An Efficient Conversion of Catechols into 6*H*-Benzofuro[3,2-*c*][1]-benzopyran-6-one Derivatives

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Coupling of *in-situ* generated *o*-benzoquinones with 4-hydroxycoumarin as a nucleophile has been studied in the presence of potassium ferricyanide as an oxidizing agent in aqueous solution. The results indicate that the quinones derived from catechols, participate in Michael addition reactions with 4-hydroxycoumarin to form the 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one derivatives.

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The importance of compounds known as coumestans [1] has led many workers to synthesize a number of coumestan derivatives by chemical [2-5] and electrochemical [6-9] routes. These compounds are derivatives of 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one and are structural compounds of many natural products such as wedelolactone, medicagol, psoraldin, isopsoraldin, erosnin and the estrogenic coumestrol, which possess interesting physiological activites [10-11]. In this work oxidation of catechols (**1a-f**) in the presence of 4-hydroxycoumarin (**3**) as a possible nucleophile in aqueous sodium acetate solution has been performed using potassium ferricyanide as oxidizing agent. The present work has led to the development of a one pot oxidative method for the synthesis of coumestan derivatives (**6a-e**) in high yield and purity.

A suitable oxidizing agent is a compound that can selectively oxidize catechol (**1a**) to *o*-benzoquinone (**2a**) without any effect on 4-hydroxycoumarin (**3**). In order to accesses it, we have studied the electrooxidation of catechol (**1a**), 4-hydroxycoumarin (**3**) and potassium ferricyanide, using cyclic voltammetry. Cyclic voltammetry of a 1.0 mM solution of catechol (**1a**) in an aqueous solution containing 0.2 *M* sodium acetate as supporting electrolyte, shows one anodic (A_1) (at 0.26 V vs. SCE) and a corresponding cathodic peak (C_1) (at 0.07 V vs. SCE) which corresponds to the transformation of catechol (**1a**) to *o*-benzoquinone (**2a**) and *vice-versa* within a quasi-reversible two-electron process (Figure 1, curve a). Figure 1, (curve b) shows the cyclic voltammogram obtained for a 1.0 mM solution of 4-hydroxycoumarin (**3**) under the same conditions. The voltammogram exhibits two anodic peaks (A_2 and A_3) at 0.85 and 1.11 V versus SCE, within an irreversible process. In this figure, curve c is the cyclic voltammogram of 1.5 mM solution of potassium ferricyanide in the same conditions. The cyclic voltammogram shows one anodic (A_4) (at 0.24 V vs. SCE) and a corresponding cathodic peak (C_4) (at 0.15 V vs. SCE) which corresponds to the transformation of $Fe(CN)_6^{4-}$ to $Fe(CN)_6^{3-}$ and *vice-versa* within a reversible one-electron process. Comparison of the values of $E^{\circ\prime}$ evaluated from the midpoint potential between the anodic and cathodic peaks, (E_{mid}) for catechol {(0.26+0.07)/2 = 0.165} and potassium ferricyanide {(0.24+0.15)/2 = 0.195} reveals that $Fe(CN)_6^{3-}$ is a suitable agent for mild oxidation of catechol (**1a**) in the presence of 4-hydroxycoumarin (**3**).

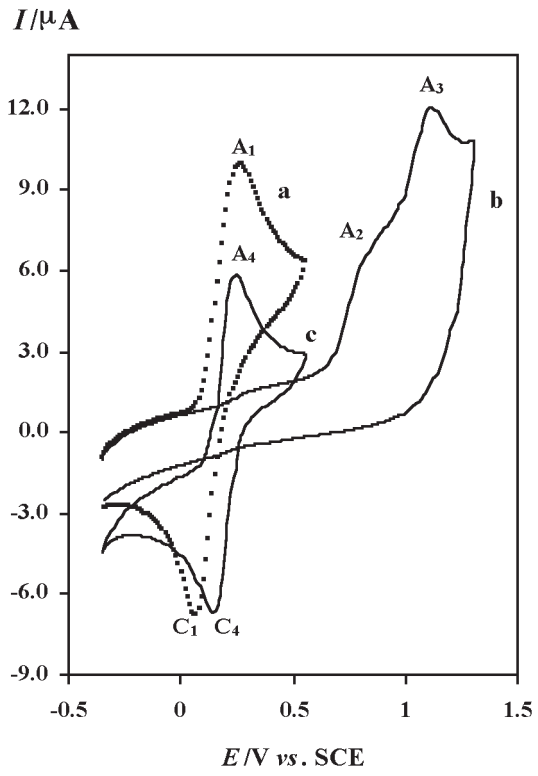
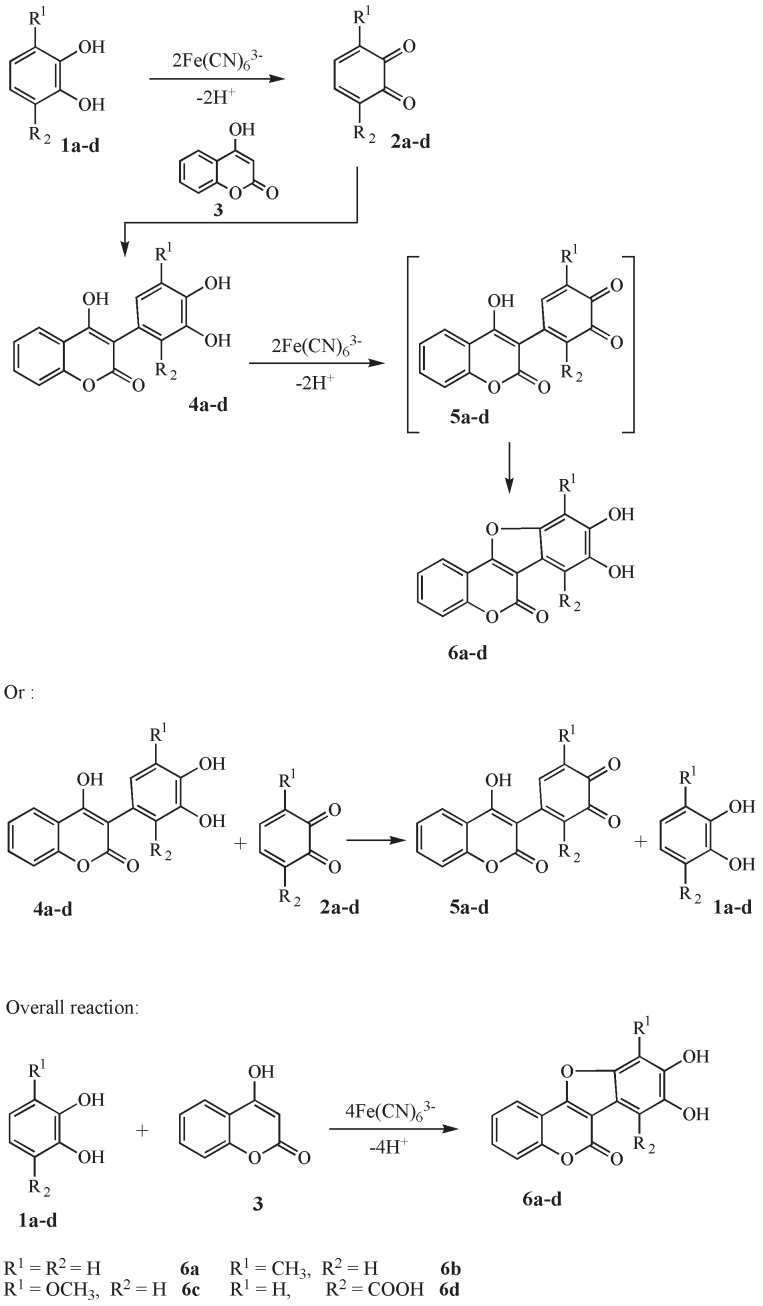


Figure 1. Cyclic voltammograms of, (a): 1.0 mM catechol (**1a**), (b) 1.0 mM 4-hydroxycoumarin (**3**) and (c) 1.5 mM potassium ferricyanide, at glassy carbon electrode (1.8 mm diameter) in aqueous solution. Supporting electrolyte 0.15 *M* sodium acetate; scan rate: 100 mVs^{-1}; *T*= 25 ± 1 °C.

When catechols (1 mmol) were treated with potassium ferricyanide (4 mmol) in an aqueous solution containing 0.2 *M* sodium acetate, coumestans were obtained in good yields (Scheme 1). In more basic solutions, the formation of anionic forms of catechols that formed by acid dissociation reaction was enhanced and the coupling of anionic

Scheme 1

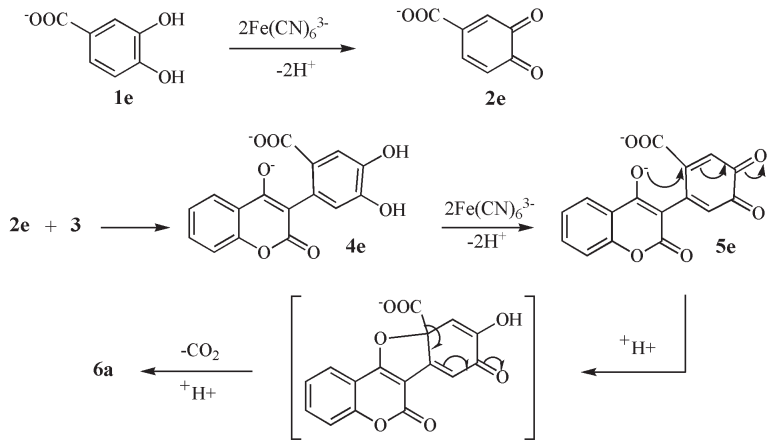


forms with *o*-quinones interfered in the Michael addition reaction of 4-hydroxycoumarin (**3**) with *o*-quinones. In other words, in aqueous solution containing 0.2 *M* sodium acetate any hydroxylation [12-14] or dimerization [11,15] reactions are too slow to interfered in the synthesis of coumestan derivatives.

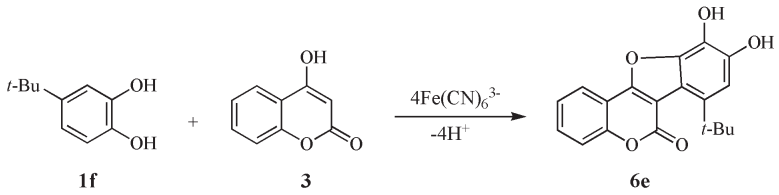
The proposed mechanism for oxidation of **1a** in the presence of **3** is presented in Scheme 1.

According to our results, it seems that the 1,4-addition (Michael) reaction of anion **3** to *o*-quinone (**2a**) leads to the intermediate (**4a**). The oxidation of this compound (**4a**) is easier than the oxidation of the parent-starting molecule (**1a**) by virtue of the presence of an electron-donating group. The reaction product (**6a**) can also be oxidized at a lower potential than the starting **1a** compound. However, over-oxidation of **6a** was circumvented during the preparative reaction because of the insolubility of the product in the water/sodium acetate solvent medium. Alternatively, it is possible that the intermediate **4a** can also be oxidized during reaction with **2a**.

Scheme 2



Scheme 3



The oxidation of **1b**, **1c** and **1d** in the presence of **3** as a nucleophile in sodium acetate solution proceeds in a similar way to that of **1a**. The existence of a methyl, methoxy or carboxylic group at the C-3 position of these compounds probably causes relevant Michael acceptors (**2b**, **2c** and **2d**) to be attacked by **3** at the C-4 and/or C-5 positions to yield two types of product in each case. Since, in the *o*-quinones **2b** and **2c** C-5, and in the *o*-quinone **2d** C-4 is more electropositive, we suggest that *o*-quinones **2b** and **2c** are selectively attacked at C-5 and *o*-quinone **2d** at C-4 position by **3** leading to the formation of the products **6b**, **6c** and **6d** respectively [8].

The oxidation of 3,4-dihydroxybenzoic acid (**1e**), in the presence of **3** as a nucleophile in sodium acetate solution proceeds in a similar way to that of **1a**. It seems that the intermolecular and intramolecular 1,4-addition of **3** followed by a decarboxylation reaction leads to the formation of **6a** as final product. The overall reaction is presented in Scheme 2.

The oxidation of 4-*tert*-buthylcatechol (**1f**), in the presence of **3** as a nucleophile in sodium acetate solution has been performed. Due to the existence of a *t*-butyl group in C-4 position of the catechol ring, it seems that the intermolecular 1,4- and intramolecular 1,6-Michael addition of

Table 1

Experimental and Preparative Data

Conversion	Solvent for Recrystallization	Chemical Name	Yield (%)
1a to 6a	Ethanol+acetone	3,4-Dihydroxy-6*H*-benzofuro[3,2-*c*][1] benzopyron-6-one	96
1b to 6b	Ethanol+acetone	3,4-Dihydroxy-2-methyl-6*H*-benzofuro [3,2-*c*][1]benzopyron-6-one	95
1c to 6c	Ethanol+acetone	3,4-Dihydroxy-2-methoxy-6*H*-benzofuro [3,2-*c*][1]benzopyron-6-one	98
1d to 6d	Water+ethanol	3,4-Dihydroxy-6-oxo-6*H*-benzofuro [3,2-*c*][1]benzopyron-5-carboxylic acid	90
1e to 6a	Ethanol+acetone	3,4-Dihydroxy-6*H*-benzofuro[3,2-*c*][1] benzopyron-6-one	90
1f to 6e	Water+ethanol	2,3-Dihydroxy-5-*tert*-butyl-6*H*-benzofuro [3,2-*c*]benzopyron-6-one	96

3, leads to the formation of **6e** as a final product (1.2 (s, 9H, *t*-Butyl), 6.6 (s, 1H, aromatic C-4), 7.5-8.0 (m, 4H, aromatic C8-C11), 9.5 (broad, 2H, hydroxy) (Scheme 3).

EXPERIMENTAL

Apparatus and Reagents.

Cyclic voltammetry was performed using an Autolab model PGSTAT 20 potentiostat/galvanostat. The working electrode used in the voltammetry experiment was a glassy carbon disc (1.8 mm diameter) and platinum wire was used as counter electrode. The working electrode potentials were measured *versus* SCE (all electrodes from AZAR electrode).

General Procedure for Synthesis.

To a stirred solution of sodium acetate (4 mmol) in distilled water (20 mL), 4-hydroxycoumarin (**3**) (0.162 g, 1 mmol) was added, and heated up to 50 °C until it dissolved and then potassium ferricyanide (1.317 g, 4 mmol) was added. In a dropping funnel, a solution of catechol (**1a-f**) (1 mmol), in 10 mL distilled water containning sodium acetate (2 mmol) was prepared and added dropwise to the stirred previous solution over a period of 1 h. The solution became dark and precipitates were formed. At the end of the reaction, a few drops of acetic acid were added and the mixture was placed in a refrigerator overnight. Solids were collected by filtration and recrystallized from an appropriate solvent (Table 1). After recrystallization, products were characterized by comparison of their spectral (IR, NMR) and physical data with the authentic samples.

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