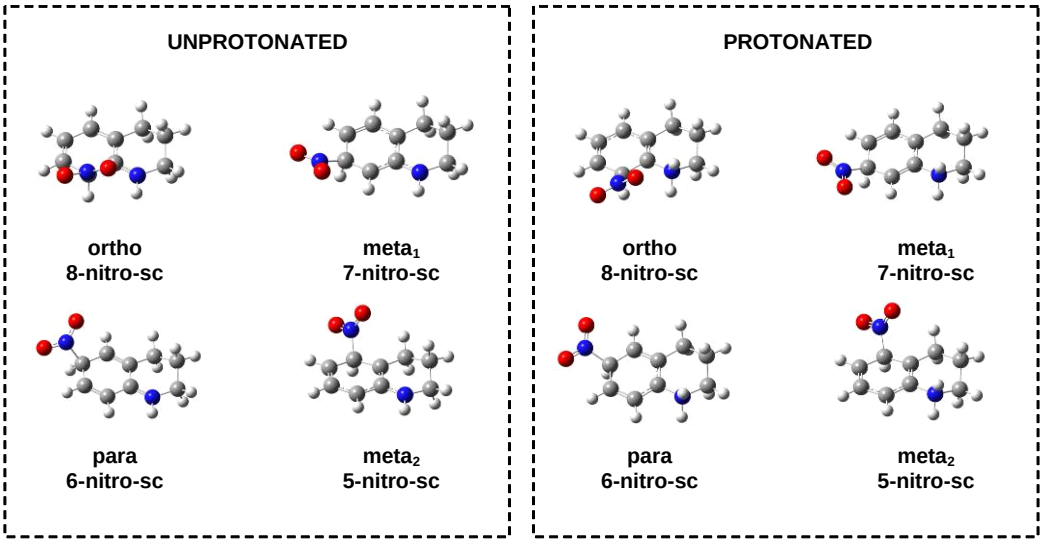



**FIGURE 9.** σ-Complexes of the unprotonated and protonated forms of all possible nitro-THQ calculated at B3LYP/6-31++G** computational level.

The corresponding calculated energies are gathered in Table 4. First, we studied the systems in gas phase and, in these conditions, only the minima corresponding to the unprotonated intermediates were localised. The σ-complexes of protonated structures: 5-nitro-sc; 6-nitro-sc

and 7-nitro-sc, were unstable and the corresponding minima were not found. This could be explained by the difficulty of stabilising two positive charges in gas-phase conditions, one corresponding to the protonation of the amine and the other resulting from the incorporation of the $NO_2^+$. In view of these results and to approach the conditions being used (acidic aqueous phase) in our parallel experimental study, the intermediates were optimised again in water condensed phase (solvated) by using the PCM solvation approach.[24]

**TABLE 4.** Total (a.u.) and relative (kJ $mol^{-1}$) energies obtained for all σ-complexes (unprotonated and protonated) calculated both in gas and solvated phases using the B3LYP/6-31++G** computational level.

| σ-complex | Gas Phase | | | Solvated Phase | | | |
|---|---|---|---|---|---|---|---|
| | Unprotonated | | Protonated | Unprotonated | | Protonated | |
| | E tot | E rel | E tot | E tot | E rel | E tot | E rel |
| **5-nitro-sc** | -609.170867 | 122.1 | Unstable[a] | -609.265468 | 134.6 | -609.684991 | 15.6 |
| **6-nitro-sc** | -609.217378 | **0.0** | Unstable[a] | -609.316745 | **0.0** | -609.683123 | 20.5 |
| **7-nitro-sc** | -609.175482 | 110.0 | Unstable[a] | -609.270778 | 120.7 | -609.690940 | **0.0** |
| **8-nitro-sc** | -609.211497 | 15.4 | -609.365654 | -609.304926 | 31.0 | -609.677669 | 34.8 |

[a] Minimum not found

Similar trends were observed in the unprotonated intermediates both in gas and solvated phase. The relative energies show that the *ortho*/*para* substitution (8- and 6-nitro σ-complexes) in these conditions are favoured, being the 6-nitro intermediate the one that shows a more stable minimum. The energy gap with the two different *meta*- substituted systems (7- and 5-nitro σ-complexes) is above 100 kJ $mol^{-1}$. Considering these energy ranges in gas and in water phases, one might assume a high degree of selectivity for the *ortho* and *para* positions, *i.e.* the nitration of unprotonated (protected in our experiments) THQ should occur mostly in positions 6- (*para*) and 8- (*ortho*) of the aromatic ring, what was in agreement with our experimental results.

In the case of the Wehland intermediates of the protonated species (Table 4), even though the differences are not as pronounced as in the unprotonated systems, there is a clear reversal in the trend of the relative energies becoming the two *meta*-substituted intermediates (5- and 7-nitro-sc) more stable than the *ortho* and *para* σ-complexes (8- and 6-nitro-sc). Attending to this, nitration of protonated THQ (unprotected in our experiments) should occur mostly in positions 5- and 7- as it was experimentally confirmed. These results validate the definitive roll of the protonation of the amine in the selectivity of the nitration of THQ.

**Conclusions**

A revision of the literature on the nitration of tetrahydroquinolines yielded a number of inconsistencies and lack of information in terms of dinitration and *N*-protecting groups. Thus, a thorough study on the nitration of THQ and some of its *N*-protected derivatives has been performed both experimentally and at theoretical level.

The favoured position for nitration of THQ depends on the protonation state of the ring amine group. Thus, the neutral THQ is favourably nitrated on the 6- and 8- positions corresponding to *para*- and *ortho*- positions whereas the *N*-protonated specie favours protonation on the 5- and 7- positions which correspond to *meta*- orientation. Nitration is carried out in acidic conditions and, thus, THQ would be normally *N*-protonated. However, if the THQ amino group is protected the neutral THQ system will be the one undergoing nitration.

Reproducing conditions already found in the literature for the nitration of unprotected THQ ($KNO_3/H_2SO_4$) we obtained similar results to those found in the literature (73:18, 7-nitro:5-nitro). However, when trying to reproduce the nitration of the *N*-acetyl protected THQ

($HNO_3/Ac_2O$) we did not achieve the reported regioselectivity (80:20) and 50:50 mixtures of the 6- and 8-nitro derivatives were obtained. Therefore, different protecting groups such as $COC(CH_3)_3$, $COCF_3$ or Fmoc were explored varying not only electronic and steric effects, but also deprotection conditions. Additionally, different reaction reagents ($KNO_3/H_2SO_4$; $HNO_3/Ac_2O$; $KNO_3/H_2SO_4$/DCM) and conditions (temperature, time) were investigated. From this study we were able to achieve total regioselectivity for the 6- position (the one object of our interest) by using Fmoc, $KNO_3/H_2SO_4$/DCM, at room temperature during 2 hours and 30 minutes.

A very detailed NMR study was required to unequivocally characterise the four nitro isomers and, hence, mono and bi-dimensional $^{1}H$ and $^{13}C$ NMR studies were carried out. The data now obtained complete with new relevant information the already known characterization of this family of compounds.

Finally, a parallel computational study has been performed and hence all the σ-complexes of the four nitro isomers neutral and *N*-protonated were optimized both in gas phase and in water condensed phase by using the B3LYP/6-31++G** level of computation. The energy results obtained, using the solvated system, confirm that the *N*-protonation facilitates nitration in the *meta*- positions whereas the neutral system yields nitration in the *ortho*- and *para*- positions. This computational study was in agreement with our experimental results.

In conclusion, the present study not only provides a regioselective method for the preparation of 6-nitro-tetrahydroquinoline but also clarifies the nitration of the THQ system, offers insights on how to obtain a particular nitro isomer and presents an unequivocal characterization of the four possible nitro isomers.

## Experimental Section

*Chemistry*

Commercially available materials were obtained from Sigma-Aldrich. Melting points were obtained using Stuart melting point (SMP3) apparatus. Infrared spectra were recorded on a Mattson Genesis II FTIR spectrometer equipped with a Gateway 2000 4DX2-66 workstation and on a Perkin Elmer Spectrum One FT-IR Spectrometer. NMR spectra were recorded in a Bruker DPX-400 Avance spectrometer, operating at 400.13 MHz and 600.1 MHz for $^{1}$H-NMR and $^{13}$C-NMR. Shifts are referenced to the internal solvent signals. NMR data were processed using Bruker Win-NMR 5.0 software. HRMS spectra were recorded on a Waters (Micromass) LCT-Tof mass spectrometer in the positive ion electrospray mode.

**5-Nitrotetrahydroquinoline (3a) and 7-nitrotetrahydroquinoline (4a)**

Concentrated sulphuric acid (5 mL) was added to a flask at 0 °C. The 1,2,3,4-tetrahydroquinoline (16 mmol) was then added dropwise to the flask while stirring. Potassium nitrate (16 mmol) was added to the solution. The mixture was stirred for 30 min at 0 °C and a further 30 min at room temperature. The reaction was quenched by pouring over ice (6 g/mmol). The solution was filtered and extracted using ethyl acetate (3 × 75 mL). The organic layer was dried over magnesium sulphate and concentrated under vacuum. Purification using silica column chromatography (Hexane:EtOAc, 4:1) yielded **4a** (1.4g, 48%) and **3a** (0.34g, 11%) as orange crystals.

**7-nitro-1,2,3,4-tetrahydroquinoline, 4a**: mp = 57–58 °C (lit.[9] 63–65 °C); $^{1}$H NMR (600 MHz, DMSO) δ: 1.81 (q, 2H, *J* = 4.0 Hz), 2.75 (t, 2H, *J* = 6.0 Hz), 3.22 (dt, 2H, *J* = 4.0 Hz, *J* = 2.0 Hz), 6.42 (s, 1H, NH), 7.07 (d, 1H, *J* = 8.0 Hz), 7.22 (dd, 1H, *J* = 8.0 Hz, *J* = 2.5 Hz), 7.27 (d, 1H, *J* = 2.5 Hz) ppm; $^{13}$C NMR (100 MHz, DMSO) δ: 20.3 ($CH_2$), 26.8 ($CH_2$), 40.2

($CH_2$), 106.2 (CH), 108.9 (CH), 127.6 (q), 129.5 (CH), 146.0 (q), 146.7 (C-$NO_2$) ppm. HRMS (ESI, MeOH) m/z found $[M + H]^+$ 179.0849, $C_9H_{10}N_2O_2$ requires $[M + H]^+$ 179.0842. IR 3416 (NH), 1511 ($NO_2$) $cm^{-1}$.

**5-nitro-1,2,3,4-tetrahydroquinoline, 3a**: lit.[9] mp = 80–82 °C; $^1$H NMR (600 MHz, DMSO) δ: 1.77 (q, 2H, *J* = 5.6 Hz), 2.75 (t, 2H, *J* = 5.6 Hz), 3.20 (dt, 2H, *J* = 5.6 Hz), 6.41 (broad s, 1H, NH), 6.73 (dd, 1H, *J* = 8.3 Hz, *J* = 1.1 Hz), 6.94 (dd, 1H, *J* = 7.9 Hz, *J* = 1.1 Hz), 7.05 (dd, 1H, *J* = 8.3 Hz, *J* = 7.9 Hz). $^{13}$C NMR (100 MHz, DMSO) δ: 20.7 ($CH_2$), 23.8 ($CH_2$), 39.8 ($CH_2$), 109.9 (CH), 110.2 (q), 117.6 (CH), 127.0 (CH), 146.0 (q), 147.7 (C-$NO_2$) ppm.

***N*-Acetyl-1,2,3,4-tetrahydroquinoline (2b)**

To a solution of THQ (3.75 mmol) in pyridine or DCM (10 mL) at 0 °C, acetyl chloride or acetic anhydride (2 equiv.) was added dropwise. After stirring for 1 h at room temperature, the solvent was evaporated under reduced pressure. The residue was taken up with ethyl acetate and washed with 1N HCl (3 × 15 mL) and brine (2 × 15 mL). The organic layer was dried ($Na_2SO_4$) and concentrated in vacuum to give 0.58 g (89%) of **2b** as a yellow oil: $^1$H NMR (400 MHz, $CDCl_3$) δ: 1.97 (q, 2H, *J* = 6.0 Hz), 2.24 (s, 3H, $CH_3$), 2.73 (t, 2H, *J* = 6.0 Hz) 3.81 (t, 2H, *J* = 6.0 Hz), 7.16 (m, 4H, arom) ppm; $^{13}$C NMR (100Hz, $CDCl_3$) δ: 22.7 ($CH_3$), 23.6 ($CH_2$), 26.4 ($CH_2$), 43.5 ($CH_2$), 124.1, 124.8, 125.6, 127.9 (arom), 134.0 (q), 139.8 (q), 169.9 (CO) ppm; HRMS (ESI, MeOH) m/z found $[M + H]^+$ 176.0991, $[M + Na]^+$ 198.0988, $C_{11}H_{13}NO$ requires $[M + H]^+$ 176.0997, $[M + Na]^+$ 198.0997. IR 1707 (CO) $cm^{-1}$.

**6-Nitro-*N*-acetyl-1,2,3,4-tetrahydroquinoline (1b) and 8-nitro-*N*-acetyl-1,2,3,4-tetrahydroquinoline (5b)**

A mixture of 70% nitric acid (1.48 equiv.) and acetic anhydride (3 mL), cooled at 0 °C, was added dropwise to a solution of *N*-acetyl-THQ **2b** in acetic anhydride (3 mL) between –10 °C and –5 °C . The mixture was stirred at 0 °C for 1 h and at room temperature for 3 h. It was diluted with water and extracted with ether. The organic extracts were washed with diluted $NaHCO_3$ and water, dried ($Na_2SO_4$) and concentrated in vacuum to give a mixture of 6-nitro **1b** (50%, brown solid) and 8-nitro **5b** (50%, brown solid) that were separated using silica column chromatography.

**6-Nitro-*N*-acetyl-1,2,3,4-tetrahydroquinoline, 1b:** $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 2.06 (q, 2H, *J* = 5.6 Hz), 2.28 (s, 3H, $CH_3$), 2.88 (t, 2H, *J* = 6.4 Hz), 3.83 (t, 2H, *J* = 6.4 Hz), 7.67 (m, 1H), 8.06 (s, 1H), 8.08 (m, 2H) ppm.

**8-Nitro-*N*-acetyl-1,2,3,4-tetrahydroquinoline, 5b:** mp = 98–100 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 2.06 (m, 2H), 2.33 (s, 3H, $CH_3$), 2.86 (m, 2H), 3.85 (m, 2H), 7.21 (t, 1H, *J* = 7.9 Hz), 7.37 (d, 1H, *J* = 7.9 Hz), 7.72 (d, 1H, *J* = 7.9 Hz) ppm. $^{13}$C NMR (100Hz, $CDCl_3$) δ: 22.2 ($CH_3$), 23.8 ($CH_2$), 26.8 ($CH_2$), 45.5 ($CH_2$), 122.3 (arom.), 124.6 (arom.), 130.5 (q), 132.5 (arom.) 135.2 (q), 145.3 (C-$NO_2$), 169.8 (CO) ppm. HRMS (ESI, MeOH) m/z found $[M + Na]^+$ 243.0834, $C_{11}H_{12}N_2O_3$, requires $[M + Na]^+$ 243.0848. IR 1668 (CO), 1528 ($NO_2$) $cm^{-1}$.

***N*-Pivaloyl-1,2,3,4-tetrahydroquinoline (2d)**

To a solution of THQ (3.75 mmol) in pyridine (10 mL) cooled at 0 °C, pivaloyl chloride (2 equiv.) was added dropwise. After stirring for 1 h at room temperature, the solvent was evaporated under reduced pressure. The residue was taken up with EtOAc and washed with

1N HCl (3 × 15 mL) and brine (2 × 15 mL). The organic layer was dried ($Na_2SO_4$) and concentrated in vacuum to give 0.65 g (80%) of **2d** as yellow crystals: mp = 96–98 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ: 1.32 (s, 9H, $3CH_3$), 2.02 (q, 2H, *J* = 6.3 Hz), 2.79 (t, 2H, *J* = 7.1 Hz) 3.81 (t, 2H, *J* = 6.3 Hz) 7.11 (m, 3H), 7.40 (d, 1H, *J* = 8.1 Hz) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): 24.1 ($CH_2$), 26.5 ($CH_2$), 28.9 ($CH_3$), 40.4 (C), 45.2 ($CH_2$), 125.1, 125.6, 125.8, 128.5 (arom), 132.0 (C=), 140.1 (C=), 178.3 (CO) ppm; HRMS (ESI, MeOH) m/z found $[M + Na]^+$ 240.1461, $C_{14}H_{19}NO$ requires $[M + Na]^+$ 240.1467. IR 1632 (CO) $cm^{-1}$.

**6-Nitro-*N*-pivaloyl-1,2,3,4-tetrahydroquinoline (1d) and 8-nitro-*N*-pivaloyl-1,2,3,4-tetrahydroquinoline (5d)**

A mixture of 70% nitric acid (1.48 equiv.) and acetic anhydride (3 mL), was added dropwise to a solution of *N*-acetyl-1,2,3,4-tetrahydroquinoline **1d** in acetic anhydride (3 mL) kept between –10 °C and –5 °C. The mixture was stirred at 0 °C for 1 h and at room temperature for 3 h. It was diluted with water and extracted with ether. The extracts were washed with diluted $NaHCO_3$ and water, dried ($Na_2SO_4$) and concentrated in vacuum to give a mixture of 6-nitro **1d** (80%, yellow solid) and 8-nitro **5d** (20%, brown solid) that were separated using silica column chromatography.

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**6-Nitro-*N*-pivaloyl-1,2,3,4-tetrahydroquinoline, 1d:** mp = 81–83 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ: 1.40 (s, 9H, $CH_3$), 2.07 (q, 2H, *J* = 5.7 Hz), 2.95 (t, 2H, *J* = 7.1 Hz), 3.87 (t, 2H, *J* = 5.7 Hz), 7.62 (d, 1H, *J* = 9.1 Hz), 7.98 (dd, 1H, *J* = 9.1 Hz, *J* = 2.9 Hz), 8.04 (s, 1H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): 23.3 ($CH_2$), 26.4 ($CH_2$), 28.6 ($CH_3$), 40.4 (C), 45.5 ($CH_2$), 120.8, 124.6, 126.2 (arom.), 130.7 (C=), 143.6 (C=), 146.3 (C-$NO_2$), 178.9 (CO) ppm. HRMS (ESI, MeOH) m/z found $[M + H]^+$ 263.1325, $[M + Na]^+$ 285.1326, $C_{14}H_{18}N_2O_3$ requires $[M + H]^+$ 263.1317, $[M + Na]^+$ 285.1317. IR 1645 (CO), 1510 ($NO_2$) $cm^{-1}$.

**8-Nitro-*N*-pivaloyl-1,2,3,4-tetrahydroquinoline, 5d:** mp = 48–50 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 1.38 (s, 9H, $CH_3$), 2.08 (m, 2H), 2.93 (t, 2H, *J* = 6.6 Hz), 3.45 (m, 2H), 7.20 (t, 1H, *J* = 7.6 Hz), 7.37 (d, 1H, *J* = 7.6 Hz), 7.72 (d, 1H, *J* = 7.9 Hz) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 23.9 ($CH_2$), 26.0 ($CH_2$), 30.9 ($CH_3$), 39.3 (C), 44.6 ($CH_2$), 122.3, 124.8, 132.9, 133.8 (C=), 134.6 (C=), 145.4 (C-$NO_2$), 177.4 (CO) ppm. HRMS (ESI, MeOH) m/z found $[M + H]^+$ 263.1311, $C_{14}H_{18}N_2O_3$ requires $[M + H]^+$ 263.1317. IR 1645 (CO), 1511 ($NO_2$) $cm^{-1}$.

***N*-Trifluoroacetyl-1,2,3,4-tetrahydroquinoline (2e)**

To a solution of trifluoroacetic anhydride (1.5 equiv.) in anhydrous THF (15 mL) at 0 °C, a solution of tetrahydroquinoline (3.75 mmol) in anhydrous THF (10 mL) was added dropwise. After stirring for 14 h at room temperature, the solvent was evaporated under reduced pressure. The residue was taken up with EtOAc and washed with 2N HCl. The organic layer was dried ($Na_2SO_4$) and concentrated in vacuum to give 0.68 g (80%) of the title compound **2e** as yellow crystals: mp = 39–41 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 2.09 (m, 2H), 2.91 (m, 2H), 3.86 (t, 2H, *J* = 6.0 Hz), 7.24 (m, 4H) ppm. HRMS (ESI, MeOH) m/z found $[M +H]^+$ 230.0723, $C_{11}H_{10}F_3NO$ requires $[M + H]^+$ 230.0714. IR 1681 (CO), 1138, 1170 ($CF_3$) $cm^{-1}$.

**6,8-dinitro-*N*-trifluoroacetyl-1,2,3,4-tetrahydroquinoline (6e)**

Concentrated sulphuric acid (5 mL) was added to a flask at 0 °C. Compound **2e** (16 mmol) was then added dropwise to the flask while stirring. Potassium nitrate (16 mmol) was added to the solution. The mixture was stirred for 30 minutes at 0 °C. The reaction was quenched by pouring over ice (6 g/mmol) and the solution filtered and extracted using ethyl acetate (3 × 75 mL). The organic layers were dried over magnesium sulphate and concentrated under vacuum. Purification using silica column chromatography (Hexane:EtOAc, 4:1) yielded **6e** as a brown solid: mp = 120–122 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 1.28 (q, 2H, *J* = 6.3 Hz),

2.27 (broad t, 2H), 3.11 (broad t, 2H, *J* = 6.3 Hz), 8.36 (s, 1H), 8.72 (s, 1H) ppm. $^{13}$C NMR (100Hz, $CDCl_3$) δ: 13.7 ($CH_2$), 23.6 ($CH_2$), 26.5 ($CH_2$), 116.0 ($CF_3$), 118.5 (CH), 120.0 (C=), 127.3 (CH), 130.0 (C-$NO_2$), 135.4 (C=), 141.0 (C-$NO_2$), 169.0 (CO) ppm. HRMS (ESI, MeOH) m/z found $[M+H]^+$ 320.0424, $C_{11}H_8F_3N_3O_5$ requires $[M + H]^+$ 320.0416. IR 1705 (CO), 1543, 1522 ($NO_2$), 1157 ($CF_3$) $cm^{-1}$.

**6-Nitro-*N*-trifluoroacetyl-1,2,3,4-tetrahydroquinoline (1e) and 8-nitro-*N*-trifluoroacetyl-1,2,3,4-tetrahydroquinoline (5e)**

A solution of **1e** (1 equiv.) in DCM was cooled at –25 °C and concentrated sulphuric acid (1 equiv.) was added. Then, potassium nitrate (1 equiv.) was added to the solution. The mixture was stirred for thirty minutes at –25 °C and was quenched by pouring over ice. The solution was extracted with DCM, and the organic layer washed with 2N HCl and dried with $Na_2SO_4$. After concentration in vacuum, a mixture of 6-nitro **1e** (75%, brown solid) and 8-nitro **5e** (25 %, brown solid) was obtained and separated using silica column chromatography.

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**6-Nitro-*N*-trifluoroacetyl-1,2,3,4-tetrahydroquinoline, 1e:** mp = 110-112 ºC; $^1$H NMR (400 MHz, $CDCl_3$) δ: 2.17 (q, 2H, *J* = 6.8 Hz), 3.03 (t, 2H, *J* = 6.8 Hz), 3.92 (t, 2H, *J* = 5.9 Hz), 7.92 (broad d, 1H, *J* = 8.0 Hz), 8.1 (broad d, 1H, *J* = 2.7 Hz), 8.11 (s, 1H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 22.9 ($CH_2$), 26.3 ($CH_2$), 45.1 ($CH_2$), 114.9 ($CF_3$), 121.5 (CH), 124.6 (CH), 125.3 (CH), 132.2 (C=), 142.3 (C-$NO_2$), 145.1 (C=), 155.9 (CO) ppm. HRMS (ESI, MeOH) m/z found $[M+H]^+$ 275.0558, $C_{11}H_9F_3N_2O_3$ requires $[M + H]^+$ 275.0565. IR 1694 (CO), 1514 ($NO_2$), 1148 ($CF_3$) $cm^{-1}$.

**8-nitro-*N*-trifluoroacetyl-1,2,3,4-tetrahydroquinoline, 5e:** $^{1}$H NMR (400 MHz, DMSO) δ: 2.03 (q, 2H, *J* = 6.6 Hz), 2.97 (t, 2H, *J* = 6.6 Hz), 3.84 (t, 2H, *J* = 6.6 Hz), 7.51 (t, 1H, *J* = 7.6 Hz), 7.56 (d, 1H, *J* = 8.4 Hz), 7.67 (d, 1H, *J* = 7.6 Hz) ppm.

***N*-Fluorenylmethyloxycarbonyl-1,2,3,4-tetrahydroquinoline (2f)**

To a solution of THQ (3.75 mmol) in DCM (10 mL) at 0 °C, fluorenylmethyloxycarbonyl chloride (1.1 equiv.) and TEA (1.1 equiv.) were added. After stirring overnight at room temperature, the solvent was evaporated under reduced pressure. The residue was taken up with EtOAc and washed with 1N HCl (3 × 15 mL) and brine (2 × 15 mL). The organic layer was dried ($Na_2SO_4$) and concentrated in vacuum to give 0.93 g (70 %) of **2f** as a yellow solid: mp = 90–92 ºC. $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 1.94 (q, 2H, *J* = 6.8 Hz), 2.79 (t, 2H, *J* = 6.8 Hz), 3.75 (t, 2H, *J* = 6.8 Hz), 4.31 (t, 1H, CH, *J* = 6.4 Hz), 4.61 (d, $CH_2$, *J* = 6.4 Hz), 7.03 (m, 2H), 7.10 (m, 2H), 7.32 (t, 2H, *J* = 7.6 Hz.), 7.43 (t, 2H, *J* = 7.6 Hz), 7.58 (d, 2H, *J* = 7.6 Hz), 7.80 (d, 2H, *J* = 7.6 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 23.4 ($CH_2$), 27.2 ($CH_2$), 44.8 ($CH_2$), 47.3 (CH-Fmoc), 67.5 ($CH_2$-Fmoc), 120.0, 123.7, 124.1, 124.9, 125.9, 127.1, 127.7, 128.5, 130.1, 137.9 (C=), 141.4 (C=), 143.9 (C=), 154.7 (CO). HRMS (ESI, MeOH) m/z found $[M + H]^+$ 356.1575, $C_{24}H_{21}NO_2$ requires $[M + H]^+$ 356.1572. IR 1702 (CO) $cm^{-1}$.

**6-Nitro-*N*-fluorenylmethyloxycarbonyl-1,2,3,4-tetrahydroquinoline (1f)**

To a solution of **2e** (1 equiv.) in DCM (5 mL) at room temperature, concentrated sulphuric acid (1 equiv.) was added. Then, potassium nitrate (1 equiv.) was added to the solution, the mixture was stirred for 2:30 h and was quenched by pouring over ice. The solution was extracted with DCM, and the organic layer washed with water and dried with $Na_2SO_4$. Finally, after concentration in vacuum, 100% of **1f** was obtained as brown syrup. $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 1.91 (q, 2H, *J* = 6.1 Hz), 2.81 (t, 2H, *J* = 6.1 Hz), 3.71 (t, 2H, *J* = 6.1

Hz), 4.30 (t, 1H, CH, *J* = 5.5 Hz), 4.74 (d, 2H, $CH_2$, *J* = 5.5 Hz), 7.35 (t, 2H, *J* = 7.2 Hz), 7.44 (t, 2H, *J* = 7.2 Hz), 7.55 (broad d, 1H), 7.58 (d, 2H, *J* = 7.3 Hz), 7.80 (d, 2H, *J* = 7.3 Hz), 7.84 (d, 1H, *J* = 7.7 Hz), 7.94 (s, 1H) ppm; $^{13}$C NMR (100Hz, $CDCl_3$) δ : 22.3($CH_2$), 27.5 ($CH_2$), 45.1 ($CH_2$), 47.1 (CH-Fmoc), 67.6 ($CH_2$-Fmoc), 119.9 (Fmoc), 121.5 (arom), 123.4 (arom), 123.8 (arom), 124.5 (Fmoc), 127.0 (Fmoc), 127.7 (Fmoc), 130.0 (C=), 141.3 (C=), 143.4 (C=), 143.6 (C-$NO_2$), 154.1 (CO); HRMS (ESI, MeOH) m/z found $[M + Na]^+$ 423.1429, $C_{24}H_{20}N_2O_4$ requires $[M + Na]^+$ 423.1423. IR 1707 (CO), 1511 ($NO_2$) $cm^{-1}$.

***Deprotection of 6-nitro-N-Protected-THQ (1b, 1d, 1e and 1f) and 8-nitro-N-Protected-THQ (5c) derivatives***

**Deprotection of 6-nitro-*N*-acetyl-1,2,3,4-tetrahydroquinoline (1b)** or **6-nitro-*N*-pivaloyl-1,2,3,4-tetrahydroquinoline (1d):** After dilution of **1b** (0.5 g) or **1d** (0.5 g) with ethanol (5 mL), water (2.5 mL) and HCl (1 mL) were added, and the mixture refluxed for 4 h. Then, the mixture was diluted with water and **1a** precipitated as a red solid in a 90% yield.

**Deprotection of 6-nitro-*N*-trifluoroacetyl-1,2,3,4-tetrahydroquinoline (1e)**

After dilution of **1e** (0.6 g) in 25 mL of MeOH a solution of $K_2CO_3$ (1.5 equiv.) in 20 mL of water was added. The mixture was refluxed for 1 h, MeOH was then evaporated and the residue washed three times with EtOH. The organic solution was dried ($Na_2SO_4$) and concentrated under vacuum. Compound **1a** was obtained by crystallization as red crystals (85%).

**Deprotection of 6-nitro-*N*-fluorenylmethyloxycarbonyl-1,2,3,4-tetrahydroquinoline (1f)**: Compound **1f** (0.1 g) was dissolved in 10 mL of DCM. Then, 5 mL of pyrrolidine were added. After 5 min, the reaction was finished yielding **1a** as red crystals (85%).

**6-Nitro-1,2,3,4-tetrahydroquinoline, 1a:** mp = 160–162 °C (lit.[9] 161–162 °C); $^{1}$H NMR (600 MHz, DMSO) δ: 1.79 (q, 2H, $CH_2$, *J* = 6.3 Hz), 2.72 (t, 2H, *J* = 6.3 Hz), 3.29 (q, 2H, *J* = 3.3 Hz), 6.48 (d, 1H, *J* = 8.9 Hz), 7.43 (broad s, 1H, NH), 7.76 (d, 1H, *J* = 2.7 Hz), 7.78 (dd, 1H, *J* = 2.7 Hz, *J* = 8.9 Hz) ppm; $^{13}$C NMR (150 MHz, DMSO) δ: 20.0 ($CH_2$), 26.3 ($CH_2$), 40.5 ($CH_2$), 111.7 (arom), 119.1 (C=), 124.1 (arom), 125.2 (arom), 134.7 (C-$NO_2$), 151.6 (C=).

$^{1}$H NMR (600 MHz, $CDCl_3$) δ: 1.97 (q, 2H, $CH_2$, *J* = 6.0 Hz), 2.81 (t, 2H, *J* = 6.0 Hz), 3.43 (q, 2H, *J* = 6.0 Hz), 4.76 (broad s, 1H, NH), 6.38 (dd, 1H, *J* = 8.9 Hz, *J* = 3.7 Hz), 7.90 (m, 2H) ppm.

HRMS (ESI-, MeOH) m/z found $[M - H]^+$ 177.0732, $C_9H_{10}N_2O_2$ requires $[M - H]^+$ 177.0742. IR 3374 (NH), 1514 ($NO_2$) $cm^{-1}$.

**Deprotection of 8-nitro-*N*-acetyl-1,2,3,4-tetrahydroquinoline (5c)** After dilution of **5c** (0.5 g) with EtOH (5 mL), water (2.5 mL) and HCl (1 mL) were added and the mixture was refluxed for 4 h. After that, the mixture was diluted with water and **5a** precipitated as a red (90%).

**8-Nitro-1,2,3,4-tetrahydroquinoline, 5a:** mp = 48–50 °C (lit.[9] 71 °C); $^{1}$H NMR (600 MHz, DMSO) δ: 1.83 (q, 2H, $CH_2$, *J* = 5.8 Hz), 2.79 (t, 2H, *J* = 6.2 Hz), 3.46 ( broad q, 2H), 6.51 (dd, 1H, *J* = 8.5 Hz, *J* = 6.8 Hz), 7.21 (d, 1H, *J* = 6.8 Hz), 7.85 (d, 1H, *J* = 8.5 Hz), 8.46 (broad s, 1H, NH) ppm; $^{13}$C NMR (150 MHz, DMSO): 19.8 ($CH_2$), 27.6 ($CH_2$), 41.4 ($CH_2$), 114.3 (arom.), 124.2 (arom.), 125.6 (C-$NO_2$), 130.1 (arom.), 135.3 (arom.), 143.3 (arom.) ppm.

$^{1}$H NMR (600 MHz, $CDCl_3$) δ: 2.00 (q, 2H, $CH_2$, *J* = 6.0 Hz), 2.86 (t, 2H, *J* = 6.0 Hz), 3.55 (t, 2H, *J* = 6.0 Hz), 6.51 (d, 1H, *J* = 7.0 Hz), 7.14 (dd, 1H, *J* = 7.0 Hz, *J* = 1.7 Hz), 7.99 (dd, 1H,

*J* = 7.0 Hz, *J* = 1.7 Hz), 8.36 (broad s, 1H, NH) ppm; $^{13}$C NMR (150 MHz, $CDCl_3$): 20.1 ($CH_2$), 27.8 ($CH_2$), 41.3 ($CH_2$), 114.3 (arom.), 124.7 (arom.), 128.8 (C-$NO_2$), 130.9 (arom.), 134.9 (arom.), 143.4 (arom.).

HRMS (ESI, MeOH) m/z found $[M]^+$ 178.0746, $C_9H_{10}N_2O_2$ requires $[M + H]^+$ 178.0742. IR 3375 (NH), 1511 ($NO_2$) $cm^{-1}$.

*Computational details*

Geometries of the stationary structures were fully optimized at the B3LYP theoretical level with the 6-31++G** basis set as implemented in the Gaussian 03 program.[25] Frequency calculations have been carried out at the same computational level to confirm that all relevant structures correspond to energetic minima or real transition states. For the condensed-phase calculations, the PCM as implemented in Gaussian was employed to account for continuum solvation effects.

**Supporting Information Available**

Copies of $^1$H and $^{13}$C NMR spectra of all compounds **1**, **2**, **3**, **4** and **5** derivatives, HSQC and HMBC spectra and cartesian coordinates of the optimized structures at B3LYP/6-31++g(d,p) Level available free of charge via the Internet at http://pubs.acs.org.

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