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Synthesis of catecholthioethers by the selective oxidation of catechols in competition with 2-mercaptobenzoxazole

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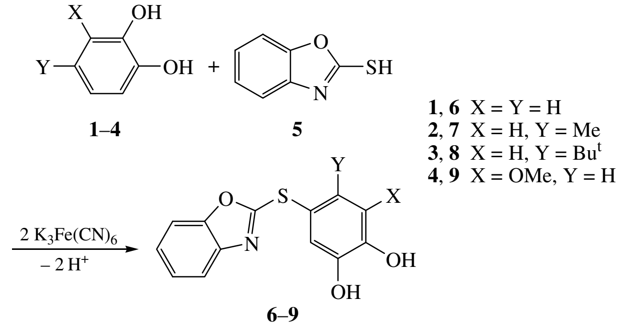
Potassium ferricyanide acts as a selective oxidising agent for the oxidation of catechols even in the presence of 2-mercaptobenzoxazole, as an easily oxidisable thiol to produce related catechol thioethers.

The investigation of the toxicity properties of catechol and quinone thioethers is of considerable importance. They can be found in animal and plant cells as catechol metabolites. They are widely used as anticancer, antibacterial, or antimalarial drugs and fungicides.[1] Quinones exert biological activities through both redox cycling and alkylation of DNA and proteins.[2] Quinones are both oxidants and electrophiles, and they can bind to cellular nucleophiles as Michael acceptors.[3] The cytotoxicity of quinones can be attributed to their binding with cellular nucleophiles such as protein and nonprotein sulfhydryls and/or their ability to redox cycle with the creation of oxidative stress.[4] On the other hand, the existence of sulfhydryl thiols (RSH) in biological media makes their investigations very interesting, particularly from their anti-oxidation and/or pro-oxidation properties when they attach to cellular species.[5] Therefore, in order to develop a simple, fast and green method for the synthesis of catechol thioethers, the oxidation of catechols **1–4** by potassium ferricyanide in the presence of 2-mercaptobenzoxazole **5** as a thiol in aqueous solution at physiologic pH was performed.



Scheme 1

As a typical procedure, to a stirred solution of water–acetonitrile (4:1) and a 0.2 M phosphate buffer (pH 7.2) containing catechols **1–4** (1 mmol) and 2-mercaptobenzoxazole **5** (1 mmol), potassium ferricyanide (2 mmol) was added dropwise for about 20 min. The yellow colour of the ferricyanide solution disappeared and precipitates were formed. At the end of the reaction, a few drops of phosphoric acid were added and the mixture was filtered after about 1 h. The collected product was recrystallised from an appropriate solvent. All compounds are known,[6] and they were characterised by physical properties and spectroscopic data.

The electrochemical properties of a 1.0 mM solution of catechols, 2-mercaptobenzoxazole **5** and potassium ferricyanide in a water–acetonitrile (9:1) solution containing a 0.2 M phosphate buffer (pH 7.2) at a bare glassy carbon electrode have been studied using cyclic voltammetry (Figure 1).† Cyclic voltammetry of 1 mM catechol **1** shows one anodic peak (A_1) at 0.14 V *vs.* SCE and a corresponding cathodic peak (C_1), which corresponds to the transformation of catechol **1** to its related *o*-benzoquinone and *vice versa* within a quasi-reversible two-electron process (Figure 1, curve *1*). The cyclic voltammogram of 2-mercaptobenzoxazole (Figure 1, curve *2*) shows one anodic peak (A_2) at 0.2 V *vs.* SCE, which corresponds to the irreversible oxidation of SH followed by the dimerization of 2-mercaptobenzoxazole.[7] The oxidation potential of potassium ferricyanide (0.24 V *vs.* SCE) is shown in Figure 1 (curve *3*). A preliminary comparison of oxidation peaks indicates the ability of potassium ferricyanide to both catechol and 2-mercaptobenzoxazole oxidation.[8,9] However, the analysis of synthesis products obtained from the addition of potassium ferricyanide to the solution containing catechols and 2-mercaptobenzoxazole, verifies the selectivity of catechol oxidation by potassium ferricyanide in competition with 2-mercaptobenzoxazole. Therefore, potassium ferricyanide acts as a selective oxidising agent for the oxidation of catechol to related *o*-benzoquinone in the presence of 2-mercaptobenzoxazole, which can be oxidised to its dimer.

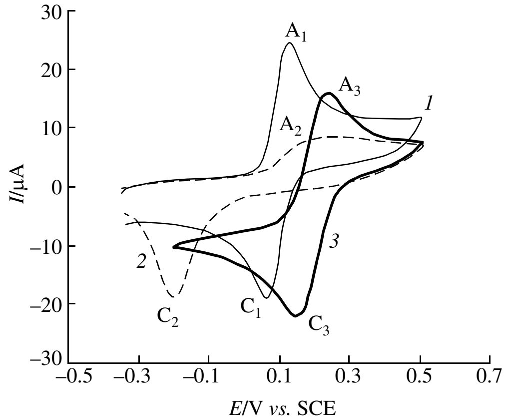


Figure 1 Cyclic voltammograms of (*1*) 1 mM catechol **1**, (*2*) 1 mM 2-mercaptobenzoxazole **5** and (*3*) 2 mM $K_3Fe(CN)_6$ at a glassy carbon electrode in solution containing 0.2 M phosphate buffer (pH 7.2). Scan rate: 100 mV s^{-1}; $T = 25$ °C.

When catechols (1 mmol) were treated with potassium ferricyanide (2 mmol) (dropwise) in an aqueous solution containing a 0.2 M phosphate buffer (pH 7.2) in the presence of **5**, catechol thioethers **6–9** were obtained in good yields (Scheme 1). In more basic solutions, the formation of the anionic forms of catechols is enhanced and the coupling of the anionic forms with *o*-quinones interfers in the Michael reaction of 2-mercapto-

Table 1 Oxidation of catechols by $K_3Fe(CN)_6$ in the presence of 2-mercaptobenzoxazole.[a]

Substrate	Product	Isolated yield (%)	mp/°C
1	**6**	75	125–126
2	**7**	80	199–200
3	**8**	81	169–171
4	**9**	65	158–160

[a]All products were crystallised from water–acetonitrile and identified by comparison with authentic samples (IR, ^{1}H and ^{13}C NMR spectroscopy, melting points).

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† Cyclic voltammetry was performed using an Autolab model PGSTAT 20 potentiostat/galvanostat. The working electrode used in voltammetry was a glassy carbon disc (1.8 mm in diameter), and platinum wire was used as a counter electrode. The working electrode potentials were measured *vs.* SCE. Catechols and 2-mercaptobenzoxazole (Merck) were reagent-grade materials. Potassium ferricyanide and phosphate salts (Merck) were of analytical grade.

benzoxazole with the *o*-quinones. In other words, in an aqueous solution containing a 0.2 M phosphate buffer (pH 7.2) any hydroxylation[10] or dimerization[11] reactions are too slow to interfere in the synthesis of **6**–**9**.

In the case of 4-methylcatechol **2**, the related formed *o*-quinone can convert to its quinone methide tautomeric form,[12] but it seems that its fast nucleophilic reaction in the presence of **5** inhibits tautomerization and proceeds in a similar way to that of **1**. The reaction products **6**–**9** can also be oxidised at higher potentials than starting compounds **1**–**4**, but because of the insolubility of the product in the reaction medium, overoxidation of **6**–**9** was circumvented during the preparative reaction. Other advantages of the presented method consist in the use of water as an environmentally friendly solvent and potassium ferricyanide as a mild commonly available oxidising agent, short reaction times and good yields of products.

These results complete the previous report[6] on the synthesis of catechol thioether derivatives. The overall reaction is presented in Scheme 1. The Michael reaction of nucleophile **5** with *o*-quinones leads to the formation of catechol thioether derivatives as final products (Table 1).

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