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$KAl(SO_4)_2 \cdot 12H_2O$ (alum) a reusable catalyst for the synthesis of some 4-substituted coumarins *via Pechmann* reaction under solvent-free conditions

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Abstract A simple, efficient, and practical procedure for the *Pechmann* condensation using $KAl(SO_4)_2 \cdot 12H_2O$ (alum) as a non-toxic, reusable, inexpensive, and easily available catalyst is described under solvent-free condition at 65°C. These improved reaction conditions allow the preparation of a wide variety of some new substituted coumarins in high yields (86–96%) and purity under mild reaction conditions. Compared to the classical *Pechmann* condensation, this new method consistently has the advantage of high yields.

Keywords *Pechmann* condensation; Coumarins; $KAl(SO_4)_2 \cdot 12H_2O$ (alum); Phenols; Solvent-free.

Introduction

Polyheterocyclic systems with coumarin ring skeleton, for example calanolides [1] and hydroxylomatin [2], have been isolated from *Calophyllum* genus and roots of *Angelica purpuraefolia*. They are well-known for their antitumor and anti-HIV activities [1, 2]. In addition, coumarins show some pharmacological and biological activities including inhibition of platelet aggregation [3], anticancer [4], inhibition of steroid 5α-reductase [5], antibacterial [6], and anticoagulant [7]. Also, they are used as additives in food and cosmetics [8], in preparation of insecticides, optical brighteners [9], dispersed fluorescent and laser dyes [10], and intermediates for the synthesis of furocoumarins, chromenes, coumarones, and 2-acylresorcinols [11].

Coumarins could be synthesized by various methods, such as *Pechmann* [12], *Perkin* [13], *Knoevenagel* [14], *Reformatsky* [15], and *Witting* [16] reactions. However, the *Pechmann* reaction is one of the simplest and direct methods for the synthesis of coumarin since it proceeds from very simple starting materials, namely, phenols and β-keto esters or α,β-unsaturated carboxylic acids employing various catalysts, such as sulfuric acid [12], trifluoroacetic acid [17], phosphorus pentoxide [18], $ZrCl_4$ [19], $TiCl_4$ [20], ionic liquids [21], and Amberlyst [22]. However, these catalysts have to be used in excess; for example, H_2SO_4 in 10–12 equiv. [23], CF_3CO_2H in 3–4 equiv. [17], and phosphorus pentoxide in a five-fold excess [18]. Further, such reaction requires long duration (24 h [24], 20 h [25]), or high temperature (150°C) [25] and also microwave irradiation [26].

Very recently, we have reported the ability of $KAl(SO_4)_2 \cdot 12H_2O$ (alum) as an effective catalyst in the synthesis of benzimidazole [27], *cis*-isoquinolonic acid [28], and dihydropyrimidinones [29]. Herein, we describe a high-yielding protocol for the *Pechmann* condensation of phenols and β-keto esters for the synthesis of the some new coumarins **3**

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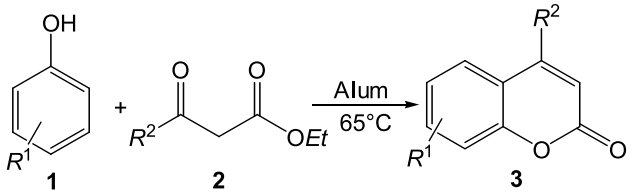

Scheme 1

using $KAl(SO_4)_2 \cdot 12H_2O$ (alum) under mild conditions (Scheme 1).

Results and discussion

In a typical experiment, a solvent-free mixture of phenols and β-keto esters was heated at 65°C in presence of catalytic amount of alum (20 mol%). The reaction was monitored by TLC (ethyl acetate/petroleum ether, 1/1). Then, the reaction mixture was poured into ice-cold water and stirred for 5 min. The solid product was obtained by simple filtration and recrystallization from ethanol.

We found that the *Pechmann* condensation is affected by various solvents as is evident from Table 1. Most excitingly, the *Pechmann* condensation could also be carried out under solvent-free condition in excellent yield. Moreover, the best results are observed when the molar ratio of phenols 1 and β-keto esters 2 was 1:1.2. In addition, the activity of the recycled alum was also examined according to the typical experiment conditions. We obtained the desired product in 96, 95, 93, 90, and 88% yields within five runs (Table 1, entry 5).

Table 1 $KAl(SO_4)_2 \cdot 12H_2O$ (alum)-catalyzed condensation of 1,3,5-trihydroxybenzene (**1a**) and ethyl acetoacetate (**2a**) under different reaction conditions[a]

Entry	Solvent	Amount of catalyst/mol%	Yield of **3a**/%[b]
1	H_2O	20	50
2	CH_3CH_2OH	20	80
3	toluene	20	68
4	CH_3CN	20	65
5[c]	none	20	96, 95, 93, 90, 88
6	none	30	95
7	none	10	92

[a] The reaction were carried out in the presence of 1,3,5-trihydroxybenzene (**1a**) (1 mmol), ethyl acetoacetate (**2a**) (1.2 mmol), and $KAl(SO_4)_2 \cdot 12H_2O$ at 65°C for 120 min
[b] Isolated yield
[c] Catalyst was reused for five times

In order to study the generality of this procedure, a series of *Pechmann* condensation were performed similarly. The results are summarized in Table 2. The two-component condensation reaction proceeded smoothly at 65°C and completed in 2–3.20 h under these conditions. We carried out this reaction with a series of substituted phenols bearing either electron-donating or electron-withdrawing substituents, with β-keto esters in the presence of alum to obtain the corresponding coumarins. The

Table 2 $KAl(SO_4)_2 \cdot 12H_2O$ (alum)-catalyzed synthesis of coumarins[a]

Entry	Compound **1**[b]	Compound **2**	Coumarin **3**	Time/min	Yield[c]/%	Ref.
1[d]	**1a**	ethylacetoacetate (**2a**)	**3a**	120	96	[20]
2	**1a**	diethyl 1,3-acetonedicarboxylate (**2b**)	**3b**	100	95	–
3	**1a**	ethyl 2-chloroacetoacetate (**2c**)	**3c**	130	94	[24]
4	**1a**	ethyl cyclopentanone-2-carboxylate (**2d**)	**3d**	120	93	[30]
5	**1a**	ethyl benzoylacetate (**2e**)	**3e**	120	92	[19]
6	**1b**	**2a**	**3f**	150	91	[31]
7	**1b**	**2b**	**3g**	130	92	–
8	**1b**	**2c**	**3h**	120	93	[24]
9	**1b**	**2d**	**3i**	130	92	[32]
10	**1b**	**2e**	**3j**	130	91	[19]
11	**1c**	**2a**	**3k**	210	88	[25]
12	**1c**	**2b**	**3l**	200	86	–

[a] Reaction conditions: phenol (1 mmol), β-keto esters (1.2 mmol), and $KAl(SO_4)_2 \cdot 12H_2O$ (20 mol%), 65°C
[b] 1,3,5-Trihydroxybenzene (**1a**), 1,3-dihydroxybenzene (**1b**), 1-naphthol (**1c**)
[c] Isolated yield
[d] The reaction was carried out in the presence of 1,3,5-Trihydroxybenzene (**1a**), (0.1 mol), ethyl acetoacetate (**2a**) (0.12 mol), and $KAl(SO_4)_2 \cdot 12H_2O$ at 65°C for 260 min

experimental procedure with this catalyst is very simple and the catalyst can be removed easily (see Experimental). Hence there will not be any unnecessary acidic waste stream to create environmentally hazardous pollution. However, substrates having electron-donating groups in the *para* position to the site of electrophilic substitution gave maximum yields under reaction conditions in shorter times. Interestingly, we have found that this method is useful for large scale preparation (Table 2, entry 1). All products were identified by comparison of analytical data (IR, NMR, MS, and CHN) with those reported for authentic samples.

In conclusion, we describe a mild, convenient method for the preparation of some new coumarins by the *Pechmann* cyclocondensation reaction of phenols and β-keto esters using cheap, non-toxic, very soluble in water, recyclable, and easily available $KAl(SO_4)_2 \cdot 12H_2O$ (alum) catalyst under solvent-free conditions. Additionally, this new reaction might be a useful tool for high-throughput organic synthesis.

Experimental

Melting points were obtained in open capillary tubes and were measured on an electrothermal 9200 apparatus. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. IR spectra were recorded on KBr pellets on a Shimadzu IR-470 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300 and 75 MHz.

General procedure for preparation of 4-substituted coumarins
A mixture of 1 mmol substituted phenol, 1.2 mmol β-keto ester, and 0.1 g $KAl(SO_4)_2 \cdot 12H_2O$ (20 mol%) was stirred at 65°C. After completion of reaction, as indicated by TLC (ethyl acetate/petroleum ether, 1/1), the reaction mixture was cooled to room temperature and the contents were poured into ice-cold water,and stirred for 5 min. The products were collected by filtration, washed with water, and then recrystallized from ethanol to afford the coumarin derivative.

General procedure for catalyst recovery
The catalyst in the aqueous phase could be recovered by removing the water under vacuum then washing with acetone and drying at rt.

Ethyl 2-(5,7-dihydroxycoumarin-4-yl)acetate
(**3b**, $C_{13}H_{12}O_6$)
White powder; mp 205–207°C (dec); IR (KBr): $\bar{\nu} = 3479$, 1717, 1690 cm^{-1}; ^{1}H NMR (*DMSO*-d$_6$): $\delta = 1.17$ (t, $J =$ 7.0 Hz, CH_3), 3.86 (s, CH_2), 4.07 (q, $J = 7.0$ Hz, CH_2), 5.98 (s, C=CH), 6.20 (s, *Ar*H), 6.21 (s, *Ar*H),10.34 (s, OH), 10.71 (s, OH) ppm; ^{13}C NMR (*DMSO*-d$_6$): $\delta = 14.49$, 41.54, 60.56, 95.05, 99.41, 102.06, 111.59, 150.64, 156.94, 157.60, 160.60, 161.68, 170.20 ppm; MS: m/z (%) = 264 (M$^+$, 50), 219 (100), 190 (45), 162 (90), 134 (30), 69 (50), 45 (50).

Ethyl 2-(7-hydroxycoumarin-4-yl)acetate (**3g**, $C_{13}H_{12}O_5$)
White powder; mp 155–157°C; IR (KBr): $\bar{\nu} = 3225$, 1713, 1680 cm^{-1}; ^{1}H NMR (*DMSO*-d$_6$): $\delta = 1.17$ (t, $J = 7.1$ Hz, CH_3), 3.92 (s, CH_2), 4.10 (q, $J = 7.1$ Hz, CH_2), 6.24 (s, C=CH), 6.73 (d, $J = 2.2$ Hz, *Ar*H), 6.79 (dd, $J = 2.2$, 8.7 Hz, *Ar*H), 6.82 (d, $J = 8.7$ Hz, *Ar*H), 7.49 (d, $J = 8.7$ Hz, *Ar*H), 10.61 (s, OH) ppm; ^{13}C NMR (*DMSO*-d$_6$): $\delta = 14.42$, 37.35, 61.33, 102.80, 111.66, 112.57, 113.48, 127.15, 150.07, 155.50, 160.60, 161.73, 169.62 ppm; MS: m/z (%) = 248 (M$^+$, 75), 220 (30), 192 (25), 176 (30), 147 (100), 91(30), 65 (30), 39 (30).

Ethyl 2-(benzo[h]coumarin-4-yl)acetate (**3l**, $C_{17}H_{14}O_2$)
White powder; mp 134–136°C; IR (KBr): $\bar{\nu} = 1718$, 1611 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.27$ (t, $J = 7.1$ Hz, CH_3), 3.87 (s, CH_2), 4.21 (q, $J = 7.1$ Hz, CH_2), 6.49 (s, C=CH), 7.56 (m, 5H, *Ar*H), 8.57 (m, 1H, *Ar*H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.10$, 38.66, 61.85, 114.30, 116.29, 120.09, 122.68, 123.22, 124.41, 127.31, 127.67, 128.88, 134.83, 149.05, 151.04, 160.50, 168.73 ppm; MS: m/z (%) = 282 (M$^+$, 80), 254 (30), 208 (35), 181 (95), 152 (100), 77 (10), 63 (30), 39 (30).

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