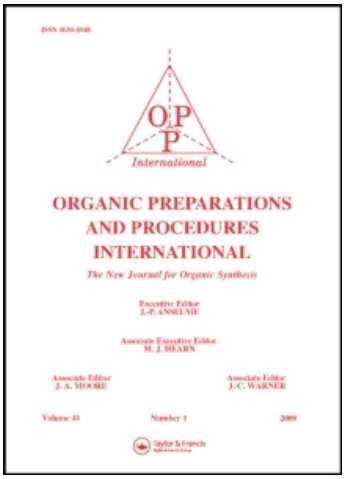

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FACILE SYNTHESIS OF 3-CHLOROCOUMARINS

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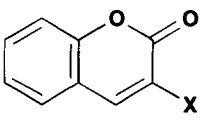
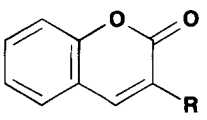
3-Substituted coumarins constitute an important class of coumarins. Apart from their natural occurrence,[1] several 3-substituted coumarins are known to possess anthelmintic, hypnotic and insecticidal properties.[2] 3-Halocoumarins[3] (**1**) also possess insecticidal and fungicidal properties and are useful intermediates for the synthesis of various compounds[3] such as **2** and some furocoumarins[4] and isocoumestans.[5] Several methods have been reported for the synthesis of 3-chlorocoumarins e. g. the chlorination[3] of coumarins, the von Pechmann condensation[6] of ethyl 2-chloroacetoacetate with

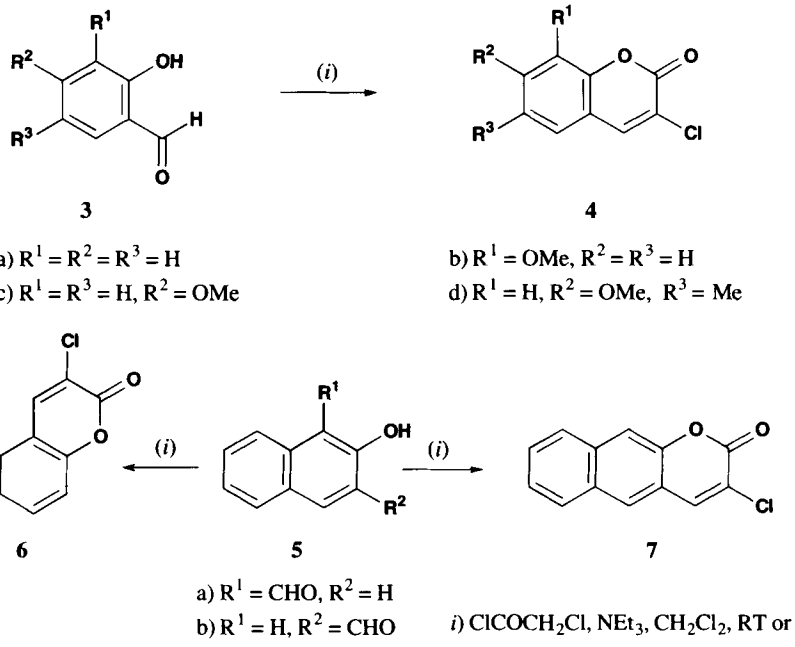


1 X = Cl, Br



2 R = CHO, Ar

phenol and the condensation[7] of sodium phenoxide with trichlorocrotonaldehyde. Reaction of 2-hydroxybenzaldehydes with α–chlorocarbethoxymethylene triphenylphosphorane[8] or the Vilsmeier-Haack complex[5] prepared from $POCl_3$ and N,N-diethylchloroacetamide also provide 3-chloro-coumarins. The cycloaddition of chloroketene to α-methoxymethylenecyclohexanones as the key step has also been reported for 3-chlorocoumarins. Most of these methods either involve multistep sequences[4-5] or provide the final product in low yield.[5-9] This paper reports a convenient method for the synthesis of 3-chlorocoumarins (**4a-d**) and 3-chlorobenzocoumarins (**6** and **7**).



3 **4**

a) $R^1 = R^2 = R^3 = H$ b) R^1 = OMe, $R^2 = R^3 = H$

c) $R^1 = R^3 = H$, R^2 = OMe d) $R^1 = H$, R^2 = OMe, R^3 = Me

6 **5** **7**

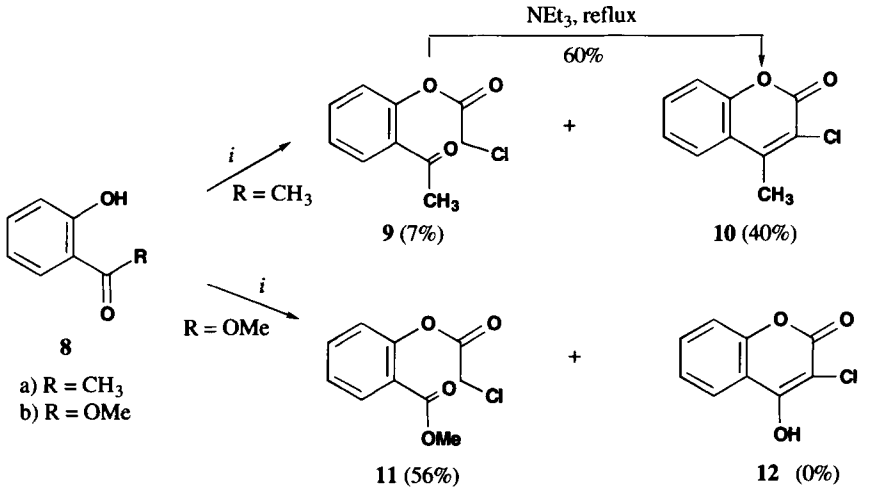
a) R^1 = CHO, $R^2 = H$

b) $R^1 = H$, R^2 = CHO *i*) $ClCOCH_2Cl$, NEt_3, CH_2Cl_2, RT or reflux

Scheme 1

In our approach, salicylaldehyde (**3a**) was treated with chloroacetyl chloride in the presence of triethylamine in methylene chloride at room temperature for 24 hrs to give 3-chlorocoumarin (**4a**) in 45% yield. Similar reaction of benzaldehydes (**3b-d**) and naphthaldehydes (**5a** and **5b**) provided 3-chlorocoumarins (**4b-d**) and 3-chlorobenzocoumarins (**6** and **7**) in 20-70% yield. When the reaction was carried out at reflux, the coumarins (**4a-d, 6** and **7**) were obtained in 40-90% yield, except for **4d** which is obtained in only 37% yield.These results led us to synthesize 4-substituted 3-chloro-coumarins (**10** and **12**).

2-Hydroxyacetophenone (**8a**) at reflux provided coumarin **10** in 40% yield along with minor amount (7%) of **9** which upon reflux with triethylamine in methylene chloride gave **10** in 60% yield. On the other hand, methyl salicylate (**8b**) under similar conditions gave **11** (56%) and not the desired 3-chlorocoumarin **12**; **11** could not be converted to 3-chloro-4-hydroxycoumarin (**12**) under a variety of conditions. The structures of all compounds were established on the basis of their analytical and spectral data.



i) $ClCOCH_2Cl$, NEt_3, CH_2Cl_2, RT or reflux

Scheme 2

The present method is simple and does not require preformed coumarins. It provides 3-chlorocoumarins from 2-hydroxybenzaldehydes in better yields than previously reported (Tables 1 and 2).[5-9]

EXPERIMENTAL SECTION

All mps are uncorrected. IR spectra were recorded in nujol on a Perkin Elmer-337 IR spectrometer and ^1H NMR in $CDCl_3$ solution on a Jeol FX 90 Q instrument. Chemical shifts are expressed in δ (ppm) downfield from TMS as an internal standard and coupling constant in Hertz.

General Procedure for 3-Chlorocoumarins (4a-d, 6, 7 and 10). - To a stirred and cooled (0°) solution of 2-hydroxyaldehyde or ketone (**3a-d, 5a-b, 8a,** 3.75 mmoles) in methylene chloride (4 mL) was added triethylamine (8.6 mmoles) and a solution of chloroacetyl chloride (5.02 mmoles) in methylene chloride (2 mL). The mixture was stirred at room temperature for 30 min. and then heated to reflux for 6-8 hrs. (monitored by TLC). The solvent was removed under reduced pressure and the dark brown oily residue was chromatographed over silica gel (100-200 mesh) using *n*-hexane as an eluent to give some amount of starting compound and 3-chlorocoumarins (**4a-d, 6, 7** and 10) as crystalline products.

The yields reported are based on recovered starting compound. All 3-chlorocoumarins (**4a-d, 6, 7** and **10**) were recrystallized from *n*-hexane. Coumarins **4** and **10** were obtained as white crystalline products while **6** and **7** were slightly yellow in color.

TABLE 1. Yields, mp, spectral data and Lliterature Comparison of **4**.

Compd	Yield (%)	mp. (°C)	Lit. mp. (°C)	IR (cm^{-1})	^{1}HNMR Data (δ)	Lit. Yield (no of steps)
4a	73	121	121[5]	1730 1740	7.3 - 7.7 (m, 4H, Ar-H), 7.9 (s, 1H, C_4-H).	26(2)[5], 51(3)[7] 20(2)[8],30(3)[9]
4b	67	153	153[5]	1735	3.94 (s, 3H, - OCH_3), 6.90-7.32 (m, 3H, Ar-H), 7.86 (s, 1H, C_4-H).	35(2)[5]
4c	40	163	164[5]	1735	3.9 (s,3H,-OCH_3), 6.80 (bs, 1H, C_8-H), 7.02 (dd, J = 9 and 2 Hz, 1H, C_6-H), 7.45 (d, J = 9 Hz,1H, C_5-H), 7.9 (s, 1H, C_4-H).	30(2)[5]
4d	37	179	a	1725	2.28 (s, 3H, -CH_3), 3.92 (s, 3H, - OCH_3), 6.88 (s, 1H, C_8-H), 7.43 (s, 1H· C_5-H), 7.91 (s, 1H, C_4-H).	—

a) *Anal.* Calcd. for $C_{11}H_9ClO_3$: C, 58.79; H, 4.00. Found : C, 58.58; H, 4.18

TABLE 2. Yields, mp, spectral data and Literature comparison of **6**, **7**, **9** and **10**.

Compd	Yield (%)	mp. (°C)	Lit. mp. (°C)	IR (cm^{-1})	^{1}HNMR Data (δ)	Lit. Yield (no of steps)
6	91	164-165	166-167[5]	1730	7.58 - 8.42 (m, 6H, Ar-H) 8.81 (s, 1H, C_4-H).	24(2)[5], 61 (3)[7]
7	87	192	b	1730	7.63 - 8.3 (m,7H, Ar-H).	—
9	7	77	c	1765 1682	2.60 (s,3H, -CH_3), 4.48 (s, 2H, -CH_2-), 7.22 -7.77 (m,3H, Ar-H), 8.02 (dd, J =9 and 2 Hz,1H, Ar-H).	—
10	40	142	d	1730	2.63 (s, 3H, -CH_3), 7.42 (m, 4H, Ar-H).	—

b) *Anal.* Calcd. for $C_{13}H_7ClO_2$: C, 67.67; H, 3.03. Found : C, 67.44; H,3.29. c) *Anal.* Calcd. for $C_{10}H_9ClO_3$: C, 56.47; H, 4.23 .Found : C, 56.33 ; H, 4.40. d) *Anal.* Calcd. for $C_{10}H_7ClO_2$: C, 61.69 ; H, 3.59 .Found : C,61.48; H, 3.79.

Conversion of 9 into 3-Chloro-4-methylcoumarin (10).- Triethylamine (0.57g, 0.56 mmoles) was added to a solution of ester (**9**, 0.40g, 1.80 mmoles) in methylene chloride and the reaction mixture

was heated to reflux for 4 hrs. The solvent was removed and the light brown oily residue obtained was chromatographed over silica gel (100-200 mesh) using *n*-hexane as an eluent to yield **10** (0.22g, 60%), mp. 142°, identical (mp., TLC, IR and ^{1}H NMR) with authentic sample obtained above.

Preparation of 3-Chloro-4-methylcoumarin (10) from 2-Hydroxy-acetophenone (8a). - To a solution of **8a** (0.510g, 3.75 mmoles) in methylene chloride (4 mL) was added triethylamine (1.21g, 12 mmoles) and a solution of chloroacetyl chloride (0.565g, 5.02 mmoles) in methylene chloride (2mL). The reaction mixture was stirred at room temperature for 30 min. and then heated to reflux for 12 hrs. Work-up as described in general procedure gave coumarin **10** (0.145g, 42% on the basis of recovered starting compound.), mp.142° identical with authentic sample.

Preparation of Ester (11). - A solution of methyl salicylate **8b** (0.570g, 3.75 mmoles) in methylene chloride (4 mL) was reacted with a solution of chloroacetyl chloride (0.567g, 5.02 mmoles) in methylene chloride (2 mL) in presence of triethylamine (0.871g, 8.6 mmoles) at reflux temperature for 8 hrs. The work-up as described above provided white crystals of ester **11** (0.290g, 56% on the basis of recovered starting compound), mp. 67°. IR: 1778, 1722 cm^{-1}. ^{1}H NMR : δ 3.94 (s, 3H, –OCH_3), 4.54 (s, 2H, –CH_2–), 7.31-7.94 (m, 3H, Ar-H), 8.31 (dd, J = 9 and 2 Hz, 1H, Ar-H).

Anal. Calcd. for $C_{10}H_9ClO_4$: C, 52.51; H, 3.93. Found : C, 52.73; H, 3.93

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