Condensation of 4-Hydroxycoumarin with Aldehyde under Knoevenagel Conditions

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Summary: Reactions of 4-hydroxycoumarin(I) with aldehydes under Knoevenagel conditions initially form intermediates (3) which subsequently react with additional quantity of (1) or thiophenol to yield biscoumarins (2) or (benzo-4-hydroxy-2-oxo-2H-pyran-3-yl) (aryl) phenylthiomethane (4a,b,c) in excellent yields.

Introduction

Electrophilic substitution reactions of 4-hydroxycoumarin (1) at the 3-positions are well known [1-7]. However, reactions with aldehydes have been only scarcely reported [8,9].

During the course of our synthetic investigations we have found that the reactions of 4-hydroxycoumarin(1) with aldehyde under Knoevenagel conditions using piperidine and acetic acid in ethanol give excellent yields of biscoumarins (2). The results obtained are summarized in the Table. The reaction involves the initial formation of an highly reactive electrophilic species (3) via aldol condensation in the presence of piperidinium acetate [10] formed in the reaction mixture which subsequently condenses with additional quantity of 4-hydroxycoumarin(1) through Michael type reaction to form biscoumarin (2).

Attempsts to stop the reaction at the product (3) and to isolate it were unsuccessful. However, the trapping of the intermediate (3) with thiosphenol to form 3-substituted coumarins of type (4) was considered feasible. As anticipated the reactions of 4-hydroxycoumarin (1) with benzaldehyde or 2-nitrobenzaldehyde or 2-chlorobenzaldehyde and thiophenol (molar ratio 1:1:2) under Knoevenagel conditions afforded the products (4a,b,c) in good yields. These reactions provide a simple and convenient method not only for the synthesis of biscoumarins (2) but also for 3-substituted-4-hydroxycoumarins (4) which are of synthetic importance and possess physiological properties [11- 13].

Experimental

4-Hydroxycoumarin (Fluka) m.p. 211-213°C and aldehydes used were of technical grade, purified where necessary.

Infrared spectra were recorded on JASCO-IRA-1 spectrophotometer in Nujol. ^{1}H-NMR spectra were recorded on R-24B, 60-MH spectrometer (Hitachi) using tetramethyl silane as internal reference and are quoted in ppm (δ). Melting points were recorded on Gallenkamp melting point apparatus.

General procedure for the preparation of biscoumarin(2)

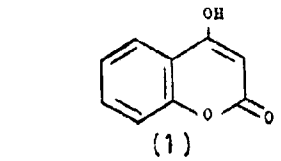
A solution of 4-hydroxycoumarin (1, 0.02 mol) in dry ethanol (15 ml) was gradually added to a solution of appropriate aldehyde (0.01 mol), acetic acid (0.5 ml) and piperidine (0.5 ml) in ethanol (15 ml). The reaction mixture was refluxed which on cooling gave solid product. The products were crystallized from ethanol-chloforom mixture. The reaction conditions, spectral data and analytical data are given in Table 1

(Benzo-4-hydroxy-2-oxo-2H-pyran-3-yl)phenylphenyl thiomethane (4a)

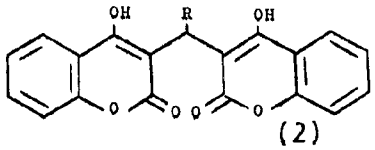
4-Hydroxycoumarin (1, 0.05 mol) in dry ethanol (20 ml) was added to a stirred solution of benzaldehyde (0.01 mol), thiophenol (0.02 mol), acetic acid (0.5 ml) and piperidine (0.5 ml) in ethanol (15 ml). The reaction mixture was vigorously stirred at ambient temperature for 6 hours. The

Table: 1. Physical and analytical data of compound (2a-h)

Compd	Reflux time (hours)	m.p.	Yield %	νmax cm^{-1} CO	-C=C-	Mol. formula	Analysis Calcd./Found C%	H%	N%	Cl	^{1}H-NMR
2a	3	229-230 (lit.m.p. 228-229) [9]	85	1700,1680	1600	$C_{25}H_{16}O_6$	72.82 72.70	3.82 3.92	-	-	5.8 (s, 1H), 6.6-7 (m, 14H, aromatic)
b	3.5	230-232	75	1700,1680	1600	$C_{25}H_{15}NO_8$	65.64 65.30	3.28 3.08	3.06 3.30	-	5.8 (s, 1H), 6.6-7.5 (m, 12H aromatic)
c	4	224-225	80	1700,1690	1610	$C_{25}H_{15}NO_8$	65.64 65.45	3.28 3.08	3.06 3.20		5.9 (s,1H), 6.8-8.7 (m, 12H aromatic).
d	3	234-235	85	1700,1680	1600	$C_{25}H_{15}ClO_6$	67.18 67.43	3.36 3.50	- -	7.95 7.88	5.8 (s, 1H), 6.8-8.75 (m, 12H aromatic).
e	4	144-145 (lit. m.p. 144-145) [9]	70	1710,1700	1610	$C_{21}H_{16}O_6$	69.23 69.50	4.4 4.5	- 6.5	- -	1.1 (t, 3H), 2.2 (q, 2H), 6.0 (s, 1H), 76 (m, 8H, aromatic).
f	3.5	123-124	80	1710, 1700	1600	$C_{22}H_{18}O_6$	69.84 69.85	4.74 4.85	- 6.5	- -	1.2 (t, 3H), 2.1 (q, 4H), 5.8 (s, 1H), 7.7 (m, 8H aromatic).
g	4	198-199 (lit. m.p. 199-200) [9]	75	1700,1690	1600	$C_{22}H_{18}O_6$	69.84 69.56	4.74 4.60	-	-	1.1 (d, 6H), 4.2 (m, 1H), 5.8 (s, 1H), 6.6-7.5 (m, 8H, aromatic).
h	4	240-241	80	1710,1690	1610	$C_{26}H_{18}O_6$	70.59 70.85	4.0 4.35	-	-	3.5 (s, 3H), 6.0 (s, 1H), 6.5-7.6 (m, 12H aromatic).

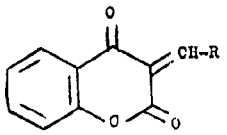


(1)

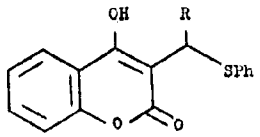


(2)

R-Ph(a), 2-NO_2Ph(b), 3-NO_2Ph(c),2-ClPh(d), Ch_3CH_3-(e),$CH_3(CH_2)_2$- (f),$(CH_3)_2$-CH-(g), 4-CH_3OPh(h).



(3)



(4)

R = Ph(a), 2-NO_2Ph(b),2-ClPh(c).

solid product was filtered out and washed with hexane-ethylacetate mixture (20:1) to remove unreacted thiophenol. Crystallisation from chloroform gave solid (80%) m.p. 157-158°C; ν_{max}. 1680, 1660 (CO), 1600 (-C=C-); ^{1}H-NMR: (d_6DMSO) δ 5.8 (s, 1H), 6.9-7.7 (m, 14H-aromatic) 9.5 (broad, 1H of -OH); calc for $C_{22}H_{16}SO_3$; C, 73.33; H, 4.44; S, 8.88. Found; C, 73.50, H, 4.60, S, 8.65.

The following compounds (4b, 4c) were prepared by the similar method.

Benzo-4-hydroxy-2-oxo-2H-pyran-3-yl (2-nitrophenyl) (phenyl-thiomethane (4b)

This compound was prepared in 85% yield by stirring the reaction mixture for 8 hours at room temperature. Crystallization from chloroform-ethanol gave solid m.p. 161-162°C; ν_{max}. 1680 (CO); 1600 (-C=C-); ^{1}H-NMR (d_6, DMSO); δ 5.8 (s, 1H); 7-7.5 (m, 13H aromatic), 9.8 (broad, 1H of -OH); calcd for $C_{22}H_{15}SNO_5$; C, 65.18; H, 3.70; S, 7.90; N, 3.45; Found C, 65.35; H, 3.6; S, 8.00; N, 3.35.

Benzo-4-hydroxy-2-oxo-2H-pyran-3-yl (2-chlorophenyl)phenyl-thiomethan (4c)

This compound was obtained in 70% yield by stirring the reaction mixture at room temperature for 6 hours. Crystallization from chloroform-ethanol mixture afforded white solid m.p. 180-182°C. ν_{max}. 1680 (CO), 1610 (-C=C-); ^{1}H-NMR (d_6, DMSO): δ 5.9 (s, 1H), 7.1-7.5 (m, 13H aromatic), 8.5 (broad, 1H, of -OH); calcd. for $C_{22}H_{15}SClO_3$: C, 66.92; H, 3.80; S, 8.11; Cl, 8.99. Found: C 66.65; H, 3.6; S, 8.4; Cl, 8.85.

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