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NUCLEOPHILIC ADDITION REACTIONS ON 3-CARBETHOXY- 5,7-DIMETHOXYCOUMARIN

M. A. Hassan ^a, S. A. Shiba ^a, N. S. Harb ^a, M. K. Abou-El-Regal ^a & S. A. El-Metwally ^a

^a Chemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt

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NUCLEOPHILIC ADDITION REACTIONS ON 3-CARBETHOXY- 5,7-DIMETHOXYCOUMARIN

M. A. Hassan,* S. A. Shiba, N. S. Harb,
M. K. Abou-El-Regal, and S. A. El-Metwally

Chemistry Department, Faculty of Science,
Ain Shams University, Cairo, Egypt

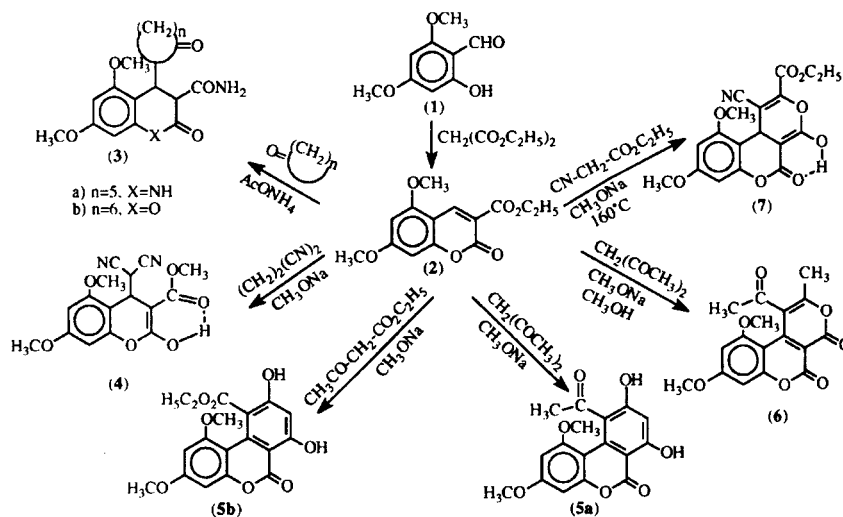
ABSTRACT

3-Carbethoxy-5,7-dimethoxycoumarin (**2**) underwent Michael addition and addition–cyclization of some active methylene compounds under different reaction conditions to give the adducts (**3–7**). Addition of phenylmagnesium bromide onto (**2**) yielded the tertiary alcohol (**8**). Addition of ammonia derivatives on (**2**) afforded the 3-carboxamides (**9a–c**) and azine (**10**). Furthermore, alcoholysis and hydrolysis yielded the coumarins (**11a–c**).

In continuation of our interest^{1–3} on the synthesis and reactions of novel coumarins, we report here the synthesis of 3-carbethoxy-5,7-dimethoxycoumarin (**2**) and its reactions with some nucleophilic reagents aiming to synthesis some new coumarin derivatives which might have enhanced biological activities.

*Corresponding author.

Knoevenagel condensation of 4,6-dimethoxy-2-hydroxy-benzaldehyde (1) with diethyl malonate in the presence of piperidine afforded the coumarin (2) in quantitative yield (Scheme 1).



Scheme 1.

Base catalyzed addition–cyclization^{4,5} of some active methylene compound, such as cycloalkanone, malononitrile, acetylacetone, ethyle aceto or cyanoacetate have been investigated under different reaction conditions.

Addition of cyclohexanone on coumarin (2) in the presence of ammonium acetate at 160°C underwent Michael addition with nucleophilic addition of ammonia to the carbonyl pyrone followed with ring closure and subsequent ammonolysis of the ester group to its corresponding amide to give 5,7-dimethoxy-4-(1'-oxo-cyclohexan-2'-yl)-1,2,3,4-tetrahydroquino- lin-2-one-3-carboxamide (3a) (Scheme 1), while cycloheptanone proceeds by normal Michael addition with ammonolysis of the ester group to give 5-7-dimethoxy-4-(1'-oxo-cycloheptanon-2'-yl)-3,4-dihydro-coumarin-3- carboxamide (3b) (Scheme 1).

Base-catalyzed addition of malononitrile to (2) in the presence of sodium methoxide in boiling methanol proceeds by normal Michael addition with transesterification⁶ to give 3-carbethoxy-4-dicyanomethyl- 3,4-dihydro-5,7-dimethoxycoumarin (4) (Scheme 1).

Treatment of coumarin (2) with acetylacetone and/or ethyl aceto- acetate in the presence of sodium methoxide at 160°C yielded 10-acetyl



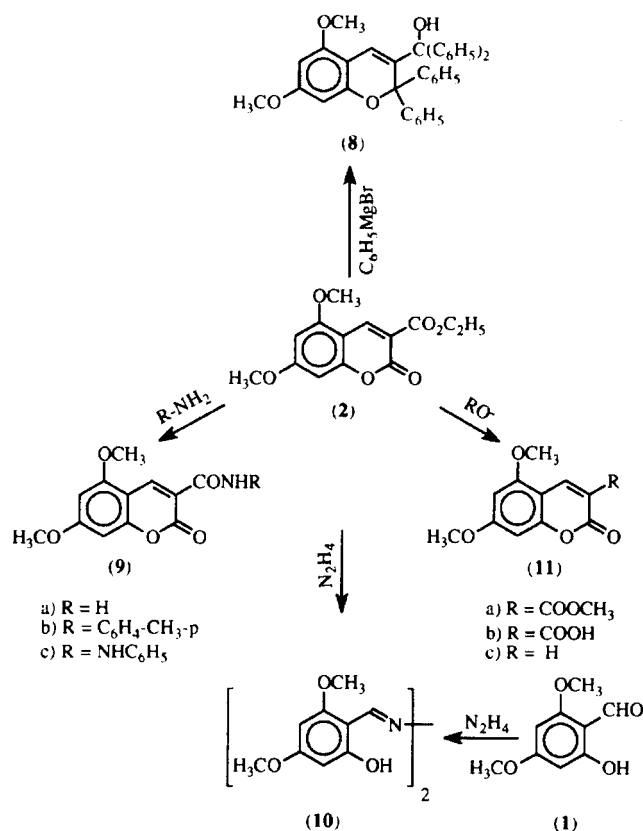
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and/or 10-carbethoxy-7,9-dihydroxy-1,3-dimethoxy-6-oxo-6H-dibenzo(b,d)-pyrans (**5a,5b**) respectively (Scheme 1). The reaction proceeds via base-catalyzed addition–cyclization with subsequent dehydrogenation under reaction conditions.

On the other hand, base-catalyzed addition–cyclization of acetylacetone on coumarin (**2**) in the presence of sodium methoxide in boiling methanol afforded acetyl-8,10-dimethoxy-2-methyl-4,5-dihydro-4,5-dioxopyrano[3,4-c]-benzopyran (**6**) (Scheme 1).

Furthermore, coumarin (**2**) underwent base-catalyzed addition–cyclization of ethyl cyanoacetate in the presence of sodium methoxide at 160°C to give 1-cyano-8,10-dimethoxy-2-ethoxy-4-hydroxy-5-oxo-4,4a,5,10a-tetrahydropyrano-[3,4-c]-benzopyran (**7**) (Scheme 1).



Scheme 2.



Table 1. Physical Data of Prepared Compounds (2–11)

Compound No.	M.P. (°C) Solvent	Color Yield (%)	Molecular Formula (M.Wt.)	Analysis, Calc./Found (%)		
				C	H	N
2	160 E	Yellow (96)	C ₁₄ H ₁₄ O ₆ (278.30)	60.43 60.39	5.07 5.05	—
8	190–3 E	Yellow (55)	C ₃₆ H ₃₀ O ₄ (526.63)	82.11 82.26	5.74 5.71	—
3a	225 E	Colorless (74)	C ₁₈ H ₂₂ N ₂ O ₅ (346.39)	62.41 62.41	6.40 6.54	8.09 8.18
3b	218–22 E	Colorless (68)	C ₁₉ H ₂₃ NO ₆ (361.38)	63.14 63.03	6.42 6.47	3.87 3.88
4	220 E	Yellow (33)	C ₁₆ H ₁₄ N ₂ O ₆ (330.30)	58.18 57.95	4.24 4.16	8.48 8.40
5a	252–4 A	Yellow (73)	C ₁₇ H ₁₄ O ₇ (330.26)	61.45 61.63	4.85 4.86	—
5b	225 A	Colorless (78)	C ₁₈ H ₁₆ O ₈ (360.29)	60.00 60.30	4.48 4.82	—
6	220–5 EA	Pale yellow (37)	C ₁₇ H ₁₄ O ₇ (330.27)	61.82 61.98	4.24 4.30	—
7	194–6 E	Orange (76)	C ₁₇ H ₁₅ NO ₇ (345.30)	59.13 59.23	4.38 4.36	4.06 3.93
9a	235–7 A	Yellow (64)	C ₁₂ H ₁₁ NO ₅ (249.22)	57.83 57.91	4.45 4.53	5.62 5.70
9b	243 A	Yellow (82)	C ₁₉ H ₁₇ NO ₅ (339.35)	67.25 67.36	5.05 5.19	4.13 4.24
9c	222–4 EA	Brown (50)	C ₁₈ H ₁₆ N ₂ O ₅ (340.34)	63.51 63.50	4.73 4.84	8.23 8.33
10	280–2 A	Yellow (77)	C ₁₈ H ₂₀ N ₂ O ₆ (360.37)	59.95 60.11	5.59 5.64	7.78 8.02
11a	188–90 EA	Yellow (63)	C ₁₃ H ₁₂ O ₆ (264.20)	59.09 59.18	4.58 4.77	—
11b	235–7 A	Yellow (88)	C ₁₂ H ₁₀ O ₆ (250.19)	57.60 57.44	4.03 3.93	—
11c	141–3 M	Pale yellow (57)	C ₁₁ H ₁₀ O ₄ (206.12)	64.07 64.19	4.88 5.07	—

A—acetic acid; E—ethanol; EA—ethylacetate; M—methanol.



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Treatment of coumarin (**2**) with excess phenylmagnesium bromide (1 : 8) afforded (5,7-dimethoxy-2,2-diphenylbenzo-2H-pyran-3-yl)diphenylcarbinol (**8**) (Scheme 2). The reaction proceeds with nucleophilic addition of Grignard reagent on both carbonyl groups of ester and lactone to give the ditertiary alcohols followed by ring closure to give (**8**).

Heating of (**2**) with ammonium acetate at 160°C and/or treatment of it with *p*-toluidine in boiling ethanol yielded the corresponding 3-carboxamide derivatives (**9a,b**) respectively (Scheme 2).

Reaction of coumarin (**2**) with hydrazine hydrate or phenylhydrazine in boiling ethanol gave 2-hydroxy-4,6-dimethoxybenzalazine⁷ (**10**) and/or 5,7-dimethoxy-3-phenylcarbohydrazide coumarin (**9**), respectively (Scheme 2). Formation of azine (**10**) may be attributable for the formation of 2-hydroxy-4,6-dimethoxy-benzaldehyde (**1**) as an intermediate product, which is condensed with hydrazine hydrate giving (**10**), which is proved authentically⁷ giving same product.

With oxygen nucleophiles, like, methoxide or hydroxide, coumarin (**2**) underwent transesterifications,⁶ hydrolysis of ester group and/or hydrolysis of ester group with decarboxylation depending on the reaction conditions to give the corresponding coumarins (**11a-c**) respectively (Scheme 2).

EXPERIMENTAL

Melting points reported are uncorrected. IR spectra were recorded on Pye-Unicam SP 2000 Spectrophotometer, Perkin-Elmer 983 Spectrophotometer and Maltson-1000 Series FT-IR Spectrophotometer using KBr Wafer technique. The ¹H- and ¹³C-NMR spectra were determined on Gimini 200 MHz, and Bruker AC 200, AMX 300 and DRX 500, using TMS as internal standard. ¹³C-signals assigned on the basis of the DEPT 135/90 spectra. The chemical shifts are recorded in δ -scale in ppm. The mass spectra were measured by AMD 604 Spectrophotometer using single focusing mass spectrophotometer with direct inlet at Beam energy 70 eV. Elemental analysis were estimated by Perkin-Elmer 2400 CHN analyzer and Carlo-Erba 1106 CHN analyzer.

3-Carbethoxy-5,7-dimethoxycoumarin (**2**)

A mixture of dimethoxysalicylaldehyde (**1**) (3.6 g, 0.02 mol), diethyl malonat (3.8 ml, 0.02 mol) and piperidine (0.5 ml) was heated on water-bath for 1 h. The mixture was left at room temperature for 3 h, and then washed with cold hydrochloric acid (3 \times 30 ml 10%). The solid was filtered,



Table 2. Spectral Data of Prepared Compounds (2–11)

Compound (Solvent)	IR (cm ⁻¹)	¹ H-NMR, δ (ppm)	<i>m/e</i> : Ms. (Abundance %)
2	1710, 1780 (V _{C=O})	(CDCl ₃), 1.40 (t, 3H, CH ₃), 3.88 (s, 3H, OCH ₃), 3.93 (s, 3H, OCH ₃), 4.38 (q, 2H, CH ₂), 6.26 (d, 1H, Ar-H), 6.38 (d, 1H, Ar-H), 8.79 (s, 1H, C ₄ H).	—
8	3420 (V _{OH})	(CDCl ₃), 3.25 (s, 3H, OCH ₃), 3.74 (s, 3H, OCH ₃), 5.64 (d, 1H, Ar-H), 6.15 (d, 1H, Ar-H), 6.22 (s, 1H, OH), 6.92–7.77 (m, 21H, 4 × C ₆ H ₅ and C ₄ H).	526 (M ⁺ , 52), 421 (23), 359 (100), 267 (45), 167 (21), 105 (74), 91 (44).
(3a)	3200–3510 (V _{NH}) 1670 (V _{C=O})	(CDCl ₃), 1.13–2.06 (m, 10H, cyclohex. H + C ₄ H), 2.61 (d, 1H, C ₃ H), 3.12 (s _{br} , 1H, NH), 3.75 (s, 3H, OCH ₃), 3.77 (s, 3H, OCH ₃), 5.99 (d, 1H, Ar-H), 6.07 (d, 1H, Ar-H), 6.26 (s _{br} , 1H, NH), 6.49 (s _{br} , 1H, NH).	346 (M ⁺ , 5), 304 (20), 303 (100), 207 (86), 150 (59).
(3b)	3200–3400 (V _{NH}) 1730, 1670 (V _{C=O})	(CDCl ₃), 1.22–2.13 (m, 11H, cyclohept. H), 2.58 (m, 1H, C ₄ H), 3.03 (s _{br} , 2H, NH ₂), 3.74 (s, 3H, OCH ₃), 3.76 (s, 3H, OCH ₃), 3.90 (d, 1H, C ₃ H), 6.00 (d, 1H, Ar-H), 6.06 (d, 1H, Ar-H).	361 (M ⁺ , 6), 317 (100), 300 (14), 249 (73), 207 (52), 164 (71).
4	2200 (V _{C≡N}) 1690, 1745 (V _{C=O})	(CDCl ₃), 3.92 (s, 3H, OCH ₃), 3.94 (s, 3H, OCH ₃), 3.96 (s, 3H, CH ₃), 4.03 (d, 1H, C ₄ H), 4.18 (d, 1H, CH-CN), 6.37 (d, 1H, Ar-H), 6.52 (d, 1H, Ar-H), 9.17 (s, H, OH).	330 (M ⁺ , 4), 250 (100), 206 (42), 178 (35).
5a	3420 (V _{OH}) 1670 (V _{C=O}) (chelated)	—	330 (M ⁺ , 69), 315 (100), 300 (20), 271 (8).
5b	3485 (br, V _{OH}) 1670 (V _{C=O}) (chelated)	(CDCl ₃), 1.49 (t, 3H, CH ₃), 3.86 (s, 3H, OCH ₃), 3.89 (s, 3H, OCH ₃), 4.49 (q, 2H, CH ₂), 6.40 (d, 1H, Ar-H), 6.44 (d, 2H, Ar-H), 7.87 (s, 1H, Ar-H).	—



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6	1750, 1690 ($\nu_{\text{C=O}}$)	—	330 (M^+ , 16), 315 (24), 250 (100), 206 (53), 178 (46), 163 (26).
7	3480 (ν_{OH}), 2220 ($\nu_{\text{C=N}}$), 1740 ($\nu_{\text{C=O}}$)	(CDCl_3), 1.39 (t, 3H, CH_3), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.94 (s, 1H, CH), 4.39 (q, 2H, CH_2), 6.29 (d, 1H, Ar-H), 6.42 (d, 2H, Ar-H), 8.5 (s, 1H, OH).	—
9a	3420, 3180 ($\nu_{\text{N-H}}$), 1730, 1650 ($\nu_{\text{C=O}}$)	(CDCl_3), 3.89 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.30 (d, 1H, Ar-H), 6.44 (d, 1H, Ar-H), 6.79 (s_{br} , 1H, NH), 8.58 (s_{br} , 1H, NH), 9.13 (s, 1H, $\text{C}_4\text{-H}$).	249 (M^+ , 100), 233 (62), 231 (36), 221 (15), 206 (16), 203 (19).
9b	3280 ($\nu_{\text{N-H}}$), 1710, 1650 ($\nu_{\text{C=O}}$)	(DMSO), 2.28 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.63 (d, 1H, Ar-H), 6.78 (d, 1H, Ar-H), 7.19 (d, 2H, Ar-H), 7.60 (d, 2H, Ar-H), 8.86 (s, 1H, $\text{C}_4\text{-H}$), 10.55 (s, 1H, NH).	—
9c	3320, 3280 ($\nu_{\text{N-H}}$), 1720, 1665 ($\nu_{\text{C=O}}$)	(CDCl_3), 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.32 (d, 1H, Ar-H), 6.48 (d, 1H, Ar-H), 6.47 (d, 1H, NH), 6.9–7.21 (m, 5H, C_6H_5), 9.14 (s, 1H, $\text{C}_4\text{-H}$), 10.27 (d, 1H, NH).	340 (M^+ , 31), 233 (91), 45 (59), 43 (100).
10	3450 (ν_{OH})	(DMSO), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.16–6.17 (m, 3H, Ar-H + OH), 8.93 (s, 1H, CH=).	360 (M^+ , 100), 343 (11), 197 (28), 180 (31), 137 (15).
11a	1770, 1720 ($\nu_{\text{C=O}}$)	(CDCl_3), 3.87 (s, 3H, CH_3), 3.91 (s, 6H, $2 \times \text{OCH}_3$), 6.26 (d, 1H, Ar-H), 6.39 (d, 1H, Ar-H), 8.84 (s, 1H, $\text{C}_4\text{-H}$).	—
11b	3560 (ν_{OH}), 1745, 1685 ($\nu_{\text{C=O}}$)	(CDCl_3), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.37 (d, 1H, Ar-H), 6.51 (d, 2H, Ar-H), 9.17 (s, 1H, $\text{C}_4\text{-H}$).	250 (M^+ , 100), 233 (8), 222 (8), 206 (59), 178 (53), 163 (32).
11c	1720 ($\nu_{\text{C=O}}$)	(CDCl_3), 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.16 (d, 1H, $\text{C}_3\text{-H}$), 6.28 (d, 1H, Ar-H), and 6.41 (d, 1H, Ar-H), 7.96 (d, 1H, $\text{C}_4\text{-H}$).	206 (M^+ , 100), 178 (74), 163 (41), 135 (19).



washed with sodium bicarbonate (3×50 ml, 10%) and finally with water (3×30 ml), dried and crystallized to give (2).

**Addition of Cyclohexanone and Cycloheptanone to Coumarin (2)
in the Presence of Ammonium Acetate. Formation of (3a,b)**

A mixture of dimethoxycoumarin (2) (1.4 g, 0.005 mol), ammonium acetate (5.0 g, 0.06 mol), cyclohexanone or cycloheptanone (0.006 mol) was heated at 160°C for 5 h, then triturated with hot water (30 ml). The solid was filtered, dried and crystallized to give (3a,b).

**Addition of Malononitrile and Acetylacetone in the Presence of
Sodium Methoxide in Boiling Methanol. Formation of (4,6)**

General procedure: To a solution of sodium methoxide (0.5 g, 0.01 mol) in absolute methanol (30 ml), malononitrile and/or acetylacetone (0.006 mol) was added and the solution was refluxed for 15 min, then dimethoxycoumarin (2) (1.40 g, 0.005 mol) was added and the reaction mixture was refluxed for 4 h. The solid product was filtered, washed with cold hydrochloric acid (2×30 ml, 10%), and water (2×30 ml), dried and crystallized to give (4) and (6) respectively.

**Addition of Acetylacetone, Ethyl Acetoacetate and
Ethyl Cyano-Acetate to (2) in the Presence of
Sodium Methoxide at 160°C . Formation of (5a,b, and 7)**

General procedure: A mixture of (2) (1.4 g, 0.005 mol), active methylene compounds (0.006 mol) and sodium methoxide (0.5 g, 0.01 mol) was heated without solvent at 160°C for 5 h. The reaction mixture was cooled triturated with cold hydrochloric acid (30 ml, 10%). The solid was filtered, washed with water (2×20 ml), dried and crystallized to give (5a,b) and (7) respectively.

**5,7-Dimethoxy-2,2-diphenyl-3-(diphenyl,hydroxy)
Methyl Coumarin (8)**

To a solution of 3-carbethoxy-5,7-dimethoxycoumarin (2) (0.2 g, 0.001 mol) in dry THF (100 ml) phenylmagnesium bromide (0.008 mol in



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30 ml dry ether) was added dropwise with stirring. After complete addition the reaction mixture was refluxed for 24 h. After cooling the reaction mixture was extracted with saturated solution of ammonium chloride (2×30 ml) and then water (2×30 ml). The ethereal layer was separated and dried over anhydrous sodium sulphate. Ether was then evaporated and the solid product obtained was crystallized to give (8).

3-Carboxamide-5,7-dimethoxycoumarin (9a)

In dry RB flask, a mixture of carbethoxycoumarin (2) (1.4 g, 0.005 mol) and ammonium acetate (5 g, 0.06 mol) was heated at 160°C for 4 h. The reaction mixture was then cooled and the solid product was filtered, washed with water (2×30 ml), dried, and finally crystallized from appropriate solvent to give (9a).

3-(*N-p*-Tolyl)carboxamide-5,7-dimethoxycoumarin (9b)

A mixture of carbethoxycoumarin (2) (1.4 g, 0.005 mol) and *p*-toluidine (1.10 g, 0.01 mol) in absolute ethanol (40 ml) was boiled under reflux for 5 h. The crystalline product was filtered and crystallized from the appropriate solvent to give (9b).

2-Hydroxy-4,6-dimethoxybenzalazine (10) and/or 5,7-Dimethoxycoumarin-3-phenylhydrazide (9c)

A mixture of carbethoxycoumarin (2) (1.4 g, 0.005 mol) and hydrazine hydrate or phenyl hydrazine (0.01 mol) in absolute ethanol (40 ml) was boiled under reflux for 5 h, then the reaction mixture was left to cool. The crystalline product formed on cooling was filtered and crystallized to give (10) and (9c) respectively.

5,7-Dimethoxy-3-carbomethoxycoumarin (11a)

A mixture of dimethoxycoumarin (2) (1.40 g, 0.005 mol) in sodium methoxide solution (0.5 g, 0.12 mol, in 30 ml methanol) was boiled under reflux for 4 h to precipitate a yellow crystals after cooling. The product was filtered and crystallized from appropriate solvent to give (11a).



Synthesis of 5,7-Dimethoxycoumarin (11c)

A mixture of dimethoxycoumarin (**2**) (1.40 g, 0.005 mol) and sodium hydroxide (0.5 g, 0.13 mol) was heated at 160°C for 4 h. The reaction mixture was cooled, acidified with dilute hydrochloric acid (10%). The solid separated was filtered, washed with water (2 × 30 ml), dried and crystallized from appropriate solvent to give (**11c**).

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