

Improved Synthesis of Some Hydroxycoumarins

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(Received 28 April 1995; accepted 22 June 1995)

ABSTRACT

An improved synthesis of some 7-hydroxycoumarin derivatives is reported. Hydroxybenzenes reacted with β -ketoesters or d,l-malic acid in HClO_4 to give good yields of 7-hydroxycoumarins. IR and ^1H NMR data for the products are also reported.

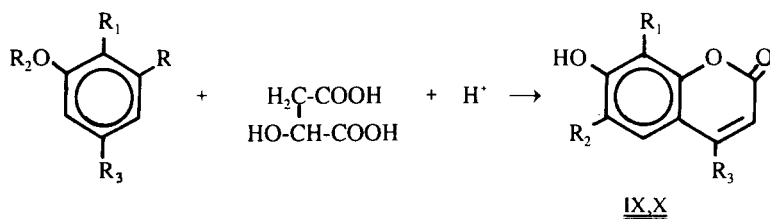
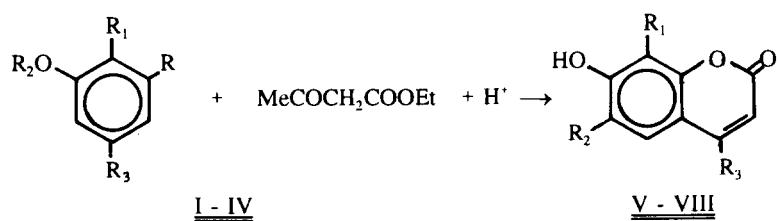
INTRODUCTION

There is much current interest in coumarins and several reviews of the chemistry of these compounds are available.^{1–3} The initial syntheses of such molecules stemmed from the studies of Perkin⁴ and von Pechmann.⁵ Perkin prepared the coumarins by condensing *o*-hydroxyaldehydes with acetic anhydride,⁴ whilst von Pechmann and Duisburg⁶ reported the reaction between phenols and β -ketoesters in the presence of strong acids. Lacey⁷ described the preparation of some coumarin derivatives following similar but updated procedures. However, most of the earlier procedures afforded only low yields.⁸ We have reported the synthesis of crown ether derivatives of coumarin using H_2SO_4 as acid catalyst.^{9–14}

In this present work, we describe a modified procedure for the synthesis of hydroxycoumarins by reaction, in HClO_4 , of hydroxybenzenes, with β -ketoesters in excellent yields, and with *d,l*-malic acid in good yield (Scheme 1).

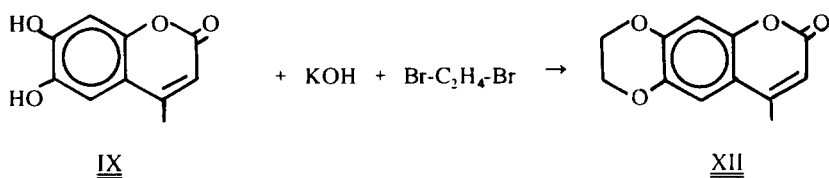
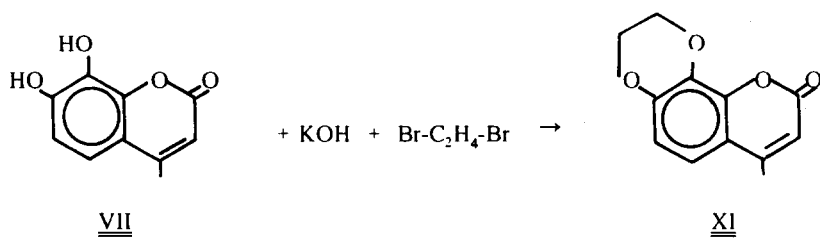
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	R	R ₁	R ₂	R ₃
I	OH	H	H	H
II	OH	OH	H	H
III	OH	CH ₃ CO	H	H
IV	H	OCOCH ₃	CH ₃ CO	OCOCH ₃

	R ₁	R ₂	R ₃
V	H	H	CH ₃
VI	OH	H	CH ₃
VII	CH ₃ CO	H	CH ₃
VIII	H	OH	CH ₃
IX	H	H	H
X	OH	H	H



Scheme 1

RESULTS AND DISCUSSION

The well established coumarin synthesis,¹⁻⁵ in which H_2SO_4 is predominantly used in the reaction system, were found by us to be generally unsatisfactory. The products obtained were difficult to purify due to resinous by-products, and after removal of dark-coloured material, yields less than 20% were obtained for compounds **V**–**VIII**.⁹⁻¹² Higher yields of 35–82%, and absence of tarry components, were, however, obtained in the presence of 50–70% HClO_4 .

The overall yields for compounds **IX** and **X** obtained in HClO_4 , were similar to those obtained in H_2SO_4 ,¹³ but pale-coloured pure products were obtained in most cases when allowing the reaction mother liquors to crystallise on cooling.

The new dimethylenedioxy derivatives **XI** and **XII** were obtained from source materials prepared by this HClO_4 procedure. These compounds were more stable and neutral luminescent compounds compared to the coumarin starting materials and the fluorescence spectra of such ethers are not pH-dependent.¹⁵

On the other hand, attempts to react hydroquinone, catechol and 2,4-dihydroxyacetophenone with ethylacetoacetate failed to give coumarins in the presence of HClO_4 as was the case using H_2SO_4 . These compounds are more satisfactorily obtained in the presence of AlCl_3 or POCl_3 .⁸

EXPERIMENTAL

Melting points are uncorrected. ^1H NMR spectra were obtained on a Bruker WA-200 using TMS as internal standard. The reported data are given in ppm. IR spectra were determined (KBr) with a Perkin-Elmer, Model 598 and mass spectra with a Hewlett-Packard, Model MS Engine-5989 with CI source. Compounds **I**–**V** were obtained from Fluka or Merck and were used without purification. Elementary analyses were conducted by Tubitak laboratories at Gebze, Turkey.

7-Hydroxy-4-methyl-2(*H*)-1-benzopyran-2-one (**V**)

A mixture of HClO_4 (100 ml, 70%), resorcinol (**I**) (55 g, 500 mmol) and ethyl acetoacetate (65 g, 500 mmol) was heated at 80–90°C for 3 h. The liquor was cooled and, after dilution with water, filtered and the product recrystallized from methanol as pale yellow crystals (49 g, 56%), m.p. 185°C; IR: 3400, 1670, 1600, 1390, 1275 cm^{-1} ; ^1H NMR (acetone- d_6) 9.55 (1H, s, OH), 7.61 (1H, d), 6.86 (1H, q), 6.74 (1H, d), 6.08 (1H, s), 2.41 (3H, s, CH_3).

7,8-Dihydroxy-4-methyl-2(*H*)-1-benzopyran-2-one (VI)

A mixture of pyrogallol (**II**) (38 g, 300 mmol), ethyl acetoacetate (78 g, 600 mmol) and HClO_4 (70%, 100 ml) was heated at 90°C for 4 h with stirring. The liquor was poured into ice-water and the resultant crude product was dissolved in hot ethanol and recrystallized as pink needles (48 g, 85%), m.p. 244°C;⁷ IR: 3400, 1650, 1570, 1510, 1060, 1000, 800 cm^{-1} ; ^1H NMR (CDCl_3); 9.0 (s, 1H, OH), 7.08 (d, 1H), 6.85 (d, 1H), 6.04 (s, 1H), 2.37 (s, 3H, CH_3).

8-Acetyl-7-hydroxy-4-methyl-2(*H*)-1-benzopyran-2-one (VII)

A mixture of 2,6-dihydroxyacetophenone (**III**) (10 g, 65 mmol), ethyl acetoacetate (8.5 g, 65 mmol) and HClO_4 (70%, 50 ml) was heated on a water bath for 4 h. The mixture was allowed to cool for one day, then filtered and the product crystallized from methanol as grey leaflets (7.0 g, 49%), m.p. 163°C; IR: 3400, 2920, 1725, 1705, 1600, 1380, 1295, 1100 cm^{-1} ; ^1H NMR (CDCl_3); 13.56 (1H, s, OH), 7.68 (1H, s, H), 7.26 (1H, s, H), 6.92 (1H, s, H), 6.16 (1H, s, H), 2.97 (3H, s, COCH_3), 2.42 (3H, s, CH_3).

6,7-Dihydroxy-4-methyl-2(*H*)-1-benzopyran-2-one (VIII)

A mixture of 1,2,4-triacetoxybenzene (**VI**) (50.4 g, 300 mmol), ethyl acetoacetate (78 g, 600 mmol) and HClO_4 (70 ml, 70%) was stirred for 4 h at 95°C. The mixture was poured into ice-water, filtered, and the dried product dissolved in boiling ethanol and filtered, giving yellowish-green needles (50 g, 87%), m.p. 275°C acetone; IR: 3400, 1670, 1560, 1400, 1270, 1160, 1100 cm^{-1} ; ^1H NMR (CDCl_3); 7.08 (s, 1H), 6.85 (s, 1H), 6.04 (s, 1H), 2.37 (s, 3H, CH_3).

7-Hydroxy-2(*H*)-1-benzopyran-2-one (IX)

A mixture of resorcinol (**I**) (5.5 g, 50 mmol), *d,l*-malic acid (6.7 g, 50 mmol) and HClO_4 (50 ml, 70%) was heated at 90°C for 4 h. The product was obtained as orange needles from ethanol (6.0 g, 81%), m.p. 232°C;⁷ IR: 3400, 1770, 1230, 1130, 830 cm^{-1} ; ^1H NMR (acetone- d_6); 7.83 (d, 1H), 7.46 (d, 1H), 6.82 (q, 1H), 6.73 (d, 1H), 6.14 (d, 1H).

7,8-Dihydroxy-2(*H*)-1-benzopyran-2-one (X)

Pyrogallol (**II**) (3.8 g, 30 mmol), *d,l*-malic acid (8.0 g, 60 mmol) and HClO_4 (70%, 25 ml) were heated at 95°C for 4 h while the mixture was stirred. The mixture was poured into ice-water, the product filtered, dissolved in hot

ethanol and filtered. Crystallization from acetone gave 3.1 g (60%), m.p. 256°C;⁶ IR: 3450, 1670, 1560, 1400, 1150, 350 cm⁻¹; ¹H NMR (CDCl₃); 7.62 (d, 1H), 7.14 (d, 1H), 6.58 (d, 1H), 6.28 (d, 1H).

7,8-Ethylenedioxy-4-methyl-2(*H*)-1-benzopyran-2-one (XI)

Dioxane (100 ml), compound VI (3.84 g, 20 mmol), 1,2-dibromoethane (3.74 g, 20 mmol), KOH (2.24 g, 40 mmol) and water (25 ml) were refluxed for 48 h. The mixture was acidified, filtered, and the product dried and extracted with CHCl₃ (100 ml). Recrystallization from CH₂Cl₂ gave 1.52 g (35%), m.p. 163°C. IR: 1700, 1550, 1430, 1120, 950 cm⁻¹. ¹H NMR (CDCl₃); 7.04 (d, 1H), 6.78 (d, 1H), 6.10 (s, 1H), 4.34 (s, 4H), 2.36 (s, 3H, CH₃). ¹³C NMR (CDCl₃) 160.25, 152.71, 146.25, 143.42; 131.51; 115.94; 114.27; 113.10; 112.19; 77.65; 77.01; 76.38; 64.53; 64.16; 18.74. MW (218) CI (NH₃ reagent gas), 219 (MH)⁺; 236 (M . NH₄)⁺.

Calcd for C₁₂H₁₀O₄: C, 66.0; H 4.59. Found: C, 66.1; H, 4.51.

6,7-Ethylenedioxy-4-methyl-2(*H*)-1-benzopyran-2-one (XII)

DMF (50 ml), compound VIII (1.95 g, 10 mmol), 1,2-dibromoethane (1.9 g, 10 mmol), K₂CO₃ (1.12 g, 20 mmol) and water (5 ml) were stirred under reflux for 36 h. The mixture was acidified, the product filtered, dried and extracted with chloroform (75 ml) to give white crystals (0.55 g, 25%), m.p. 151°C. IR: 2965, 1730, 1630, 1565, 1060 cm⁻¹. ¹H NMR (CDCl₃); 7.02 (s, 1H), 6.80 (s, 1H), 6.12 (s, 1H), 4.32 (m, 4H), 2.32 (s, 3H, CH₃), ¹³C NMR (CDCl₃) 161.74, 152.52, 149.12, 147.39, 141.05, 114.54, 113.31, 112.11, 78.17, 77.54, 76.89, 65.23, 64.55, 19.19. MW (218) CI (NH₃ reagent gas), 219 (MH)⁺; 236 (M . NH₄)⁺.

Calcd for C₁₂H₁₀O₄: C, 66.0; H 4.59. Found: C, 66.6; H, 4.69.

ACKNOWLEDGEMENT

Financial support from the Istanbul Technical University Research Foundation is gratefully acknowledged by Ç. E.

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