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One-pot synthesis of substituted catechols from the corresponding phenols

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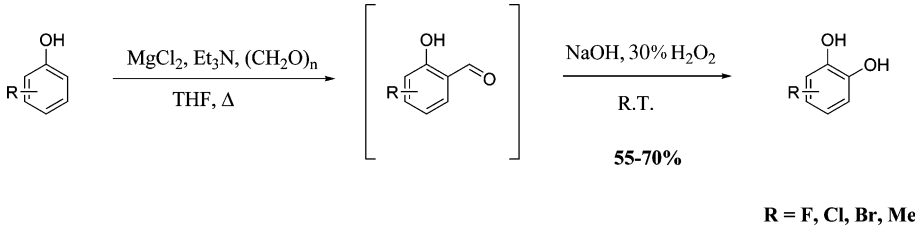
Abstract—Phenols are converted to salicylaldehydes with paraformaldehyde, $MgCl_2$–Et_3N in THF, and when subsequently treated with aqueous NaOH and H_2O_2 afford the corresponding catechols. The sequence is conveniently carried out as a one-pot procedure.

The catechol structural entity is present in a number of important naturally occurring compounds and in other molecules with interesting biological activity. Hence synthetic methods leading to substituted catechols are of considerable interest. Several methods of preparation are known.[1] The copper ion catalyzed substitution of 2-halophenols with hydroxide can lead to the corresponding catechols in good yields, but the conditions are quite harsh.[2] The most versatile methods are probably the oxidation of salicylaldehydes or acetophenone derivatives with either hydrogen peroxide or peracids, the Dakin and Bayer–Villiger reactions, respectively.[3,4] In the last two decades fermentation methods have been introduced with considerable success.[5] Benzene derivatives are converted to the corresponding optically pure cyclohexadiene-1,2-diols, which are readily transformed into catechols. In the present paper we describe an efficient one-pot method for the conversion of phenols to catechols.

We recently described a simple procedure for the selective *ortho*-formylation of phenols that involves heating a mixture of the phenol, anhydrous $MgCl_2$, triethylamine, and paraformaldehyde under reflux in acetonitrile or THF. For alkyl and halogen substituted phenols excellent yields of salicylaldehydes were obtained.[6] Moreover, we have shown that the reaction products from this formylation reaction can, without isolation, be reacted with (+)-(*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt, thus giving rise to a convenient high yielding and one-pot method for the preparation of salen ligands.[7] A similar approach seemed feasible for the preparation of catechols; the formylation reaction is followed by the Dakin oxidation with H_2O_2 as a one-pot procedure (Scheme 1).

Accordingly, to the THF solution from the formylation reaction, aqueous NaOH was added followed by 30% H_2O_2. After 4–8 h at room temperature the reaction



Scheme 1.

Keywords: *ortho*-Formylation of phenols; Dakin reaction; Substituted catechols.
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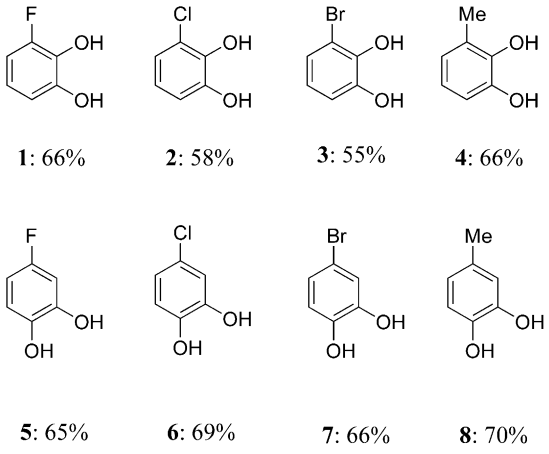

Figure 1.

was complete and normal work-up furnished the crystalline catechol derivative. The reactions were carried out with both 2- and 4-substituted phenols as starting materials. The catechols **1**–**8**, prepared by this method, are shown in Figure 1. Except for compound **3**, they are all commercially available compounds that were identified by comparison with authentic samples.[8] The recorded yields are for recrystallized materials, based on the phenols, and are not optimized. Experimental details for the preparation of **3** are given below and are typical.[9]

Substituted phenols are readily available, and the present method appears to be a convenient way of transforming them into the corresponding catechols.

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9. *Preparation of* **3**: A mixture of 2-bromophenol (1.73 g, 10 mmol), $MgCl_2$ (1.90 g, 20 mmol), Et_3N (2.02 g, 20 mmol) and paraformaldehyde (0.90 g, 30 mmol) under argon and in THF (15 mL) was heated under reflux for 3 h. The reaction mixture was cooled to room temperature and sodium hydroxide (0.05 N, 30 mL) was added dropwise. When all components had dissolved, H_2O_2 (30%, 4 mL) was added dropwise. After 2 h, another portion of 30% H_2O_2 (4 mL) was added and the reaction mixture was stirred for 4 h until complete conversion (TLC). The reaction mixture was acidified (1.0 N HCl, 25 mL) and extracted with CH_2Cl_2. The extract was washed with NaS_2O_4, the solvent removed under reduced pressure and the residue dissolved in a small amount of MeOH. Filtration and washing (CH_2Cl_2, 50 mL) through a plug of silica followed by evaporation of the solvent gave a solid residue, that was recrystallized from pentane to give 3-bromocatechol **3** as white crystals (1.03 g, 55%): mp 40–41 °C, lit.[8a] mp 40.5–41.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.65 (bs, 2H), 6.72 (t, J = 7.8 Hz, 1H), 6.85 (dd, J = 1.5, 7.8 Hz, 1H), 6.98 (dd, J = 1.5, 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.5, 114.9, 121.9, 123.3, 140.3, 144.6; HRMS calcd for $C_6H_5BrO_2$ (M^+): 187.9473, found 187.9485.