Vicarious Nucleophilic Amination of Nitroquinolines by 1,1,1-Trimethylhydrazinium Iodide

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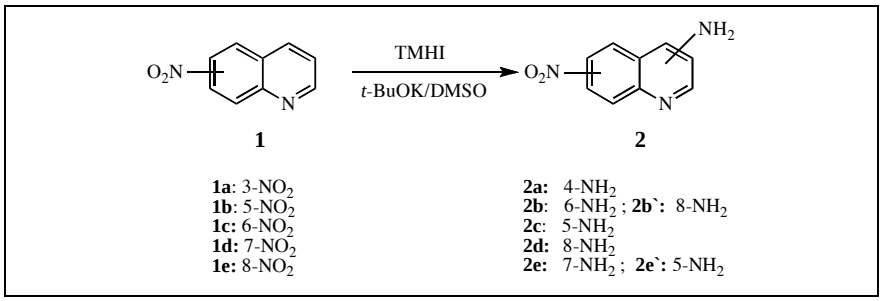
Received February 25, 2008



The amination of 3-, 5-, 6-, 7- and 8-nitroquinoline *via* the vicarious nucleophilic substitution of hydrogen (VNS) with 1,1,1-trimethylhydrazinium iodide (TMHI) in the presence of *t*-BuOK in DMSO was studied. The amination occurs regioselectively giving *ortho* or *ortho* and *para* isomers relative to the nitro group with a high yield (95-86%). 2-Nitroquinoline does not undergo vicarious amination but displacement of the labile nitro group by an amino group occurs and then transformation to an imine compound and hydrolysis gives 2(1*H*)-quinolinone.

J. Heterocyclic Chem., **45**, 1879 (2008).

INTRODUCTION

Vicarious nucleophilic substitution (VNS) of hydrogen [1,2] is now a well-established general method for the introduction of a variety of substituents into electrophilic arenes, particularly those containing nitro groups. Besides, widely examined carbanions, the introduction of oxygen, nitrogen, sulphur and halogen substituents are also possible.

The direct amination by VNS methodology requires suitable amine nucleophiles, which contain a good leaving group at the nucleophilic centre. These effective amination reagents are hydroxylamine [3], 1,1,1-trimethylhydrazinium iodide (TMHI) [4-6], 4-amino-[7,8] or 4-alkylamino-1,2,4-triazoles [9] and sulfenamides [10,11].

Application of the vicarious nucleophilic amination seems to be of special interest in considering high regioselectively and good yields for this type of reaction. The products of VNS amination, particularly those with amino substituents in the *ortho* position to the nitro group, can serve as convenient and versatile starting material for the synthesis of heterocyclic compounds.

The efficacy of TMHI as a VNS aminating reagent was tested by reacting them with a variety of nitroarenes [4,6,12,13] and nitroazoles [13] giving excellent yields. These results induced studing the possibility of using the 1,1,1-trimethylhydrazinium iodide as a VNS reagent for the amination of nitroquinolines. Additionally, the vicarious nucleophilic amination appeared to be of special interest with regard to the conditions of reactions, which are comparatively simple. Many derivatives of amino-quinolines exhibit a wide spectrum of pharmacological and biological activities. They also establish important intermediates in organic synthesis.

This paper reports the results of the vicarious nucleophilic amination of x-mononitroquinolines (x = 2-8) by 1,1,1-trimethylhydrazinium iodide (TMHI).

The literature quoted below describes some examples of synthesis of aminonitroquinolines. At first they were obtained from halogenonitroquinolines by the classical method of nucleophilic substitution S_NAr of halogen, with amines [14-16] and then, by the dehydroamination of nitroquinolines. These reactions can proceed by nucleophilic replacement of aromatic hydrogen, S_NH substitution, by oxidative (ONSH) or vicarious amination (VNS). Woźniak *et al.,* aminated x-mononitroquinolines (x = 2-8) [15,17] in a solution of potassium permanganate in liquid ammonia -33 °C. The oxidative amination occurs very selectively giving only *ortho* substitution relative to the nitro group, aminonitroquinolines with moderate to low yields [15,17], except 2-nitro- and 8-nitroquinoline, which was found to be unreactive [15]. Hasegawa *et al*., [3] reported the amination of 5-nitro-, 6-nitro-, 7-nitro- and 8-nitroquinoline using hydroxylamine in potassium hydroxide as an aminating agent, obtaining a novel product, furazanoquinoline, besides the known amino derivatives substituted in *ortho* and/or *para* positions to the nitro group [3]. Mąkosza and Białecki [11] used sulfenamides as aminating agents. With 5-nitroquinoline obtained a mixture of 6-amino-5-nitro- (52%), 8-amino-5-

nitro- (17%) and 6-amino-5-nitrosoquinoline (29%) and with 6-nitroquinoline, 5-amino-6-nitroquinoline (98%) [11].

RESULTS AND DISCUSSION

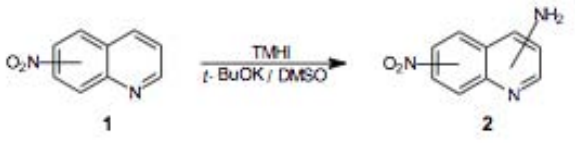
The amination of the mononitroquinolines **1a**-**f** by 1,1,1-trimethylhydrazinium iodide was carried out in base-solvent system: potassium *tert*-butoxide-dimethyl sulfoxide at room temperature. The results of reactions are compiled in Scheme 1. The structure of the obtained amino products (known compounds), has been established on the basis of spectroscopic data, in particular ^{1}H NMR and IR and also by comparing their properties with the data given in the literature or with independently synthesised reference samples.

Amination of 3-nitroquinoline (**1a**) with 1,1,1-trimethylhydrazinium iodide affords 4-amino-3-nitroquinoline (**2a**) with high yield. This determined unequivocally the position of the amino group in **2a** (2 or 4) carried out by comparison of its properties (R_F, mp and ^{1}H NMR and IR spectrum) with reference to the sample obtained by oxidative amination [17] (Scheme 1).

Amination of 5-nitroquinoline (**1b**) with TMHI gives a mixture of 6-amino- (**2b**) and 8-amino-5-nitroquinoline (**2b'**) with a ratio of **2b**:**2b'** = 70:30 likewise as 8-nitroquinoline (**1e**), gave 7-amino- (**2e**) and 5-amino-8-nitroquinoline (**3e'**) with a ratio of 79:21 respectively. The ratio of *ortho/para* isomers was determined on the basis of chromatographic separation (Scheme 1).

Treatment of 6-nitro- (**1c**), and 7-nitroquinoline (**1d**) with TMHI give 5-amino-6-nitroquinoline (**2c**) and 8-amino-7-nitroquinoline (**2d**) respectively with high yields (Scheme 1).

Scheme 1

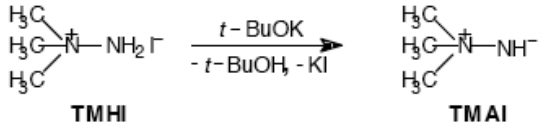


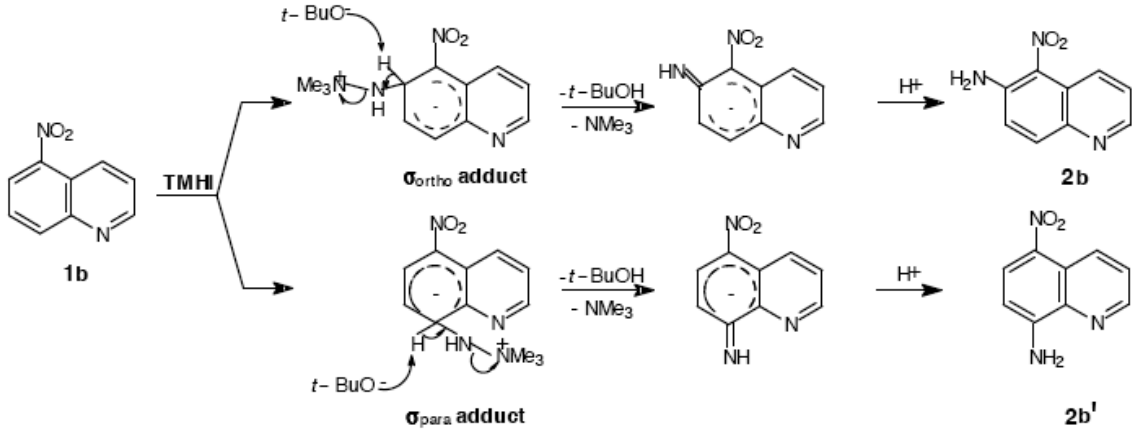
1a: 3-NO_2 — **2a**: 3-NO_2, 4-NH_2 (92%)
1b: 5-NO_2 — **2b**: 5-NO_2, 6-NH_2 (61%)
2b`:5-NO_2, 8-NH_2 (26%)
1c: 6-NO_2 — **2c**: 6-NO_2, 5-NH_2 (95%)
1d: 7-NO_2 — **2d**: 7-NO_2, 8-NH_2 (92%)
1e: 8-NO_2 — **2e**: 8-NO_2, 7-NH_2 (68%)
2e`:8-NO_2, 5-NH_2 (18%)

The results of amination of nitroquinolines **1a-e** with 1,1,1-trimethylhydrazinium iodide (TMHI) confirm that the amination proceeds in accordance with the vicarious S_NAr^H mechanism given by Mąkosza [1,2]. The course of reaction was presented with the example of reaction 5-nitroquinoline (**1b**) with TMHI (Scheme 2).

Generally, the reaction process takes place between nitroquinolines **1a**-**e** and the ylide generated from 1,1,1-trimethylhydrazinium iodide (Scheme 2). In the presence of a strong base (*t*-BuOK), deprotonation of TMHI occurs, giving trimethylammonium imide (TMAI). In the first step, addition of the ylide TMAI to the nitroquinolines **1a**-**e** results in formation of σ adducts in the *ortho* or *ortho* and *para* position relative to the nitro group. The σ adducts undergo base-induced deprotonation

Scheme 2

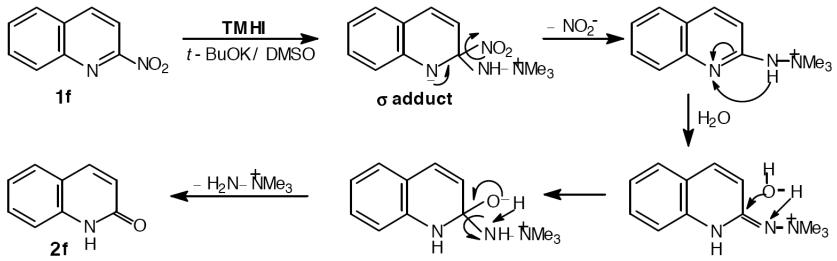




with simultaneous elimination of trimethylamine to form carbanions which are protonated during the work up procedure, giving products **2a**-**e**.

The substantial predominance of the *ortho* isomers in the case of amination of **1b** and **1e** is presumably connected with the stability of the σ adduct. The addition of the nucleophile to the *ortho* position relative to the NO_2 group will give a more stable adduct than in the *para* position. In contrast to other studied nitroquinolines **1a-e**, 2-nitroquinoline (**1f**) does not undergo vicarious amination by treatment with THMI, giving 2(1*H*)-quinolinone (**2f**). The nucleophilic displacement of the highly labile nitro group at the C-2 position by trimethylamonium imide (TMAI) take place more easily than the vicarious substitution of hydrogen at an adjacent carbon atom to the nitro group. A possible mechanistic pattern for the substitution of the nitro group is presented in Scheme 3.

Scheme 3



The substitution of the nitro group occurs by the addition of the trimethylammonium imide anion (TMHI) followed by the departure of NO_2^- anion. The reaction proceeds *via* an anionic σ adduct that can be formed by analogy to the σ^H adduct. The transformation of the substituted amino group to imine and then its hydrolysis, gives 2(1*H*)-quinolinone (**1f**).

In conclusion, the THMI reagent is effective for direct amination of nitroquinolines in VNS reactions. These reactions proceed selectively under mild conditions and can be synthetically useful with regard to excellent yields (95-86%) and high pure obtained amino products.

EXPERIMENTAL

Melting points (uncorrected) were determined on a Boetius apparatus. The ^{1}H NMR spectra were recorded on Tesla BS-587A (80 MHz) spectrometers using TMS as an internal standard; the chemical shifts are given in ppm (δ); and coupling constants are taken from the expanded spectra. The infrared spectra were recorded on Bio-Rad FTS-175C spectrophotometer (in potassium bromide pellets). The progress of reactions was monitored by thin-layer chromatography (TLC) on aluminum foil plates with aluminum oxide 60F 254 (Merck) using chloroform as eluent. Preparative chromatography was performed on a column packed with Aluminum oxide type 507 C (Fluka). The ratio of *ortho*/*para* isomers **2b**/**2b'** and **2e**/**2e'** was established by preparative chromatography.

Starting materials and Reagents. 3-Nitro-(**1a**) [18] and 2-nitroquinolines (**1f**)[15] were obtained according to literature procedures. 5- (**1b**), 6- (**1c**), 7- (**1d**) and 8-Nitroquinolines (**1e**) [19] were prepared by Skraup reaction from the respective aminonitrobenzenes. Other reagents, 1,1,1-trimethylhydrazinium iodide (TMHI), *t*-BuOK, DMSO were commercial product from Aldrich.

General Procedure for Amination of Mononitroquinolines 1a-f. To a solution of 0.35 g (2 mmol, 1 equiv.) of the respective mononitroquinolines **1a-f** and 0.61g (3 mmol, 1.5 equiv.) TMHI in anhydrous DMSO (10-15 mL) was added the solid of *t*-BuOK (0.67 g, 6 mmol, 3 equiv.). The reaction mixture was stirred at room temperature until the starting material was completely reacted, as indicated by TLC monitoring (1-8 h). The resulting dark-red solution was poured into saturated aqueous NH_4Cl. The obtained precipitate was collected by filtration, washed with water, dried and purified by recrystallization. Additionally, in the case of reactions **1b**, **1e** and **1f,** the filtrate was periodically extracted with chloroform (3 x 30 mL). The combined chloroform phases were washed with water (30 mL) and dried ($MgSO_4$). After evaporation of the solvent, the residue was combined with the obtained precipitate and was separated by column chromatography or recrystallized.

Amination of 3-nitroquinoline (1a). The yellow precipitate was isolated after 4 h and recrystallized from ethanol to give 0.35 g (92%) of 4-amino-3-nitroquinoline (**2a**), yellow needles with mp 276-277 °C (lit. [14] 261 °C, lit.[17] 274-275 °C, lit. [18] 270-272 °C); ir (potassium bromide): 3385, 3304, 3175 (NH), 1537 (NO_2, as), 1337 (NO_2, s) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 9.18 (s, 1H, 2-H), 9.01 (broad s, 2H, NH), 8.58 (dd, 1H, 5-H or 8-H, $J_{5,6}$ = 8.56, $J_{5,7}$ = 2.4 Hz), 7.96-7.51 (m, 3H, 6-H, 7-H, $J_{6,7}$ = 4.40, $J_{7,8}$ = 8.56 Hz and 5-H or 8-H, $J_{6,8}$ = 2.4 Hz).

Amination of 5-nitroquinoline (1b). The amination of **1b** was carried out for 8 h according to the general procedure. The yellow residue was dissolved in chloroform and separated by column chromatography using the same solvent as the eluent. The first fraction afforded 0.10 g (26%) of 8-amino-5-nitroquinoline (**2b'**), orange needles with mp 195-197 °C (lit. [11] 195-197 °C, lit. [14,18] 194-195 °C); ir (potassium bromide): 3404, 3310, 3213 (NH), 1524 (NO_2, as). 1392 (NO_2, s) cm^{-1} ; ^{1}H nmr (DMSO-d_6): δ 9.28 (dd, 4-H), 8.84 (dd, 2-H, $J_{2,3}$ = 4.16, $J_{2,4}$ = 1.68 Hz), 8.48 (d, 6-H), 7.80 (dd, 3-H, $J_{3,4}$ = 8.96 Hz), 6.85 (d, 7-H).

The second fraction, after removing of the eluent by evaporation, gave 0.23 g (61%) of 6-amino-5-nitroquinoline (**2b**), yellow needles with mp 176-178 °C (lit. [15,18] 176-178 °C); ir (potassium bromide): 3432, 3412, 3295 (NH), 1511 (NO_2, as), 1375 (NO_2, s) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.90 (dd, 4-H), 8.63 (dd, 2-H, $J_{2,3}$ = 4.40, $J_{2,4}$ = 1.44 Hz), 8.23 (broad s, 2H, NH), 7.94 (d, 8-H), 7.58 (dd, 3-H, $J_{3,4}$ = 8.80 Hz), 7.42 (d, 7-H, $J_{7,8}$ = 9.52 Hz).

Amination of 6-nitroquinoline (1c). 5-Amino-6-nitroquinoline (**2c**) obtained after 1 h as yellow needles, yield 0.36 g (95%) with mp 285-287 °C (without purification, chromatographically pure) (lit. [15] 287-288 °C); ir (potassium bromide): 3404, 3295, 3168 (NH), 1584 (NO_2, as), 1324 (NO_2, s) cm^{-1} ; ^{1}H nmr (DMSO-d_6): δ 9.10-8.90 (m, 2H, 2-H, 4-H, $J_{2,3}$ = 4.40 Hz), 8.74 (broad s, 2H, NH), 8.22 (d, 7-H, $J_{7,8}$ = 9.64 Hz), 7.60 (dd, 3-H, $J_{3,4}$ = 8.00 Hz), 7.15 (d, 8-H).

Amination of 7-nitroquinoline (1d). 8-Amino-7-nitroquinoline (**2d**) obtained after 2 h as orange needles, yield 0.35 g (92%) with mp 188-189 °C (without purification, chromatographically pure) (lit.[14] 185-185.5 °C, lit.[15] 188-189 °C). The compound showed properties identical (mp, ir spectrum) with reference sample. Ir (potassium bromide): 3477, 3359 (NH), 1523 (NO_2, as), 1321 (NO_2, s) cm^{-1} ; ^{1}H nmr (DMSO-d_6): δ 8.91 (dd, 2-H, $J_{2,3}$ = 4.16, $J_{2,4}$ = 1.76 Hz) , 8.43 (broad s, 2H, NH), 8.34 (dd, 4-H), 8.04 (d, 6-H), 7.76 (dd, 3-H, $J_{3,4}$ = 8.16 Hz), 7.93 (d, 5-H, $J_{5,6}$ = 9.36 Hz).

Amination of 8-nitroquinoline (1e). The amination of **1e** was carried out for 4 h according to the general procedure. The yellow residue (0.37 g) separated by the column chromatography using the mixture of chloroform and ethyl acetate (1:1) as eluent. The first fraction gave 0.26 g (68%) of 7-amino-8-nitroquinoline (**3e**), orange needles with mp 203- 205 °C (lit. [20] 203-204.5 °C); ir (potassium bromide): 3433, 3313, 3185 (NH), 1507 (NO_2, as), 1284 (NO_2, s) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.74 (dd, 2-H, $J_{2,3}$ = 4.4, $J_{2,4}$ = 1.68 Hz), 8.20 (dd, 4-H), 7.84 (d, 5-H, $J_{5,6}$ = 8.08 Hz), 7.32 (dd, 3-H, $J_{3,4}$ = 8.16 Hz), 7.21 (d, 6-H), 6.87 (broad s, 2H, NH).

The second fraction, after removing of the eluent, afforded 0.07 g (18%) of 5-amino-8-nitroquinoline (**2e '**), orange needles with mp 253-255 °C (lit. [21] 252-253 °C); ir (potassium bromide): 3456, 3438, 3324, 3204 (NH), 1576 (NO_2, as), 1298 (NO_2, s) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.97 (dd, 2-H, $J_{2,3}$ = 4.12, $J_{2,4}$ = 1.52 Hz), 8.70 (dd, 4-H), 8.19 (d, 7-H), 7.54 (dd, 3-H, $J_{3,4}$ = 8.68 Hz), 7.39 (broad s, 2H, NH), 6.67 (d, 6-H, $J_{6,7}$ = 8.80 Hz).

Amination of 2-nitroquinoline (1f). The amination of **1f** was carried out for 4 h according to general procedure. A small amount of precipitate was filtered off and filtrate solution was extracted by chloroform. After evaporation of solvent the residue combined with precipitate and crystallized from methanol, yielding 0.18 g (62%) of creme crystals of 2(1*H*)-quinolinone (**2f**) mp 198-200 °C (lit. [22] 199-200 °C); ir (potassium bromide): 3255 (NH), 3126 - 2848 (OH), 1651(CO) cm^{-1} ; ^{1}H nmr (DMSO-d_6): δ 11.73 (broad s, 1H, OH), 7.91, (d, 4-H), 7.66 (d, 8-H or 5-H), 7.48, (dd, 7-H or 6-H), 7.29 (d, 5-H or 8-H, $J_{5,6}$ = 7,6 Hz), 7.12 (dd, 6-H or 7H, $J_{6,7}$ = 6.72, $J_{7,8}$ = 7.6 Hz), 6.51 (d, 3-H, $J_{3,4}$ = 9.52 Hz).

Acknowledgements. I am thankful to Dr. Cholewka for measuring the ^{1}H NMR and IR spectra.

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