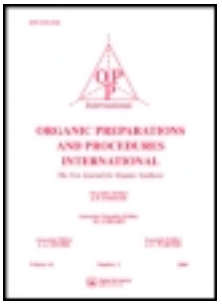

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EFFICIENT PREPARATION OF 4-SUBSTITUTED-6-ACYL-7-METHOXYCOUMARINS

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EFFICIENT PREPARATION OF 4-SUBSTITUTED-6-ACYL-7-METHOXYCOUMARINS

Submitted by M. V. Paradkar*, M. S. Kulkarni, S. A. Kulkarni and H. M. Godbole
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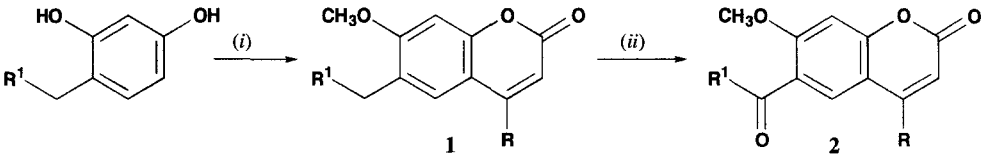
The acyl group of 6-and 8-acylcoumarins is an important feature in naturally occurring coumarins.[1-3] Their synthesis involves either the Pechmann condensation[4,5] or the Fries rearrangement[6] which, usually provides a mixture of products in which the 6-acylated product is formed in low yield. The yields of 6-acylated products are improved by the use of the photoFries rearrangement[7] of 7-acyloxycoumarins. However, this modification was successful only for acyl groups containing two or three carbons and failed with higher members. Recently Harwood *et al.*[8,9] reported another approach for the 6-acyl-7-methoxycoumarins which again involves the Fries rearrangement of methyl 2-acyloxy-4-methoxydihydrocinnamate, an open chain analogue of the dihydrocoumarin ring system. This paper describes a general and convenient synthesis of 6-acyl-7-methoxycoumarins bearing either a phenyl or an alkyl substituent at the 4-position.

The key step involves a facile and efficient conversion of 6-alkyl-4-phenylcoumarins into corresponding 6-acylcoumarins using ceric ammonium nitrate (CAN). The starting alkylcoumarins



a) R = Ph, R^1 = Me b) R = Ph, R^1 = $(CH_2)_2Me$ c) R = Ph, R^1 = CH_2CHMe_2
d) R = Me, R^1 = Me e) R = Me, R^1 = CH_2Me f) R = Me, R^1 = $(CH_2)_2Me$
g) R = Me, R^1 = CH_2CHMe_2 h) R = $(CH_2)_2Me$, R^1 = Me (**1h** was obtained by a different route (see text)

(*i*) $RCOCH_2CO_2Et$, H^+ then Me_2SO_4, K_2CO_3, acetone. (*ii*) CAN

(**1a-g**) were obtained by reaction of 4-alkylresorcinols with the appropriate β-ketoesters followed by methylation while coumarin **1h** was obtained by treatment of 1-[2'-hydroxy-4'-methoxy-5'-ethyl-phenyl]butane-l-one with carbethoxymethylene triphenylphosphorane. The starting ketone which to our knowledge is so far unreported, was obtained by acylation of 4-ethyl-resorcinol with butyric acid in presence of $ZnCl_2/POCl_3$ followed by methylation of the non-chelated hydroxy group. This methodology was extended for the 4,6-dialkylcoumarins bearing two oxidizable groups. Oxidation of 6-ethyl-7-methoxy-4-methylcoumarin (**1d**) with CAN afforded a compound whose NMR exhibited two singlets at δ 2.46 and 2.69 for the two methyl groups clearly indicating that the benzylic methyl-ene underwent oxidation while the allylic methyl group remained intact.

EXPERIMENTAL SECTION

All the melting points are uncorrected. ^{1}H NMR spectra were recorded on a Jeol FX 90 Q instrument in $CDCl_3$. IR spectra were determined on Perkin Elmer FT IR 1600 instrument as nujol mulls. Chemical shifts are expressed in δ downfield from TMS as an internal standard and coupling constants in Hz.

General Procedure for the Preparation of 6-Alkylcoumarins (1a-g).- A solution of 4-alkylresorcinol (0.05 mole) in ethyl benzoylacetate or ethyl acetoacetate (0.05 mole) was added dropwise to 80% sulfuric acid (25 mL) cooled to 0° with stirring. After the addition was complete, the reaction mixture was left overnight. It was then poured over crushed ice to give a solid, the corresponding crude 6-alkyl-7-hydroxycoumarin (60-70%).

Dimethyl sulfate (0.012 mole) and anhydrous potassium carbonate (0.015 mole) were added to a solution of the crude 7-hydroxycoumarin (0.01 mole) in distilled acetone (35 mL). The mixture was refluxed for 7 hrs. The reaction mixture was filtered and the residue washed with acetone. The combined filtrate was concentrated to provide a crude solid which was chromatographed on silica gel using hexane as eluent. The solid was crystallized from hexane to yield the pure **1a-g** (60-80%).

TABLE 1. *Mps, Yields, IR and Elemental Analyses*

Compd.	mp. (°C)	Yield (%)	IR (cm^{-1})	Elemental Analyses (Found) C	H
1a	135	70	1740	77.20 (77.00)	5.76 (5.81)
1b	114	67	1740	77.92 (77.69)	6.47 (6.40)
1c	101	71	1739	78.23 (78.10)	6.87 (6.80)
1d	160, lit.[10] 162-163	72	1740	71.54(71.28)	6.47(6.15)
1e	168, lit.[5] 172.4-172.8	94	1740	72.39 (72.30)	6.97 (6.87)
1f	172, lit.[5] 172.3	80	1740	73.14 (73.20)	7.37 (7.26)
1g	168	73	1740	73.82 (73.61)	7.74 (7.70)
1h	Liquid	70	1740	73.14 (73.00)	7.37 (7.30)
2a	201	57	1690, 1738	73.46 (73.39)	4.79 (4.82)
2b	85	57	1690, 1736	74.51 (74.48)	5.62 (5.58)
2c	110	60	1690. 1739	74.97 (74.89)	5.99 (5.92)
2d	180, lit.[11] 209-210	86	1689, 1738	67.26(67.12)	5.21 (5.04)
2e	172, lit.[12] 180	94	1690, 1738	68.28 (68.10)	5.73 (5.86)
2f	150	65	1688, 1738	69.21 (69.16)	6.20 (6.12)
2g	134-136	70	1689, 1738	70.05 (69.82)	6.61 (6.52)
2h	89	67	1690. 1738	69.21 (69.18)	6.20 (6.24)

6-Ethyl-7-methoxy-4-propylcoumarin (1h).- A solution of 1-[2'-hydroxy-4'-methoxy-5'-ethylphenyl]butane-1-one (0.88g, 0.004 mole), carbethoxy methylenetriphenylphosphorane (2.62g, 0.006 mole) and xylene (25 mL) was refluxed for 48 hrs. Removal of the solvent under vacuum provided a

dark colored solid mass which was chromatographed on silica gel using hexane as eluent. The initial fractions on concentration provided the desired coumarin (**1h**) as a pale yellow oil.

TABLE 2. *^{1}H NMR Spectra*

Cmpd	^{1}H NMR (δ)
1a	1.05, t, 3H, (J = 8.0), -C<u>H</u>$_3$; 2.62, q, 2H, (J = 8.0), -C<u>H</u>$_2$-; 4.05, s, 3H, -OC<u>H</u>$_3$; 6.45, s, 1H, H-3; 7.17, s, 1H, H-8; 7.37, s, 1H, H-5; 7.74-8.00, bs, 5H, Ar<u>H</u>.
1b	0.85, t. 3H, (J = 8.0), -C<u>H</u>$_3$; 1.05-1.54, m, 4H, 2x-C<u>H</u>$_2$; 2.54, t, 2H, (J = 8.0), -C<u>H</u>$_2$Ar; 3.97, s, 3H, -OC<u>H</u>$_3$; 6.37, s, 1H, H-3; 7.02, s, 1H, H-8; 7.37, s, 1H, H-5; 7.50-7.85, bs, 5H, Ar<u>H</u>.
1c	0.88, d, 6H, (J = 5.0), -C<u>H</u>(Me)$_2$; 1.14-1.51, m, 3H, -CH$_2$, -C<u>H</u>(Me)$_2$; 2.6, t, 2H, (J = 8.0). -C<u>H</u>$_2$Ar; 3.97, s, 3H, -OC<u>H</u>$_3$; 6.37, s, 1H, H-3; 7.02, s, 1H, H-8; 7.37, s, 1H, H-5; 7.62-7.80. bs. 5H, Ar<u>H</u>.
1d	1.14, t, 3H, (J = 8.0), -CH$_2$-C<u>H</u>$_3$; 2.34, s, 3H, -C<u>H</u>$_3$; 2.62, q, 2H, (J = 8.0), -C<u>H</u>$_2$-CH$_3$; 3.88, s, 3H, -OC<u>H</u>$_3$; 6.17, s, 1H, H-3; 6.82, s, 1H, H-8; 7.37, s, 1H, H-5.
1e	0.91, t, 3H, (J = 8.0), -C<u>H</u>$_3$; 1.36-1.77, m, 2H, -C<u>H</u>$_2$-CH$_3$; 2.39, s, 3H, -C<u>H</u>$_3$; 2.63, t. 2H, (J = 8.0). -C<u>H</u>$_2$Ar; 3.86, s, 3H, -OC<u>H</u>$_3$; 6.17, s, 1H, H-3; 680, s, 1H, H-8; 7.37, s, 1H, H-5.
1f	0.91, t, 3H, (J = 8.0), -CH$_2$-C<u>H</u>$_3$; 1.2-1.74, m, 4H, 2x-C<u>H</u>$_2$; 2.42, s, 3H, -C<u>H</u>$_3$; 2.65, t, 2H, (J = 8.0), -C<u>H</u>$_2$Ar; 3.94, s, 3H, -OC<u>H</u>$_3$; 6.25, s, 1H, H-3; 6.94, s, 1H, H-8; 7.45, s, 1H, H-5.
1g	1.0, d, 6H, (J = 6.0), -C<u>H</u>(Me)$_2$; 1.11-1.77, m, 3H, -C<u>H</u>-, -C<u>H</u>$_2$; 2.43, s, 3H, -C<u>H</u>$_3$; 267. t. 2H, (J = 6.0), -C<u>H</u>$_2$Ar; 3.93, s, 3H, -OC<u>H</u>$_3$; 6.23, s, 1H, H-3; 6.89, s, 1H, H-8; 7.43, s, 1H, H-5.
1h	0.88-1.37, m, 6H, -CH$_2$-C<u>H</u>$_3$, -CH$_2$-CH$_2$-C<u>H</u>$_3$; 1.51-1.94, m, 4H, -C<u>H</u>$_2$-C<u>H</u>$_2$-; 2.74, q, 2H, (J = 8.0). Ar-C<u>H</u>$_2$-CH$_3$; 4.0, s, 3H, -OC<u>H</u>$_3$; 631, s, 1H, H-3; 7.0, s, 1H, H-8; 7.51, s, 1H, H-5.
2a	2.2, s, 3H, -CO-C<u>H</u>$_3$; 4.14, s, 3H, -OC<u>H</u>$_3$; 6.82, s, 1H, H-3; 7.48, s, 1H, H-8; 7.65-8.05, m, 5H, Ar<u>H</u>; 8.68, s, 1H, H-5.
2b	0.91, t, 3H, (J = 8.0), -CH$_2$-C<u>H</u>$_3$; 1.51-1.77, m, 2H, -C<u>H</u>$_2$-CH$_3$; 3.0, t, 2H, (J = 8.0). -C<u>H</u>$_2$-CO-; 4.11, s, 3H, -OC<u>H</u>$_3$; 6.51, s, 1H, H-3; 7.54, s, 1H, H-8; 7.64-7.94, bs, 5H, Ar<u>H</u>; 8.17, s, 1H, H-5.
2c	0.9, d, 6H, (J = 6.0), -CH(<u>Me</u>)$_2$; 2.2-2.6, m, 1H, -C<u>H</u>-; 2.94, d, 2H, (J = 6.0). -C<u>H</u>$_2$; 4.10, s, 3H, -OC<u>H</u>$_3$; 6.82, s, 1H, H-3; 7.44, s, 1H, H-8; 7.54 - 7.85, bs, 5H, Ar<u>H</u>; 8.3, s, 1H, H-5.
2d	2.46, s, 3H, -C<u>H</u>$_3$; 2.69, s, 3H, -C<u>H</u>$_3$; 4.10, s, 3H, -OC<u>H</u>$_3$; 6.46, s, 1H, H-3; 7.13, s, 1H, H-8 8.40, s, 1H, H-5.
2e	0.9, t, 3H, (J = 8.0), -C<u>H</u>$_3$; 2.46, s, 3H, -C<u>H</u>$_3$, 3.04. q, 2H, (J = 8.0). -C<u>H</u>$_2$; 4.04, s, 3H, -OC<u>H</u>$_3$. 6.21, s, 1H, H-3; 6.93, s, 1H, H-8; 8.10, s, 1H, H-5.
2f	0.95. t, 3H, (J = 8.0), -CH$_2$-C<u>H</u>$_3$; 1.51-1.94, m, 2H, -C<u>H</u>$_2$-CH$_3$; 2.45, s, 3H, -C<u>H</u>$_3$; 3.05, t, 2H, (J = 8.0). -C<u>H</u>$_2$CO-; 4.07, s, 3H, -OC<u>H</u>$_3$; 6.37, s, 1H, H-3; 7.05, s, 1H, H-8; 8.22, s, 1H, H-5.
2g	1.0, d, 6H, (J = 6.0). -CH(<u>Me</u>)$_2$; 2.2-2.6, m, 4H, -C<u>H</u>-, -C<u>H</u>$_3$; 2.94, d, 2H, (J = 6.0), -C<u>H</u>$_2$; 4.10, s, 3H, -OC<u>H</u>$_3$, 6.34, s, 1H, H-3; 7.04, s, 1H, H-8; 8.14, s, 1H, H-5.
2h	1.02, t, 3H, (J = 8.0), -CH$_2$-C<u>H</u>$_3$; 1.45-1.91, m, 2H, -C<u>H</u>$_2$; 2.62-2.97, m, 5H, -CO-C<u>H</u>$_3$, -C<u>H</u>$_2$-; 4.08, s, 3H, -OC<u>H</u>$_3$; 6.37, s, 1H, H-3; 7.12, s, 1H, H-8; 8.4, s, 1H, H-5.

General Procedure for the Oxidation of 4-Substituted-6-alkyl-7-methoxycoumarins (1a-h).- To a well stirred solution of coumarin (**1a-h**) (0.001 mole) in glacial acetic acid (15 mL), ether (15 mL)

water (15 mL), CAN (0.006 mole) in small portions was added over a period of 10 minutes. The contents were heated on a steam bath with frequent shaking till the characteristic color change from orange to pale yellow was observed (20-30 min). The reaction mixture was then cooled, diluted with cold water and extracted with ether (50 mL). The organic phase was washed successively with cold water, saturated bicarbonate solution and again with cold water. Drying of the organic phase over anhydrous sodium sulfate followed by removal of the solvent furnished a pale yellow colored product. Further purification by column chromatography on silica gel using hexane-ethyl acetate as eluent provided desired coumarins (**2a-h**).

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