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Synthesis of Zwitterionic 4-Hydroxycoumarin Derivatives through a Unique Reaction of 4-Hydroxycoumarins with *p*-Benzoquinone and Pyridine

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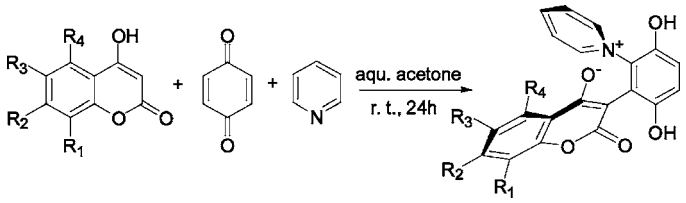
ABSTRACT



A unique reaction of 4-hydroxycoumarins with *p*-benzoquinone and pyridine was found, and through the reaction, six zwitterionic 4-hydroxycoumarin derivatives were synthesized. The structures of these compounds were determined by IR, MS(ESI), ^{1}H NMR, ^{13}C NMR, and single-crystal X-ray diffraction studies.

4-Hydroxycoumarin is an important component of many synthetic and natural products[1] with wide ranging biological activities that include anticoagulant and HIV protease inhibition effects.[2] These special properties have stimulated considerable interest in this class of compounds, and various 2,3- or 3,4-fused polycycles or open-chain derivatives have been synthesized. A number of 4-hydroxycoumarin derivatives can be synthesized through the Michael addition of 4-hydroxycoumarins to α,β-unsaturated carbonyl compounds utilizing the nucleophilicity of C-3.[3]

The reaction of 4-hydroxycoumarins with quinone is illustrative in this regard. It has been reported that 4-hy-

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droxycoumarins react with *o*-quinone to give the corresponding coumestans.[4] In contrast, the reaction of 4-hydroxycoumarin with *p*-quinone has been less well studied with only a few products having been reported from such reactions (Figure 1).[5]

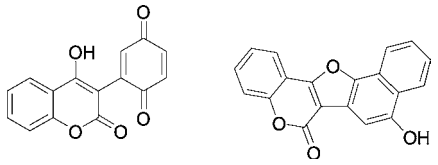
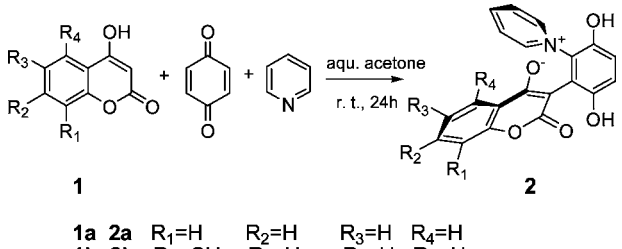


Figure 1. Structures of the products from the reaction of 4-hydroxycoumarin with *p*-benzoquinone and naphthoquinone, respectively.

In the present work we now report an interesting reaction of 4-hydroxycoumarins with *p*-benzoquinone that is mediated by excess pyridine in aqueous acetone (v:v = 1:1) (Scheme 1). The reaction of 4-hydroxycoumarin with *p*-benzoquinone

Scheme 1. Preparation of Compounds **2**



1 **2**

1a	**2a**	R_1=H	R_2=H	R_3=H	R_4=H
1b	**2b**	R_1=CH_3	R_2=H	R_3=H	R_4=H
1c	**2c**	R_1=H	R_2=CH_3	R_3=H	R_4=H
1d	**2d**	R_1=H	R_2=H	R_3=H	R_4=CH_3
1e	**2e**	R_1+R_2=-CH=CH-CH=CH-		R_3=H	R_4=H
1f	**2f**	R_1=H	R_2=H	R_3+R_4=-CH=CH-CH=CH-	

and pyridine gives a pale yellow product **2a**,[6] which we have shown to be a pyridinium-zwitterionic compound by IR, MS-(ESI), ^{1}H NMR, ^{13}C NMR, and X-ray crystallographic studies.

Pyridinium zwitterions are often reactive species that are widely used in organic synthesis.[7] The preparation of zwitterions via the addition of pyridine derivatives to reactive double bonds or carbenes has been reported.[8] In most cases, the negative charge in the zwitterionic compound is on the atom adjacent to that attached to the pyridinium nitrogen and is delocalized by the presence of electron-withdrawing substituents to improve the stability of the compound. Yet, the result is usually unsatisfactory. Recently, charge-separated pyridinium zwitterions have been prepared and proved to be stable.[9]

Under similar reaction conditions for the synthesis of **2a**, five other zwitterions were also prepared. The proposed zwitterionic structures for these compounds are consistent with the ^{1}H NMR(500 MHz, DMSO-d_6) spectroscopic data.[10] The unusual downfield signals of the pyridine ring of **2b** showed the presence of the pyridinium structure. The presence of the oxyanion on the lactone ring of **2b** was corroborated by the absence of a broad OH signal at δ 12.37 ppm, which appears in the ^{1}H NMR of 8-methyl-4-hydroxycoumarin. The quadruple peaks of the AB system for two protons of the phenolic ring at δ 6.95−6.98 ppm indicated that the pyridinium moiety and the 4-hydroxycoumarin moiety were on the same side of the hydroquinone ring. The different shift of the two α-protons located on the pyridine ring of **2b**, at δ 8.95 and 8.59 ppm, respectively, was caused by the uneven shielding of the negative ion attached to the pyrano ring. Similarly, the signals of the two β-protons were also unequal. Thus, these compounds might exist as atropisomers due to the restricted rotation about the C6−N1 bond.

The unambiguously determined structure of **2a** via single-crystal X-ray diffraction also lent support to the proposed structures of the other related compounds.[11] (Figure 2)

The positive charge located on the pyridinium cation and the negative charge was delocalized on the 1,3-dicarbonyl structure of the 4-hydroxycoumarin fragment. The delocalization of the negative charge on the 1,3-dicarbonyl structure

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(6) **Preparation of Compounds 2a−f: General Procedure.** A mixture of 4-hydroxycoumarin **1a** (0.81 g, 5 mmol), *p*-benzoquinone (1.08 g, 10 mmol), and pyridine (0.79 g, 10 mmol) in 60 mL aqueous acetone (v:v = 1: 1) was magnetically stirred at room temperature for 24 h. The reaction mixture was filtered to afford a brown crude product that was purified by column chromatography (silica gel, methanol/trichloromethane = 1:10) to give the yellow compound **2a** (0.79 g, 2.3 mmol) in 46% yield: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.89 (1H, s), 9.62 (1H, s), 8.97 (1H, d, J = 6 Hz), 8.57 (1H, d, J = 6 Hz), 8.51 (1H, t, J = 8 Hz), 8.06 (1H, t, J = 7 Hz), 7.86−7.89 (2H, m), 7.42 (1H, t, J = 7 Hz), 7.17(1H, t, J = 8 Hz), 7.07 (1H, d, J = 8 Hz), 6.98 ppm (2H, q, δ_{Ha} = 6.99 ppm, δ_{Hb} = 6.97 ppm, J_{AB} = 9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.7, 162.2, 153.2, 150.3, 150.1, 146.7, 145.7, 142.9, 130.8, 130.4, 126.2, 125.9, 124.8, 122.4, 121.9, 121.9, 120.7, 115.4, 115.1, 92.6 ppm; IR (KBr) 3064, 1626, 1599, 1522, 1502 cm^{-1}; MS(ESI) 346 (M − 1)$^-$.

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(10) **Compound 2b:** ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.87(1H, s), 9.58(1H, s), 8.95(1H, d, J = 6 Hz), 8.59(1H, d, J = 6 Hz), 8.51(1H, t, J = 7.5 Hz), 8.06(1H, t, J = 8 Hz), 7.89(1H, t, J = 8 Hz), 7.70(1H, d, J = 8 Hz), 7.28(1H, d, J = 7 Hz), 7.05(1H, t, J = 7.5 Hz), 6.96(2H, q, AB system, dδ_{Ha} = 6.97 ppm, dδ_{Hb} = 6.95 ppm, J_{AB} = 9 Hz), 2.21 ppm (3H, s); ^{13}C NMR (DMSO-d_6) δ 173.9, 162.3, 151.6, 150.3, 149.9, 146.9, 145.6, 142.9, 131.8, 130.4, 126.2, 126.0, 123.9, 122.5, 121.9, 121.848, 121.4, 120.6, 114.9, 92.4, 15.1 ppm; IR (KBr) 3067, 1623, 1596, 1523, 1504 cm^{-1}; MS(ESI) 360 (M − 1)$^-$.

(11) **Crystal Data for 2a:** $C_{20}H_{15}NO_6$, MW = 365.33, monoclinic *P*21/*c*, a = 7.142(10), b = 16.314(2), c = 16.054(2) Å, α = 90°, β = 111.45(3)°, γ = 90°, V = 1741.0(4) Å^3, Z = 4, D_{calcd} = 1.394 g/cm^3, R_1 = 0.047, wR_2 = 0.110 [$I > 2\sigma(I)$], R_1 = 0.085, wR_2 = 0.128 (all data), S = 1.03.

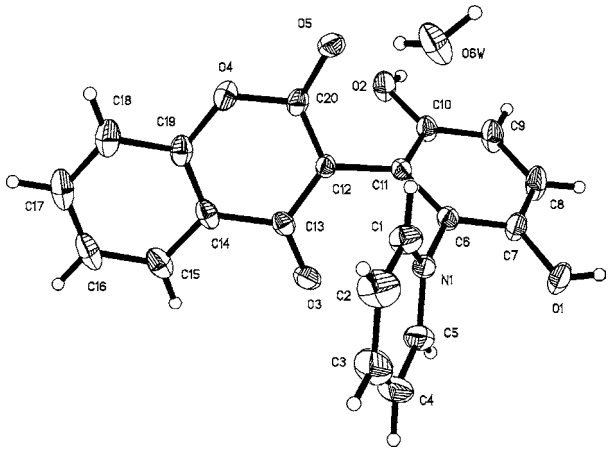

Figure 2. X-ray structure of compound **2a**.

was consistent with the observation that the C(20)−O(5) bond length [1.251(2) Å] was similar to the C(13)−O(3) bond length [1.255(2) Å] and shorter than the C−O bond length [1.348(5) Å] of the enol form in the 4-hydroxycoumarin fragment.[12] Neither the pyridine ring nor the pyrano ring of the 4-hydroxycoumarin fragment was found to conjugate to the hydroquinone ring. The dihedral angles for C(11)−C(6)−N(1)−C(1) and C(10)−C(11)−C(12)−C(20) were found to be 65.2 and 62.5°, respectively.

A possible mechanism of **2a** formation is presented in Scheme 2. The Michael addition of 4-hydroxycoumarin into *p*-benzoquinone first gives unstable intermediate **3**, which is subsequently autooxidized to generate quinone derivative **4**. **4** is attacked by pyridine at the 3-position to form **2a**, which is in a hydroquinone form due to the electron-withdrawing effect of the pyridinium moiety.

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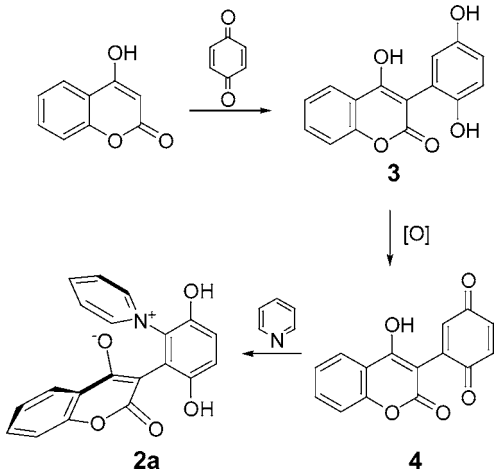
Scheme 2. Possible Mechanism of Adduct Formation of **2a**



In summary, we described here an unexpected and interesting reaction of 4-hydroxycoumarins with *p*-benzoquinone and pyridine in aqueous acetone (v:v = 1:1). Six stable zwitterionic compounds have been synthesized via this reaction.

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Supporting Information Available: X-ray data for compound **2a**; spectral data of compounds **2a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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