

Study of the regioselectivity of vicarious nucleophilic amination of mononitroquinolines with 1,1,1-trimethylhydrazinium iodide (TMHI)

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Dedicated to Professor Henk C. van der Plas on the occasion of his 80th anniversary

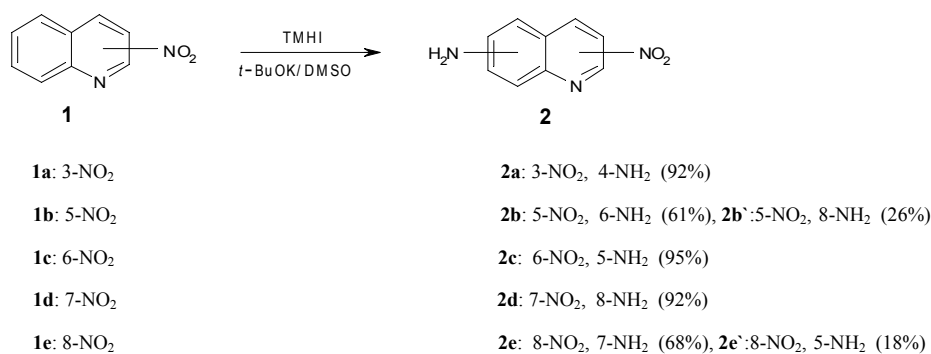
Abstract

The intermediary, covalent σ adducts formed in the reaction of nitroquinolines with the ylide generated from 1,1,1-trimethylhydrazinium iodide (TMHI) were detected by ^1H NMR spectroscopy. Quantum-chemical calculations of the transition state (TS) energy and heats of formation of the σ adducts were done. The results of the calculations agree with high regioselectivity observed for the amination of 3-, 5-, 6-, 7- and 8-nitroquinolines with (TMHI) via a vicarious nucleophilic substitution (VNS) reaction. High yields of the products substituted with amino substituent, mainly in the *ortho* position relation to the nitro group, are obtained.

Keywords: Nitroquinolines, 1,1,1-trimethylhydrazinium iodide (TMHI), vicarious nucleophilic substitution of hydrogen (VNS), covalent σ adducts, quantum-chemical calculations, PM3 method

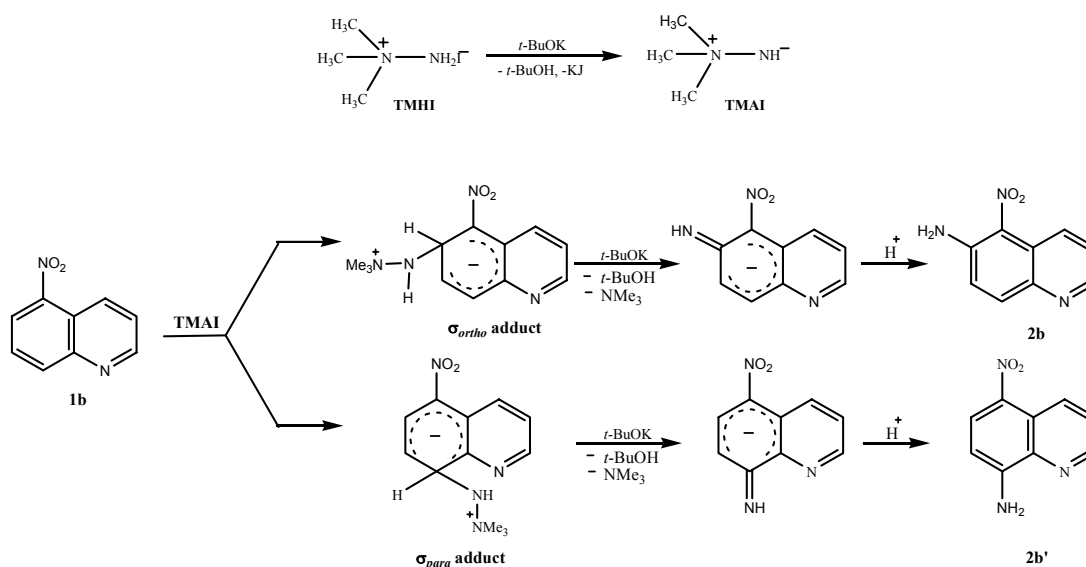
Introduction

In a previous paper¹ we reported that x-nitroquinolines (x = 3, 5-8) **1a-e** undergo direct amination with 1,1,1-trimethylhydrazinium iodide (TMHI) via vicarious nucleophilic substitution of hydrogen (VNS). The amination occurs regioselectively giving mainly the products with the amino groups in *ortho* position to the nitro group in high yields (61-95%) and small amounts of the corresponding *para* isomers (Scheme 1)¹.



Scheme 1. The results of amination of mononitroquinolines **1a-e** with TMHI¹.

The reaction of nitroquinolines **1a-e** with 1,1,1-trimethylhydrazinium iodide (TMHI) proceeds in accordance with the vicarious S_NAr^H mechanism, given by Małosza^{2,3} which is exemplified in Scheme 2. The reaction occurs between 5-nitroquinoline (**1b**) and the ylide (TMAI) generated from TMHI in the base-solvent system: potassium *tert*-butoxide – dimethyl sulfoxide at room temperature. In the initial step, TMAI adds to 5-nitroquinoline (**1b**) in the *ortho* and *para* positions relative to the nitro group to form σ adducts with the structure comparable to Meisenheimer complexes. Next, these σ adducts deprotonate with simultaneous elimination of trimethylamine to form anions, which upon protonation to yield the corresponding amino derivatives (Scheme 2).



Scheme 2

Results and Discussion

To elucidate the mechanism of the vicarious dehydroamination (Scheme 2), we were able to detect the intermediary covalent σ adducts and to determine their structures by ^1H NMR spectroscopy. We recorded the ^1H NMR spectra of the σ adducts of nitroquinolines (**1a-e**) with the TMAI ylide, generated from 1,1,1-trimethylhydrazinium iodide in of *t*-BuOK/DMSO- d_6 solution.

Comparison of the spectra of σ adducts with those of the corresponding compounds **1a-e** in a neutral solvents, such as DMSO- d_6 , shows that all proton signals in the σ adducts are shifted to lower δ -values in particular the signals of the protons at the carbon atoms, where the ylide (TMAI) was attached. The results are compiled in Table 1.

Table 1. ^1H NMR data of mononitroquinolines **1a-e** and their σ adducts with TMAI

| Compound | Solvent $\Delta \delta$ | Chemical shifts (δ values) | | | | | | |
|--|--------------------------------|------------------------------------|------|-------------|-------------|---------------|-------------|-------------|
| | | 2-H | 3-H | 4-H | 5-H | 6-H | 7-H | 8-H |
| 3-Nitroquinoline (1a) | DMSO- d_6 | 9.66 | - | 9.04 | | 8.34 – 7.62* | | |
| 4-NH-N $^+$ (CH $_3$) $_3$ σ adduct of 1a | <i>t</i> -BuOK/ DMSO- d_6 | 8.79 | - | 5.80 | | 8.41 – 7.10* | | |
| | $\Delta \delta$ | 0.87 | - | 3.24 | | -0.07 – 0.52* | | |
| 5-Nitroquinoline (1b) | DMSO- d_6 | 9.10 | 7.83 | 8.85 | - | 8.36 | 8.01 | 8.36 |
| 6-NH-N $^+$ (CH $_3$) $_3$ σ adduct of 1b | <i>t</i> -BuOK/ DMSO- d_6 | 8.14 | 7.16 | 9.34 | - | 4.22 | 7.03 | 6.80 |
| | $\Delta \delta$ | 0.96 | 0.66 | -0.49 | - | 4.14 | 0.98 | 1.56 |
| 6-Nitroquinoline (1c) | DMSO- d_6 | 9.15 | 7.78 | 8.73 | 9.08 | - | 8.50 | 8.23 |
| 5-NH-N $^+$ (CH $_3$) $_3$ σ adduct of 1c | <i>t</i> -BuOK/ DMSO- d_6 | 8.50 | 7.15 | 7.64 | 4.19 | - | 7.74 | 6.20 |
| | $\Delta \delta$ | 0.65 | 0.63 | 1.09 | 4.89 | - | 0.76 | 2.03 |
| 7-Nitroquinoline (1d) | DMSO- d_6 | 9.13 | 7.78 | 8.59 | 8.31 | 8.33 | - | 8.81 |
| 8-NH-N $^+$ (CH $_3$) $_3$ σ adduct of 1d | <i>t</i> -BuOK/ DMSO- d_6 | 8.48 | 7.35 | 7.74 | 6.11 | 7.62 | - | 3.59 |
| | $\Delta \delta$ | 0.65 | 0.43 | 0.85 | 2.20 | 0.71 | - | 5.22 |
| 8-Nitroquinoline (1e) | DMSO- d_6 | 9.07 | 7.78 | 8.61 | 8.36 | 7.79 | 8.26 | - |
| 7-NH-N $^+$ (CH $_3$) $_3$ σ adduct of 1e | <i>t</i> -BuOK/ DMSO- d_6 | 8.31 | 6.83 | 7.52 | 6.89 | 6.58 | 4.24 | - |
| | $\Delta \delta$ | 0.71 | 0.95 | 1.09 | 1.47 | 1.21 | 4.02 | - |

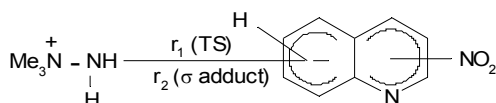
* The signals of these protons form a complex multiplet and can not be exactly assigned.

Addition of TMAI to the sp^2 carbon atom of nitroquinoline induces change of its hybridization from sp^2 to sp^3 (tetrahedral centre of σ adduct) which is reflected in a substantial shift of the NMR signals of the corresponding hydrogen atoms. These changes of the chemical shifts ($\Delta\delta = 3.24 - 5.22$ ppm) are comparable to those reported earlier for the amino σ adducts detected in oxidative dehydroamination of nitroquinolines⁴⁻⁶. In the case of 5-nitro-(**1b**) and 8-nitroquinoline (**1e**) we did not observe NMR signals from the σ adducts linked at the position

para to the nitro group. This indicates, their concentration was too low to be detectable by the NMR technique.⁷

In order to explain the high regioselectivity of the reactions studied, we carried out quantum-chemical calculations of the reaction path using PM3 method. We calculated heats of formation of the σ adducts linked at the *ortho* and *para* positions, relative to the nitro group. Moreover, we calculated the transition state (TS) energies for the reactions studied (Table 2).⁸

Table 2. Results of PM3 calculations: of bond lengths [a] and heats of formation (ΔH) of the transition states (TS) and the σ adducts of the compounds **1a-e** with TMAI



| Compound | | Transition State (TS) ΔH [kcal/mol] | r_1 Å | σ adduct ΔH [kcal/mol] | r_2 Å |
|-----------|-----|--|------------|--|------------|
| 1a | C-2 | 99.94 | 2.01 | 94.51 | 1.56 |
| | C-4 | 96.17 | 2.04 | 88.04 | 1.53 |
| 1b | C-6 | 102.26 | 1.98 | 96.17 | 1.54 |
| | C-8 | 103.47 | 2.07 | 91.69 | 1.52 |
| 1c | C-5 | 98.12 | 2.01 | 88.79 | 1.53 |
| | C-7 | 102.84 | 1.89 | 97.64 | 1.54 |
| 1d | C-6 | 103.68 | 1.87 | 99.18 | 1.54 |
| | C-8 | 98.95 | 2.02 | 90.21 | 1.53 |
| 1e | C-5 | 101.93 | 1.96 | 95.73 | 1.54 |
| | C-7 | 101.37 | 1.93 | 97.48 | 1.55 |

[a] r_1 , r_2 – distance between the corresponding C atom in nitroquinoline **1a-e** and the N atom in the ylide anion (TMAI) in transition state (TS) and σ adduct respectively.

The calculated transition states energy and the heats of formation of the σ adducts are in good agreement with the observed experimental results. In the case of 3-nitro- (**1a**), 6-nitro-(**1c**) and 7-nitroquinoline (**1d**), where two *ortho* positions relative to the nitro group are available, the substitution only in the *ortho* position with lower TS energy is observed. The calculated differences of TS energies for the formation of particular *ortho* products, are 3.77, 4.72 and 4.73 kcal/mol for **1a**, **1c** and **1d** respectively. Substantial differences are also observed for the heats of formation of the respective σ adducts.

On the other hand, small TS energy difference for the reaction at the positions C-6 (*ortho*)

and C-8 (*para*) (1.21 kcal/mol), calculated for 5-nitroquinoline (**1b**), agrees well with the experimental product distribution. In this case, the reaction mixture contained both isomers, while 6-amino-5-nitroquinoline (**2b**) with lower TS energy was the main product. Likewise, in the case of 8-nitroquinoline (**1e**), where the TS energy difference for the reaction at C-5 (*para*) and C-7 (*ortho*) positions is 0.56 kcal/mol, we obtained two products with 7-amino-8-nitroquinoline (**2e**) being the main isomer.

The good agreement between the calculated transition states energies and the experimental results let us conclude that the reactions studied are under kinetic control.

Conclusions

In conclusion, the ¹H NMR study of the intermediate σ adducts shows that for the studied nitroquinolines **1a-e**, the position *ortho* to the nitro group is strongly favoured for nucleophilic attack. Additionally, the calculated energy of transition states (TS) and the heats of formation of the σ adducts are consistent with experimentally observed regioselectivity of the vicarious amination of nitroquinolines with 1,1,1-trimethylhydrazinium iodide.

References and Notes

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7. The ¹H NMR spectra were recorded on Varian Mercury 300 (300 MHz) spectrometer; the chemical shifts are given in ppm (δ).
8. The PM3 method was used for the semiempirical MO calculations using MOPAC- version 6, molecular orbital package. The starting geometries and intermediary structures were obtained from the corresponding molecular models, fully optimized using keyword PRECISE. The transition states TS were calculated using SADDLE subroutine. NLLSQ procedure was used for gradient optimization (< 0.1 kcal/mol/Å). The calculations of TS were performed until at least one negative Hessian was obtained. Cartesian coordinates of the transition state TS for mononitroquinolines **1a-e** involved in the reaction with TMAI are given in Supplementary Material S1.