New Route for Preparation of Nitrosubstituted 1,2-Phenylenediamines

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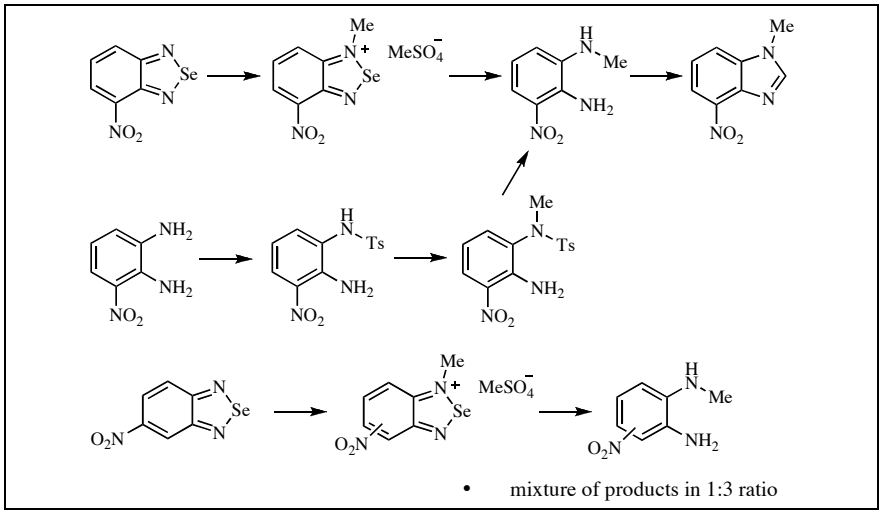
Dedicated to Prof. Miha Tišler on the occasion of his 80th birthday



4-Nitrobenzoselenadiazole was methylated with dimethylsulphate to give corresponding 1-*N*-methyl-4-nitrobenzoselenadiazolium methylsulphate which after alkaline ring-opening afforded 1-*N*-methyl-3-nitro-1,2-phenylenediamine in 90% yield. This compound was also prepared from 3-nitro-1,2-phenylenediamine by monomethylation through tosylation, methylation and detosylation and was confirmed and characterised as 1-methyl-4-nitrobenzimidazole. Methylation of 5-nitrobenzoselenadiazole and subsequent alkaline ring-opening led to unseparable mixture of both methylated products.

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INTRODUCTION

Substituted nitro-1,2-phenylenediamines are important starting materials for synthesis of nitrosubstituted nitrogen containing heterocycles such as benzimidazoles, benztriazoles, benzthiadiazoles, benzoselenadiazoles, quinoxalines [1] *etc*.

Preparation of nitro-1,2-phenylenediamines is based on Zinin partial reduction [2] of dinitroanilines or partial hydrogenation using expensive catalysts such as Pd or Ru [3,4]. Reductive deselenation of appropriate benzoselenadiazole derivatives also leads to nitro-1,2-phenylenediamines. Partial reduction of 2,4-dinitroaniline in presence of ammonium sulfide leads to 4-nitro-1,2-phenylenediamine [5]. Analogically, 2,6-dinitroaniline is partially reduced in 98% yield to 3-nitro-1,2-phenylenediamine using sodium sulfide and sodium bicarbonate as reducing agents [6]. Another approach to 3-nitro-1,2-phenylenediamine employs readily available 4-nitrobezoselenadiazole as starting material. This compound is selectively reduced with excess of hydroiodic acid to 3-nitro-1,2-phenylenediamine without affecting the nitro group [7].

Synthesis of substituted nitro-1,2-phenylenediamines is often difficult and laborious with many reaction steps. However, method described by Grivas *et al.* [8-11] is very efficient route to substituted 3-nitro-1,2-phenylenediamines. This method is based on protection of appropriate 1,2-phenylenediamine derivatives by ring closure with selenium dioxide to form benzoselenadiazoles. Subsequent nitration of the these compounds affords corresponding 4-nitrobenzoselenadiazoles or its 5-methoxy derivative which are selectively reduced to substituted 3-nitro-1,2-phenylenediamines in presence of hydroiodic acid or ammonium sulfide (in case of using hydroiodic acid also total demethoxylation is observed).

Nitro-1,2-phenylenediamines can also be used as starting materials for preparation of their *N*-methylated analogues. Selective monomethylation is described only for 4-nitro-1,2-phenylenediamine through tosylation followed by methylation and detosylation to afford 2-*N*-methyl-4-nitro-1,2-phenylenediamine [12]. 1-*N*-Methyl-

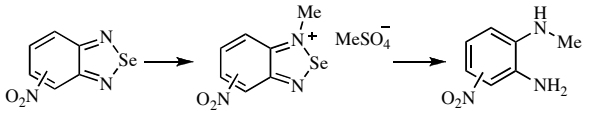
ated derivative could be easily prepared from 2,4-dinitrochlorobenzene, which is first treated with methylamine followed by partial reduction using sodium sulfide and sodium bicarbonate replacing sodium hydrogensulfide as reducing agents. Synthesis of *N*-methylated-3-nitro derivatives is somewhat complicated due to limited availability of starting materials 2,3-dinitroaniline or *N*-methyl-2,6-dinitroaniline. Treatment 2,3-dinitroaniline with dimethylsulphate, subsequent partial reduction using sodium sulfide and sodium bicabonate provides to 1-*N*-methyl-3-nitro-1,2-phenylene-diamine [13]. Partial reduction of *N*-methyl-2,6-dinitro-aniline with different reducing reagent such as ammonium sulfide [14] or sodium sulfide with sodium bicarbonate [15] leads to a 2-*N*-methyl-3-nitro-1,2-phenylenediamine.

Ralph and Nunn [16,17] found out that benzoselena-diazole and benzothiadiazole react with dialkylsulphates to afford *N*-alkyl benzoselenadiazolium or benzothia-diazolium alkylsulphates. Ring-opening of these alkyl quaternary salts with water or sodium hydroxide solution provides to *N*-alkyl-1,2-phenylene-diamines.

RESULTS AND DISCUSSION

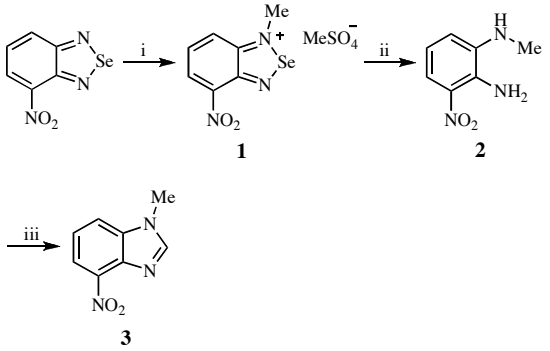
In our synthesis towards *N*-methylated nitrosubstituted 1,2-phenylenediamines we used readily available nitrobenzoselenadiazoles (Scheme 1).

Scheme 1



Both, 4- and 5-nitrobenzoselenadiazole were treated with excess of freshly distilled dimethylsulphate at about 130°C for 1 hour to produce *N*-methyl benzo-selena-diazolium methylsulphates in good yields. After increasing temperature above 130°C or prolonging reaction time the yields of methylation decreased. At temperatures above 140°C we have obtained black tar from which we were not able to isolate desired products. *N*-Methyl benzoselenadiazolium methylsulphates were used without futher purification to alkaline ring-opening. Alternative methylation using ecological friendly dimethylcarbonate has been unsuccessful. After alkaline ring-opening starting from 5-nitrobenzoselenadiazole we have obtained mixture of two *N*-methylated 4-nitro-1,2-phenylenediamines in 1:3 ratio (from ^{1}H NMR). In case when the starting material 4-nitrobenzoselenadiazole has been used we have obtained only one *N*-methylated 3-nitro-1,2-phenylenediamine in 90% yield. To establish the position of the methyl group on the amino groups in relation to the nitro group we have converted this *N*-methylated 3-nitro-1,2-phenylene-diamine to corresponding 1-methylnitrobenzimidazole by a simple cyclisation with formic acid [17] (Scheme 2). Then we compared the set of values for ^{1}H NMR and ^{13}C NMR signals with known data for 1-methyl-4- or -7-nitro-benzimidazole. Our spectral data were in good agreement with the published data for 1-methyl-4-nitro-benzimidazole [18,19]. Thus, the starting material for cyclisation 1-*N*-methyl-3-nitro-1,2-phenylenediamine has been used. We can also conclude that nitrogen of 4-nitrobenzoselenadiazole in position 1 is methylated, probably due to steric hindrance of the nitro group.

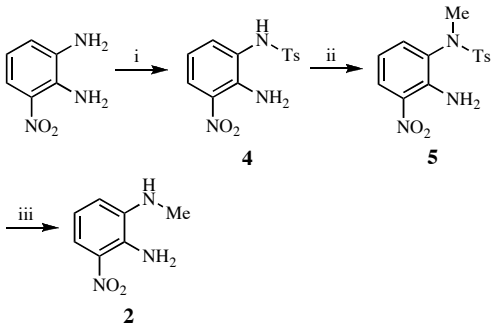
Scheme 2



Reagents and conditions: (i) Me_2SO_4, 120-130°C, 1 h; (ii) 2M NaOH, r.t. 0.5 h; (iii) HCOOH, reflux, 12 h

We have also prepared 1-*N*-methyl-3-nitro-1,2-phenylenediamine starting from 3-nitro-1,2-phenylene-diamine by monomethylation *via* tosylation followed by methylation and detosylation [12,20] (Scheme 3). Repeated addition of reagent (sodium hydroxide and dimethylsulphate) is necassary in methylation of tosyl derivative to increase yields to about 80%. Detosylation of methylated tosyl compound gave 1-*N*-methyl-3-nitro-1,2-phenylenediamine in moderate yields, which was again confirmed and characterized as 1-methyl-4-nitro-benzimidazole.

Scheme 3



Reagents and conditions: (i) TsCl, pyridine, reflux, 7 h; (ii) Me_2SO_4/NaOH, 30-40°C; (iii) 80% H_2SO_4, 100°C, 7 h

Monomethylation of 3- or 4-nitro-1,2-phenylene-diamine using Katritzky's protocol [21] did not lead to desired products.

EXPERIMENTAL

Melting points were determined on Koffler's apparatus using digital thermometer (DT012C) and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury 300-MHz spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as internal standard. Chemical shifts (δ) and coupling constants *J* are given in ppm and Hz, respectively. Reaction monitoring and purity of products was accomplished by TLC on silica-gel plates.

1-*N*-Methyl-4-nitrobenzo[2.1.3]selenadiazolium methylsulphate (1). A mixture of 4-nitrobenzo[2.1.3]selenadiazole (4.56 g, 20 mmol) and freshly distilled dimethylsulfate (20 mL, 0.21 mol) was heated at 120-130°C in oil bath within 1 h. After cooling down the reaction mixture to room temperature, the precipitated solid was separated by suction, washed with diethylether and dried to give **1** as light brown crystals (6.2 g, 87%), mp 182-185°C. **1** was used to the next reaction without further purification and spectral characterization.

1-*N*-Methyl-3-nitro-1,2-phenylenediamine (2). To a stirred NaOH solution (2 *M*, 25 mL) compound **1** (3.54 g, 10 mmol) was added portionwise. The formed dark red suspension was stirred for 30 minutes at room temperature. The dark red solid was collected by suction, washed with water and dried. Dry solid was dissolved in CH_2Cl_2 (20 mL), insoluble material was filtred off and the filtrate was evaporated to dryness under reduced pressure to afford **2** as dark red solid (1.4 g, 90%), mp 87-90°C (lit.[13] 78°C). ^{1}H nmr (DMSO-d_6, 300 MHz): 2.78 (d, *J* = 4.6 Hz, 3H); 5.46 (d, *J* = 4.8 Hz, 1H); 6.56 (m, 2H); 7.06 (s, 2H); 7.32 (dd, *J* = 7.8, 2.4 Hz, 1H). ^{13}C nmr (DMSO-d_6, 75 MHz): δ 30.4, 111.8, 112.1, 115.9, 130.5, 135.7, 138.8.

1-*N*-Tosyl-3-nitro-1,2-phenylenediamine (4). A mixture of 3-nitro-1,2-phenylenediamine (4 g, 26 mmol), tosylchloride (5 g, 26 mmol) and pyridine (30 mL) was refluxed for 5 h. Hot reaction mixture was poured into ice (100 g) and yellow-orange solid formed was collected by suction, washed with water and dried. Recrystallization from ethanol gave **4** as yellow needles (5.62 g, 70%) mp 198-200°C (lit. [20] 192-193°C). ^{1}H nmr (DMSO-d_6, 300 MHz): 2.37 (s, 3H); 6.50 (dd, *J* = 7.55 Hz, 1H); 6.87 (dd, *J* = 7.52, 1.54 Hz, 1H); 7.01 (s, 2H); 7.36-7.62 (dd, *J* = 8.20 Hz, 4H); 7.89 (dd, *J* = 8.74, 1.54 Hz, 1H); 9.66 (s, 1H). ^{13}C nmr (DMSO-d_6, 75 MHz): δ 21.0, 114.2, 124.5, 124.7, 127.0, 129.7, 131.7, 133.6, 136.3, 142.8, 143.5.

1-*N*-Methyl-1-*N*-tosyl-3-nitro-1,2-phenylenediamine (5). Derivative **4** (4.37 g, 14 mmol) was dissolved in NaOH solution (2 *M*, 16 mL) and to this solution water (200 mL) was added. Orange-red solution was heated to 30-40°C and freshly distilled dimethylsulfate was added dropwise. After the addition was completed the yellow precipitate was formed and colour of solution changed to yellow. Addition of the same amounts of reagents (16 mL of NaOH solution and 5 mL dimethylsulfate) was repeated for 4 times. Yellow precipitate was separated by suction, washed with water and dried. Recrystallization from ethanol yielded **5** as yellow needles (3.85 g, 84%) mp 184-189°C. ^{1}H nmr (DMSO-d_6, 300 MHz): 2.43 (s, 3H, Ph-CH_3); 3.07 (s, 3H, N-CH_3); 6.50 (dd, *J* = 7.57 Hz, 1H); 6.67 (dd, *J* = 7.51, 1.41 Hz, 1H); 7.44-7.62 (dd, *J* = 8.20 Hz, 4H); 7.99 (dd, *J* = 8.70, 1.52 Hz, 1H). ^{13}C nmr (DMSO-d_6, 75 MHz): δ 21.1, 38.9, 114.0, 126.0, 127.9, 129.9, 130.0, 131.7, 133.3, 134.0, 144.1, 144.3. *Anal.* Calcd. for $C_{14}H_{15}N_3O_4S$: C, 52.33; H, 4.70; N, 13.08. Found: C, 52.16; H, 4.66; N, 13.11.

1-*N*-Methyl-3-nitro-1,2-phenylenediamine (2). A mixture of **5** (4 g, 12.4 mmol) and 80% sulfuric acid (30 mL) was stirred at 100°C for 7 h. Hot reaction mixture was poured into ice (50 g) and neutralized with 10% NaOH solution while cooling. Dark red precipitate was collected by suction, washed with water and dried. Recrystallization from *n*-heptane afforded **2** as dark red needles (0.98 g, 47%) mp 91-94°C (lit.[13] 78°C). ^{1}H nmr (DMSO-d_6, 300 MHz): 2.76 (d, *J* = 4.2 Hz, 3H); 5.44 (d, *J* = 4.8 Hz, 1H); 6.56 (m, 2H); 7.04 (s, 2H); 7.32 (dd, *J* = 7.8, 2.4 Hz, 1H). ^{13}C nmr (DMSO-d_6, 75 MHz): δ 30.4, 111.8, 112.1, 115.9, 130.5, 135.6, 138.8.

1-Methyl-4-nitrobenzimidazole (3). A mixture of **2** (0.5 g, 3 mmol) and formic acid (6 mL) was refluxed for 12 h. After cooling down the reaction mixture was diluted with water (6 mL) and then alkalized with 27% NH_4OH solution. Resulting precipitate was collected by filtration, washed with water and dried. Recrystalization from toluene yielded **3** as yellowish needles (0.24 g, 45%), mp 168-169°C (lit. [15,22] 168°C). ^{1}H nmr ($CDCl_3$, 300 MHz): 3.95 (s, 3H); 7.40 (t, *J* = 8.07 Hz, 1H); 7.73 (d, *J* = 8.05 Hz, 1H); 8.11 (s, 1H); 8.14 (d, *J* = 8.07 Hz, 1H). ^{13}C nmr ($CDCl_3$, 75 MHz): δ 31.6, 116.1, 119.3, 122.1, 137.0, 137.2, 139.1, 146.8.

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