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A Facile Synthesis of Functionalized Catechols

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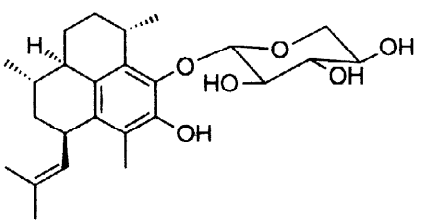
Abstract: A general route to functionalized catechols is achieved by the reaction of 3,6-di(chloromethyl)-4,5-dimethyl-catechol with various nucleophiles in the presence of a base. The reactions are proposed to occur by way of a dehydrochlorinated intermediate which undergoes Michael additions to give the catechol products.

Keywords: Catechol; Michael reactions.

Catechols, and their oxidized form, *o*-quinones, are important components of many natural products, e.g., pseudopterosin A (**1**) from the caribbean soft coral *Pseudopterogorgia Elisabethae*[1-3]. In addition, reactivities of the diene and ketone functionalities of *o*-quinones have attracted the interest of synthetic chemists[4]. In our studies we were interested in catechols as ligands for the separation of metal ions. It is known that the equilibrium binding constant (K) for the coordination of the deprotonated form of the catechol, Tiron (4,5-



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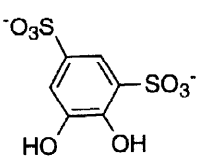

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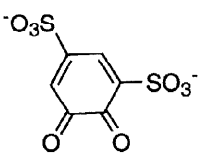

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dihydroxybenzene-1,3-disulfonate, **2**)[5], to the uranyl dication (UO_2^{2+}) is orders of magnitude larger than that for coordination to the quinone form **3**[6]. Thus, it seemed possible to incorporate into a ligand a catechol unit that would strongly bind a metal ion but would release the metal ion when the catechol unit was oxidized to the quinone form. With the goal of synthesizing catechol ligands that also incorporate other coordinating groups, we developed the route to functionalized catechols that is described in this letter.

The 3,6-difunctionalized catechols **9** were the targets of these syntheses. Their preparation began with the chloromethylation of commercially available 3,4-dimethoxytoluene (**4**) using chloromethyl methyl ether[7] (Scheme 1). Reduction with $LiAlH_4$ gave **5** in 77% yield. Further treatment of **5** with chloromethyl methyl ether using conc. H_2SO_4 as the catalyst gave the di-chloromethylated product **6** in 95% yield[8].

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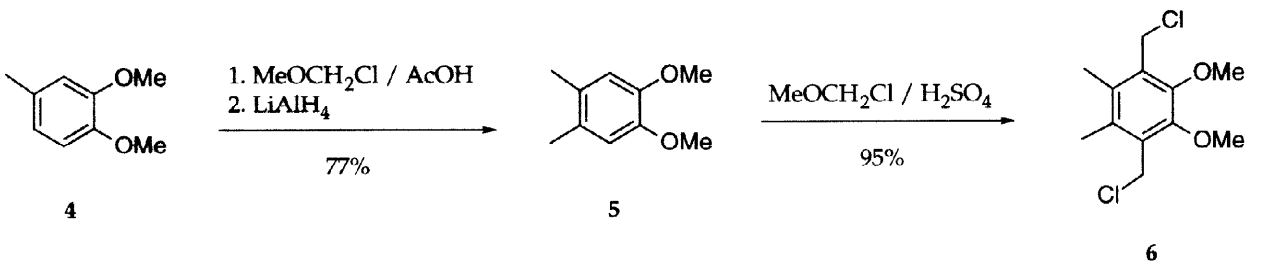
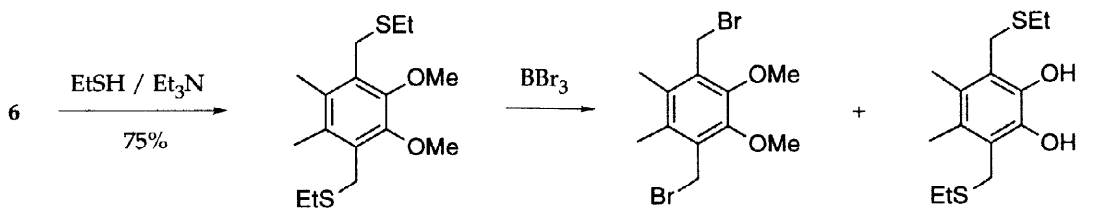
Scheme 1.



4 5 6

Direct reaction of **6** with nucleophiles such as EtSH gave the corresponding substitution product **7**. However, the demethylation of **7** using BBr_3[9] led to the formation of dibromide **8** in high yield rather than the catechol **9a** (Scheme 2). Other demethylating agents such as iodide[10], thioethoxide[11], or even diphenylphosphide[12] failed to give **9a** in reactions with **7**.

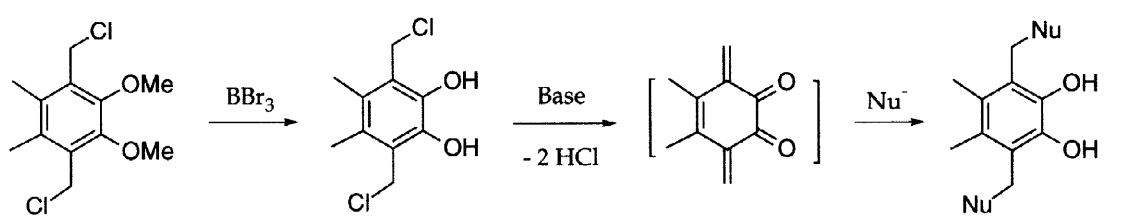
Scheme 2



7 8 (80%) 9a (0%)

In order to prepare catechols **9**, **6** was first demethylated with BBr_3 to give a high yield of **10**, which was then reacted with nucleophiles in the presence of a base to give the functionalized catechols **9** without needing to protect the two hydroxyl groups (Scheme 3). The conversion of **10** to **9** could proceed through intermediate **11** or a quinone methide resulting from loss of only one equivalent of HCl. Evidence for the intermediacy of **11**

Scheme 3



6 10 11 9

or a quinone methide is the observation that compound **10** reacted with methanol in the presence of K_2CO_3 as the base (r.t. for 48 h, 40%) to give **9i**, while the methyl-protected compound **6**, which is incapable of undergoing dehydrochlorination, failed to react with methanol under the same experimental conditions. Related *o*-quinone methides have been proposed in other reactions[13,14]. The formation of **9** from **11** (Scheme 3) would

presumably occur by Michael addition of the nucleophile at the β-position of the intermediate diketone **11**. Alternatively, the conversion of **10** to **9** could proceed by two sequential HCl elimination - nucleophilic addition reactions.

Table 1. Synthesis of catechols **9** from **6**

Entry	Nucleophiles (Nu-H) (equiv)[a]	Base (equiv)[a]	Temp (°C) / Time(h)	Yield (%)[b]
a	EtSH (3)	Et_3N (4)	20 / 5	90
b	Me_2CHSH (3)	Et_3N (4)	20 / 5	86
c	$HS(CH_2)_3SH$ (4)	Et_3N (4)	20 / 5	70
d	$HS(CH_2CH_2O)_4CH_2CH_2SH$ (5)	Et_3N (4)	20 / 5	50
e	$HOCH_2CH_2S$-H (3)	Et_3N (4)	20 / 5	65
f	Et_2NH (4)	Et_2NH (4)	20 / 8	82
g	$PhNH_2$ (4)	Et_3N (6)	20 / 8	64
h	$H_2NCH_2CH_2NH_2$ (4)	Et_3N (6)	20 / 8	62
i	MeOH[c]	NaOMe (4)	0 / 4	73
j	EtOH[c]	NaOEt (4)	0 / 4	71
k	$HOCH_2CH_2OH$ (10)	NaH (6)	0 / 8	55
l	H_2O (3)	NaOH (4)	20 / 15	85

[a] 1 equivalent of **6** was used.
[b] Isolated yield based on the starting **6**.
[c] Also used as solvent.

The reactions were run under mild conditions with various nucleophiles to give the 3,6-difunctionalized catechols **9** in good to high yield (Table 1). With 2-mercaptoethanol as the nucleophile, the reaction occurred exclusively at the sulfur. When the nucleophile has two nucleophilic centers (entries c, d, h, and k in Table 1), an excess of the nucleophile is required to avoid cyclization or oligomerization. A typical preparation of **9** is as follows: Boron tribromide (3.0 mL, 3 mmol, 1 M solution in CH_2Cl_2) was added to a dry CH_2Cl_2 (20 mL) solution of compound **6** (0.263 g, 1 mmol) at -70°C. The mixture was stirred at -70°C for 1 h and then at 0°C for 2 h. Water (5 mL) was added to quench the reaction. The resulting mixture was extracted with CH_2Cl_2 (20 mL), and the organic phase was washed with water (5 mL) and then dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, the residue was redissolved in CH_2Cl_2 (20 mL) and ethanethiol (0.22 mL, 3 mmol) was added followed by the addition of triethylamine (0.56 mL, 4 mmol). The mixture was stirred at r.t. for 5 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography on silica with ethyl acetate / hexanes (1 / 2, v / v) as the eluent to give pure product **9a** as a yellow liquid. Yield: 0.255 g (90%). ^{1}H NMR ($CDCl_3$) δ 1.276 (6H, t, J = 7.5 Hz, CH_3), 2.212 (6H, s, CH_3), 2.535 (4H, q, J = 7.5 Hz, CH_2), 3.873 (4H, s, CH_2), 6.220 (2H, br, OH); ^{13}C NMR ($CDCl_3$) δ 14.80, 15.74, 25.83, 28.09, 121.82, 127.40, 140.91. EIMS: m/z 286 (M^+, 30), 257 (18), 225 (40), 164 (35), 146 (10), 61 (100). HRMS calcd for $C_{14}H_{22}O_2S_2$: 286.10613. Found: 286.10607. The other derivatives of **9** were prepared by very similar procedures[15].

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8. Sulfuric acid (2 mL) was added to a mixture of **5** (2.49 g, 15 mmol) and chloromethyl methyl ether (25 mL), and the mixture was refluxed for 12 h. The resulting solution was concentrated in vacuo and the residue dissolved in ether (200 mL). The ether solution was washed successively with water (10 mL), $NaHCO_3$ solution (20 mL), brine (20 mL) and then dried over anhydrous $MgSO_4$.After removal of the solvent, the crude product was purified by column chromatography on silica with ethyl acetate / hexanes (1 / 8, v / v) as the eluent to give the pure product **6** as a white solid. Yield: 3.75 g (95%). m.p 109-111°C. ^{1}H NMR ($CDCl_3$) δ 2.287 (6H, s, CH_3), 3.895 (6H, s, CH_3O), 4.717 (4H, s, CH_2); ^{13}C NMR ($CDCl_3$) δ 15.52, 38.46, 61.27, 131.06, 132.91, 149.44. EIMS: *m/z* 262 (M^+, 100), 227 (83), 212 (46), 177 (29), 133 (22), 91 (30), 43 (33). HRMS calcd for $C_{12}H_{16}O_2Cl_2$: 262.0527. Found: 262.0531.
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15. All compounds **9** gave satisfactory ^{1}H NMR, ^{13}C NMR, EIMS and HRMS data. Data for selected compounds: **9c**. colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.327 (2H, t, *J* = 7.5 Hz, SH), 1.847-1.941 (4H, m, CH_2), 2.209 (8H, s, CH_3 and OH), 2.592-2.636 (8H, m, CH_2S), 3.858 (4H, s, CH_2S); ^{13}C NMR ($CDCl_3$) δ 15.83, 23.52, 28.34, 30.06, 33.38, 121.89, 127.63, 140.92. EIMS: m/z 378 (M^+, 1), 272 (3), 164 (23), 106 (57), 74 (32), 41 (100). HRMS calcd for $C_{16}H_{26}O_2S_4$: 378.08157. Found: 378.08172. **9f**. yellowish oil. ^{1}H NMR ($CDCl_3$) δ 1.133 (12H, t, *J* = 7.2 Hz, CH_3), 2.094 (6H, s, CH_3), 2.646 (8H, q, *J* = 7.2 Hz, CH_2), 3.823 (4H, s, CH_2N), 9.477 (2H, br, OH); ^{13}C NMR ($CDCl_3$) δ 11.25, 15.09, 46.46, 53.69, 118.92, 123.68, 144.40. EIMS: m/z 308 (M^+, 1), 236 (34), 164 (48), 91 (37), 43 (100); HRMS calcd for $C_{18}H_{32}N_2O_2$: 308.25472. Found: 308.25453. **9k**: colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.155 (10H, s, CH_3 and OH), 3.593 (4H, t, *J* = 6.4 Hz, CH_2), 3.699 (4H, t, *J* = 6.4 Hz, CH_2), 4.545 (4H, s, CH_2O); ^{13}C NMR ($CDCl_3$) δ 15.75, 61.35, 61.82, 71.39, 129.18, 133.04, 148.95. EIMS: m/z 286 (M^+, 15), 224 (40), 157 (20), 91 (18), 58 (19), 43 (100); HRMS calcd for $C_{14}H_{22}O_6$: 286.14166. Found: 286.14157.