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An efficient procedure for the synthesis of coumarin derivatives using $TiCl_4$ as catalyst under solvent-free conditions

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Abstract—The ability of titanium(IV) chloride as a catalyst to promote the Pechmann condensation reaction with a range of phenols and β-keto esters is described.The reaction was carried out by addition of $TiCl_4$ to a mixture of the phenol and the β-keto ester with thorough stirring in the absence of a solvent and represents an improvement on the classical Pechmann conditions. The yields of coumarins obtained via this novel protocol were significantly higher than those using the conventional method and the reaction duration was reduced to a few minutes or even a few seconds.

1. Introduction

Coumarins have been both widely studied and widely used but still generate much interest. Coumarins are well known as natural products and many exhibit high levels of biological activity.[1] Coumarins are also used as food additives, in cosmetics,[2] as optical brightening agents[3] and dispersed fluorescent and laser dyes.[4] In addition, some coumarins are of interest because of their toxicity,[5] carcinogenity[6] and photodynamic effects.[7] Coumarins also act as intermediates for the synthesis of furocoumarins, chromenes, coumarones and 2-acylresorcinols.[8]

The drive towards clean technology has encouraged the application of solvent-free conditions.[9] A move away from the use of solvents in organic synthesis has led in some cases to improved results and more benign synthetic procedures.[10] Adopting the principles of 'Green Chemistry', we have established that using solvent-free conditions for Knoevenagel[11] and Wittig[12] reactions results in a dramatic improvement in yields. Our approach reduces the use of organic solvents, which are potentially toxic and hazardous[13] and uses simple and mild conditions, with inherently lower costs.[14]

Coumarins can be synthesised by various methods including the Perkin,[15] Pechmann,[16] Knoevenagel,[17] Reformatsky[18] and Wittig[19] reactions. Among these, the Pechmann reaction has been the most widely used method since it proceeds from very simple starting materials and gives good yields of variously substituted coumarins. Substituted phenols are condensed with β-keto esters in the presence of an acid to afford coumarins. Various acids have been used to carry out this reaction.[20] In some methods, several hours or even days are required to complete the reaction even when heated above 150 °C. Undesired by-products such as chromones are sometimes formed.[21] Recently, cation exchange resins[22] and solid acid catalysts[23] have been used, however, such reactions require, either a reaction temperature of about 150 °C or higher or long reaction times and in some cases give low yields. More recently, there have been reports on the use of microwave irradiation[24] for accelerated synthesis of different coumarins.

In view of the current emphasis on solid state synthesis[25] and on 'green chemistry'[26] we set out to develop a solvent-free preparation of coumarins using an inexpensive and non-polluting catalyst. We have recently used 3 Å molecular sieves as promoting agents in the synthesis of coumarins.[27] In continuation of our interest in organic synthesis in solvent-free systems[12,28] we report here a method for the preparation of coumarins **3** and **5** using $TiCl_4$ as the catalyst in the Pechmann reaction of a neat mixture of a phenol and a β-keto ester (Scheme 1).

Keywords: Pechmann condensation; Titanium(IV) chloride; Coumarin; Solvent-free system.

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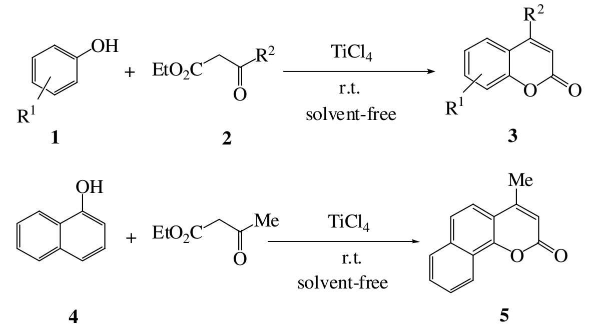

Scheme 1.

Attempted TiCl$_4$-catalysed reactions in the presence of solid supports and MW irradiation proved to be unsuccessful, the reactions were sluggish and considerable amounts of starting materials were recovered even after prolonged exposure to microwave irradiation. After some experimentation with respect to the molar ratios of reagents, we developed the conditions that generally gave the coumarins in good to excellent yields (Table 1). These conditions employed a 1:1.5 ratio of the phenol and the β-keto ester using TiCl$_4$ as catalyst. As shown in Table 1 the time of reaction was reduced to a few minutes or even a few seconds. The work-up involved simply quenching with water then filtration and recrystallisation from a suitable solvent.

In conclusion, we have demonstrated an efficient and simple alternative for the preparation of substituted coumarins via the TiCl$_4$-catalysed Pechmann reaction in solvent-free conditions. Prominent among the advantages of this new method are operational simplicity, good yields, short reaction times and an easy work-up.

2. General procedure

The phenol (20 mmol) and the β-keto ester (30 mmol) were mixed thoroughly and titanium(IV) chloride (10 mmol) was added to the mixture with stirring at room temperature. The reaction was essentially complete after addition of the TiCl$_4$ (up to 80 s). The reaction mixture was poured onto crushed ice and the resulting crude product was filtered off and recrystallised from hot ethanol/water (9/1) to give the pure product.

2.1. Selected spectroscopic data

Compound **3a**: ^{1}H NMR δ (DMSO-d_6): 2.65 (s, 3H, Me), 6.41 (s, 1H, C=CH), 6.91–7.72 (m, 3H, ArH), OH not observed, IR, ν (KBr): 3260–3080, 1690 cm^{-1}. EIMS: *m*/*z*: 176 (M$^+$). Compound **3b**: ^{1}H NMR δ (CDCl$_3$): 2.59 (s, 3H, Me), 4.22 (s, 3H, OMe), 6.51 (s, 1H, C=CH), 7.01–7.51 (m, 3H, ArH), IR, ν (KBr): 1685 cm^{-1}. EIMS: *m*/*z*: 190 (M$^+$). Compound **3c**: ^{1}H NMR δ (CDCl$_3$): 2.62 (s, 3H, Me), 2.80 (s, 3H, Me), 6.41 (s, 1H, C=CH), 7.10–7.60 (m, 3H, ArH), IR, ν (KBr): 1685 cm^{-1}. EIMS: *m*/*z*: 174 (M$^+$). Compound **3d**: ^{1}H NMR δ (CDCl$_3$): 1.71 (t, $J = 6.98$, 3H, Me), 2.64 (s, 3H, Me), 4.30 (q, $J = 6.98$, 2H, OCH$_2$), 5.35 (s, 2H, OCH$_2$), 6.45 (s, 1H, C=CH), 7.20–7.81 (m, 3H, ArH), IR, ν (KBr): 1730, 1650 cm^{-1}. EIMS: *m*/*z*: 262 (M$^+$). Compound **3e**: ^{1}H NMR δ (CDCl$_3$): 2.65 (s, 3H, Me), 5.50 (s, 2H, CH$_2$), 6.51 (s, 1H, C=CH), 7.01–8.20 (m, 8H, ArH), IR, ν (KBr): 1700, 1630 cm^{-1}. EIMS: *m*/*z*: 294 (M$^+$). Compound **3f**: ^{1}H NMR δ (CDCl$_3$): 1.90 (d, $J = 6.65$, 3H, Me), 2.60 (s, 3H, Me), 2.91 (s, 3H, Me), 5.10 (q, $J = 6.65$, 1H, CH), 6.60 (s, 1H, C=CH), 7.10–7.81 (m, 3H, ArH), IR, ν (KBr): 1730, 1668 cm^{-1}. EIMS: *m*/*z*: 230 (M$^+$). Compound **3g**: ^{1}H NMR δ (DMSO-d_6): 2.65 (s, 3H, Me), 6.25 (d, $J = 2.61$, 1H, ArH), 6.35 (d, $J = 2.61$, 1H, ArH), 6.40 (s, 1H, C=CH), OH not observed, IR, ν (KBr): 3160, 1670 cm^{-1}. EIMS: *m*/*z*: 192 (M$^+$). Compound **3h**: ^{1}H NMR δ (DMSO-d_6): 6.24 (d, $J = 2.62$, 1H, ArH), 6.34 (d, $J = 2.62$, 1H, ArH), 6.50 (s, 1H, C=CH), OH not observed, IR, ν (KBr): 3158, 1665 cm^{-1}. EIMS: *m*/*z*: 246 (M$^+$). Compound **3i**: ^{1}H NMR δ (DMSO-d_6): 5.11 (s, 2H, CH$_2$Cl), 6.25 (d, $J = 2.60$, 1H, ArH), 6.29 (d, $J = 2.60$, 1H, ArH), 6.35 (s, 1H, C=CH), OH not observed, IR, ν (KBr): 3157, 1655 cm^{-1}. EIMS: *m*/*z*: 226 (M$^+$). Compound **3j**: ^{1}H NMR δ (DMSO-d_6): 2.65 (s, 3H, Me), 2.95 (s, 3H, Me), 6.25 (d, $J = 2.60$, 1H, ArH), 6.35 (d, $J = 2.60$,

Table 1. Titanium(IV) chloride-catalysed Pechmann condensations in the absence of solvent

Product	R^1	R^2	Time (s)	Mp (°C)	Yield (%)[a]
3a	7-OH	Me	50	184–186	97
3b	7-OMe	Me	40	156–158	96
3c	7-Me	Me	60	131–132	92
3d	7-OCH$_2$CO$_2$Et	Me	55	98–100	89
3e	7-OCH$_2$COPh	Me	70	173–174	87
3f	7-OCHMeCOMe	Me	80	231–233	90
3g	5,7-Di OH	Me	50	283–285	96
3h	5,7-Di OH	CF$_3$	60	250–252	97
3i	5,7-Di OH	CH$_2$Cl	60	242–244	95
3j	7-OH–5-Me	Me	50	243–245	92
3k	H	Me	70	83–84	60
3l	4-NO$_2$	Me	No reaction	—	—
3m	4-Cl	Me	No reaction	—	—
5			70	155–157	90

[a] After recrystallisation.

1H, ArH), 6.41 (s, 1H, C=CH), OH not observed, IR, *v* (KBr): 3159, 1665 cm^{-1}. EIMS: *m*/*z*: 190 (M^+). Compound **3k**: ^{1}H NMR δ ($CDCl_3$): 2.62 (s, 3H, Me), 6.48 (s, 1H, C=CH), 7.30–7.65 (m, 4H, ArH), IR, *v* (KBr): 1665, 1610, 1450, 1400 cm^{-1}. EIMS: *m*/*z*: 160 (M^+). Compound **5**: ^{1}H NMR δ ($CDCl_3$): 2.71 (s, 3H, Me), 6.51 (s, 1H, C=CH), 7.50–8.91 (m, 6H, ArH), IR, *v* (KBr): 1675 cm^{-1}. EIMS: *m*/*z*: 210 (M^+).

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