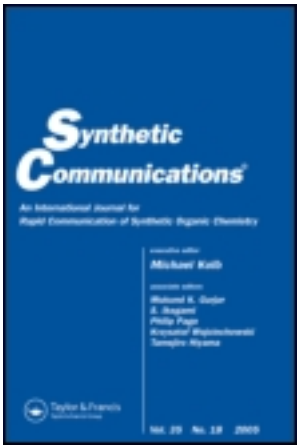

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$ZrCl_4$-Catalyzed Pechmann Reaction: Synthesis of Coumarins Under Solvent-Free Conditions

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$ZrCl_4$-Catalyzed Pechmann Reaction: Synthesis of Coumarins Under Solvent-Free Conditions

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ABSTRACT

Zirconium (IV) chloride is used as an efficient catalyst in the Pechmann condensation reaction of phenols with β-keto esters leading to the formation of coumarin derivatives in good yields under solvent-free conditions.

Key Words: Phenol; Keto ester; Zirconium (IV) chloride; Pechmann reaction; Coumarin.

Coumarin and its derivatives occur widely in nature, particularly in plants; most of them show wide biological activities like anthelmintic,

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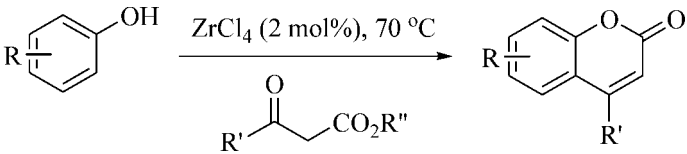
hypnotic, insecticidal, and anticoagulant properties.[1] They are widely used as additives in food and cosmetics, agrochemicals, optical brightening agents, dispersed fluoroscent and tunable dye lasers,[2] and also act as intermediates for the synthesis of fluoro coumarins, chromenes, coumarones, 2-acyl resorcinols, and others.[3] Many routes have been reported for the synthesis of coumarins including the Perkin,[4] Pechmann,[5] Knoevenagel,[6] Reformatsky,[7] and the Wittig[8] reactions. The Pechmann reaction involves the condensation of phenols with β-ketonic esters in the presence of variety of acidic condensing agents such as sulfuric, hydrochloric, and phosphoric acids, phosphorous pentoxide, trifluroacetic acid, and Lewis acids such as $ZnCl_2$, $FeCl_3$, $AlCl_3$[9] and exchange resins,[10] solid acid catalysts[11] have also been used. Recently, there have been reports on the use of microwaves,[12] ionic liquid as a Lewis acid catalyst and solvent,[13] Zn/I_2,[14] *p*-TsOH,[15] $InCl_3$,[16] and $Yb(OTf)_3$[17] as acid catalysts for the synthesis of coumarins.

In connection with our work on catalytic applications of $ZrCl_4$,[18] we report herein a mild and convenient method for the synthesis of coumarins under the Pechmann reaction conditions using $ZrCl_4$ as an efficient catalyst (Sch. 1).

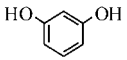
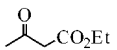
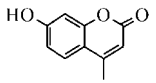
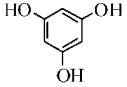
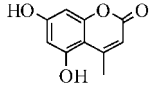
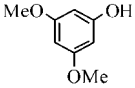
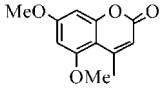
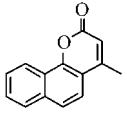
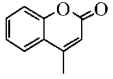
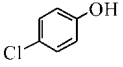
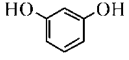
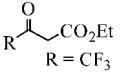
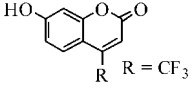
Thus, treatment of resorcinol with ethyl acetoacetate in the presence of 2 mol% of $ZrCl_4$ under solvent-free conditions at 70°C for 8 min afforded the 7-hydroxy-4-methyl coumarin in 95% yield (entry 1). In order to study substituent effects, we have tested several combinations of phenol derivatives, and β-keto esters were examined and the results are summarized in Table 1. The condensation reaction with 4-chloro phenol failed to afford the corresponding coumarin (entry 6). The electron donating group on phenol promoted the reaction while the electron withdrawing group inhibited the reaction. An alkyl group is not strong enough to furnish the activation needed and thus gives a low yield. In contrast, electron-withdrawing groups inhibit the reaction.

In summary, this paper describes a simple and efficient method for the synthesis of coumarins via $ZrCl_4$-catalyzed Pechmann condensation of phenol and β-keto esters.



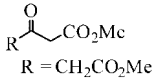
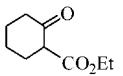
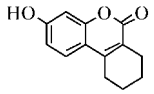
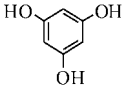
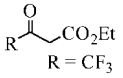
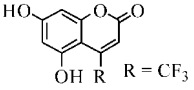
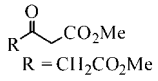
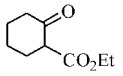
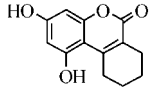
Scheme 1.

Table 1. $ZrCl_4$-catalyzed Pechmann reaction.

Entry	Phenol	β-Keto ester	Time (min)	Product	Yield (%)[a]	Mp °C[b]
1			8		95	183–185 (185)[19]
2		”	5		93	281–282 (280)[19]
3		”	10		91	171–173 (172)[19]
4		”	15		78	155–156 (155)[12]
5		”	30		56	82–84 (83–84)[11]
6		”	60	no reaction	—	—
7			5		94	186–188 (187)[19]

(*continued*)

Table 1. Continued.

Entry	Phenol	β-Keto ester	Time (min)	Product	Yield (%)[a]	Mp °C[b]
8	”	R = CH_2Cl	8	R = CH_2Cl	92	142–144 (143)[3b]
9	”	 R = CH_2CO_2Me	8	R = CH_2CO_2Me	93	221–223 (221)[3c]
10	”		10		91	223–225 (225)[3d]
11		 R = CF_3	5	 R = CF_3	93	251–253 (251)[3e]
12	”	R = CH_2Cl	6	R = CH_2Cl	90	243–245
13	”	 R = CH_2CO_2Me	5	R = CH_2CO_2Me	91	234–236
14	”		8		89	265–267 (267)[3f]

[a]Isolated yields.
[b]The literature references are given for known products.

EXPERIMENTAL

General Procedure for the Synthesis of Coumarins

A mixture of phenolic substrate (10 mmol) and keto ester (10 mmol) was heated at 70°C in the presence of zirconium (IV) chloride (46 mg, 2 mol%). After completion of the reaction at the desired time as indicated in the table, the reaction mixture was cooled to room temperature and poured onto crushed ice (50 g). The solid product obtained was filtered off, washed with ice-cold water, and recrystallized from hot ethanol to obtain the pure product. All the products were characterized by IR, ^{1}H NMR, and mass spectroscopy and compared with the literature data for known products.

4-(Chloromethyl)-5, 7-dihydroxy-*2H*-chromen-2-one (entry 12): White solid, m.p. 243–245°C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.35 (s, 1H), 6.29 (s, 1H), 6.25 (s, 1H), 5.0 (s, 2H); ^{13}C NMR (DMSO-d_6, 400 MHz): δ 162.0, 160.5, 157.6, 157.0, 152.5, 109.2, 100.2, 99.7, 95.3, 45.5; IR (Neat): 3159, 1654, 1601, 1374, 1170, 820 cm^{-1}; EIMS (m/z): 226 (M^+); Anal. Calcd. for $C_{10}H_7ClO_4$: C, 53.00; H, 3.11. Found C, 53.06; H, 3.15.

Methyl 2-(5-7-dihydroxy-2-oxo-2H-chromen-4-yl)acetate (entry 13): White crystalline solid, m.p. 234–236°C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.75 (s, 1H, OH), 10.37 (s, 1H, OH), 6.35 (s, 1H), 6.21 and 6.2 (2s, 2H), 5.98 (s, 1H), 3.88 (s, 2H), 3.6 (s, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz): δ 170.8, 161.7, 160.6, 157.6, 156.9, 150.5, 111.6, 102.0, 99.4, 95.1, 52.1, 41.3; IR (Neat): 3200, 1701, 1601, 1362, 1158, 825 cm^{-1}; EIMS (m/z): 250 (M^+); Anal. Calcd. for $C_{12}H_{10}O_6$: C, 57.60; H, 4.03. Found C, 57.62; H, 4.07.

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