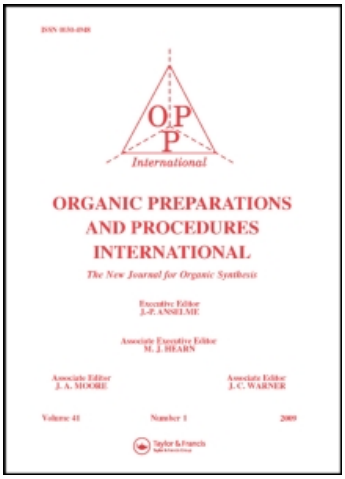

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A CONVENIENT METHOD FOR THE PREPARATION OF 2,5-*bis*-(4-AMINOPHENYL)-1,3,4-OXADIAZOLE

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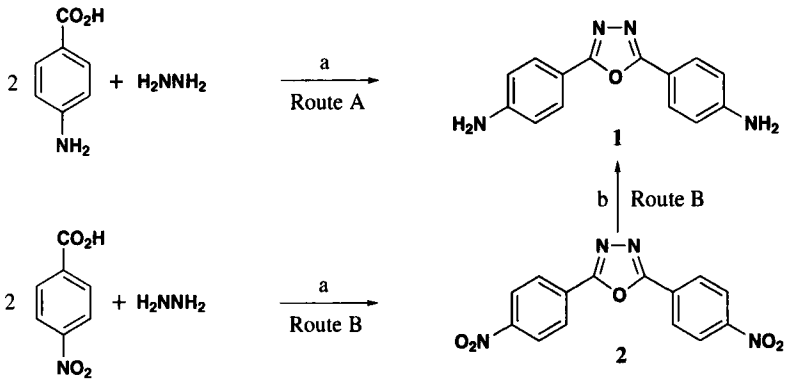
2,5-*bis*-(4-Aminophenyl)-1,3,4-oxadiazole (**1**) is useful in polymer synthesis because it confers electron-transporting-capabilities. Although **1** is commercially available,[1] polymer synthesis studies here required an inexpensive and plentiful source of **1**. We report herein a reliable and efficient method for the preparation of **1** in two-steps with an overall yield of 85%.



a) PPA, 160°C; b) H_2, Pd/C, THF/DMF, 60°C

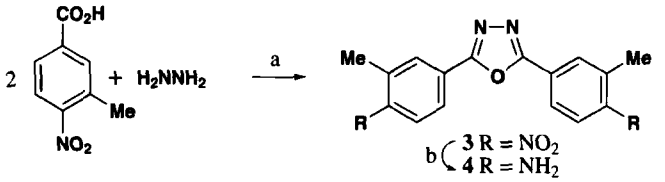
Scheme 1

Our initial effort focused on a literature report for the synthesis of **1** in a single step from 4-aminobenzoic acid.[2] We attempted this reaction (Route A) as described as well as with minor modifications, *Scheme 1*.[3] The crude product from this reaction consistently contained an impurity that could not be removed by recrystallization, in contrast to the report. We found that sublimation was the only procedure effective for the purification of this material. Our best yields by this route were approximately 60%. The need for a large scale apparatus for sublimation made purification tedious and time-consuming and led us to seek another procedure.

The reports of the reduction[4,5,6] of the dinitro compound **2** to **1** and the easy preparation of **2**[7] made Route B attractive. For the reduction step, only one report gave experimental details for 2,5-*bis*-(3-aminophenyl)-1,3,4-oxadiazole in only a 62% yield.[4] Another procedure only reported a 48% yield of **1** with Raney® nickel catalyst, a fire hazard during filtrations.[5] The most recent report[6] did not include experimental details or the yield for **1** and employed Fe and HCl, inconvenient for our needs.

The preparation of **2** scaled-up to over 100 grams uneventfully and provided an efficient preparation of **2** proceeding in 87% yield.[8] In the reduction, DMF was chosen as solvent because it presented a low fire hazard and was the best solvent for **2**. Although the reduction proceeded very smoothly, removal of the catalyst was troublesome. The remaining catalyst could be removed by dissolution of the crude product in a mixture of DMF/THF and filtration of the solution again through diatomaceous earth. Thus, in subsequent experiments, the solvent for reduction was changed to a mixture of DMF and THF (1:2, v:v). Using this solvent mixture, all the catalyst could be removed in a single filtration through diatomaceous earth. The product was obtained in 97% yield.

In order to assist in the elucidation of NMR spectra of polymers containing **1**, we prepared the previously unreported **4**, *Scheme* 2. Both the cyclization and reduction reactions proceeded uneventfully using the same sequence.



a) PPA, 160°C; b) H_2, Pd/C, THF/DMF, 60°C

Scheme 2

EXPERIMENTAL SECTION

Mps were collected on a capillary melting point apparatus and are not corrected. NMR spectra were obtained on a Bruker AC-200 spectrometer (^1H at 200 MHz, ^{13}C at 50 MHz) and are referenced to solvent or tetramethylsilane. The substituted benzoic acids were purchased from Aldrich Chemical Co. (Milwaukee, WI). Polyphosphoric acid (PPA) was a product of Riedel-de Haën (Seelze, DEU) and purchased through Sigma-Aldrich (St.Louis, MO). The 5% palladium on carbon catalyst (Lot # 0712) was purchased from Lancaster Synthesis Ltd (Windham, NH). Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA). All other reagents were obtained commercially and used as received. ***Caution: Anhydrous hydrazine is carcinogenic and must be handled by the operator with appropriate body protection in a well-ventilated hood.***

Preparation of 2,5-*bis*-(4-Aminophenyl)-1,3,4-oxadiazole (1) from 4-Aminobenzoic Acid.- A 1 L beaker containing 200 g PPA and a magnetic stir bar was heated to 150°C and stirred on a hot plate/stirrer. Then 2.33 mL (0.073 mol) anhydrous hydrazine was carefully added to the PPA followed immediately by 20 g (0.146 mol) 4-aminobenzoic acid. The mixture was stirred at 150°C for 2 h after which time, the mixture became a pale yellow homogenous solution. The hotplate was shut off and, while the mixture was hot, it was carefully diluted with 600 mL distilled H_2O, this resulted in a pale yellow solution. The solution was then made basic to pH 8 by the portionwise addition of powdered NaOH. The precipitated yellow solid was collected on a

coarse porosity glass frit and the filter cake was washed three times with 500 mL portions of distilled H_2O. It was then air dried on the frit for 8 h by drawing air through the filter cake. Purification of the crude product was performed by sublimation (250-300°C, 0.1 Torr) and provided a total of 10.8 g (58%) of a pale yellow solid, mp. 245-250°C, *lit.*[2] mp. 251-253°C. ^{1}H NMR (DMSO-d_6): δ 7.74 (d, ^2J = 8.9 Hz, 4H), 6.71 (d, ^2J = 8.3 Hz, 4H), 5.87 (bs, 4H). ^{13}C NMR (DMSO-d_6): δ 163.44, 151.97, 127.83, 113.62, 110.28.[9]

Anal. Calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21; O, 6.34

Found: C, 66.44; H, 4.82; N, 22.17; O, 6.55

2,5-*bis*-(4-Nitrophenyl)-1,3,4-oxadiazole (2).- A 4 L heavy-walled Erlenmeyer flask was charged with 1.2 kg of PPA and a magnetic stir bar. The flask was heated on a hot plate/stirrer and after reaching ~120°C, could be readily stirred. 4-Nitrobenzoic acid (179 g, 1.07 mol, 2 equiv) was added in three portions to the hot PPA allowing 10 min to pass between additions. The mixture was stirred 15 min further to generate an evenly dispersed suspension. Anhydrous hydrazine (17.2 mL, 0.54 mol, 1 equiv) was added to the mixture, dropwise over 20 min, using an addition funnel. After the addition was completed, the mixture was heated to 160°C for 6 h. To the hot and vigorously stirred mixture, 1 L of distilled H_2O was added, carefully, and in portions of 25 mL initially, then increasing gradually as the PPA hydrolyzed. During this process a tan solid precipitated. Another 1 L of distilled H_2O was added and the mixture was allowed to cool to ambient temperature (~3 hr). The mixture was then collected (12.5 cm porcelain filter, Whatman® 541) and air-dried on the filter for 10 hr by drawing air through the filter cake. The crude product was dissolved in 2 L of boiling DMSO and allowed to cool slowly and crystallize. The fine, pale yellow needles were collected on a medium porosity glass frit, then transferred to a 2 L beaker and 1 L of distilled H_2O was added. The crystals were stirred for 1 hr and filtered with a coarse porosity glass frit. The filter cake was washed twice with 300 mL portions of distilled H_2O. Finally, the crystals were air-dried for 12 h on the frit by drawing air through the filter cake. The total mass of the recrystallized product was 146.5 g (88%), mp. 299-301°C, *lit.*[7] mp. 312-314°C. Because of the low solubility of **2**, NMR spectroscopy was not performed.

Anal. Calcd for $C_{14}H_8N_4O_5$: C, 53.85; H, 2.58; N, 17.94

Found: C, 54.10; H, 2.55; N, 17.99

2,5-*bis*-(4-Aminophenyl)-1,3,4-oxadiazole (1).- To a 500 mL round bottom flask equipped with a magnetic stir bar was added 2 g of 5% palladium on carbon (~7 wt% catalyst) followed by 80 mL of DMF and 160 mL of THF; care was taken to cover the catalyst completely. Then compound **2** (30 g, 0.096 mol) was added and a condenser was attached which was then connected to a near-atmospheric pressure hydrogenation apparatus;[10] the mixture was then purged/flushed three times before placing the contents under a static H_2 atmosphere of approximately 2.5 psi. The mixture was stirred as rapidly as possible and heated to 60°C for 24 h. The flask was removed from the hydrogenator and purged with N_2 while it was cooled to ambient temperature. The mixture was filtered through 12 g Celite® 521 on a 7 cm diameter coarse

porosity glass frit (the diatomaceous earth was approximately 12 cm deep) to remove the catalyst. The flask was rinsed with 20 mL of THF and the collected catalyst was washed with 50 mL of THF. The pale yellow filtrate was then poured into 2 L of vigorously stirred, distilled H_2O and the product precipitated as a white solid. After stirring for 3 h, the solids were collected on a 14 cm diameter porcelain filter (Whatman® 541 filter paper). The crude product was air-dried on the filter for 1 hr by drawing air through the filter cake. The solid was transferred to a 2 L beaker and dissolved in a boiling mixture of 400 mL of 1,4-dioxane and 300 mL of H_2O. The solution took on a yellow tint during this process. The beaker was allowed to cool slowly (8 h), leading to precipitation of the product as pale yellow needles. The product was collected on a coarse porosity glass frit and transferred to a tared crystallizing dish, which was placed in a vacuum oven (100 Torr, 100°C) for 8 hr to remove residual H_2O and 1,4-dioxane. After drying, the purified product weighed 22.9 g. A second crop of product, 700 mg, was obtained after diluting the mother liquor with 300 mL H_2O and drying similarly. The total yield was 23.6 g (97%), mp. 254°C, *lit.*[2] mp. 251-253°C. The ^1H and ^{13}C NMR spectra of the product were identical to the spectra of the product from the 4-aminobenzoic acid route above.[9]

Anal. Calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21
Found: C, 66.45; H, 4.75; N, 22.35

2,5-*bis*-(3-Methyl-4-nitrophenyl)-1,3,4-oxadiazole (3).- Using similar conditions as for the preparation of **2** above: 185 g PPA, 25 g (0.138 mol) 3-methyl-4-nitrobenzoic acid and 2.2 mL (0.69 mol) anhydrous hydrazine gave 15.44 g (66%) of the title compound as pale yellow microcrystals after recrystallization from DMSO, mp. 203°C (shrinks) 210°C melts. ^1H NMR (DMSO-d_6): δ 8.31 (s, 2H), 8.21 (s, 4H), 2.64 (s, 6H).

Anal. Calcd for $C_{16}H_{12}N_4O_5$: C, 56.4; H, 3.55; N, 16.46
Found: C, 56.21; H, 3.56; N, 16.32

2,5-*bis*-(3-Methyl-4-aminophenyl)-1,3,4-oxadiazole (4).-Using similar conditions as for the preparation of **1** above: 3.5 g 5% Pd/C, 20 g (0.059 mol) **3** gave 14 g (85%) of the title compound as light tan powder after recrystallization from 1,4-dioxane, mp. 255-260°C. ^1H NMR (DMSO-d_6): δ 7.7-7.57 (m, 4H), 6.74 (d, J = 8.1 Hz, 2H), 5.62 (bs, 4H), 2.14 (s, 6H). ^{13}C NMR (DMSO-d_6): δ 163.45, 150.06, 128.21, 125.46, 121.05, 113.58, 110.52, 17.28.

Anal. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99
Found: C, 68.45; H, 5.79; N, 19.96

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