Facile Synthesis of Catechol Azo Dyes

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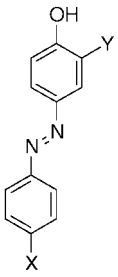
Results and Discussion

Azo dyes of catechol (1,2-dihydroxybenzene) are of interest due to their chromophoric nature and the bidentate character of their ortho phenolic hydroxyl groups. These properties have made them useful for metal complexation studies[1] and for spectroscopic measurement of cation concentrations.[2,3] Their wider utility is limited by a lack of generally applicable, yet efficient, methods for their synthesis. The limitations of existing methods[4−8] became obvious in our attempts to prepare catechol azo compounds **2a**−**d** for use as chromophoric substrates for redox enzymes.



2) Y = OH
3) Y = OCH_3
4) Y = H

a) X = NO_2
b) X = SO_2NH_2
c) X = H
d) X = CH_3

The coupling reaction of catechol with a diazonium salt (Scheme 1) is accompanied by side reactions that have not been thoroughly studied. An important aspect to consider for catechol in a diazo coupling reaction is its tendency to oxidize to unstable *o*-quinone. Oxidation of catechol becomes increasingly rapid with increasing alkaline pH. However, a high pH also increases the reactivity of catechol to diazo coupling. It is the balancing of these two characteristics of catechol which leads to compromises in the yield of reaction. Several methods have been reported to address these two aspects of diazo coupling with catechol. These have included alkaline conditions,[4] an acetate-buffered solution at pH 4 using fluoroborate diazonium salts,[5] strong acidic conditions in a mixture of water and ethanol,[6] and the addition of $Al_2(SO_4)_3$.[7]

Scheme 1

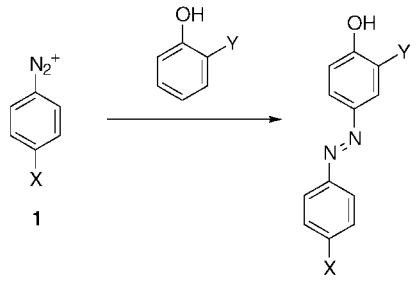


Table 1. Yields (%) of Azo Compounds 2−4 Obtained from Reaction of the Appropriate Diazonium Salt with Catechol, Guaiacol, and Phenol, Respectively

	2	3	4
a	30	92	quantitative
b	35	90	quantitative
c		85	90
d		78	85

When the direct coupling method was used for the synthesis of compounds **2**−**4**, it was found that apart from the consideration of pH the efficiency of diazo coupling reactions is dependent on the nature of the substituents on the aryldiazonium salts (Table 1). Aryldiazonium salts with electron-withdrawing substituents, such as nitro and sulfonamide, gave higher yields of diazo product than phenyldiazonium, whereas aryldiazonium salts with electron-donating substituents, such as methyl or methoxy, gave only intractable dark material. Regardless of the substituent on the diazonium salt, the yield of catechol diazo compound was low and substantial amounts of impurities were produced.

The low yields are not surprising when it is taken into account that aryldiazonium salts undergo homolytic dediazotization reactions under certain reducing conditions. It has been reported that *p*-hydroquinone and ascorbic acid can reduce diazonium salts.[9] EPR studies have shown that even under acidic conditions catechol can reduce 4-methoxyphenyldiazonium through a one-electron reduction to form the aryl radical intermediate.[10]

There are at least two factors affecting the dediazotization reaction. One factor concerns the structure of the reducing agent, which determines the transition state of the redox reaction. The primary factor, however, is the reducing ability of the reducing agent. It has been shown that molecules with oxidation potentials higher than 1 V versus normal hydrogen electrode (NHE) are poor reducing agents for diazonium salts.[11] Taking the dediazotization reaction into account, it was not unexpected that phenol gave the highest yield from diazo coupling compared to guaiacol (2-methoxyphenol) and catechol (Table 1). Guaiacol, which has a peak current potential

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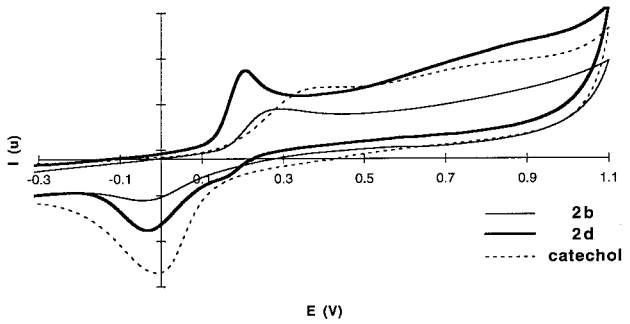

Figure 1. Cyclic voltammograms (SCE) of azo dyes **2b**,**d** and catechol, measured at pH 6.8, showing the lower oxidation potentials of the catechol azo dyes.

(0.52 V) lower than that of phenol (0.60 V) but higher than that of catechol (0.42 V), gave yields in diazo coupling between that obtained for catechol and phenol. The peak current potential for catechol is comparable to that of *p*-hydroquinone. Presumably, guaiacol can reduce diazonium salts, albeit to a lesser extent than catechol.

The dependency of the yield of diazo product on the nature of the diazonium salt (Table 1) is in agreement with the premise that electron-withdrawing groups increase the reactivity of diazonium salts. However, these groups also promote the ability of the diazonium salt to accept an electron in homolytic dediazotization reactions.[12] The results in Table 1 show the expected effect of the various substituents on the efficiency of the coupling reaction between aryl diazonium salt with phenol, guaiacol, and catechol. However, the fact that **1a**,**b** formed the corresponding azo compounds with catechol while **1c**,**d** did not appears to contradict the expected trend for substituent effects on homolytic dediazotization reactions. From peak current potentials catechol is expected to be midway in reducing ability between phenol and *p*-hydroquinone. This indicates that diazo coupling and dediazotization reactions are in competition in reactions between catechol and diazonium salts. To the extent that the reactivity of the diazonium salt is enhanced by electron-withdrawing groups, the chance of diazo compound formation increases. By decreasing the activity of the diazonium salt, the dediazotization reaction becomes progressively dominant.

Another factor which limits the yield of catechol diazo coupling reactions is the lower oxidation potential of catechol azo compounds relative to that of catechol (Figure 1). Apparently the products may be oxidized more readily than catechol. Therefore, they are able to dediazotize diazonium salts and lead to byproducts.

The high efficiency of the direct diazo coupling of guaiacol led to the consideration that the guaiacol azo dyes be used as precursors to the desired catechol azo dyes (Scheme 1). An indirect method for the preparation of catechol dyes has been reported previously which involved protection of one of the hydroxyl groups of catechol as a benzoate ester prior to coupling with diazonium salts.[8] However, this method requires alkaline hydrolysis of the benzoyl protecting group with KOH which promotes the autoxidation of the catechol azo dye product.

To cleave the methyl ether bond of the guaiacol azo dyes, chlorotrimethylsilane with sodium iodide in refluxing acetonitrile[13] was tried but gave no reaction after 48 h. Boron tribromide in methylene chloride[14] could effect the demethylation of the guaiacol azo dyes with electron-donating groups but was completely ineffective for the nitro and sulfonamide derivatives **3a**,**3b**. The method which was applicable to all of the guaiacol dyes tested was treatment with aluminum trichloride and pyridine in refluxing chloroform. The workup of the $AlCl_3$/pyridine procedure is under acidic conditions which decreases the possibility of autoxidation. The results are shown in Table 2.

Table 2. Recovery (%) of Catechol Dyes 2 Obtained from Demethylation of Guaiacol Dyes 3 with BBr_3 and $AlCl_3$/Pyridine

	BBr_3	$AlCl_3$/pyridine
2a	incomplete reaction	80
2b	incomplete reaction	85
2c	72	72
2d	65	65

Many factors in catechol diazo coupling reactions serve to lower the yield of azo product. Given the nature of catechol and of diazonium salts, these factors are generally unavoidable. The indirect method described above affords high yields and uses reaction conditions which allow the product to be readily purified. Moreover it is applicable to systems with electron-donating as well as electron-withdrawing groups.

Experimental Section

General. ^{1}H NMR spectra were recorded as dilute solutions in deuteriochloroform. Cyclic voltammetry was carried out at 20 °C using a 0.7-mm diameter platinum disk electrode, platinum wire auxiliary electrode, and aqueous KCl-saturated calomel reference electrode (SCE).

General Procedure for Preparation of Diazonium Chloride Solutions of Sulfanilamide (1b), Aniline (1c), and *p*-Toluidine (1d). The desired aromatic amine (0.01 mol) was dissolved in a mixture of concentrated HCl (5 mL) and distilled water (20 mL). A solution of sodium nitrite (0.83 g, 0.012 mol) in distilled water (5 mL) was prepared in a test tube. Sodium nitrite solution was added dropwise to the acidic solution of amine over 5 min at 0 °C. The mixture was stirred at 0 °C for 40 min.

Procedure for Preparation of Diazonium Chloride Solutions of *p*-Nitroaniline (1a). *p*-Nitroaniline (1.38 g, 0.01 mol) was dissolved in a mixture of methanol (20 mL) and concentrated HCl (5 mL). Isoamyl nitrite (1.34 mL, 0.01 mol) was added to this solution at 0 °C. A yellow precipitate gradually appeared. The reaction mixture was kept stirring at 0 °C for 45 min.

General Procedure for Preparing Diazo Derivatives of Catechol (2) through Direct Diazo Coupling. The desired deoxygenated benzonium salt solution was injected dropwise to a deoxygenated solution of catechol (1.1 g, 0.01 mol) at 0 °C under an N_2 atmosphere while the pH of the reaction mixture was kept between 6 and 7 by addition of the appropriate amount of deoxygenated K_2CO_3 (1 M) solution. The reaction mixture was kept stirring under N_2 at 0 °C for 30 min by which time the product precipitated. Precipitation was driven to completion by the addition of a few drops of dilute HCl (10%). The precipitate was extracted with diethyl ether and evaporated to dryness under reduced pressure. The resulting solid was washed with heptane.

4-[(4-Nitrophenyl)azo]-1,2-benzenediol (2a). Using the direct coupling procedure described above, compound **2a** was obtained in 30% yield: mp 232−234 °C; λ_{max} 396 nm (ϵ 13 000, 5% 2-propanol−H_2O); ^{1}H NMR (acetone-d_6) δ 7.05 (d, J = 8.0

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Hz, 1H), 7.54 (m, 2H), 8.03 (d, J = 9.0 Hz, 2H), 8.40 (d, J = 9.0 Hz, 2H), 8.53 (s, 1H), 8.91 (s, 1H); LRMS (EI) 259 (M^+), 242 ($M^+ - OH$), 137 ($M^+ - C_6H_4NO_2$), 122 ($M^+ - C_6H_5N_2O_2$).

4-[(4-Sulfonamidophenyl)azo]-1,2-benzenediol (2b). Using the direct coupling procedure described above, compound **2b** was obtained in 35% yield: mp 240−242 °C; λ_{max} 381 nm (ϵ 15 730, 5% 2-propanol−H_2O); ^{1}H NMR (acetone-d_6) δ 6.70 (s, 2H), 7.02 (d, J = 9.1 Hz, 1H), 7.50 (m, 2H), 7.94 (d, J = 9.0 Hz, 2H), 8.37 (d, J = 9.0 Hz, 2H), 8.52 (s, 1H), 8.82 (s, 1H). Anal. Calcd for $C_{12}H_{11}N_3O_4S$: C, 49.14; H, 3.75; N, 14.33; S, 10.92. Found: C, 49.14; H, 3.96; N, 14.68; S, 10.91.

General Procedure for Preparation of Diazo Derivatives of Guaiacol (3). Guaiacol (1.24 g, 0.01 mol) was dissolved in ethanol (15 mL), and the mixture was added to a solution of K_2CO_3 (1.4 g in 50 mL). A solution of the desired arylazonium salt was added to the guaiacol solution under an N_2 atmosphere at 0 °C. The resultant mixture was stirred under an N_2 atmosphere for 40 min at 0 °C.

2-Methoxy-4-[(4-nitrophenyl)azo]phenol (3a). From the general procedure described above, the reaction mixtures were acidified by addition of cold HCl (10%) and the resulting precipitate was dissolved in ethanol and reprecipitated by the addition of water to afford **3a** in 92% yield: mp 167−169 °C; λ_{max} 396 nm (ϵ 22 910, 15% ethanol−H_2O); ^{1}H NMR ($CDCl_3$), δ 4.01 (s, 3H), 6.10 (s, 1H), 7.09 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 2.1 Hz, 1H), 7.68 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.98 (d, J = 8.7 Hz, 2H), 8.36 (d, J = 8.7 Hz, 2H). Anal. Calcd for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 56.92; H, 4.05; N, 15.65.

2-Methoxy-4-[(4-sulfonamidophenyl)azo]phenol (3b). The same procedure as described for **3a** was used to afford **3b** in 90% yield: mp 241−243 °C; λ_{max} 378 nm (ϵ 20 120, 15% ethanol−H_2O); ^{1}H NMR (acetone-d_6) δ 3.95 (s, 3H), 6.58 (s, 1H), 6.97 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.52 (dd, J = 8.2, 2.2 Hz, 1H), 7.88 (q, J = 8.5 Hz, 2H), 7.98 (q, J = 8.5 Hz, 2H). Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 50.8; H, 4.26; N, 13.67; S, 10.43. Found: C, 50.42; H, 4.41; N, 13.47; S, 10.47.

2-Methoxy-4-(phenylazo)phenol (3c). Using the general procedure described above, a black precipitate was collected after decreasing the pH of the reaction mixture to 4 by addition of HCl (10%). This precipitate was dissolved in acetone, and an excess amount of water (8 times in volume) was slowly added to the acetone solution. The resulting mixture was left overnight at room temperature to allow the product to precipitate. Compound **3c** was obtained in 85% yield: mp 69−71 °C; λ_{max} 364 nm (ϵ 17 280, 15% ethanol−H_2O); ^{1}H NMR ($CDCl_3$), δ 4.00 (s, 3H), 5.95 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 7.41−7.54 (m, 4H), 7.60 (q, J = 2.2 Hz, 8.4 Hz, 1H), 7.867 (dd, J = 8.1 Hz, 1.3 Hz, 2H). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.3; N, 12.27. Found: C, 68.18; H, 5.18; N, 12.47.

2-Methoxy-4-[(4-methylphenyl)azo]phenol (3d). From the general procedure described above, the reaction mixture was acidified by the addition of dry ice which caused precipitation of the product. The collected dye was dissolved in ethanol and precipitated by the addition of water. Compound **3d** was obtained in 78% yield: mp 75−771 °C; λ_{max} 363 nm (ϵ 22 840, 15% ethanol−H_2O); ^{1}H NMR ($CDCl_3$), δ 2.44 (s, 3H), 4.00 (s, 3H), 5.92 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 2.0 Hz, 1H), 7.60 (dd, J = 8.4 Hz, 2.0 Hz), 7.78 (d, J = 8.4 Hz, 2H). Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.4; H, 5.82; N, 11.56. Found: C, 69.3; H, 5.57; N, 11.47.

General Procedure for the Preparation of Diazo Derivatives of Phenol (4). Phenol (0.94 g, 0.01 mol) was dissolved in a solution (20 mL) of sodium hydroxide (4 g, 0.1 mol) and cooled to 0 °C. The appropriate aryldiazonium salt solution was added slowly to the phenolic solution at 0 °C. The resultant colored mixture was stirred for 1 h at 0 °C. The product was precipitated by addition of HCl solution (20%). For further purification the phenolic dye was dissolved in acetone and recrystallized by addition of water.

4-[(*p*-Nitrophenyl)azo]phenol (4a). Using the general procedure described above, compound **4a** was obtained in quantitative yield: mp 190−192 °C; λ_{max} 377 nm (ϵ 25 230, 15% ethanol−H_2O); ^{1}H NMR ($CDCl_3$) δ 5.28 (1H, s), 6.98 (2H, d, J = 9.1 Hz), 7.81 (2H, q, J = 8.9 Hz), 7.88 (2H, d, J = 8.9 Hz), 8.34 (2H, d, J = 9.1 Hz). Anal. Calcd for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.14; H, 3.56; N, 17.54.

4-[(4-Hydroxyphenyl)azo]benzenesulfonamide (4b). Using the general procedure described above, compound **4b** was obtained in quantitative yield: mp 254−256 °C; λ_{max} 359 nm (ϵ 30 510, 15% ethanol−H_2O); ^{1}H NMR (in alkaline D_2O) δ 6.57 (2H, d, J = 8.7 Hz), 7.59 (2H, d, J = 6.0 Hz), 7.62 (2H, d, J = 6.0 Hz), 7.79 (2H, d, J = 8.7 Hz). Anal. Calcd for $C_{12}H_{11}N_3O_3S$: C, 51.98; H, 4.00; N, 15.15; S, 11.56. Found: C, 51.84; H, 4.02; N, 15.20; S, 11.53.

4-(Phenylazo)phenol (4c). Using the general procedure described above, compound **4c** was obtained in 90% yield: mp 149−151 °C; λ_{max} 348 nm (ϵ 20 350, 5% 2-propanol−H_2O); ^{1}H NMR ($CDCl_3$) δ 5.21 (1H, s), 6.93 (2H, d, J = 8.7 Hz), 7.46−7.52 (3H, m), 7.86−7.90 (4H, m). Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.55; H, 4.89; N, 14.16.

4-[(4-Methylphenyl)azo]phenol (4d). Using the general procedure described above, compound **4d** was obtained in 85% yield: mp 143−144 °C; λ_{max} 352 nm (ϵ 20 800, 5% 2-propanol−H_2O); ^{1}H NMR ($CDCl_3$) δ 2.44 (3H, s), 5.40 (1H, s), 6.93 (2H, d, J = 8.3 Hz), 7.30 (2H, d, J = 8.3 Hz), 7.78 (2H, q, J = 9.1 Hz), 7.86 (2H, d, J = 9.1 Hz). Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.62; H, 5.45; N, 13.27.

BBr_3 Reaction with Diazo Guaiacol Derivatives. An excess of BBr_3 (10 mol equiv) was added to a solution of the appropriate guaiacol dye (1.0 mmol) in dried acetonitrile (25 mL) under N_2. The mixture was left stirring overnight at room temperature. The resulting solution was poured slowly onto ice (300 g) which resulted in the formation of a precipitate. The product was extracted from the collected precipitate with diethyl ether. The solvent was removed by evaporation under reduced pressure, and the resulting solid was washed with heptane.

4-(Phenylazo)-1,2-benzenediol (2c). Using the BBr_3 procedure described above, compound **2c** was obtained in 72% yield: mp 145−147 °C, λ_{max} 364 nm (ϵ 15 650, 5% 2-propanol−H_2O); ^{1}H NMR (acetone-d_6) δ 7.00 (1H, d, J = 8.2 Hz), 7.44−7.60 (5H, m), 7.82 (2H, dd, J = 7.7 Hz, J = 1.8 Hz), 8.62 (1H, s), 8.91 (1H, s). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.29; H, 4.7; N, 13.08. Found: C, 67.13; H, 4.49; N, 13.11.

4-[(4-Methylphenyl)azo]-1,2-benzenediol (2d). Using the BBr_3 procedure described above, compound **2d** was obtained in 65% yield: mp 180−182 °C, λ_{max} 364 nm (ϵ 15 400, 5% 2-propanol−H_2O); ^{1}H NMR (acetone-d_6) δ 2.40 (3H, s), 6.99 (1H, d, J = 8.4 Hz), 7.33 (2H, d, J = 8.2 Hz), 7.40 (1H, dd, J = 8.4 Hz, 2.1 Hz), 7.49 (1H, d, J = 2.1 Hz), 7.75 (2H, d, J = 8.2 Hz), 8.54 (s, 1H), 8.83 (s, 1H). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.4; H, 5.30; N, 12.27. Found: C, 68.30; H, 5.25; N, 12.17.

$AlCl_3$/Pyridine Reaction with Diazo Guaiacol Derivatives 3a,b. To a solution of the desired guaiacol dye (1.0 mmol) in dry chloroform (20 mL) was added an excess of anhydrous $AlCl_3$ (1 g). The resultant mixture was kept under an N_2 atmosphere and was heated to 50 °C. Pyridine (2.1 mL) was added dropwise, and the mixture was refluxed for 30 h and then cooled to room temperature. Hydrochloric acid (10%) was added, and the product was extracted from the aqueous phase with diethyl ether. The solvent was removed under reduced pressure, and the resulting solid was washed with chloroform to give **2a**,**b** in 80% and 85% yields, respectively.

$AlCl_3$/Pyridine Reaction with Diazo Guaiacol Derivatives 3c,d. A similar method as mentioned above for the preparation of **2a**,**b** from the corresponding guaiacol dyes was applied for **3c**,**d**, except that acetonitrile was used in place of chloroform. The product was extracted with diethyl ether, and the solvent was removed under reduced pressure. The resulting solid was washed with heptane to give **2c**,**d** in 75% and 68% yields, respectively.

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