An Improved Procedure for the Nitration of Benzo-2,1,3-selenadiazoles and Their Reduction to *ortho*-Phenylenediamines

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A method for the nitration of benzo-2,1,3-selenadiazoles using nitric acid dissolved in a mixture of methanesulfonic acid and phosphorus pentoxide at room temperature is presented. The S_N2Ar displacement of fluoride that is observed when sulfuric acid is used as solvent is prevented and yields are high. Sodium nitrate could be used in place of nitric acid with no loss in yield. Following nitration, the 2,1,3-selenadiazole ring is cleaved with hydriodic acid to afford a 3-nitro-*ortho*-phenylenediamine. The method is applied to the multi-gram preparation of 4-fluoro-3-nitrobenzene-1,2-diamine.

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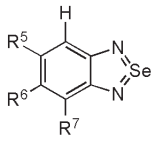
Ortho-Phenylenediamines are useful intermediates for the construction of a variety of benzo-fused heterocyclic ring systems, particularly benzimidazoles and quinoxalines, which are found in a number of important pharmaceutical and agricultural agents. The strongly electron-releasing nature of the 1,2-diamine substituents renders the benzene ring especially susceptible to attack and degradation by aggressive electrophilic reagents, which necessitates the protection of the 1,2-diamine functionality during synthetic manipulations on the ring with such reagents. The 2,1,3-selenadiazole ring is a particularly suitable protecting group in this regard. Readily formed in high yield from the diamine by reaction with selenium dioxide, the 2,1,3-selenadiazole ring is resistant to many electrophilic reagents and attenuates the electron releasing character of the latent diamine. The 2,1,3-selenadiazole may be subsequently cleaved by hydriodic acid to regenerate the phenylenediamine in high yield.

Recently we required access to 4-fluoro-3-nitrobenzene-1,2-diamine in preparatively useful quantities. This compound had been reported in the literature as having been prepared, albeit in poor (37%) yield, by the nitration of 5-fluorobenzo-2,1,3-selenadiazole (**1a**; R^5 = F; R^6, R^7 = H) with 100% nitric acid in concentrated sulfuric acid, followed by reduction of the product 5-fluoro-4-nitrobenzo-2,1,3-selenadiazole **2a** (R^5 = F; R^6, R^7 = H) with hydriodic acid [1]. We repeated the reported procedure and obtained results similar to those reported, obtaining the desired nitration product **2a** in 32% yield. As was reported to be the case in the previous work, the primary product of the nitration (66% yield) was the undesired 5-hydroxy-4-nitrobenzo-2,1,3-selenadiazole **2b** (R^5 = OH; R^6, R^7 = H), presumably arising from either solvolysis of the desired product **2a** or from solvolysis of **1a** followed by nitration. Surprisingly, separation of the desired **2a** from the undesired **2b** by chromatography proved to be tedious. An extractive separation could be achieved with aqueous potassium hydroxide; however, repeated consecutive washings with dilute potassium hydroxide were required to remove **2b**.

Experimentation with purified samples of **2a** showed that the solvolysis of the fluoro substituent to form **2b** occurred primarily in the reaction mixture, rather than as a consequence of the quenching and workup procedure [2]. We postulated that the solvolysis of the fluoro substituent could occur in the nitration mixture in the absence of water by protonation of the heterocycle, followed by S_N2Ar displacement of fluoride by bisulfate, resulting in the loss of the considerably weaker acid hydrogen fluoride. The putative sulfate ester intermediate (R^5 = OSO_3H; R^6, R^7 = H) presumably would hydrolyze upon workup. If so, we reasoned that the outcome of the nitration could be improved if the nitration were carried out in a weaker, monoprotic acid medium such as methanesulfonic acid. Because methanesulfonic acid does not have the powerful dehydrating properties of concentrated sulfuric acid that are required to generate the nitronium ion NO_2^+ from nitric acid, we decided to use Eaton's reagent, a 10% solution of phosphorus pentoxide in methanesulfonic acid, as a substitute for concentrated sulfuric acid. Eaton's reagent has solvent and dehydrating properties similar to concentrated sulfuric acid, but in contrast to the latter reagent it is non-oxidizing and is less prone to promote the sulfonation of substrates dissolved in it. The presence of phosphorus pentoxide in the nitration mixture was of additional importance as we wished to use commercially available 90%



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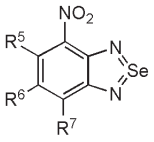

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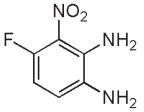

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nitric acid (d = 1.48), in order to avoid the tedious and potentially hazardous preparation of 100% fuming nitric acid (d = 1.51) as used in the reported procedure.

The 2,1,3-selenadiazoles used in this work were prepared from commercially available *ortho*-phenylenediamines (or *ortho*-nitro anilines after reduction to the known *ortho*-phenylenediamines) by reaction with selenium dioxide in aqueous ethanol [1]. The 2,1,3-selenadiazole **1c** was prepared from 3-fluoro-2-methylaniline by a multi-step sequence of acetylation, nitration, amide hydrolysis, reduction, and reaction with selenium dioxide [3]. The nitration of the 2,1,3-selenadiazoles was found to proceed smoothly in Eaton's reagent at room temperature [4] with 4 equivalents of 90% nitric acid to afford the expected nitration products in high yield (Table 1). The progress of the nitration reactions was followed by thin layer chromatography and/or GC/MS. Following the successful application of these nitration conditions to a variety of 2,1,3-selenadiazoles, we investigated the effects of various modifications of the reaction conditions. We found that methanesulfonic acid alone, without dissolved phosphorus pentoxide, was unsatisfactory, as the nitration reaction proceeded at an almost negligible rate. Likewise, the use of 70% nitric acid (d = 1.41), even if used with a compensating excess of Eaton's reagent, failed to afford the nitrated product **2a** in any more than trace amounts. We were gratified, however, to find that sodium nitrate could be used in place of the 90% nitric acid with no loss in yield (Entry 9, Table 1).

Following this, we turned our attention to improving the reductive cleavage of **2a** to regenerate the phenylenediamine functionality. Reductive cleavage of the 2,1,3-selenadiazole **2a** with aqueous 57% hydriodic acid [5] was followed by reduction of the iodine produced by sulfur dioxide gas. Sulfur dioxide gas was used instead of aqueous sodium bisulfite to minimize the aqueous volume and attendant product losses resulting from the appreciable solubility of the product 4-fluoro-3-nitro-benzene-1,2-diamine (**3**) in water. The complete reduction of iodine present in the reaction was confirmed by the use of potassium iodide - starch paper [6]. The mixture was allowed to stand overnight to allow the elemental selenium that formed to precipitate then heated to expel residual sulfur dioxide. After cooling and filtration, treatment with ammonium hydroxide caused crystalline **3** to precipitate in high yield. This procedure was considerably easier to apply on a large scale than the extraction and chromatography previously used to obtain pure **3**. Furthermore, we found that the crude 2,1,3-selenadiazole **2a** could be used directly in the reduction reaction following filtration and washing, without need to dry or recrystallize **2a** prior to the reduction.

In summary, we have found the reagent combinations methanesulfonic acid – phosphorus pentoxide – nitric acid and methanesulfonic acid – phosphorus pentoxide – sodium nitrate to provide a convenient, high yielding method for the nitration of benzo-2,1,3-selenadiazoles at room temperature without competing solvolysis of halogen substituents on the benzo ring.

EXPERIMENTAL

All reactions were carried under an atmosphere of dry nitrogen. All starting materials including Eaton's reagent were commercial reagents and were used as received without additional purification. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on Varian Unity Inova 400 spectrometers. Mass spectra were recorded on a Hewlett Packard Model 5989 mass spectrometer using electron impact ionization; ions for isotopes other than ^{80}Se are not reported. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York, USA.

General Procedure for the Nitration of 2,1,3-Selenadiazoles.

The 2,1,3-selenadiazole **1** (5 mmol) was dissolved in 5 mL of Eaton's reagent and cooled in ice while an ice - cold solution of 1.0 mL (20 mmol) of 90% nitric acid (d = 1.48) in 2 mL of

Table 1

Entry	Substrate	R^5	R^6	R^7	Product	Yield	R^5	R^6	R^7	mp, °C (lit. mp)
1	**1a**	F	H	H	**2a**	94%	F	H	H	237 –239 (150 – 151 [a])
2	**1c**	H	F	CH_3	**2c**	81%	H	F	CH_3	209 – 210 (198 – 200 [a])
3	**1d**	Cl	H	H	**2d**	85%	Cl	H	H	228 – 230 (230 – 232 [b])
4	**1e**	Cl	Cl	H	**2e**	85%	Cl	Cl	H	209 – 212 (111 – 112 [c])
5	**1f**	Br	H	H	**2f**	86%	Br	H	H	236 – 238 (226 – 230 [b])
6	**1g**	F	H	CH_3	**2g**	90%	F	H	CH_3	184 – 185 (182 – 183 [a])
7	**1h**	H	H	H	**2h**	90%	H	H	H	214 – 216 (220 – 221 [b])
8	**1i**	CH_3	H	H	**2i**	93%	CH_3	H	H	194 – 196 (192 – 194 [b])
9 [d]	**1i**	CH_3	H	H	**2i**	91%	CH_3	H	H	194 – 196 (192 – 194 [b])

[a] W. Tian, S. Grivas and K. Olsson, *J. Chem. Soc., Perkin Trans. I*, 257 (1993); [b] V. G. Pesin, V. A. Sergev and A. G. Nesterova, *Chem. Heterocyclic Compounds, Eng. Trans.*, 75 (1966); [c] V. G. Pesin, V. A. Sergev and M. P. Papirnik, *J. Org. Chem. USSR, Eng. Trans.*, **25**, 1629 (1989); [d] Powdered sodium nitrate (1.70 g, 20 mmol) was used in place of 90% nitric acid.

Eaton's reagent was added dropwise with stirring. Once the addition of nitric acid was complete, the cooling bath was removed and the mixture was stirred at room temperature until the reaction was complete as judged by the disappearance of the starting material **1** by tlc or GC/MS analysis, typically 18 to 24 h. The reaction mixture was poured into 70 mL of ice water and stirred until the ice had melted. The precipitate was collected by filtration, washed well with water and dried on the filter. The dried product was recrystallized from 1,4-dioxane to afford the final product.

5-Fluoro-4-nitrobenzo-2,1,3-selenadiazole (**2a**).

This compound was obtained in 94% yield as white crystals, mp 237 – 239 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.28 (m, 1 H); 7.88 (t, 1 H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 157, 155, 151, 129, 128, 120; ^{19}F nmr (dimethyl sulfoxide-d_6): δ -117; ms: m/z 247 (M^+, 100%).

Anal. Calcd. for $C_6H_2FN_3O_2Se$: C, 29.29; H, 0.82; N; 17.08. Found: C, 29.30; H, 0.93; N, 17.14.

5-Fluoro-4-methyl-7-nitrobenzo-2,1,3-selenadiazole (**2c**).

This compound was obtained as yellow crystals, mp 209 – 210 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.58 (d, $^3J_{F-H}$ = 9.6 Hz, 1 H); 2.58 (s, 3 H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 159, 156, 148, 126, 120, 119, 12; ^{19}F nmr (dimethyl sulfoxide-d_6): δ -117; ms: m/z 261 (M^+, 100%).

Anal. Calcd. for $C_7H_4FN_3O_2Se$: C, 32.33; H, 1.55; N, 16.16. Found: C, 31.98; H, 1.76; N, 15.86.

5-Chloro-4-nitrobenzo-2,1,3-selenadiazole (**2d**).

This compound was obtained in 85% yield as white crystals, mp 228 – 230 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.09 (d, J = 9.5 Hz, 1 H); 7.78 (d, J = 9.5 Hz, 1 H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 158, 150, 129, 127, 126; ms: m/z 263 (M^+, 100%).

Anal. Calcd. for $C_6H_2ClN_3O_2Se$: C, 27.45; H, 0.77; N, 16.01; Cl 13.51. Found: C, 27.71; H, 0.65; N, 16.05; Cl, 13.72.

5,6-Dichloro-4-nitrobenzo-2,1,3-selenadiazole (**2e**).

This compound was obtained in 85% yield as off-white crystals, mp 209 – 212 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.57 (s, 1H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 157, 149, 132, 126, 125; ms: m/z 297 (M^+, 100%).

Anal. Calcd. for $C_6HCl_2N_3O_2Se$: C, 24.27; H, 0.34; N, 14.15; Cl 23.88. Found: C, 24.33; H, 0.34; N, 14.50; Cl, 23.94.

5-Bromo-4-nitrobenzo-2,1,3-selenadiazole (**2f**).

This compound was obtained in 86% yield as yellow crystals, mp 236 – 238 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.00 (d, J = 9.5 Hz, 1 H); 7.87 (d, J = 9.5 Hz, 1 H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 158, 151, 132, 127, 126, 116; ms: m/z 307 (M^+, 100%).

Anal. Calcd. for $C_6H_2BrN_3O_2Se$: C, 23.48; H, 0.66; N, 13.69; Br 26.03. Found: C, 23.79; H, 0.50; N, 13.76; Br, 26.30.

5-Fluoro-7-methyl-4-nitrobenzo-2,1,3-selenadiazole (**2g**).

This compound was obtained in 90% yield as off-white crystals, mp 184 – 185 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.69 (d, $^3J_{F-H}$ = 11.6 Hz, 1 H); 2.66 (s, 3 H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 19; ^{19}F nmr (dimethyl sulfoxide-d_6): δ -116; ms: m/z 261 (M^+, 100%).

Anal. Calcd. for $C_7H_4FN_3O_2Se$: C, 32.33; H, 1.55; N 16.16. Found: C, 32.63; H, 1.60; N, 15.94.

4-Nitrobenzo-2,1,3-selenadiazole (**2h**).

This compound was obtained in 90% yield as white crystals, mp 214 – 216 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.42 (d, J = 7.4 Hz, 1 H); 8.25 (d, J = 8.7 Hz, 1 H); 7.71 (m, 2 H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 161, 151, 130, 127, 126, 120; ms: m/z 229 (M^+, 100%).

Anal. Calcd. for $C_6H_3N_3O_2Se$: C, 31.60; H, 1.33; N, 18.42. Found: C, 31.40; H, 1.15; N, 18.24.

5-Methyl-4-nitrobenzo-2,1,3-selenadiazole (**2i**).

This compound was obtained in 93% yield as off-white crystals, mp 194 – 196 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.97 (d, J = 9.1 Hz, 1 H); 7.58 (d, J = 9.1 Hz, 1 H); 2.41 (s, 3 H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 158, 151, 132, 131, 126, 17; ms: m/z 243 (M^+, 100%).

Anal. Calcd. for $C_7H_5N_3O_2Se$: C, 34.73; H, 2.08; N, 17.36. Found: C, 34.82; H, 1.78; N, 17.18.

4-Fluoro-3-nitro-benzene-1,2-diamine (**3**).

2,1,3-Selenadiazole **2a** (12.30 g, 50 mmol) was dissolved in 50 mL of Eaton's reagent and cooled in ice while an ice - cold solution of 9.6 mL (200 mmol) of 90% nitric acid (d = 1.48) in 20 mL of Eaton's reagent was added dropwise with stirring. Once the addition of nitric acid was complete, the cooling bath was removed and the mixture was stirred for 24 h at room temperature until the reaction was complete. The reaction mixture was poured into 500 mL of ice and stirred until the ice had melted. The precipitate was collected by filtration and washed three times with water. The damp filter cake was transferred to a 1000 mL Erlenmeyer flask, dissolved in 150 mL of 57% hydriodic acid, and stirred overnight at room temperature. The mixture was then diluted with 200 mL of water. Sulfur dioxide gas was passed in until a negative test was obtained with potassium iodide – starch paper. The mixture was then heated to 95 °C and held at that temperature for 10 minutes with stirring. Stirring was continued while the mixture cooled, after which it was filtered through Celite. The filtrate was adjusted to pH = 6 with concentrated ammonium hydroxide (about 150 mL required) and cooled in ice to 5 °C. The precipitate was filtered, washed with ice water and dried to afford 8.16 g (95%) of **3** as purple needles, mp 136 - 137 °C (lit. mp 137 – 139 °C [1]); ^{1}H nmr (methanol-d_4): δ 6.76 (d of d, J = 8.7 Hz, $^3J_{F-H}$ = 5.0 Hz, 1 H), 6.32 (d of d, J = 8.7 Hz, $^3J_{F-H}$ = 11.2 Hz, 1 H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 149, 147, 134, 133, 115, 102; ^{19}F nmr (dimethyl sulfoxide-d_6): δ -136; ms: m/z 171 (M^+, 100%).

Anal. Calcd. for $C_6H_6FN_3O_2$: C, 42.11; H, 3.53; N, 24.55. Found: C, 42.04; H, 3.43; N, 24.45.

REFERENCES AND NOTES

[1] W. Tian, S. Grivas and K. Olsson, *J. Chem. Soc., Perkin Trans. I*, 257 (1993).

[2] The original reference [2] suggested that **2b** was formed during the quenching of the reaction mixture with ice water and that the amount of **2b** formed was a function of the time and temperature of the quenching step. We found that **2b** was formed directly in the reaction mixture in the absence of an aqueous quench. Aliquots of the nitration mixture analyzed by GC/MS showed the presence of **2b** in the nitration mixture, in amounts that increased as a function of time. Likewise, the formation of **2b** could be observed directly in the reaction mixture by ^{13}C NMR.

[3] I. Achiwa, T. Shiozawa, H. Nukaya and Y. Terao, *Chem. Pharm. Bull.*, **42**, 408 (1994); S. Grivas, *Acta Chem. Scand. B*, **39**, 213 (1985); M. S. Newman and E. H. Wiseman, *J. Org. Chem.*, **26**, 3208 (1961).

[4] We wished to avoid heating the nitration mixture, as has been reported for the nitration of certain 2,1,3-selenadiazoles (see V. G. Pesin, V. A. Sergev and A. G. Nesterova, *Chem. Heterocyclic Compounds, Eng. Trans.*, 75 (1966)) as we wished to avoid any possibility of initiating an uncontrollable exothermic decomposition of the nitration mixture.

[5] E. Sawicki and A. Carr, *J. Org. Chem.*, **22**, 503 (1957).

[6] It is important to ensure that the iodine is completely reduced prior to neutralization of the reaction mixture by ammonium hydroxide. If free iodine remains, it may react with ammonium hydroxide to precipitate the highly sensitive explosive nitrogen triiodide. Due to the intense violet - red color of the product **3**, the color of the solution cannot be taken to indicate the absence of iodine.