A Novel Method for the Synthesis of Oxazolocoumarin Derivatives

Essam Abdelghani,* Ali Abd El-Aal, Wesam Shehab, Medhat El-Mobayed

Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt
E-mail: e_abdelghani58@hotmail.com

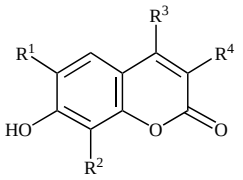
Received 24 February 2003; revised 15 April 2003

Abstract: Anodic oxidation of 7-hydroxycoumarin derivatives **1a**–**f** in anhyd acetonitrile–lithium perchlorate at constant potential between 1.70–1.80 V (vs. Ag/10^{-2} M Ag^+) using an undivided cell and platinium gauze electrodes leads to the formation of the corresponding oxazolocoumarin derivatives **2** and/or **3** according to the position of the second OH group in the benzene ring of the coumarin derivatives **1e**,**f**. The formation of these oxidation products is discussed.

Key words: oxidations, carbocations, coumarins, electrochemistry, quinones

Coumarin derivatives have aroused considerable interest from the viewpoint of their versatile practical applications as well as their biological activity.[1] In the case of 7-hydroxycoumarins, electrophilic substitution reactions usually take place quite easily at the C6-position, while nucleophilic attack at the same position has not been reported. Variations in methodology make comparison of the published results[2–4] difficult. We have sought to establish definite trends by examining oxidation of some substituted phenolic compounds as hydroxycoumarins.

The preparation of the following 7-hydroxycoumarin derivatives **1a**–**f** (Figure 1) was carried out as described in the literature.[5–7]



1

1a, R^1 = H; R^2 = H; R^3 = CH_3; R^4 = H
1b, R^1 = H; R^2 = H; R^3 = Ph; R^4 = H
1c, R^1 = H; R^2 = H; R^3 = CH_3; R^4 = C_3H_7
1d, R^1 = H; R^2 = H; R^3 = CO_2CH_3; R^4 = H
1e, R^1 = H; R^2 = OH; R^3 = Ph; R^4 = H
1f, R^1 = OH; R^2 = H; R^3 = CH_3; R^4 = H

Figure 1

In these cases, anodic oxidation can be regarded as an 'umpolung' reaction in a sense, as demonstrated below. Thus, we wish to describe the anodic oxidation of 7-hydroxycoumarin derivatives **1a**–**f** leading to the formation of the corresponding oxazolocoumarins. It would be quite difficult to synthesize some of these compounds in one step without using electrochemical methods.

Typical cyclic voltammetry, anodic oxidation followed by cathodic reduction for some phenols was performed.[8,9] Figure 2a shows the cyclic voltammogram (CV) of coumarin derivative **1b**. Inspection of this figure reveals that, on positive-going scan, the cathodic current density corresponding to hydrogen evolution, reaction decreases exponentially until it reaches the zero current potential $E_i = 0$. Beyond this potential the current changed to be anodic. The anodic excursion span is characterized by one anodic current peak AI. The returning potential scan does not exhibit any cathodic peaks. The CVs of coumarin derivatives **1a**,**c**,**d** have all the same features as that of Figure 2a.

However, the CV of hydroxycoumarin derivative **1e** (Figure 2b) exhibits two anodic peaks AI and AII and one cathodic peak CI. The current of the second anodic peak AII is three times larger than that of AI. Comparing these results with that of Figure 2a, we can conclude that the second anodic peak AII and the cathodic peak CI are due to oxidation and reduction of the hydroxy group at the 8-position. However, the first anodic peak AI corresponds to the oxidation of the hydroxy group at the 7-position, whose reduction does not appear in the voltammogram because of its transformation to the oxazolo ring formed.

Therefore, the anodic oxidation of compounds **1a**–**f** was performed in pure MeCN[10] containing $LiClO_4$ as the supporting electrolyte, using two Pt-electrodes at the measured oxidation potential (vs. Ag/10^{-2} M Ag^+) in a nitrogen atmosphere. Various synthesized compounds **2a**–**e** and **3** are depicted in Scheme 2.

Thus, we noticed that the anodic oxidation of 7-hydroxy-4-methylcoumarin (**1a**) at 1.75 V (vs. Ag/10^{-2} M Ag^+) gave the adduct oxazolo[4,5-*g*]coumarin derivative **2a** in 33% yield. The MS spectrum of **2a** revealed the molecular ion peak at *m*/*z* 215 and base peak at *m*/*z* = 176, while its IR spectrum showed υ (C=N) at 1608 cm^{-1}. The mechanism of the reaction involves the formation of a 7-oxocoumarin 6-carbocation by the loss of two electrons and one proton followed by nucleophilic attack of nitrogen atom of the solvent acetonitrile to the formed carbocation at the 6-position and regioselective cyclization to give 2,8-dimethyloxazolo[4,5-*g*]coumarin (**2a**) (Scheme 2). The attack of the solvent acetonitrile to the formed carbocations was also observed in other cases.[11,12] The product **2a** was proved authentic by the reaction of 4-aminoresorcinol

Synthesis 2003, No. 9, Print: 03 07 2003.
Art Id.1437-210X,E;2003,0,09,1373,1376,ftx,en;T01803SS.pdf.

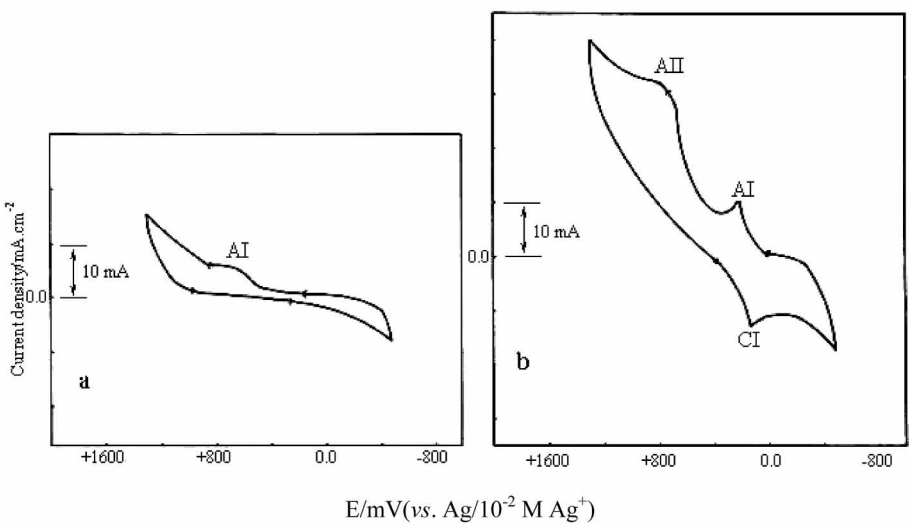


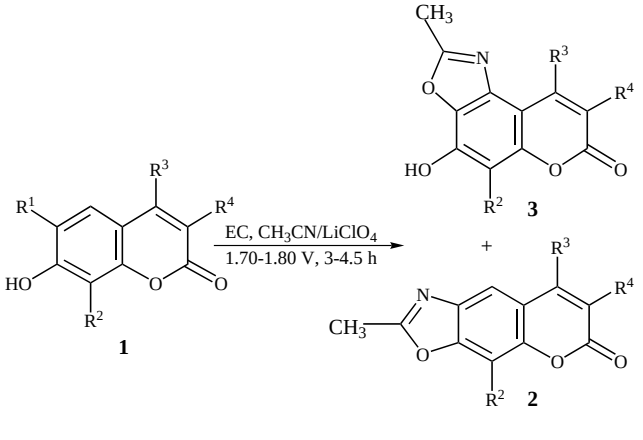
Figure 2 Cyclic voltammograms of compounds **1b** (Figure 2a) and **1e** (Figure 2b) with scan rate 0.03 Vs^{-1}.

with P_2O_5–HOAc to form the hydroxybenzoxazole which in turn cyclized with ethyl acetoacetate in concd H_2SO_4 to form the product **2a**.

Another noteworthy result was the anodic oxidation of compound **1b** which afforded the oxazolocoumarin derivative **2b** in 43% yield. The phenyl group at the 4-position increases the stability of the intermediate cation. In case of compound **1c**, the product of the anodic oxidation was 2,8-dimethyl-7-propyloxazolo[4,5-*g*]coumarin (**2c**) in 34% yield. Also, the anodic oxidation of 4-carbomethoxy-7-hydroxycoumarin (**1d**) afforded the adduct oxazolo[4,5-*g*]coumarin derivative **2d** in 38% yield.

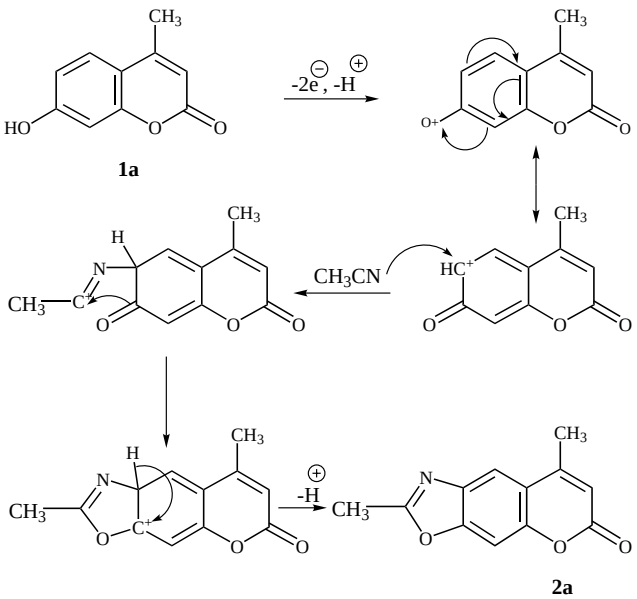
Interestingly, the anodic oxidation of 7,8-dihydroxy-4-phenylcoumarin (**1e**) results in the formation of 4-hydroxy-2-methyl-8-phenyloxazolo[4,5-*g*]coumarin (**2e**) in 39% yield. The mechanism of this reaction involves two possible ways for the addition of acetonitrile to the formed *o*-quinone derivative. The formation of **2e** can be interpreted in terms of the acetonitrile acting as a nucleophile via its nitrogen atom and attacking the formed cationic center at the C6-position, followed by cyclization with the formation of oxazolocoumarin derivative **2e**. On the other hand, the lack of formation of **4** is due to the absence of water in the pure acetonitrile used. Therefore, the formed adduct cannot undergo ring closure which affords the amide derivative **4**.

Furthermore, the electrochemical oxidation of compound **1f** was performed and among different products we can identify the product **3** as a major product. The CV of **1f** indicated that two distinct oxidative processes were occur-



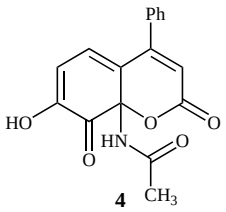
2a, R^2 = H; R^3 = CH_3; R^4 = H
2b, R^2 = H; R^3 = Ph; R^4 = H
2c, R^2 = H; R^3 = CH_3; R^4 = C_3H_7
2d, R^2 = H; R^3 = CO_2CH_3; R^4 = H
2e, R^2 = OH; R^3 = Ph; R^4 = H
3, R^2 = H; R^3 = CH_3; R^4 = H

Scheme 1



Scheme 2

ring, both of which resulted in the formation of the same *o*-quinone derivative, and more quantitative electrochemical studies were difficult because of secondary dimerization reactions and filming of the electrode surface.[13] However, according to our results, it seems that the intermolecular addition of acetonitrile to the formed *o*-quinone derivative and intramolecular cyclization was faster than other secondary dimerization reactions, leading presumably to the formation of 4-hydroxy-2,9-dimethyloxazolo[4,5-*f*]coumarin (**3**) as a major product. The structures of the isolated oxidation products as oxazolocoumarin derivatives **2a**–**e** and **3** were unambiguously determined on the basis of their IR, ^{1}H NMR, MS spectra and correct analytical data.



4

Figure 3

Table 1 Physical Data of Prepared Compounds[a]

Compd	Mp (°C) (Solvent)	Pot. (V) vs. Ag/ 10^{-2} M Ag^+	Time (h)	Yield (%)
2a	160 Toluene	1.75	3	33
2b	187 Toluene	1.70	3.5	43
2c	176 Toluene	1.70	3	34
2d	200 Toluene	1.80	3.5	38
2e	145 Benzene	1.80	4	39
3	150 EtOH (95%)	1.80	4.5	33

[a] All Compounds gave satisfactory microanalyses: C, H, N ± 0.4.

Mps are uncorrected. IR spectra (KBr discs) were recorded on a Pye Unicam (SP-1000) spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer in DMSO-d_6 using TMS as internal standard. The EIMS were obtained with a Varian MAT 311A instrument. Elemental analyses were performed at the microanalytical unit of Cairo University. Compounds **1a**–**f** were prepared by reported procedure.[5–7]

Cyclic voltammetry of 7-hydroxycoumarin derivatives **1a**–**f** were recorded using MeCN as a solvent and $LiClO_4$ as supporting electrolyte at 25°C. The experiments were carried out using three electrodes as one compartment cell. Both working and counter electrodes were Pt-gauze. The potential of the working electrode was measured versus Ag/10^{-2} M Ag^+ reference electrode and scanned from –0.4 to 1.3 V at a scan rate of 0.03 Vs^{-1}. Solutions were de-aerated by N_2 bubbling before each experiment for 30 min. The gas flow was maintained at low rates during the experiments.

Electrochemical Oxidation; General Method

In a de-aerated (N_2 gas) stirred solution of pure MeCN (175 mL) as a solvent and lithium perchlorate (2.13 g, 20 mmol) as a supporting electrolyte, anodic oxidation of each 7-hydroxycoumarin derivatives **1a**–**f** (5 mmol) was performed by fixing the electrode potential at the values indicated in Table 1 using two Pt-electrodes and the reference electrode as Ag/10^{-2} M Ag^+ electrode. During electrolysis, the products were checked using TLC to see the reaction path and how many products were formed. At different time intervals, the two Pt-gauze electrodes were removed from the cell and cleaned using nitric acid and then DMF, distilled water, acetone and then dried to remove the anodically formed non-conductive passive films on the anode. After the oxidation, the MeCN was evaporated using the rotatory evaporator, extracted with $CHCl_3$, washed with H_2O and dried (Na_2SO_4). After evaporation of $CHCl_3$ the semi-solid produced was crystallized from suitable solvent and detected as usual.

Compound 2a

IR: 1716, 1677, 1608 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.80 (s, 1 H, ArH), 7.22, 7.20 (s, 2 H, ArH), 3.40 (s, 3 H, CH_3), 2.60 (s, 3 H, CH_3).

MS: *m*/*z* = 215 (M^+), 192, and the base peak at 176.

Compound 2b

IR: 1695, 1620, 1605 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.70–6.55 (m, 7 H, ArH), 6.10 (s, 1 H, C=CH), 2.25 (s, 3 H, CH_3).

MS: *m*/*z* = 277 (M^+), 253, 239, 238.

Compound 2c

IR: 1680, 1620, 1608 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.45, 7.40 (s, 2 H, ArH), 2.62–2.54 (t, 2 H, $CH_2CH_2CH_3$), 2.37 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 1.65–1.45 (m, 2 H, $CH_2CH_2CH_3$), 1.01–0.94 (t, 3 H, $CH_2CH_2CH_3$).

MS: *m*/*z* = 257 (M^+) and the base peak at 231 ($M^+ - C_2H_2$).

Compound 2d

IR: 1720, 1690, 1618 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.95, 7.91 (s, 2 H, ArH), 6.50 (s, 1 H, ArH), 3.90 (s, 3 H, CH_3), 3.70 (s, 3 H, CH_3).

MS: *m*/*z* = 259 (M^+), 220, 192, 161.

Compound 2e

IR: 3412, 1727, 1611, 1575 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 7.64 (s, 1 H, OH), 7.61–7.41 (m, 5 H, ArH), 6.17 (s, 1 H, C=CH), 3.32 (s, 3 H, CH_3).

MS: *m*/*z* = 293 (M^+), 279, 255, 238 and the base peak at 226.

Compound 3

IR: 3423, 1729, 1640, 1607 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 8.42 (s, 1 H, OH), 7.66 (s, 1 H, ArH), 6.43 (s, 1 H, C=CH), 3.47

(s, 3 H, CH_3), 3.43 (s, 3 H, CH_3).

MS: *m*/*z* = 231 (M^+ and the base peak), 205, 192, 176, 164.

Alternative Synthesis of 2a[5,14]

A mixture of 4-aminoresorcinol (1.25 g, 10 mmol) and phosphorus pentoxide (2 g) and glacial HOAc (30 mL) was refluxed at 200 °C for 6 h. After cooling the reaction mixture was poured into ice–H_2O and extracted with Et_2O, the Et_2O layer dried (Na_2SO_4) and evaporated to give 2-methyl-1,3-benzoxazol-6-ol.

Yield: 67%.

A solution of 2-methyl-1,3-benzoxazol-6-ol (1.49 g, 10 mmol) in redistilled ethyl acetoacetate (1.30 g, 10 mmol) was added dropwise into concd H_2SO_4 (50 mL) in a 250 mL three necked flask cooled in an ice bath, fitted with a thermometer, mechanical stirrer and a dropping funnel with stirring for 2 h. The reaction mixture was kept at r.t. for about 18 h, then poured with vigorous stirring into a mixture of crushed ice (100 g) and H_2O (150 mL). The precipitated solid was filtered off at the pump, washed with cold H_2O (4×25 mL), dried, and recrystallized from toluene to give **2a**.

Yield: 30%; pale brown crystals; mp 160 °C.

References

(1) Goto, T.; Yamamura, S. *Pyran Compounds*, In *Methodicum Chimicum*, Part 3, Vol. 11; Korte, F.; Goto, M., Eds.; Academic Press: New York, **1978**.
(2) Suttie, A. B. *Tetrahedron Lett.* **1969**, 953.
(3) Popp, G.; Retiz, N. G. *J. Org. Chem.* **1972**, *37*, 3646.
(4) El-Mobayed, M.; Ismail, N.; Abo-El-Enein, G.; Abdel-Haleem, E. *J. Chem. Soc. Pak.* **1986**, *8*, 305.
(5) Furniss, B. S.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 4th ed.; Addison-Wesley: Reading MA, **1978**.
(6) Chatterji, D.; Chakraborty, D. P. *J. Indian Chem. Soc.* **1972**, *49*, 1045.
(7) Jiarong, L.; Ailion, T.; Mingshi, W. *Zhong Caoyao* **1982**, *13*, 493.
(8) Hutinec, A.; Ziogas, A.; El-Mobayed, M.; Rieker, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2201.
(9) Reischl, G.; El-Mobayed, M.; Beisswenger, R.; Regier, K.; Mossmer, C. M.; Rieker, A. *Z. Naturforsch., B: Chem. Sci.* **1998**, *53*, 765.
(10) Coetzee, J. F.; Gunningham, G. P.; McCuire, D. K.; Padmanabhan, G. R. *Anal. Chem.* **1962**, *34*, 1138.
(11) Domschke, G.; Oelmann, H. *J. Prakt. Chem.* **1969**, *311*, 800.
(12) Dreher, E. L.; Brancht, J.; El-Mobayed, M.; Winter, W.; Rieker, A. *Chem. Ber.* **1982**, *115*, 288.
(13) Papauchado, L.; Petrie, G.; Adams, R. N. *J. Electroanal. Chem.* **1972**, *38*, 389.
(14) El-Farargy, A. F. *J. Chem. Soc. Pak.* **1991**, *13*, 59.