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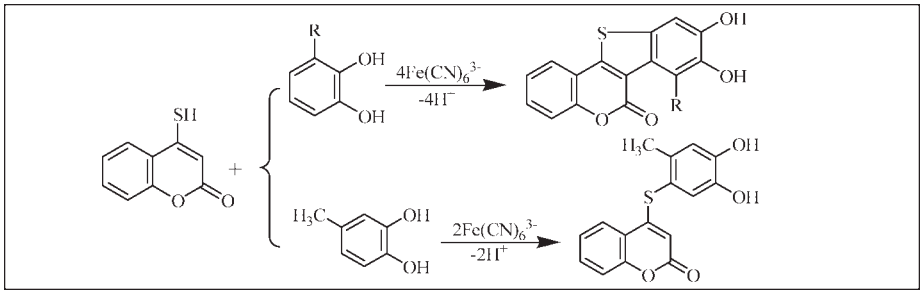

An efficient synthesis of thiocoumestan derivatives, starting from catechols and 4-mercaptocoumarin in the presence of potassium ferricyanide as an oxidizing agent (Decker oxidation) was developed. The results indicate that the 4-mercaptocoumarin participates in Michael addition reactions with *in situ* generated *o*-benzoquinones. The present work has led to the development of a one-pot oxidative method for the synthesis of the 6*H*-benzothieno[3,2-*c*][1]benzopyron-6-one derivatives.

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INTRODUCTION

Coumestans, [1] which are derivatives of 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (Fig. 1) have the basic structure of many natural products such as wedelolactone, medicagol, psoralidin, isopsoralidin, erosnin, and estrogenic cumestrol, with interesting physiological activities [2,3]. The importance of these compounds has led us and many workers to synthesize a number of these compounds by chemical [4–10] and electrochemical [11–14] routes. Following our experiences in oxidation of catechols in the presence of nucleophiles [15–23], we envisaged that synthesis of thiocoumestans (6*H*-benzothieno[3,2-*c*][l]benzopyran-6-one) (Fig. 1) might cause an enhancement of physiological activities.

In this direction, some workers synthesize a number of thiocoumestan derivatives [10,24,25]. But, to the best of our knowledge, no reaction of *in situ* generated *o*-benzoquinones (**2**) with 4-mercaptocoumarin (**3**) has been previously reported. Therefore, we now discover a facile and one-pot synthetic route to thiocoumestans involving oxidation of catechols (**1**) in the presence of 4-mercapto-coumarin (**3**), using potassium ferricyanide as an oxidizing agent (Decker oxidation), in high yield and purity.

RESULTS AND DISCUSSION

In our earlier work, comparison of the values of half wave potential ($E_{1/2}$), evaluated from the midpoint potential between anodic and cathodic peaks for catechol (0.165 V *vs*. SCE) and potassium ferricyanide (0.195 V *vs*. SCE), using cyclic voltammetry, revealed that potassium ferricyanide was a suitable agent (Decker agent) for mild oxidation of catechols to their corresponding *o*-benzoquinones without any effect on the nucleophile [8]. Therefore, in this work we used potassium ferricyanide as a stable, easily handled, and commercially available oxidizing agent. This agent has also been used in Decker oxidation. During Decker oxidation, 1,3-disubstituted pyridinium salts converts to isomeric pyridones [26].

The reaction for oxidation of (**1a-c**) in the presence of **3** is presented in Scheme 1. As can be seen, when catechols (**1a-c**) (1 mmol) was treated with potassium ferricyanide (4 mmol) in water/acetonitrile mixture (70/30 v/v) containing 4-mercaptocoumarin (**3**) (1 mmol) and sodium acetate (0.2 *M*), thiocoumestans (**4a-c**) were obtained in good yields (Scheme I). In more basic solutions, the formation of anionic forms of catechols formed by an acid dissociation reaction was enhanced and the coupling of anionic

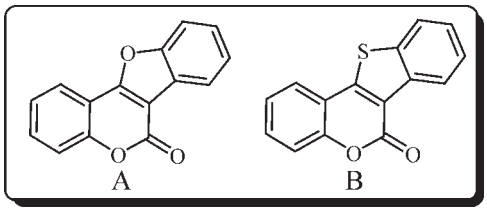


Figure 1. Structures of 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (A) and 6*H*-benzothieno[3,2-*c*][l]benzo pyran-6-one (B).

forms with *o*-benzoquinones interfered in the Michael reaction of 4-mercaptocoumarin (**3**) with *o*-benzoquinones (Scheme 2) [23,27,28]. In other words, in an aqueous solution containing 0.2 *M* sodium acetate, any dimerization [27,28] or hydroxylation [29–31] reactions are too slow to interfere in the synthesis of **4a-c**.

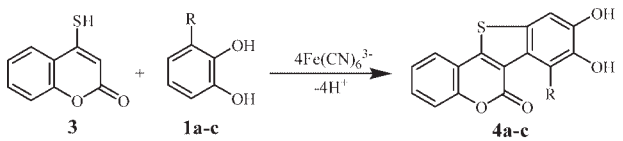
Following our experiences in oxidation of catechols in the presence of nucleophiles [15–23], it seems that in water/acetonitrile mixture (70/30 v/v), the inter and intra Michael addition reactions of anion of 4-mercapto coumarin (**3**) to *o*-benzoquinone (**2a-c**) is faster than other secondary reactions [27–31], leading to the thiocoumestan derivatives (**4a-c**) as final products.

The oxidation of **1b** and **1c** in the presence of **3** proceeded in a similar fashion to that of **1a** (Scheme 2). The existence of a methyl or methoxy group at the C-3 position of these compounds probably causes relevant Michael acceptors (**2b** and **2c**) to be attacked by **3** at the C-4 or C-5 positions to yield two types of product in each case. As in the *o*-benzoquinones **2b** and **2c** C-5 more electropositive, we suggest that *o*-benzoquinones **2b** and **2c** are selectively attacked at C-5 position by **3** leading to the formation of the products **4b** and **4c**, respectively [15–18].

Interestingly, oxidation of 4-methylcatechol (**1d**) in the presence of **3** in aqueous sodium acetate/acetonitrile (70/30) solution, because of the existence of methyl group at C-4 position of it that is a reactive site of cyclization, proceeds in a different manner to that of **1a-c** (Scheme 3).

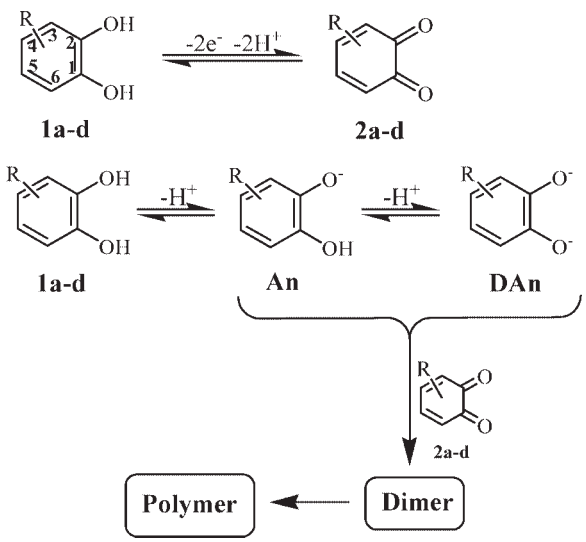
According to Scheme 3, generation of *o*-benzoquinone **2d** is followed by an intermolecular Michael addition of **3** to the *o*-benzoquinone **2d**, producing

Scheme 1



	R	Isolated Yield (%)
4a	H	82
4b	CH_3	75
4c	OCH_3	70

Scheme 2



the catechol derivative (4-(4,5-dihydroxy-2-methylphenylthio)-2*H*-chromen-2-one) **4d** as final product.

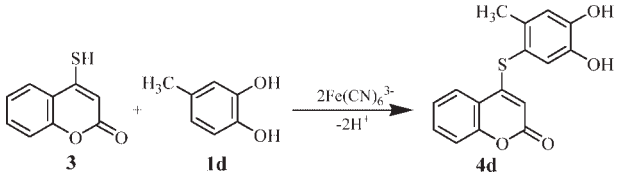
The synthesis of 4-phenylthio-2*H*-chromen-2-ones has been reported previously by us and several groups using different approaches [32–36]. However, to the best of our knowledge, no reaction of *o*-benzoquinone **2d** with 4-mercaptocoumarin (**3**) has been reported and this method described an efficient and one-pot method for the synthesis of 4-(4,5-dihydroxy-2-methylphenylthio)-2*H*-chromen-2-one (**4d**).

EXPERIMENTAL

Reagents. All chemicals were reagent grade materials. Sodium acetate, solvents, and reagents were of proanalysis. These chemicals were used without further purification. 4-mercaptocoumarin was prepared by the procedure reported previously [37].

General procedure for the synthesis of 4a-d. To a stirred solution of aqueous sodium acetate 0.2 *M*/acetonitrile (70/30), 4-mercaptocoumarin (**3**) (1 mmol) was added potassium ferricyanide (4 mmol in the cases of **1a-c** and 2 mmol in the case of **1d**). A solution of catechols (**1a-d**) (1 mmol) in relevant solution was prepared and added dropwise to the stirred solution over a period of 20–30 min. The reaction mixture was kept at r.t., with occasional stirring (1 h for **1a** and 2.5 h for **1b-d**). The solution become dark and formed precipitates. At

Scheme 3



Isolated Yield = 68 %

the end of the reaction, a few drops of acetic acid were added and the mixture was placed in a refrigerator overnight. The solid formed were collected by filtration and washed several times with water. The final products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS spectroscopy.

8,9-Dihydroxy-6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one ($C_{15}H_8O_4S$) (4a). mp 265–268° (dec); ir (potassium bromide): 3367, 3253, 1703, 1628, 1474, 1352, 1322, 1274, 1224, 1201, 1086, 1032, 989, 867, 836, 810, 752 cm^{-1}; ^{1}H nmr: δ(300 MHz, acetone-d_6) 7.29 (s, 1H, aromatic), 7.48 (s, 1H, aromatic), 7.52 (t, 2H, aromatic), 7.69 (t, 1H, aromatic), 8.03 (dd, 1H, aromatic), 8.8 (broad, OH, this peak observed in DMSO-d_6); ^{13}C nmr: δ (75.4 MHz, DMSO-d_6) 99.7, 105.7, 106.0, 112.9, 114.6, 117.8, 122.0, 125.9, 132.3, 145.3, 147.1, 150.2, 153.0, 158.6, 158.9; ms: *m*/*z* (relative intensity) 284 [M]$^+$ (95), 266 (73), 233 (60), 177 (45), 144 (10), 140 (35), 121 (30), 89(100), 43 (25).

8,9-Dihydroxy-7-methyl-6*H*-benzothieno[3,2-*c*][1]benzo pyran-6-one ($C_{16}H_{10}O_4S$) (4b). mp 230–232° (dec); ir (potassium bromide): 3374, 3163, 2929, 1708, 1603, 1546, 1448, 1343, 1289, 1124, 1170, 1030, 961, 859, 760, 639 cm^{-1}; ^{1}H nmr: δ(300 MHz, DMSO-d_6) 2.40 (s, 3H, methyl); 7.19 (s, 1H, aromatic); 7.48 (t, 1H, aromatic); 7.57 (d, 1H, aromatic); 7.66 (t, 1H, aromatic); 8.04 (dd, 1H, aromatic), 8.04 (broad, OH) 8.7 (broad, OH); ^{13}C nmr: δ (75.4 MHz, DMSO-d_6) 20.7 (methyl), 104.6, 112.7, 113.0, 122.4, 125.5, 129.2, 129.8, 132.2, 132.8, 136.1, 138.1, 151.0, 152.7, 163.9, 164.3; ms: *m*/*z* (relative intensity) 298 [M]$^+$ (100), 280 (40), 265 (45), 178 (40), 144 (23), 121 (321), 89 (50), 63 (15).

8,9-Dihydroxy-7-methoxy-6*H*-benzothieno[3,2-*c*][1]enzo pyran-6-one ($C_{16}H_{10}O_5S$) (4c). mp 245–248° (dec); ir (potassium bromide): 3641, 3521, 3359, 2923, 2852, 1704, 1628, 1605, 1596, 1466, 1442, 1418, 1396, 1345, 1265, 1204, 1081, 955, 932, 890, 857, 797, 757,746 cm^{-1}; ^{1}H nmr: δ(300 MHz, acetone-d_6) 4.23 (s, 3H, OMe); 7.21 (s, 1H, aromatic); 7.53 (m, 2H, aromatic); 7.70 (t, 1H, aromatic); 8.11 (dd, 1H, aromatic); 8.80 (broad, OH, this peak observed in DMSO-d_6); ^{13}C nmr: δ (75.4 MHz, acetone-d_6) 60.7 (methoxy), 100.1, 106.4, 113.2, 115.8, 117.4, 121.7, 125.1, 131.7, 137.9, 142.4, 142.5, 145.7, 153.5, 157.8, 159.0; ms: *m*/*z* (relative intensity) 314 [M]$^+$ (100), 298(15), 281(60), 271(30), 253 (9), 189 (6), 178 (80), 138 (20), 121 (61), 63 (30), 43 (7).

4-(4,5-Dihydroxy-2-methylphenylthio)-2*H*-chromen-2-one ($C_{16}H_{12}O_4S$) (4d). mp 273–275° (dec); ir (potassium bromide): 3344, 1686, 1600, 1546, 1519, 1445, 1414, 1344, 1320, 1270, 1187, 1158, 950, 869, 841, 824, 767, 743 cm^{-1}; ^{1}H nmr: δ(300 MHz, DMSO-d_6) 2.29 (s, 3H, methyl), 5.41 (s, 1H, aromatic), 7.01 (s, 1H, aromatic), 7.10 (s, 1H, aromatic), 7.44 (m, 2H, aromatic), 7.69 (d, 1H, aromatic), 7.94 (d, 1H, aromatic), 8.5 (broad, 2H,OH); ^{13}C nmr: δ (75.4 MHz, acetone-d_6) 19.2, 107.3, 113.4, 117.2, 118.1, 118.7, 123.5, 124.2, 124.6, 132.9, 135.6, 145.0, 148.9, 152.9, 157.5, 158.5; ms: *m*/*z* (relative intensity) 300 [M]$^+$ (38), 272 (8), 267 (16), 178 (24), 145 (30), 121 (44), 89 (100), 77 (40), 63 (78), 39 (50).

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