Synthesis of 3-substituted coumarins from 2-(acyloxy)arylaldehydes using the $TiCl_4/R_3N$ reagent system

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3-Substituted coumarins are formed in 37–63% yields by the reaction of 2-(acyloxy)arylaldehydes with the TiC_4/R_3N reagent system. The structure of the compound **2c** was determined by single crystal X-ray analysis.

Keywords: titanium tetrachloride, tertiary amines, 2-(acyloxy)arylaldehydes, coumarins

The titanium reagents have been widely used in several important C–C bond forming reactions[1] namely aldol additions[2] *e.g.* Mukaiyama aldol addition,[2e-h] Mannich-type reactions,[3] Michael additions,[4] Baylis–Hillmann reactions,[5] Diels–Alder cycloadditions,[6] ene reactions,[7] oxidative and reductive coupling reactions[8] and alkylations.[9] Also, titanium reagents are very much useful in olefinic bond forming reactions like deoxygenative coupling of carbonyl compounds (*e.g.* McMurry reaction),[10] hydrometalation and carbometalation of alkynes,[11] Wittig-type alkylidenations,[12] aldol[2a,f] and Knoevenagel condensations.[13] Several interesting and useful applications of the $TiCl_4$/tertiary amine in organic synthesis have been reported from this laboratory.[14,3h-j,8e-g] During the course of these investigations, we have develped a new method of synthesis of 3-substituted coumarins using the $TiCl_4/R_3N$ reagent system under mild conditions. The results are reported here.

2-(Butyryloxy)benzaldehyde **1c**, easily accessed using salicylaldehyde and ^{n}butyryl chloride, was reacted with $TiCl_4$ in combination with different organic bases like Et_3N, $^iPr_2NEt$, $^nBu_3N$ and pyridine (Scheme 1, Table 1). 3-Ethyl coumarin **2c** was obtained in all these reactions. The $TiCl_4/Et_3N$ reagent system gives the coumarin **2c** acceptable yields (Table 1, Entry 1).

The structure of the coumarin **2c** was confirmed by the X-ray structure analysis.[15] The ORTEP diagram of 3-ethyl coumarin **2c** is shown in Fig. 1.

With an objective of combining both the acylation and cyclisation steps, we have carried out the reaction of salicylaldehyde with butyryl chloride in presence of $TiCl_4$ and excess Et_3N. In this case, the corresponding coumarin **2c** was isolated in only 32% yield (Scheme 2).

Hence, we have carried out the reactions of different 2-(acyloxy)arylaldehydes with the TiC_4/Et_3N reagent system following the two-step procedure (Scheme 1 and Scheme 3). The results are summarised in Table 2.

The reaction of **1a** with $TiCl_4/Et_3N$ reagent gave the unsubstituted coumarin **2a** only in 42% yield (entry 1). The reactions of compounds **1b–1d** containing an α-substituent gave the corresponding 3-substituted coumarins **2b–2d** in moderate yields (60–63% entries 2–4). The reaction of **1e**, derived from 1-hydroxy-2-naphthaldehyde and acetyl chloride, with $TiCl_4/Et_3N$ reagent gave the unsubstituted benzocoumarin **2e** in 37% yield only (entry 5). The reactions of the α-substituent containing 1-acetyloxy-2-naphthaldehydes **1f–1h** delivered the corresponding benzocoumarins **2f–2h** in moderate yields (55–59% entries 6–8).

Previously, coumarins have been synthesised using reactions like the Wittig-type olefination-cyclisation,[16] condensation of Vilsmeier–Haack type of complex of suitably substituted acetamides and $POCl_3$ with substitued 2-hydroxy-arylcarbonyl compounds,[17] condensation of 2-hydroxy-arylcarbonyl compounds with appropriate

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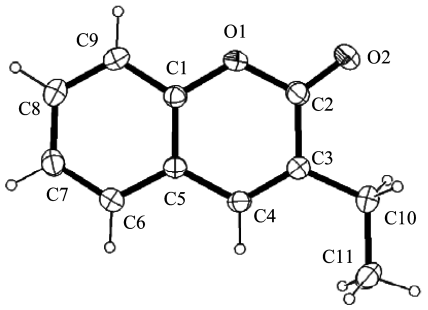
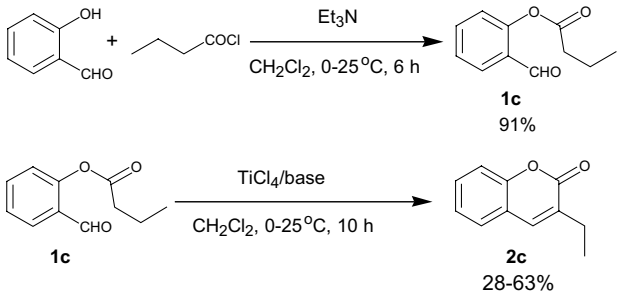


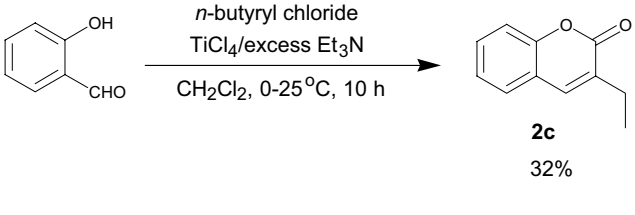
Fig. 1 ORTEP representation of the crystal structure of 3-ethyl coumarin **2c** (thermal ellipsoids are drawn at 20% probability).



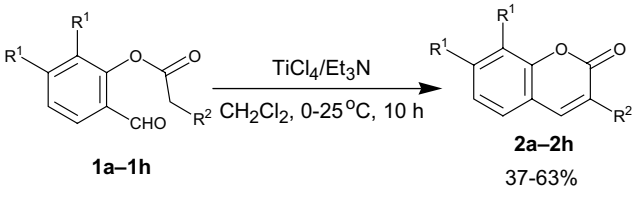
Scheme 1

Table 1 Reaction of 2-(Butyryloxy)benzaldehyde with $TiCl_4$ using different tertiary amines

Entry	Base	Yield of product **2c**/%
1	Et_3N	63
2	$^iPr_2NEt$	32
3	$^nBu_3N$	28
4	Pyridine	38



Scheme 2



Scheme 3

Table 2 Synthesis of coumarins **2** from 2-(acyloxy)arylaldehydes **1** using the $TiCl_4/Et_3N$ reagent system

Entry	R^1,R^1	R^2	Substrate	Product[a]	Yield of **2**/%[b]
1	H,H	H	**1a**	**2a**	42
2	H,H	CH_3	**1b**	**2b**	61
3	H,H	C_2H_5	**1c**	**2c**[c]	63
4	H,H	C_6H_5	**1d**	**2d**	60
5	CH=CH-CH=CH	H	**1e**	**2e**	37
6	CH=CH-CH=CH	CH_3	**1f**	**2f**	58
7	CH=CH-CH=CH	C_2H_5	**1g**	**2g**	55
8	CH=CH-CH=CH	C6H5	**1h**	**2h**	59

[a]All the structures of products were confirmed by spectral analyses (IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry).
[b]Yields are based on the amount of the substrate **1** used. Yields are for the products isolated by column chromatography and subsequent crystallisation in hexanes/EtOAc.
[c]ORTEP representation of X-ray crystal structure analysis of product **2c** is given in Fig. 1.

carboxylic acids or acid chlorides in the presence of strong bases,[18] thermal condensation of 2-hydroxyacetophenones with phenylacetic acid,[19a] or thermal rearrangement of α-(aryloxy)methylacrylic acids,[19b] and transition metal-catalysed carbonylative annulation of internal alkynes.[20] The method described here for the synthesis of 3-substituted coumarins by the reaction of 2-(acyloxy)arylaldehydes with the TiC_4/R_3N reagent system under mild conditions would serve as a good addition for the pool of hitherto known methods of preparation of this important organic skeleton of interest to medicinal chemistry.[21]

Experimental

IR spectra were recorded on Perkin-Elmer IR spectrophotometer Model 1310. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker AV-400 Spectrometers with chloroform-d as a solvent and TMS as reference. Coupling constants *J* are in Hz. The LCMS spectra were recorded on a LCMS-2010A analyser.

General procedure for the synthesis of 3-substituted coumarins:
To a solution of 2-(acyloxy)benzaldehyde **1a–1d** or 1-acyloxy-2-naphthaldehyde **1e–1h** (5 mmol) in CH_2Cl_2 (25 ml) was added Et_3N (1.0 g, 1.4 ml, 10 mmol) at 0°C. To this, a solution of $TiCl_4$ (3.8 g, 2.2 ml, 20 mmol) in CH_2Cl_2 (15 ml) was added drop-wise over 15 min at 0°C under N_2 atmosphere. The reaction mixture was stirred at 0°C for 0.5 h and then at 25°C for 10 h. It was then quenched with saturated K_2CO_3 (20 ml) and stirred for 0.5 h. The reaction mixture was filtered through a Buchner funnel, organic extract was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 ml). The combined organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel using hexanes/EtOAc (90: 10) as eluent to obtain product **2**. Thus obtained product was further purified by crystallising from hexanes/EtOAc (3 : 1) mixture.

Spectral data for **2a–h: 2a:** m.p. 70–72°C (lit.[16e] m.p. = 68–69°C); IR (KBr): 3059, 1732, 1606 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 6.45 (d, 1H, *J* = 8 Hz), 7.28–7.37 (m, 2H), 7.50–7.58 (m, 2H), 7.73 (d, 1H, *J* = 8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 116.5, 116.7, 118.8, 124.4, 127.9, 131.8, 143.5, 153.9, 160.6; MS (*m/z*): 147 (M + 1); Analyses: calculated: C-73.97%, H-4.14%; found: C-73.94%, H-4.17%; **2b:** m.p. 68–70°C (lit.[19b] m.p. = 69–70°C); IR (KBr): 3060, 2932, 1718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.22 (s, 3H), 7.24–7.51 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 17.6, 114.5, 116.5, 118.8, 124.5, 127.9, 131.4, 143.1, 154.1, 160.6; MS (*m/z*): 161 (M + 1); Analyses: calculated: C-74.99%, H-5.03%; found: C-74.96%, H-5.07%; **2c:** m.p. 66–68°C; IR (KBr) 3062, 2954, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.28 (t, 3H, *J* = 8 Hz), 2.63 (q, 2H, *J* = 8 Hz), 7.25–7.35 (m, 2H), 7.46–7.51 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 12.2, 23.8, 116.3, 119.6, 124.2, 127.1, 130.4, 131.3, 137.4, 153.0, 161.7; MS (*m/z*): 175 (M + 1); Analyses: calculated: C-75.84%, H-5.79%; found: C-75.83%, H-5.80%; **2d:** m.p. 134–136°C (lit.[19a] m.p. = 141 °C); IR (KBr) 3055, 2961, 1717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.28–7.33 (m, 2H), 7.38–7.40 (m, 1H), 7.43–7.49 (m, 3H), 7.53–7.57 (m, 2H), 7.73–7.74 (m, 1H), 7.83 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 116.1, 119.4, 124.2, 127.8, 128.2, 128.3, 128.6, 131.1, 134.5, 139.6, 153.3, 160.2; MS (*m/z*): 223 (M + 1); Analyses: calculated: C-81.07%, H-4.54%; found: C-81.12%, H-4.51%; **2e:** m.p. 118–120°C; IR (KBr): 3059, 1717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 6.60 (d, 1H, *J* = 10 Hz), 7.48 (d, 1H, *J* = 9 Hz), 7.60 (t, 1H, *J* = 8 Hz), 7.72 (t, 1H, *J* = 8 Hz), 7.95 (d, 1H, *J* = 8 Hz), 8.01 (d, 1H, *J* = 8 Hz), 8.25 (d, 1H, *J* = 9 Hz), 8.51 (d, 1H, *J* = 10 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 112.9, 115.5, 116.9, 121.3, 126.0, 128.0, 128.2, 128.9, 130.2, 133.0, 138.9, 153.8, 160.8; MS (*m/z*): 197 (M + 1); Analyses: calculated: C-79.58%, H-4.11%; found: C-79.52%, H-4.10%; **2f:** m.p. 148–150°C (lit.[16b] m.p. = 132–133°C); IR (KBr): 3058, 2962, 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.36 (s, 3H), 7.48 (d, 1H, *J* = 8 Hz), 7.58 (t, 1H, *J* = 8 Hz), 7.70 (t, 1H, *J* = 8 Hz), 7.92–7.96 (m, 2H), 8.26 (d, 1H, *J* = 8 Hz), 8.33 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 17.4, 116.5, 121.2, 124.7, 125.6, 127.6, 128.4, 128.7, 130.0, 131.3, 134.7, 152.2, 161.9; MS (*m/z*): 211 (M + 1); Analyses: calculated: C-79.98%, H-4.79%; found: C-79.79%, H-4.81%; **2g:** m.p. 108–110°C; IR (KBr) 3060, 2965, 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.37 (t, 3H, *J* = 8 Hz), 2.74 (q, 2H, *J* = 8 Hz), 7.28 (s, 1H), 7.47 (d, 1H, *J* = 8 Hz), 7.58 (d, 1H, *J* = 8 Hz), 7.70 (t, 1H, *J* = 8 Hz), 7.93 (t, 1H, *J* = 8 Hz), 8.27–8.28 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 12.3, 24.1, 113.1, 116.7, 121.1, 125.5, 127.6, 128.5, 128.7, 130.0, 130.1, 131.3, 132.8, 152.0, 161.4; MS (*m/z*): 225 (M + 1); Analyses: calculated: C-80.34%, H-5.39%; found: C-80.50%, H-5.37%; **2h:** m.p. 214–216 °C (lit.[22] m.p. = 212–213°C); IR (KBr) 3061, 1719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.45–7.55 (m, 4H), 7.61 (t, 1H, *J* = 8 Hz), 7.73 (t, 1H, *J* = 8 Hz), 7.83–7.84 (m, 2H), 7.96 (d, 1H, *J* = 8 Hz), 8.02 (d, 1H, *J* = 9 Hz), 8.34 (d, 1H, *J* = 8 Hz), 8.63 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 113.6, 116.5, 121.3, 126.0, 126.8, 128.1, 128.5, 128.8, 129.0, 130.2, 132.5, 135.0, 135.4, 152.9, 160.4; MS (*m/z*): 273 (M + 1); Analyses: calculated: C-83.81%, H-4.44%; found: C-83.83%, H-4.40%.

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15 *Crystal data:* For compound **2c**: molecular formula: $C_{11}H_{10}O_2$, MW = 174.19, monoclinic, space group: $P2_1/n$, $a = 7.3522(13)$ Å, $b = 10.4605(18)$ Å, $c = 11.731(2)$ Å, $\beta = 102.889(3)^\circ$, V = 879.5(3) Å^3, Z = 4, $\rho_c = 1.316$ Mg/m^3, Wavelength of radiation = 0.71073 Å, $\mu = 0.091$ mm^{-1}, $T = 293(2)$ K. Of the 6244 reflections collected, 1728 were unique ($R_{int} = 0.0195$). Refinement on all data converged at $R_1 = 0.0408$, $wR_2 = 0.1141$ (Deposition number CCDC 605887).

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