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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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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 several of its *N*-protected derivatives both experimentally and at theoretical level. Usually, nitration is carried out in acidic conditions and, thus, tetrahydroquinoline would be *N*-protonated; however, if the amino group is protected, the neutral system will be the one undergoing nitration. Different protecting groups have been explored varying, not only electronic and steric effects, but also deprotection conditions. Additionally, different reagents and reaction conditions have been investigated. From this study we have been able to achieve total regioselectivity for nitration at the 6-position. A very detailed NMR study has been carried out to unequivocally characterise the four nitro isomers. 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 have been optimized both in gas and water condensed phases 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).[1] The electrophilic aromatic substitution (EAS) reactivity and selectivity have been discussed in depth for a number of aromatic compounds; however, very few examples of the direct nitration of **2** were found.

Thus, the first references to THQ-nitro derivatives are found in the late ninetieth century, with the works of Hoffman and Königs[2] and subsequently Stoermer.[3] Few years later 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 (**4a**, Figure 1). In 1952, Kulka and Manske[5] reproduced the nitration of **2a** as described by Braun et al. (HNO_3/H_2SO_4 at 0 °C) yielding 65% of 7-nitro-THQ (**4a**). They also studied the nitration of the *N*-acetyl-THQ (**2c**, Figure 1) with KNO_3 in concd. H_2SO_4 obtaining, after hydrolysis, a mixture of the 6- and the 7-nitro-THQ (**1a** and **4a**) approximately in a 2:1 ratio. 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, these results were later refuted.

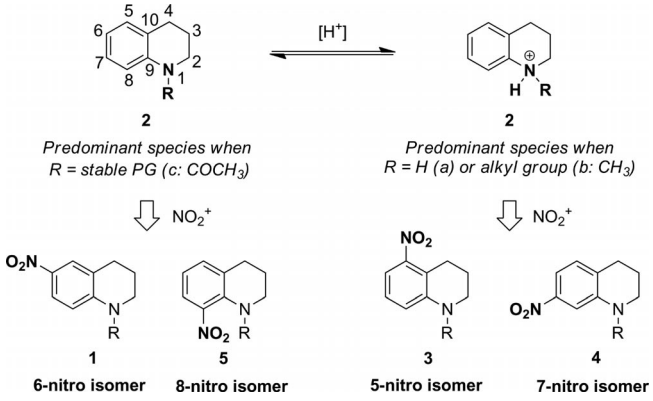

Figure 1. Structure of THQ (**2**), its nitro derivatives (**1**, **3**, **4** and **5**) and selectivity criteria for THQ nitration depending on the *N*-protective group.

Between 1970 and 1973, Levkoeva et al. published the preparation of some of the THQ nitro compounds.[7] In 1972, Utley and Vaughan studied the nitration of **2a** and some *N*-methyl-THQ derivatives in a more systematic way.[8] They observed that by using KNO_3/H_2SO_4 82%, the tertiary amino group, even though in an equilibrium be-

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tween the neutral and the protonated form, was clearly shifted to the second one (Figure 1). Under these conditions, *N*-methyl-THQ (**2b**) was nitrated on position 7 (compound **4b**) in 71% yield and a small but significant fraction of *N*-methyl-6-nitro-THQ (**1b**) (23%) was obtained. In this article, it is also reported the nitration (HNO_3/H_2SO_4) of the unsubstituted THQ (**2a**) giving, as expected, **4a** (58%) and a second product in a very low yield identified by the authors as "8-nitro-THQ" (1.1%). Besides, 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 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 by them as "5-nitro-THQ" (2.5%).

In 1976, Amit, Ben-Efrein and Patchornick,[9] realizing the discrepancies reported on the nitration of THQ, prepared the four nitro isomers (5-, 6-, 7- and 8-nitro-THQs) and reported their identification by spectroscopic properties (90-MHz ^{1}H NMR chemical shifts, experimental and calculated from substituent contribution and coupling constants). Firstly, when repeating the procedure described by Richardson and Amstutz to prepare 8-nitro-THQ (**5a**) from *N*-acetyl-THQ, they noted that two compounds were obtained; after acidic hydrolysis these were separated yielding the 6-nitro isomer (80%) and a second nitro-THQ, of melting point 71 °C, in 16% yield. Nitration of the unsubstituted THQ in concentrated sulfuric acid in their hands yielded **4a** (51%), as well as a second isomer melting at 83 °C (7.5%). They characterised all isomers obtained by ^{1}H NMR (90 MHz) confirming that the secondary product of the nitration of THQ and m.p. 83 °C was the 5-nitro-THQ (**3a**), while the secondary product of nitration of *N*-acetyl-THQ and m.p. 71 °C corresponded to the 8-nitro-THQ (**5a**). Therefore, the structural assignments previously reported by Utley and Vaughan were reversed.

Since 1980s, 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.[10]

As has just been discussed, there have been contradictions concerning the selectivity in the nitration of the THQ (**2a**) or its *N*-acetyl derivative (**2c**), as well as a lack of discussion of the use of general amino protecting groups to direct nitration. 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 several *N*-protected-THQ derivatives. Thus, nitration 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 DFT level (B3LYP/6-31++G**) were performed to provide a better understanding of the selectivity of the process.

Results and Discussion

Experimental Study of Nitration of THQ

A general scheme of the selectivity in the nitration of THQ and its *N*-substituted derivatives is presented in Figure 1. Based on the CIP criteria, from now on the orientation – *ortho*, *meta* or *para* – will be referred with respect to the C atom substituted by the amine group. In an initial approach, the 1,2 position of the two substituents in THQ, alkyl chain and amino group, produce a 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 1). Thus, in the nitration reaction of THQ 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 the expected selectivity should be on the *meta* positions producing the 5- and/or 7-nitro derivatives (**3** and **4**, respectively). Additionally, the *N*-substitution by a CO-linked protective group reduces the basicity of the amine avoiding protonation, and thus, in the nitration of *N*-CO 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.

First, the direct nitration of deprotected THQ using KNO_3 and H_2SO_4 standard conditions was carried out (Table 1, entries 1–2). 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.[4,5,8,9] Only when the reaction was carried out in larger scale, traces of the 6-nitro-THQ (**1a**) were detected by NMR and mass spectroscopic analysis.

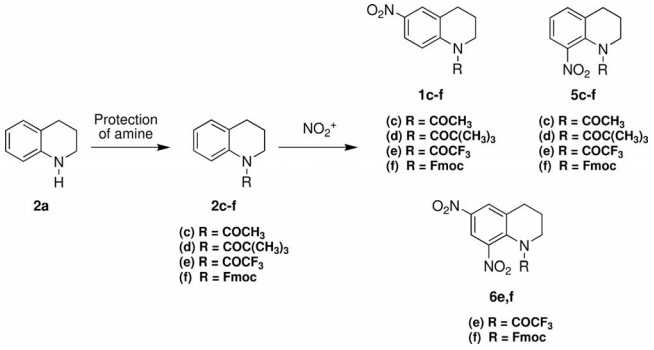
As explained before, the synthesis of our target compound (6-nitro-THQ, **1a**) by direct nitration of THQ, requires the protection of the amino group. Nitration of *N*-acetyl-THQ (**2c**) had been previously reported by the treatment of *N*-acetyl-THQ with nitric acid (1.48 equiv.) in acetic anhydride yielding a mixture of 6- and 8-nitro derivatives in a 80:20 ratio.[9] Using strictly the same conditions, we obtained 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 1, 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 were then considered to improve the selectivity of the reaction (Scheme 1).

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 the larger pivaloyl (trimethylacetyl) was explored. Reaction of **2a** with pivaloyl chloride in pyridine at

Table 1. Selectivity in percentage (%) 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	Temperature	Time	SM[a]	**3**	**1**	**4**	**5**	**6**
1	H	KNO_3/H_2SO_4	0 °C, r.t.[d]	1 h	9[b]	18[b]	–	73[b]	–	–
2	H	KNO_3/H_2SO_4	0 °C, r.t.[d]	1 h	36[b]	11[b]	5[b]	48[b]	–	–
3	$COCH_3$	1.5 equiv. HNO_3/Ac_2O	–10 °C, r.t.[d]	24 h	–	–	50	–	50	–
4	$COCH_3$	1.5 equiv. HNO_3/Ac_2O	–10 °C	4 h	–	–	50	–	50	–
5	$COCH_3$	1.2 equiv. HNO_3/Ac_2O	–10 °C, r.t.[d]	24 h	–	–	50	–	50	–
6	$COCH_3$	1.2 equiv. HNO_3/Ac_2O	–10 °C	4 h	–	–	50	–	50	–
7	$COC(CH_3)_3$	1.5 equiv. HNO_3/Ac_2O	–10 °C	4 h	–	–	80	–	20	–
8	$COCF_3$	1.0 equiv. KNO_3/H_2SO_4	0 °C	10 m	40	–	30	–	20	10
9	$COCF_3$	1.0 equiv. $KNO_3H_2SO_4$	0 °C	30 m	–	–	40	–	–	60
10	$COCF_3$	1.0 equiv. KNO_3/H_2SO_4/DCM[c]	0 °C	30 m	10	–	30	–	20	40
11	$COCF_3$	1.0 equiv. KNO_3/H_2SO_4/DCM[c]	–25 °C	30 m	–	–	75	–	25	–
12	Fmoc	1.0 equiv. KNO_3/H_2SO_4/DCM[c]	–25 °C	8 h	> 90	–	–	–	–	–
13	Fmoc	1.0 equiv. KNO_3/H_2SO_4/DCM[c]	0 °C	8 h	60	–	10	–	–	30
14	Fmoc	1.0 equiv. KNO_3/H_2SO_4/DCM[c]	r.t.[d]	2 h 30 m	–	–	> 99	–	–	–

[a] SM = starting material. [b] Total yield of isolated products. [c] Reaction diluted with dichloromethane (DCM). [d] Room temp. = 25 °C.



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

room temperature afforded the protected compound **2d**, in 80% yield. Next, the treatment of **2d** with nitric acid (1.48 equiv.) in acetic anhydride, 4 hours at –10 °C was carried out and, as postulated, a considerable increase in the selectivity was observed since the 6-nitro and 8-nitro derivatives (**1d** and **5d**) were obtained in a 80:20 ratio.

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 the presence of the 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 using KNO_3 and H_2SO_4 in acetic anhydride. As shown in Table 1 (entries 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 (see Supporting Information) 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.

To optimize the reaction conditions avoiding dinitration and favouring the selectivity towards the 6-nitro derivative the temperature influence was assessed at constant time (30 min). 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 1 (entry 11), an experiment conducted at –25 °C 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 2) evidenced the influence of temperature in the mono-

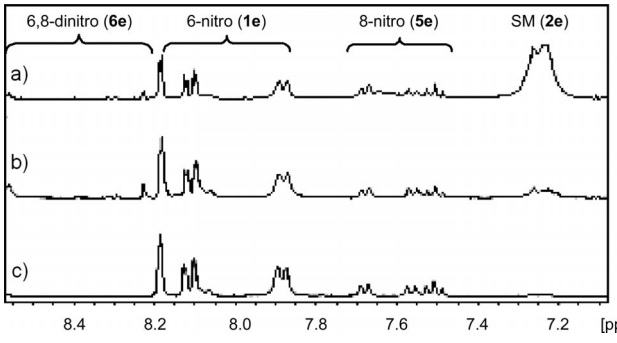


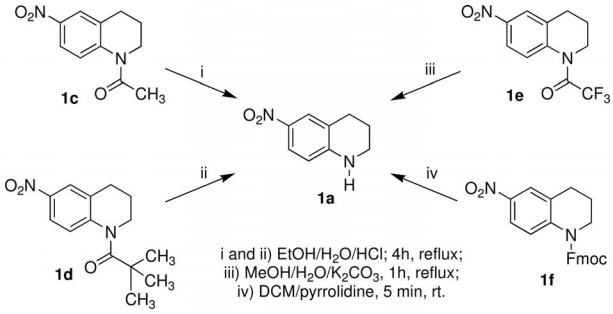
Figure 2. ^{1}H NMR spectrum of nitration of *N*-trifluoroacetyl-THQ (**2e**) at: a) 0 °C and 10 min, b) 0 °C and 30 min, and c) –25 °C and 30 min (SM = starting material).

nitration of *N*-trifluoroacetamide-THQ, showing that a temperature decrease results in the lack of formation of the dinitro compound.

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. This approach was found to be very sensitive to small experimental changes and was abandoned.

Finally, we introduced, as amine protection, an even bulkier group than pivaloyl, the fluorenylmethyloxycarbonyl (Fmoc). This group 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, yielding compound **2f** in 70%. Nitration of Fmoc-protected THQ was explored at three different conditions of temperature and time (see Table 1, entries 12–14). At –25 °C (our best conditions using $COCF_3$ as protecting group) the reaction was very slow and only starting material was recovered after 8 hours. When the reaction was performed at 0 °C, during the same amount of time, still 60% of starting material was recovered; however, the 6-nitro derivative was produced together with a significant fraction of the dinitro compound (**6f**). The best result with Fmoc was obtained when the reaction was carried out at room temperature and during only 2 hours and a half, reaching > 99% 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-Nitrotetrahydro Quinoline Derivatives

The δ and J values (^1H and ^{13}C NMR) obtained in this work for the four 5-, 6-, 7- and 8-nitro-THQs (**3a**, **1a**, **4a** and **5a**) are presented Table 2. The unambiguous assignation of each isomer has been carried out through a careful analysis of NMR using ^1H and ^{13}C NMR and techniques such as HMBC, HSQC and ROESY. 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 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 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 H^1 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 2. ^1H 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.

^1H	δH^1	δH^2	δH^3	δH^4	δH^5	δH^6	δH^7	δH^8
3a	6.41 s	3.02 q	1.77 q	2.75 t		6.94 dd $J_{6,7}$ = 7.9, $J_{6,8}$ = 1.1	7.05 dd $J_{7,8}$ = 8.3, $J_{7,9}$ = 7.9	6.73 dd, $J_{7,8}$ = 8.3, $J_{6,8}$ = 1.1
1a	7.43 s	3.29 q	1.79 q	2.72 t	7.76 d $J_{5,7}$ = 2.7		7.78 dd $J_{5,7}$ = 8.9, $J_{7,8}$ = 2.7	6.48 d $J_{7,8}$ = 8.9
4a	6.42 s	3.22 q	1.81 q	2.75 t	7.07 d $J_{5,6}$ = 8.0	7.22 dd $J_{5,6}$ = 8.0, $J_{6,8}$ = 2.5		7.27 d $J_{6,8}$ = 2.5
5a	8.46 s	3.46 q	1.83 q	2.79 t	7.21 dd[a] $J_{5,6}$ = 6.8, $J_{5,6}$ = 1.5	6.51 dd $J_{5,6}$ = 6.8, $J_{6,7}$ = 8.5	7.85 dd[a] $J_{6,7}$ = 8.5, $J_{5,6}$ = 1.5	

^{13}C	δC^2	δC^3	δC^4	δC^5	δC^6	δC^7	δC^8	δC^9	δC^{10}
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 3) were employed to discern between the isomers **1a**/**4a** (ABX) and **3a**/**5a** (ABC) respectively. The irradiation of H^1 (NH) proton at δ = 6.42 ppm in the sample corresponding to one of the ABX systems identified the signal at δ = 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 H^4 proton at δ = 2.79 ppm in the sample corresponding to one of the ABC systems identified the signal at δ = 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 3) 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 H^5 and C^4 was only present in compounds **1a**, **4a** and **5a**. This correlation is not possible in compound **3a** because it has position 5 substituted.

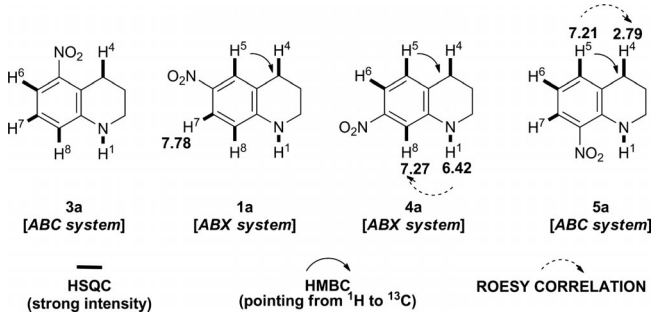


Figure 3. NMR structural elucidation of compounds **1a**, **4a**, **3a** and **5a**. Most relevant ^1H and ^{13}C chemical shifts are indicated in red and blue, respectively.

The ^1H-NMR of compounds **3a**, **1a**, **4a** and **5a** are gathered in Figure 4. 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[11] is followed, where chemical shifts of the aromatic hydrogen atoms are in the order *ortho* > *para* > *meta*. This influence is similarly manifested in the amine hydrogen atoms. The H^1 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 (δ = 7.43 ppm) is observed in compound **1a** with *para* orientation and the largest value (δ = 8.46 ppm) is shown for compound **5a** where the nitro group is located in *ortho* position 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 *ipso*-C to the nitro substituent compared with the rest of the aromatic C atoms is observed (Table 2).

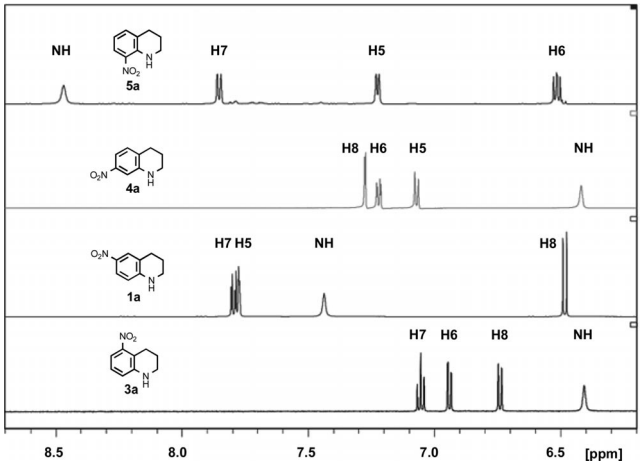


Figure 4. Aromatic region of the ^1H NMR spectra of compounds **1a**, **4a**, **3a** and **5a**.

On the contrary, it is known that the interaction by hydrogen bond produces a deshielding of the hydrogen involved.[12] Thus, the large chemical shift observed for H^1 in compound **5a** could be simultaneously influenced by the existence of an intramolecular hydrogen bond interaction between this amine hydrogen and the lone pair of one of the oxygen atoms of the nitro group.

Computational Study

In a parallel computational 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 mechanisms: the classical "Ingold–Hughe" interpretation or polar two-electron mechanism[13] and the subsequently proposed single-electron transfer (SET) mechanism.[14] One of the most thorough studies about theoretical understanding of aromatic nitration was carried out by Olah et al. in 2003.[15] 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 depending on the system and experimental conditions, the interaction between benzene and the nitronium cation could involve either a SET or a polar two-electron mechanism. 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: (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.[16]

We have considered these different mechanisms for the nitration of THQ (Figure 5) taking into account that the formation of the σ complex is the rate-determining step of the reaction, and the subsequent step of proton elimination occurs comparatively faster. Hence, the relative stability of the σ complex, and/or the oriented π complex (usually in a narrow energy range) determines the positional selectivity of the process (regioselectivity). Thus, we have focused on the relative stability of the σ complexes as a criterion of selectivity and 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) THQ nitration in both its unprotonated and protonated forms (Figure 6) 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 hybridization of the substituted carbon, showing NCH angles of about 100° 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 C atom 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.

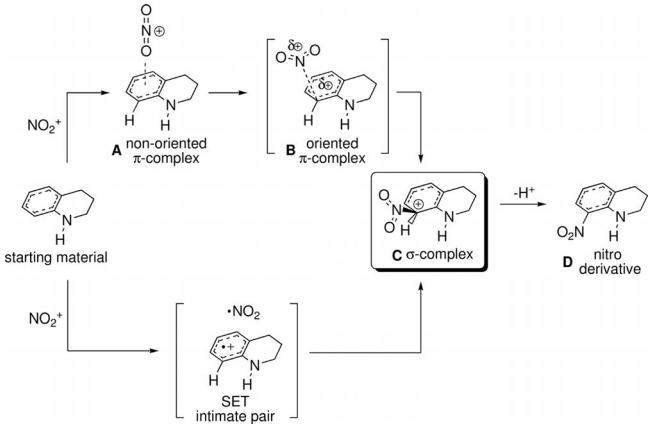


Figure 5. Different complexes and transition states involved in one of the four possible nitration processes of THQ.

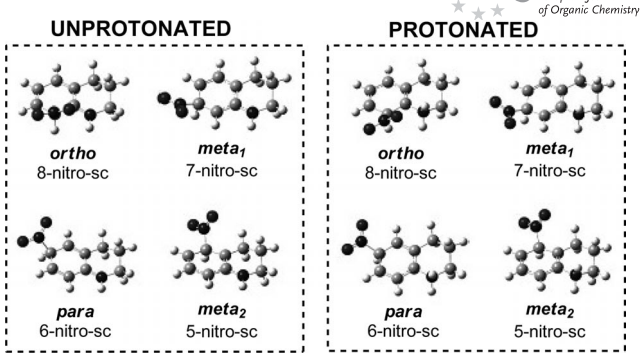


Figure 6. σ-Complexes of the unprotonated and protonated forms of all possible nitro-THQ calculated at B3LYP/6-31++G** computational level.

The corresponding calculated energies are gathered in Table 3. 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.[17]

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) is favoured in these conditions, being the 6-nitro intermediate the most stable. 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.

Table 3. Total (E_T, a.u.) and relative (E_r, kJ mol^{-1}) energies obtained for all σ complexes (U: unprotonated, P: protonated) calculated both in gas (G) and solvated (S) phases using the B3LYP/6-31++G** level.

σ Complex			5-nitro-sc	6-nitro-sc	7-nitro-sc	8-nitro-sc
G	U	E_T	–609.170867	–609.217378	–609.175482	–609.211497
		E_r	122.1	**0.0**	110.0	15.4
	P	E_T	[a]	[a]	[a]	–609.365654
S	U	E_T	–609.265468	–609.316745	–609.270778	–609.304926
		E_r	134.6	**0.0**	120.7	31.0
	P	E_T	–609.684991	–609.683123	–609.690940	–609.677669
		E_r	15.6	20.5	**0.0**	34.8

[a] Unstable, minimum not found.

In the case of the Wehland intermediates of the protonated species (Table 3), 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 rôle of the protection 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 *N*-protecting groups. Thus, a thorough study on the nitration of THQ and different *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. Nitration is often 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 (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 (object of our interest) by using Fmoc, KNO_3/H_2SO_4/DCM, at room temperature during 2 h and 30 min.

A very detailed NMR study was required to unequivocally characterise the four nitro isomers and, hence, different ^1H, ^{13}C and 2D NMR experiments 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 was performed and hence all the σ complexes of the four nitro isomers unprotonated and *N*-protonated were optimised both in gas phase and in water condensed phase by using the B3LYP/6-31++G** level of computation. The energy results, obtained using solvation, confirm that the *N*-protonation (unprotected THQ) facilitates nitration in the *meta* positions whereas the unprotonated systems (our *N*-protected THQs) yield nitration in the *ortho* and *para* positions, 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

General: Commercially available materials were obtained from Sigma–Aldrich. Melting points were obtained using a 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 ^1H-NMR and ^{13}C-NMR spectroscopy. Shifts are referenced to the internal solvent signals. NMR spectroscopic 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-Nitro-tetrahydroquinoline (3a) and 7-Nitro-tetrahydroquinoline (4a): Concentrated sulfuric 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 with magnesium sulfate and concentrated under vacuum. Purification using silica column chromatography (hexane/EtOAc, 4:1) yielded **4a** (1.4 g, 48%) and **3a** (0.34 g, 11%) as orange crystals.

7-Nitro-1,2,3,4-tetrahydroquinoline (4a): M.p. 57–58 °C (ref.[9] 63–65 °C). ^1H NMR (600 MHz, DMSO): δ = 1.81 (q, J = 4.0 Hz, 2 H), 2.75 (t, J = 6.0 Hz, 2 H), 3.22 (dt, J = 4.0, J = 2.0 Hz, 2 H), 6.42 (s, 1 H, NH), 7.07 (d, J = 8.0 Hz, 1 H), 7.22 (dd, J = 8.0, J = 2.5 Hz, 1 H), 7.27 (d, J = 2.5 Hz, 1 H) 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: $\tilde{\nu}$ = 3416 (NH), 1511 (NO_2) cm^{-1}.

5-Nitro-1,2,3,4-tetrahydroquinoline (3a): Ref.[9] m.p. 80–82 °C. ^1H NMR (600 MHz, DMSO): δ = 1.77 (q, J = 5.6 Hz, 2 H), 2.75 (t, J = 5.6 Hz, 2 H), 3.20 (dt, J = 5.6 Hz, 2 H), 6.41 (br. s, 1 H, NH), 6.73 (dd, J = 8.3, J = 1.1 Hz, 1 H), 6.94 (dd, J = 7.9, J = 1.1 Hz, 1 H), 7.05 (dd, J = 8.3, J = 7.9 Hz, 1 H) ppm. ^{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 (2c):** 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 1 N HCl (3 × 15 mL) and brine (2 × 15 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give 0.58 g (89%) of **2c** as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.97 (q, J = 6.0 Hz, 2 H), 2.24 (s, 3 H, CH_3), 2.73 (t, J = 6.0 Hz, 2 H) 3.81 (t, J = 6.0 Hz, 2 H), 7.16 (m, 4 H, arom) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 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: $\tilde{\nu}$ = 1707 (CO) cm^{-1}.

***N*-Acetyl-6-nitro-1,2,3,4-tetrahydroquinoline (1c) and *N*-Acetyl-8-nitro-1,2,3,4-tetrahydroquinoline (5c):** A mixture of 70% nitric acid (1.48 equiv.) and acetic anhydride (3 mL), cooled to 0 °C, was added dropwise to a solution of *N*-acetyl-THQ (**2c**) in acetic anhydride (3 mL) between –10 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 diethyl ether. The organic extracts were washed with diluted $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated in vacuo to give a mixture of 6-nitro **1c** and 8-nitro **5c** (50%:50% characterized by NMR) that were separated using silica column chromatography.

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

***N*-Acetyl-8-nitro-1,2,3,4-tetrahydroquinoline (5c):** Brown solid, m.p. 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (m, 2 H), 2.33 (s, 3 H, CH_3), 2.86 (m, 2 H), 3.85 (m, 2 H), 7.21 (t, J = 7.9 Hz, 1 H), 7.37 (d, J = 7.9 Hz, 1 H), 7.72 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 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: $\tilde{\nu}$ = 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 to 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 1 N HCl (3 × 15 mL) and brine (2 × 15 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give 0.65 g (80%) of **2d** as yellow crystals with m.p. 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 9 H, 3CH_3), 2.02 (q, J = 6.3 Hz, 2 H), 2.79 (t, J = 7.1 Hz, 2 H) 3.81 (t, J = 6.3 Hz, 2 H) 7.11 (m, 3 H), 7.40 (d, J = 8.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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: $\tilde{\nu}$ = 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 diethyl ether. The extracts were washed with diluted $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated in vacuo to give a mixture of 6-nitro **1d** and 8-nitro **5d** (80:20%, characterized by NMR) that were separated using silica column chromatography.

6-Nitro-*N*-pivaloyl-1,2,3,4-tetrahydroquinoline (1d): Yellow solid, m.p. 81–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, CH_3), 2.07 (q, J = 5.7 Hz, 2 H), 2.95 (t, J = 7.1 Hz, 2 H), 3.87 (t, J = 5.7 Hz, 2 H), 7.62 (d, J = 9.1 Hz, 1 H), 7.98 (dd, J = 9.1, J = 2.9 Hz, 1 H), 8.04 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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: $\tilde{\nu}$ = 1645 (CO), 1510 (NO_2) cm^{-1}.

8-Nitro-*N*-pivaloyl-1,2,3,4-tetrahydroquinoline (5d): Brown solid, m.p. 48–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 9 H, CH_3), 2.08 (m, 2 H), 2.93 (t, J = 6.6 Hz, 2 H), 3.45 (m, 2 H), 7.20 (t, J = 7.6 Hz, 1 H), 7.37 (d, J = 7.6 Hz, 1 H), 7.72 (d, J = 7.9 Hz, 1 H) 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: $\tilde{\nu}$ = 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 2 N HCl. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give 0.68 g (80%) of the title compound **2e** as yellow crystals with m.p. 39–41 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09 (m, 2 H), 2.91 (m, 2 H), 3.86 (t, J = 6.0 Hz, 2 H), 7.24 (m, 4 H) ppm. HRMS (ESI, MeOH) *m*/*z* found [M + H]$^+$ 230.0723, $C_{11}H_{10}F_3NO$ requires [M + H]$^+$ 230.0714. IR: $\tilde{\nu}$ = 1681 (CO), 1138, 1170 (CF_3) cm^{-1}.

6,8-Dinitro-*N*-trifluoroacetyl-1,2,3,4-tetrahydroquinoline (6e): Concentrated sulfuric 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 min 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 with magnesium sulfate and concentrated under vacuum. Purification using silica column chromatography (hexane/EtOAc, 4:1) yielded **6e** as a brown solid with m.p. 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (q, J = 6.3 Hz, 2 H), 2.27 (br. t, 2 H), 3.11 (br. t, J = 6.3 Hz, 2 H), 8.36 (s, 1 H), 8.72 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 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: $\tilde{\nu}$ = 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 to –25 °C and concentrated sulfuric 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 2 N HCl and dried with Na_2SO_4. After concentration in vacuo, a mixture of 6-nitro **1e** and 8-nitro **5e** (75%:25%, characterized by NMR) was obtained and separated using silica column chromatography.

6-Nitro-*N*-trifluoroacetyl-1,2,3,4-tetrahydroquinoline (1e): Brown solid, m.p. 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (q, J = 6.8 Hz, 2 H), 3.03 (t, J = 6.8 Hz, 2 H), 3.92 (t, J = 5.9 Hz, 2 H), 7.92 (br. d, J = 8.0 Hz, 1 H), 8.1 (br. d, J = 2.7 Hz, 1 H), 8.11 (s, 1 H) 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: $\tilde{\nu}$ = 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, J = 6.6 Hz, 2 H), 2.97 (t, J =

6.6 Hz, 2 H), 3.84 (t, *J* = 6.6 Hz, 2 H), 7.51 (t, *J* = 7.6 Hz, 1 H), 7.56 (d, *J* = 8.4 Hz, 1 H), 7.67 (d, *J* = 7.6 Hz, 1 H) 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 1 N HCl (3 × 15 mL) and brine (2 × 15 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give 0.93 g (70%) of **2f** as a yellow solid with m.p. 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (q, *J* = 6.8 Hz, 2 H), 2.79 (t, *J* = 6.8 Hz, 2 H), 3.75 (t, *J* = 6.8 Hz, 2 H), 4.31 (t, *J* = 6.4 Hz, 1 H, CH), 4.61 (d, *J* = 6.4 Hz, CH_2), 7.03 (m, 2 H), 7.10 (m, 2 H), 7.32 (t, *J* = 7.6 Hz, 2 H.), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.58 (d, *J* = 7.6 Hz, 2 H), 7.80 (d, *J* = 7.6 Hz, 2 H) ppm. ^{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) ppm. HRMS (ESI, MeOH) *m*/*z* found $[M + H]^+$ 356.1575, $C_{24}H_{21}NO_2$ requires $[M + H]^+$ 356.1572. IR: $\tilde{\nu}$ = 1702 (CO) cm^{-1}.

***N*-Fluorenylmethyloxycarbonyl-6-nitro-1,2,3,4-tetrahydroquinoline 1f):** To a solution of **2e** (1 equiv.) in DCM (5 mL) at room temperature, concentrated sulfuric 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 vacuo, > 99% of **1f** was obtained as brown syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (q, *J* = 6.1 Hz, 2 H), 2.81 (t, *J* = 6.1 Hz, 2 H), 3.71 (t, *J* = 6.1 Hz, 2 H), 4.30 (t, *J* = 5.5 Hz, 1 H, CH), 4.74 (d, *J* = 5.5 Hz, 2 H, CH_2), 7.35 (t, *J* = 7.2 Hz, 2 H), 7.44 (t, *J* = 7.2 Hz, 2 H), 7.55 (br. d, 1 H), 7.58 (d, *J* = 7.3 Hz, 2 H), 7.80 (d, *J* = 7.3 Hz, 2 H), 7.84 (d, *J* = 7.7 Hz, 1 H), 7.94 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 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) ppm. HRMS (ESI, MeOH) *m*/*z* found $[M + Na]^+$ 423.1429, $C_{24}H_{20}N_2O_4$ requires $[M + Na]^+$ 423.1423. IR: $\tilde{\nu}$ = 1707 (CO), 1511 (NO_2) cm^{-1}.

Deprotection of *N*-Protected 6-Nitro-THQ (1c, 1d, 1e and 1f) and *N*-Protected 8-Nitro-THQ (5c) Derivatives: Deprotection of *N*-Acetyl-6-nitro-1,2,3,4-tetrahydroquinoline (1c) or 6-Nitro-*N*-pivaloyl-1,2,3,4-tetrahydroquinoline (1d): After dilution of **1c** (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 crystals 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 (Na2SO_4) and concentrated under vacuum. Compound **1a** was obtained by crystallization as red crystals (85%).

Deprotection of *N*-Fluorenylmethyloxycarbonyl-6-nitro-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): M.p. 160–162 °C (ref.[9] 161–162 °C). ^{1}H NMR (600 MHz, DMSO): δ = 1.79 (q, *J* = 6.3 Hz, 2 H, CH_2), 2.72 (t, *J* = 6.3 Hz, 2 H), 3.29 (q, *J* = 3.3 Hz, 2 H), 6.48 (d, *J* = 8.9 Hz, 1 H), 7.43 (br. s, 1 H, NH), 7.76 (d, *J* = 2.7 Hz, 1 H), 7.78 (dd, *J* = 2.7, *J* = 8.9 Hz, 1 H) 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=) ppm. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.97 (q, *J* = 6.0 Hz, 2 H, CH_2), 2.81 (t, *J* = 6.0 Hz, 2 H), 3.43 (q, *J* = 6.0 Hz, 2 H), 4.76 (br. s, 1 H, NH), 6.38 (dd, *J* = 8.9, *J* = 3.7 Hz, 1 H), 7.90 (m, 2 H) ppm. HRMS (ESI-, MeOH) *m*/*z* found $[M - H]^+$ 177.0732, $C_9H_{10}N_2O_2$ requires $[M - H]^+$ 177.0742. IR: $\tilde{\nu}$ = 3374 (NH), 1514 (NO_2) cm^{-1}.

Deprotection of *N*-Acetyl-8-nitro-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 crystals (90%).

8-Nitro-1,2,3,4-tetrahydroquinoline (5a): M.p. 48–50 °C (ref.[9] 71 °C). ^{1}H NMR (600 MHz, DMSO): δ = 1.83 (q, *J* = 5.8 Hz, 2 H, CH_2), 2.79 (t, *J* = 6.2 Hz, 2 H), 3.46 (br. q, 2 H), 6.51 (dd, *J* = 8.5, *J* = 6.8 Hz, 1 H), 7.21 (d, *J* = 6.8 Hz, 1 H), 7.85 (d, *J* = 8.5 Hz, 1 H), 8.46 (br. s, 1 H, NH) ppm. ^{13}C NMR (150 MHz, DMSO): δ = 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, *J* = 6.0 Hz, 2 H, CH_2), 2.86 (t, *J* = 6.0 Hz, 2 H), 3.55 (t, *J* = 6.0 Hz, 2 H), 6.51 (d, *J* = 7.0 Hz, 1 H), 7.14 (dd, *J* = 7.0, *J* = 1.7 Hz, 1 H), 7.99 (dd, *J* = 7.0, *J* = 1.7 Hz, 1 H), 8.36 (br. s, 1 H, NH) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 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.) ppm. HRMS (ESI, MeOH) *m*/*z* found $[M]^+$ 178.0746, $C_9H_{10}N_2O_2$ requires $[M + H]^+$ 178.0742. IR: $\tilde{\nu}$ = 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.[18] 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 (see footnote on the first page of this article): Analytical and spectral characterization data of compounds **3a**, **4a**, **2c**, **5c**, **1d**, **2d**, **5d**, **1e**, **2e**, **5e**, **6e**, **2f**, **1f**, **1a**, and **5a**. ^{1}H NMR spectrum of the aromatic region of the crude nitration reaction of **2e** at 0 °C, isolated **6e** and isolated **1e**; and the molecular modelling coordinates of the structures optimized.

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