OXIDATIVE COUPLING OF IN-SITU GENERATED *o*-BENZOQUINONES WITH 4-HYDROXY-6-METHYL-2-PYRONE

Davood Habibi, Davood Nematollahi,* Abdolhamid Alizadeh and Mahdi Hesari
Department of Chemistry, Faculty of Sciences, University of Bu-Ali Sina, Hamadan, Iran, Post Code 65174.
E-Mail: nemat@basu.ac.ir

Abstract: A short and facile synthesis of a series of pyrano[4,3-b]benzofuran-1-one was accomplished in good yields via the inter and intramolecular oxidative coupling reaction of in-situ generated *o*-benzoquinones with 4-hydroxy-6-methyl-2-pyrone promoted by potassium ferricyanide.

Introduction

Coumestan, otherwise known as 6H-benzofuro[3,2-c]-[1]benzopyran-6-one, comprises a class of naturally occurring products with a variety of biological activities that include phytoestrogenic, antibacterial, antifungal, anti-myotoxic,and phytoalexine effects (1). The importance of these compounds has led many to synthesize a number of these compounds by chemical (2) and electrochemical (3) methods. In this work, oxidation of catechols (**1**a-e), in the presence of 4-hydroxy-6-methyl-2-pyrone (2) as a possible nucleophile in aqueous sodium acetate solution has been performed using potassium ferricyanide as the oxidizing agent. The present work has led to the development of a one pot oxidative method for the synthesis of 1H-pyrano[4,3-b]benzofuran-1-one derivatives (**4**a-c) with similar structures to some melanizing agents such as: trioxsalen and methoxsalen (4), in good yields.

Experimental

General

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). All chemicals (catechols and 4-hydroxy-6-methyl-2-pyrone) were reagent-grade materials from Aldrich. Potassium ferricyanide and sodium acetate were of pro-analysis grade from E. Merck. These chemicals were used without further purification.

Typical Procedure

To a stirred solution of sodium acetate 0.2 M (for **1**a-d) or acetate buffer 0.2 M, pH= 4.5 (for **1**e), 4-hydroxy-6-methyl-2-pyrone (2) (1 mmol) and potassium ferricyanide (4 mmol) were added. In a dropping funnel, a solution of catechols (**1**a-e) (1 mmol), in relevant solution, added dropwise to the stirred previous solution over a period of 10-20 min. 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 placed in the refrigerator overnight. Solids were collected by filtration and recrystallized from an appropriate solvent. After recrystallization, the products were characterized by comparison of their spectral (IR, ^{1}H NMR, ^{13}C NMR) and physical data with the authentic samples.

Characteristic of products

1H-Pyrano[4,3-b]benzofuran-1-one, 7,8-dihydroxy-3-methyl (**4**a). M.p. 268-270 °C (dec.) (Lit. (3f) 265-267 (dec.) °C). $IR_{(KBr)}$: 3359, 3250, 2901, 1705, 1600, 1550, 1480, 1345, 1285, 1226, 1200, 1085, 970, 895, 836, 755 cm^{-1}. ^{1}H NMR, δ (90 MHz DMSO-d_6): 2.24 (s, 3H, methyl); 6.89 (s, 1H, pyrone); 7.09 (d, J=7.1 Hz, 2H, catechol); 9.37 (d, J=4.4 Hz, 2H, hydroxy). ^{13}C NMR, δ (90 MHz DMSO-d_6): 25.4 103.4, 105.1, 109.1, 110.6, 119.1, 150.3, 151.2, 155.8 165.3, 166.1, 168.2

1H-Pyrano[4,3-b]benzofuran-1-one, 7,8-dihydroxy-3,6-dimethyl (**4b**). M.p. 258-260 °C (dec.) (Lit. (3f) 257-259 (dec.) °C). $IR_{(KBr)}$: 3471, 3055, 2915, 1710, 1610, 1557, 1478, 1288, 1203, 1090, 1053, 980, 890, 821 cm^{-1}. ^1H NMR, δ (90 MHz DMSO-d_6): 2.29 (s, 3H, methyl); 2.34(s, 3H, methyl); 6.91 (s, 1H, pyrone); 7.07 (s, 1H, catechol); 8.749 (s, 1H, hydroxy); 9.64 s, 1H, hydroxy). ^{13}C NMR, δ (90 MHz DMSO-d_6): 9.9, 26.2, 104.5, 104.7, 108.9, 110.6, 120.0, 150.3, 150.4, 157.8, 164.1, 165.2, 168.5.

1H-Pyrano[4,3-b]benzofuran-1-one, 7,8-dihydroxy-3-methyl-6-methoxy (**4c**). M.p. 223-225 °C (dec.) (Lit.(3f) 225-227 (dec.) °C). $IR_{(KBr)}$: 3465, 3087, 2905, 1695, 1625, 1560, 1478, 1352, 1275, 1230, 1210, 1090 1053, 975, 890, 840, 750 cm^{-1}. ^1H NMR, δ (90 MHz DMSO-d_6): 2.29 (s, 3H, methyl); 3.92 (s, 3H, methoxy); 6.88 (s, 1H, pyrone); 7.34 (s, 1H, catechol); 8.92 (s, 1H, hydroxy); 9.48 (s, 1H, hydroxy). ^{13}C NMR, δ (90 MHz DMSO-d_6): 20.4, 60.1, 98.4, 100.4, 105.1, 115.6, 135.3, 139.2, 142.2, 145.3, 156.7, 161.2, 165.4.

4-*tert*-Butyl-5-(4-hydroxy-6-methyl-2-pyrone)-*o*-benzoquinone (**3e**). M.p. 122-124 °C (dec.) (Lit. (3g) 124-126 (dec.) °C). UV (methanol): λ (nm): 490.9, 279.5. $IR_{(KBr)}$: 3365, 2965,1710, 1671, 1595, 1554, 1483, 1390, 1345, 1298, 1231, 1115, 1030, 970, 890, 866 cm^{-1}. ^1H NMR, δ (90 MHz DMSO-d_6): 1.19 (s, 9H, t-butyl); 2.20 (s, 3H, methyl); 6.01 (s, 1H, quinone); 6.61 (s, 1H, pyrone); 6.73 (s, 1H, quinone); 8.60 (br, 1H, hydroxy). ^{13}C NMR, δ (90 MHz DMSO-d_6): 25.3, 31.5, 31.9, 32.3, 34.1, 34.7, 113.4, 115.5, 116.1 142.2, 143.2, 145.0, 168.3. MS: m/e (relative intensity); 288(20), 232(21), 207(26), 191(17), 166(30), 151(100), 123(35), 105(20), 77(10), 41(40).

Results and discution

The electrochemical study of a 1.0 mM solution of 4-hydroxy-6-methyl-2-pyrone (**2**) in aqueous solution containing 0.2 M sodium acetate as supporting electrolyte, at a bare glassy carbon electrode, has been studied using cyclic voltammetry (Fig. 1). The voltammogram shows one anodic peak (A_1) at 1.1 V versus SCE, within an irreversible process. A suitable oxidizing agent is a compound that can only oxidize catechol to related *o*-benzoquinone without any effect on the 4-hydroxy-6-methyl-2-pyrone. Recently, we have shown the suitability of potassium ferricyanide with oxidation potential of 0.24 V vs. SCE, for the oxidation of catechols (2g). So in this work, we used potassium ferricyanide as an agent for mild oxidation of the catechol in the presence of 4-hydroxy-6-methyl-2-pyrone.

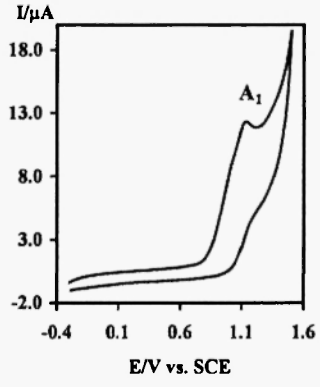
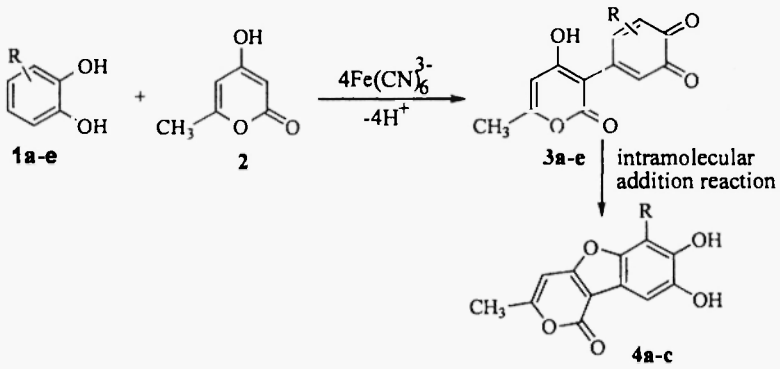


Figure 1. Cyclic voltammograms of 1.0 mM 4-hydroxy-6-methyl-2-pyrone at glassy carbon electrode (1.8 mm diameter) in aqueous solution. Supporting electrolyte 0.2 M sodium acetate; scan rate: 100 mVs^{-1}; T= 25 ± 1 °C.

When catechols (1 mmol) were treated with potassium ferricyanide (4 mmol) (dropwise) in an aqueous solution containing 0.2 M sodium acetate, 1H-pyrano[4,3-b]benzofuran-1-one derivatives (**4a-c**) were obtained in good yields (Scheme 1). In more basic solutions, the formation of anionic forms of catechols that are formed by acid dissociation reaction was enhanced, and the coupling of the anionic forms with *o*-quinones interfered in the Michael reaction of 4-hydroxy-6-methyl-2-pyrone with the *o*-quinones. In other words, in aqueous solution containing 0.2 M sodium acetate any hydroxylation (5) or dimerization (6) reactions are too slow to interfere in the synthesis of **4a-c**. The great advantages of the presented method are: using water as an environmentally friendly solvent, using mild conditions (aqueous sodium acetate), using potassium ferricyanide as a mild, common and available oxidizing agent, short time reaction and good yield of products.



R = H, **1a, 3a, 4a** R = Me (at C-3), **1b, 3b, 4b**
R = OMe (at C-3), **1c, 3c, 4c** R = COOH (at C-4) **1d, 3d, 4d**
R = *tert*-Bu (at C-4), **1e, 3e**

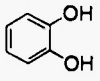
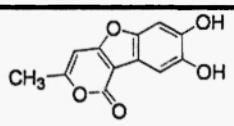
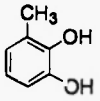
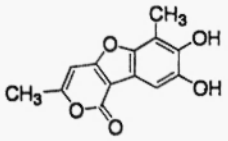
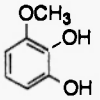
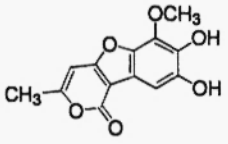
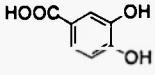
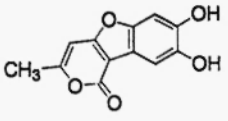
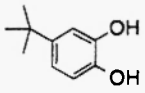
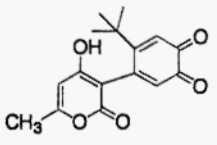
Scheme-1

The reaction products (**4a-c**) can also be oxidized at a lower potential than the starting compounds (**1a-e**). However, overoxidation of **4a-c** was circumvented during the preparative reaction because of the insolubility of the product in the water/sodium acetate solvent medium. The oxidation of 3,4-dihydroxybenzoic acid (**1d**), in the presence of **2** proceeds in a similar way to that of **1a**. It seems that the intermolecular and intramolecular 1,4-addition of **2** with a decarboxylation reaction leads to the formation of **4a** as final product. In addition, in the oxidation of 4-*tert*-buthylcatechol (**1e**), in the presence of **2**, due to the existence of a *t*-butyl group in C-4 position of the catechol ring gives *o*-quinone **3e** as the final product.

Conclusions

These results complete the previous reports on the synthesis of coumestan derivatives (2,3). The overall reaction is presented in Schemes (1). According to our results, it seems that the Michael reaction of nucleophile **2** with formed *o*-quinones leads to the formation of 1H-pyrano[4,3-b]benzofuran-1-one derivatives as final products, in good yields and purity (Table I).

Table- I Oxidation results of catechols in the presence of 4-hydroxy-6-methyl-2-pyrone.

Entry	Substrate	Reaction Time(min)	Crystallization Solvent	Product	Yield[a,5] (%)
1		10	methanol/acetone		85
2		10	methanol/acetone		80
3		10	methanol/acetone		72
4		10	methanol/acetone		75
5		20	chloroform/acetone		60

[a]Isolated yield.

[b]All products were identified by comparison with authentic samples (IR, ^{1}H NMR, ^{13}C NMR, m.p).

References

(a) F.M. Dean and M.V. Sargent, Comprehensive Heterocyclic Chemistry; in C.W. Bird and G.W.H. Cheeseman (Eds.), Pergamon Press, New York, Part 3, p 531 (1984). (b) N.A., Pereira, B.M.R., Pereira, M.C., do Nascimento, J.P., Parente and W.B. Mors : *Planta Med.* **60**, 99 (1994). (c) K.W. Gaido, L.S. Leonard and S. Lovell : *Toxicol. Appl. Pharmacol.* **143**, 205 (1997). (d) Endocrine Disrupters: A Scientific Perspective, The American Council on Science and Health, July 1999. (e) A.J.M. da Silva, P.A. Melo, N.M.V. Silva, F.V. Brito, C.D. Buarque, D.V. de Souza, V.P. Rodrigues, E.S.C. Pocas, F. Noel, E.X. Albuquerque and P.R.R. Costa : *Bioorg. Med. Chem. Lett.* **11**, 283 (2001).

2. (a) U.T. Bhalerao, C. Muralikrishna and G. Pandey : *Synth. Commun.* **19**, 1303 (1989). (b) N. Someswari, K. Srihari and V. Sundaramurthy : *Synthesis* 609 (1977). (c) B.J. Donnelly, D.M. Donnelly and A.M.O. Sullivon : *Tetrahedron* **24**, 2617 (1968). (d) K. Kurosawa and K. Nogami : *Bull. Chem. Soc. Jpn.* **49**, 1955 (1976). (e) R.R. Shah and Trivedi, K.N. : *J. Ind. Chem. Soc.* **56**, 995 (1979). (f) C.C. Li, Z.X. Xie, Y.D. Zhang, J.H. Chen and Z. Yang : *J. Org. Chem.* **68**, 8500 (2003). (g) D. Nematollahi, D. Habibi, A.H. Alizadeh and M. Hesari : *J. Heterocyclic Chem.* Submitted for publication.

3. (a) Z. Grujic, I. Tabakovic and M. Trkovnik : *Tetrahedron Lett.* 4823 (1976). (b) I. Tabakovic, Z. Gruiic and Z. Beitovic : *J. Heterocyclic Chem.* **20**, 635 (1983). (c) S.M. Golabi and D. Nematollahi : *J. Electroanal. Chem.* **420**, 127 (1997). (d) S.M. Golabi and D. Nematollahi : *J. Electroanal. Chem.* **430**, 141 (1997). (e) D. Nematollahi and S.M. Golabi : *Bull. Electrochem.* **14**, 97 (1998). (f) D. Nematollahi and Z. Forooghi : *Tetrahedron* **58**, 4949 (2002). (g) D. Nematollahi and Z. Forooghi : *Electroanalysis* **15**, 1639 (2003).

4. T.W. Rall and L.S. Schleifer, *The Pharmacological Basis of Therapeutics*, A. Gilman, L.S. Goodman, T.W. Rall and F. Murad (Eds.), Macmillan, New York, 1985; Vol. 2, 7th ed. p.952.

5. (a) L. Papouchado, G. Petrie and R.N. Adams : *J. Electroanal. Chem.* **38**, 389, (1972). (b) L. Papouchado, G. Petrie, J.H. Sharp and R.N. Adams : *J. Am. Chem. Soc.* **90**, 5620, (1968). (c) T.E. Young, J.R. Griswold and M.H. Hulbert : *J. Org. Chem.* **39**, 1980, (1974). (d) A. Brun and R.J. Rosset : *Electroanal. Chem.* **49**, 287, (1974). (e) D. Nematollahi, A. Afkhami, F. Mosaed and M. Rafiee : *Res. Chem. Intermed.* **30**, 299, (2004).

6. (a) D.I. Stum and S.N. Suslov : *Biofizika* **21**, 40, (1979). (b) M.D. Rayn, A. Yueh and C. Wen-Yu : *J. Electrochem. Soc.* **127**, 1489, (1980). (c) D. Nematollahi, M. Rafiee and A. Samadi-Maybodi : *Electrochimica Acta* **49**, 2495, (2004).

Received on October 17, 2004