A Safe Cost-Efficient Synthesis of 4,6-Diaminoresorcinol

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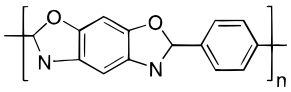
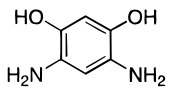
Introduction

Recent developments in the synthesis of the high-strength liquid crystalline polymer [*p*-phenylenebenzobis-(oxazole)] (PBO)[1] require a regioselective, high-yield,



PBO



DAR

inexpensive synthesis of 4,6-diaminoresorcinol (DAR) as the polymer precursor. The synthesis of DAR has been reported in moderate yield (30−50%) from nitration of resorcinol diacetate.[2]

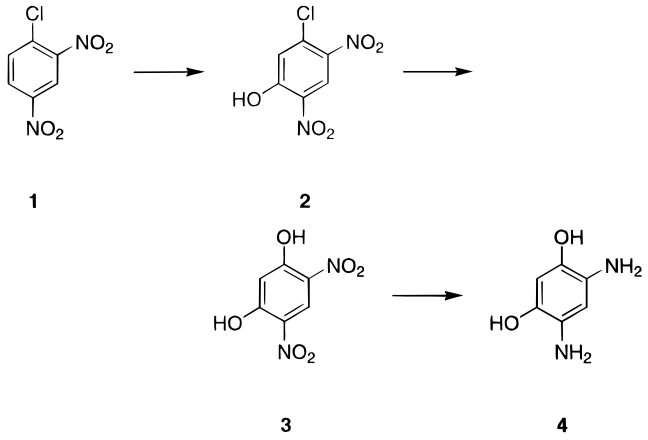
This synthesis has inherent dangers due to the formation of the explosive 2,4,6-trinitroresorcinol (styphnic acid) and suffers from low monomer yields. An alternative synthesis of DAR has been reported utilizing 1,2,3-trichlorobenzene.[3] With limited and decreasing availability of 1,2,3-trichlorobenzene, we report a safe, cost-efficient synthesis of DAR via hydroxylation of 2,4-dinitrochlorobenzene.

Results and Discussion

Makosza and Sienkiewicz reported on the hydroxylation of nitroarenes via vicarious nucleophilic substitution (VNS) of hydrogen utilizing alkyl hydroperoxides and potassium *tert*-butoxide in liquid ammonia with the substrate dissolved in tetrahydrofuran.[4] The product of the VNS reaction of 2,4-dinitrochlorobenzene (**1**) was 2,4-dinitro-5-chlorophenol (**2**), a potential precursor to DAR (Scheme 1). By utilizing a 2:1 mole ratio of base to hydroperoxide, a 93% yield of **2** was obtained. For the conversion of **1** to **4** to be commercialized, inexpensive substitutions for potassium *tert*-butoxide and tetrahydrofuran would be required, as well as the demonstration of the hydrolysis of **2** to **3**.

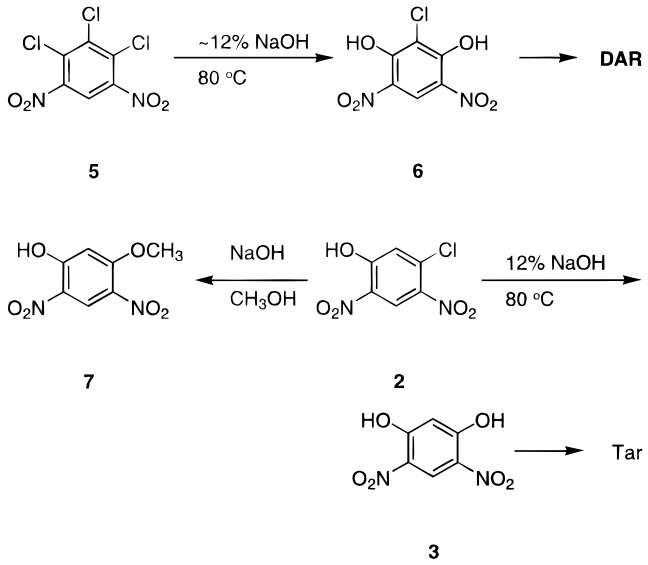
The effect of solvents on the selectivity of the VNS reaction with competing nucleophilic aromatic substitution (NAS) was investigated using anhydrous cumene hydroperoxide and powdered sodium hydroxide.[5] The product of the competing NAS reaction is 2,4-dinitrophenol. Cumene, 2-propanol, *N*-methylmorpholine, 1-methoxy-2-propanol, and 1,2-dimethoxyethane gave VNS:NAS

Scheme 1



ratios of <10. Presumably, these solvents phase-separated with the liquid ammonia−sodium hydroxide solution and the reaction, if any, was slow and nonselective. Methylene chloride, dialkyl formamides, and dimethoxymethane gave VNS:NAS ratios comparable to the results of Makosza and Sienkiewicz in tetrahydrofuran.

Although 4,6-dinitro-1,2,3-trichlorobenzene (**5**) was hydrolyzed to 2-chloro-4,6-dinitroresorcinol (**6**) in the 1,2,3-trichlorobenzene process,[3] the hydrolysis of 2,4-dinitro-5-chlorophenol (**2**) to 4,6-dinitroresorcinol (**3**) was not successful. We found that **2** is initially converted to **3**. However, in the presence of excess sodium hydroxide, **3** undergoes further degradation to intractable decomposition products.



This problem was circumvented by conversion of **2** to 2,4-dinitro-5-methoxyphenol (**7**) by the addition of methanol to the liquid NH_3 after completion of the VNS reaction.

The results for this "one pot" conversion of **1** to **7** are summarized in Table 1. Methylene chloride is the solvent of choice due to its low cost and ease of recovery. The isolation of **7** required prior removal of the cumene hydroperoxide byproducts, α-methylstyrene and cumyl alcohol, from the phenate salt of **7** by extraction with toluene. If the cumene byproducts were not separated from the phenate salt, the recovered phenol **7** would not

(1) Wolfe, J. F., Synthesis Research and Process of PBZ Polymers; final report on Contract No. AFWAL-TR-86-4025, SRI International, Sept. 1986.
(2) Schmitt, R. J.; Ross, D. S.; Hardee, J. R.; Wolfe, J. F. *J. Org. Chem.* **1988**, *53*, 5568−5569.
(3) Lysenko, Z. U. S. Patent 4,766,244, Aug 13, 1988.
(4) Makosza, M.; Sienkiewicz, K. *J. Org. Chem.* **1990**, *55*, 4979.
(5) Reference 4 mentions the use of sodium hydroxide as a base but also notes "differences in selectivity compared to potassium *tert*-butoxide presumably due to limited solubility of NaOH in liquid ammonia."

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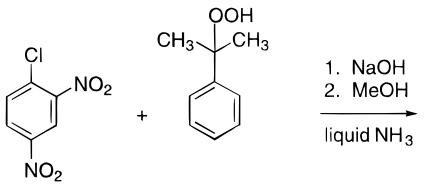
Table 1. Preparation of 2,4-Dinitro-5-methoxyphenol



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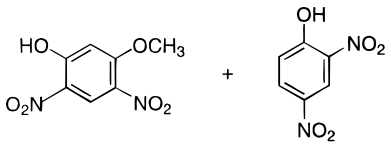


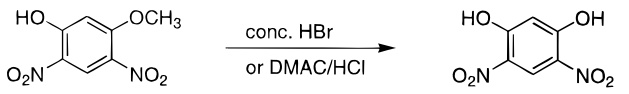
7

substrate (mol)	solvent	$C_6H_5C(CH_3)_2OOH$ (mol)	NaOH (mol)	NH_3 (mL)	**7** (% yield)
0.1	NMP	0.1	0.5	100	84
0.1	DMAC	0.1	0.5	100	82
0.1	DMF	0.1	0.5	100	80[a]
0.1	CH_2Cl_2	0.1	0.5	100	83
0.1	$(CH_3O)_2CH_2$	0.1	0.5	100	79

[a] Product contains <10% of the impurity 2,4-dinitro-5-dimethylaminophenol.

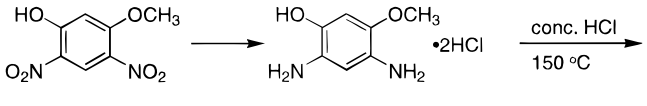
precipitate upon acidification. In this manner, crude yields in excess of 80% were obtained.

Attempted cleavage of the methyl ether **7** with HCl−perchloroethylene at 130 °C (with and without tetraphenylphosphonium chloride) or glacial acetic acid−anhydrous HCl (2:1) at 120 °C in a Parr reactor was unsuccessful. Although not an economical solution, refluxing 48% HBr (115 °C) overnight gave 100% cleavage to the desired 4,6-dinitroresorcinol (**3**). Hydrochloride salts of dialkylamides, i.e., dimethylacetamide and *N*-methylpyrrolidinone, were also effective reagents for the ether cleavage.[6] At ∼130 °C, the cleavage was complete in ∼8 h.

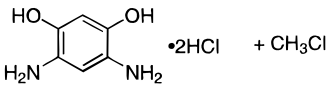


7 **3**

Although DMAC·HCl effectively produced ether cleavage, recycle of the DMAC HCl was problematic and an alternative was sought. Fortuitously, ether cleavage of 2,4-diamino-5-methoxyphenol **(8)** to **4** was more facile. Reduction of **7** to **8** was carried out with hydrogen in



7 **8**



4

aqueous propanol and 10% Pd/C as the catalyst. When **8** was subjected to concentrated HCl in a Hastelloy B reactor at 150 °C overnight, **4** was obtained in 93% yield, as the dihydrochoride salt.

(6) A paper describing this novel cleavage of ethers will be published elsewhere.

Summary

A commercially feasible process for the manufacture of 4,6-diaminoresorcinol has been demonstrated from inexpensive 2,4-dinitrochlorobenzene via vicarious nucleophilic substitution. The novel route described provides DAR monomer for PBO and eliminates the inherent dangers associated with nitration of diphenolic materials.

Experimental Section

General Procedure for the Vicarious Substitution Reaction. 2,4-Dinitrochlorobenzene (20.2 g, 0.1 mol) and cumene hydroperoxide (20 g, 80% 0.1 mol) were diluted with methylene chloride (50 mL) and added dropwise to a slurry of powdered NaOH (20 g, 0.5 mol) in (dry ice condenser) anhyd NH_3 (125 mL) at −33 °C over a period of 1 h. After the addition was complete, the reaction mixture was allowed to warm to ∼ −10 °C, and methanol (75 mL) (containing 1−2 g of sodium hypophosphite to destroy any residual hydroperoxide) was added dropwise. After this addition was complete, the reaction was allowed to warm to rt and stirred for 3−4 h (or overnight).

The reactor was equipped with a short path distillation column and the mixture heated to recover methylene chloride and, if desired, methanol. During the distillation, water was added dropwise to maintain the phenate salt in a slurry. After cooling, the contents were transferred to a separatory funnel containing 250 mL of H_2O, and the aqueous solution was extracted twice with toluene to remove cumene byproducts. After evaporation of the toluene, 18.5 g of α-methylstyrene and cumyl alcohol were recovered. The aqueous phase was acidified with concd HCl with stirring at <20 °C to precipitate the crude product 2,4-dinitro-5-methoxyphenol (18.5 g).[7,8] Recrystallization from 65% aqueous methanol afforded 15.75 g (80%) of **7**: mp 110−12 °C (lit.[9] mp 113 °C); ^{1}H NMR MHz (300 MHz, DMSO-d_6) δ 8.65 (s, 1H), 6.86 (s, 1H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.2, 157.8, 130.2, 158.6, 125.0, 120.8, 57.4; MS *m*/*z* 214 (M^+, calcd for $C_7H_6N_2O_6$ 214).

Attempted Hydrolysis of 2,4-Dinitro-5-chlorophenol (2). 2,4-Dinitro-5-chlorophenol (3.0 g) was heated at 80 °C with 25 mL of 10% NaOH. After 3 h, GC analysis indicated about 10−15% conversion. After 24 h, only traces of **2** and **3** remained.

2,4-Diamino-5-methoxyphenol Dihydrochloride (8). A 250 mL, 3-necked, round-bottomed flask was charged with 150 mL of water, 2,4-dinitro-5-methoxyphenol (21.4 g, 0.1 mol), and 1.0 g of 10% Pd/C. The reaction was stirred under a nitrogen atmosphere for 3−4 min. The stirred reaction mixture was heated to 55 °C and hydrogen gas was sparged below the surface of the reaction mixture. After 10 min, concd HCl (19.8 g, 0.2 mol) was added through the condenser and hydrogenation continued for 4 h. The catalyst was removed by filtration and the filtrate passed into a solution consisting of 0.5 g of stannous chloride dihydrate and 25 mL of concd HCl. The solution was saturated with dry HCl gas and cooled to 25 °C. The solvent was then removed under reduced pressure (15 mm) to yield a pale, off-white solid. The product was isolated as the dihydrochloride salt and dried at 40 °C, to give 2,4-diamino-5-methoxyphenol dihydrochloride (21.0 g, 93%).[7,8] ^{1}H NMR (300 MHz, D_2O) δ 7.43 (s,1H), 6.85 (s, 1H), 4.78 (bs, 7H), 3.95 (s, 3H); ^{13}C NMR (75 MHz, D_2O) δ 156.7, 154.6, 122.2, 113.3, 112.6, 103.6, 59.6; MS *m*/*z* 154 (M^+, calcd for $C_7H_{10}N_2O_2$ 154).

4,6-Diaminoresorcinol Dihydrochloride (4). 2,4-Diamino-5-methoxyphenol dihydrochloride **(8)** (15.0 g, 0.2 mol) and 150 mL of concd HCl were heated at 150 °C in a Hastelloy B bomb for 18 h. After cooling, the solids were filtered and washed with concentrated HCl to give 12.2 g (94%) of DAR·HCl. **Note: This reaction requires a Hastelloy B reactor. Hastelloy C is not stable under these conditions.**

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(8) Lysenko, Z.; Pews, R. G.; Vosejpka, P. U.S. Patent 5,414,130, May 9, 1995.
(9) Borsche, W. *Ber. Dtsch. Chem. Ges.* **1917**, *50*, 1351.