A Novel Method for the Synthesis of Oxazolocoumarin Derivatives

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Abstract: Anodic oxidation of 7-hydroxy coumarin 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 platinum 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, carboxations, 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 difficult. We have sought to establish definite trends by examining oxidation of some substituted phenolic compounds as hydroxycoumarins. The preparation of the following 7-hydroxy coumarin derivatives 1a–f (Figure 1) was carried out as described in the literature.5–7

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 Ei = 0. Beyond this potential the current changed to be anodic. The anodic excursion span is characterized by one anodic 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 MeCN10 containing LiClO4 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-methyl coumarin (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 ν (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...
with $\text{P}_2\text{O}_5\cdot\text{HOAc}$ to form the hydroxybenzoxazole which in turn cyclized with ethyl acetooacetate in concd $\text{H}_2\text{SO}_4$ 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 oxazolocoumarin 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.

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

![Diagram](image_url)

Scheme 1

![Diagram](image_url)

Scheme 2

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$_3$H$_7$
2d, R$^2$ = H; R$^3$ = CO$_2$CH$_3$; R$^4$ = H
2e, R$^2$ = OH; R$^3$ = Ph; R$^4$ = H
3, R$^2$ = H; R$^3$ = CH$_3$; R$^4$ = H
ring, both of which resulted in the formation of the same 
\( \alpha \)-quinone derivative, and more quantitative electrochem-
ical studies were difficult because of secondary dimerization
reactions and filming of the electrode surface.\(^{13}\) However,
according to our results, it seems that the inter-

teradial addition of acetonitrile to the formed \( \alpha \)-quinone
derivative and intramolecular cyclization was faster than
other secondary dimerization reactions, leading presum-
ably to the formation of 4-hydroxy-2,9-dimethyloxazo-
lo[4,5-\( \alpha \)]coumarin (3) as a major product. The structures
of the isolated oxidation products as oxazolocoumarin deriv-
atives 2a–e and 3 were unambiguously determined on the
basis of their IR, \(^1\)H NMR, MS spectra and correct analy-
tical data.

\[ \text{Figure 3} \]

\[ \text{Table 1} \]

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

\* 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 re-
corded 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 elec-
trolyte at 25°C. The experiments were carried out using three elec-

trodes 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 deriv-
atives 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 electroly-
sis, 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\(_2\)O and dried (Na\(_2\)SO\(_4\)). 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\(_6\)): \( \delta = 7.80\) (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\(_3\)): \( \delta = 7.30–6.55\) (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\(_3\)): \( \delta = 7.45, 7.40\) (s, 2 H, ArH), 2.62–2.54 (t, 2 H,
CH\(_2\)CH\(_2\)CH\(_3\)), 2.37 (s, 3 H, CH\(_3\)), 2.34 (s, 3 H, CH\(_3\)).

MS: \( m/z = 257 \) (M\(^+\)) and the base peak at 231 (M\(^+\)– C\(_2\)H\(_2\)).

**Compound 2d**

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

\(^1\)H NMR (DMSO-d\(_6\)): \( \delta = 7.95, 7.91\) (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\(_6\)): \( \delta = 7.64\) (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, 1727, 1640, 1607 cm\(^{-1}\).

\(^1\)H NMR (DMSO-d\(_6\)): \( \delta = 8.42\) (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\(_2\)O and extracted with Et\(_2\)O, the Et\(_2\)O layer dried (Na\(_2\)SO\(_4\)) 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\(_2\)SO\(_4\) (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\(_2\)O (150 mL). The precipitated solid was filtered off at the pump, washed with cold H\(_2\)O (4 × 25 mL), dried, and recrystallized from toluene to give 2a.

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

References