Dipyridine cobalt chloride: a novel catalyst for the synthesis of coumarins via Pechmann condensation

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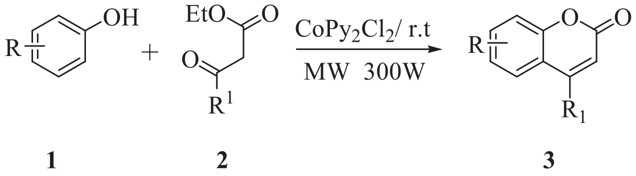
Dipyridine cobalt chloride is a novel catalyst for the Pechmann condensation involving different phenols and ethylacetoacetate under solvent-free conditions using both conventional methods and microwave irradiation. It gives the corresponding coumarins in excellent yields with high purity. The catalyst is thermally stable, inexpensive and recyclable. A faster reaction and higher yields compared to the conventional method and no side products were identified using microwave irradiation. In this reaction, electron releasing groups on the phenol ring shown more reactivity and gave high yields than simple phenol. These products were identified by ^{1}H NMR, ^{13}C NMR, MS, IR and elemental analysis.

Keywords: coumarins, phenols, β-ketoester, $CoPy_2Cl_2$, Pechmann condensation, solvent free conditions

Coumarins display a wide variety of biological properties and are used as additives in food, perfumes, cosmetics,[1] optical brighteners,[2] dispersed fluorescent and laser dyes.[3] Coumarin itself and 7-hydroxycoumarin have been reported to inhibit the proliferation of a number of human malignant cell lines *in vitro*[4,5] and have demonstrated activity against several types of animal tumors.[6-8] These compounds have also been shown in clinical trials to possess activity against prostate cancer, malignant melanoma and metastatic renal cell carcinoma.[9,10] Coumarins are synthesised by different reactions such as the Pechmann,[11] Perkin,[12] Knoevenagel,[13] Reformatsky and Wittig reactions.[14,15] Amongst these reactions, the Pechmann condensation is the most common for the synthesis of coumarins, since it proceeds from very simple starting materials and furnish good yields. It involves the condensation of phenols with β-keto esters in the presence of sulfuric acid as a cyclising agent. The reaction can also be catalysed by different acid catalysts, such as PPA,[16] $InCl_3$,[17] $ZrCl_4$,[18] $Yb(OTf)_3$,[19-22] *p*-TsOH,[23] $BiCl_3$[24] and I_2 or AgOTf[25] and $Sm(NO_3)_3$ [26] as well as chloroaluminate ionic liquids.[27,28] However, some of these Lewis acids are moisture sensitive and require special care in handling and storage. Some of these methods also need a high reaction temperature, prolonged reaction time and drastic reaction conditions. Furthermore, some of the catalysts are expensive, and in some of the existing methods the catalysts are destroyed in the work-up procedure and cannot be recovered or re-used.

In connection with our earlier reports on coumarin synthesis[29,30] now we report the use of dipyridine cobalt chloride[31] for the Pechmann condensation. Recently we have employed this catalyst for the synthesis of benzoxanthenes.[32] The Lewis acid catalyst is a solid (violet coloured crystals), soluble in water, stable in air, immiscible in common organic solvents, reusable, and it has high thermal stability. In addition, its toxicity is low. We examined the synthesis in microwave and conventional methods (Scheme 1).



Scheme 1

Results and discussion

In the microwave conditions (method-A), the phenol and β-ketoester were irradiated in the presence of $CoPy_2Cl_2$ (catalytic amount) without using any solvent at 300 W power level to afford the corresponding coumarin in 1–3 min. When the reaction was carried out by the conventional method (method-B), the phenol and β-ketoester in the presence of $CoPy_2Cl_2$ (catalytic amount), were stirred under solvent free conditions at room temperature to yield desired coumarin in 1–3 h. In comparison, the microwave technique is more advantageous than conventional method. The method-A required a shorter reaction time and yields are good with high purity. Method-B required a longer reaction time to complete the reaction. The results are given in Table 1.

In summary $CoPy_2Cl_2$ is an efficient reusable catalyst for the Pechmann condensation of phenols and β-keto esters to afford coumarins.

Experimental

Melting points were determined in open capillaries and are uncorrected. The reactions were monitored by TLC and visualised with UV light. IR spectra (KBr) were recorded on Shimadzu FTIR model 8010 spectrometer and the ^{1}H NMR spectra on Varian Gemini 200 MHz spectrometer using TMS as an internal standard. Mass spectra were recorded on a JEOL JMS D-300 Spectrometer. All solvents and reagents were purchased from Aldrich and Fluka.

Procedure for the preparation of catalyst ($CoPy_2Cl_2$):
Cobalt chloride and pyridine were mixed in a 1 : 2 mol ratio in the presence of methanol (solvent). The reaction mixture was refluxed for 7–8 h. A solid was obtained, filtered and recrystallised from 1 : 2 ratio of water and methanol to afford pure violet colour crystals of the complex.

General procedure for synthesis of coumarins
Method A (microwave irradiation): A mixture of the phenol **1** (1 mmol), β-ketoester **2** (1 mmol) and $CoPy_2Cl_2$ (0.01 mmol) was added and the mixture was inserted in a microwave oven (BPL, 800T model) on a silica gel solid support and irradiated at 300 W for the appropriate time (Table 1). The progress of the reaction was checked by TLC. The reaction mass was cooled to room temperature, water (5 ml) was added and stirred for 2 min. The mixture was filtered and recrystallised from ethanol to afford the expected products in excellent yields **3**.

Method B (conventional method): A mixture of the phenol **1** (1 mmol), β-ketoester **2** (1 mmol) and $CoPy_2Cl_2$ (0.01 mmol) was stirred at room temperature for the appropriate time (Table 1). Completion of the reaction was confirmed by TLC. After completion of the reaction, water (5 ml) was added to the reaction mixture and stirred for 2 min. The mixture was filtered and recrystallised from ethanol to afford corresponding products in good yields **3**.

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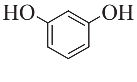
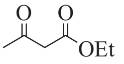
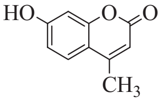
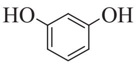
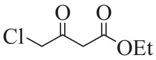
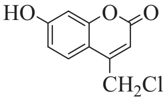
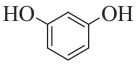
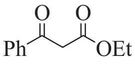
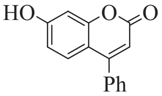
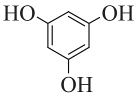
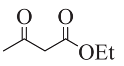
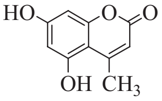
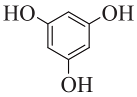
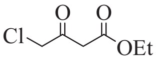
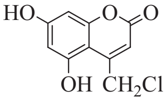
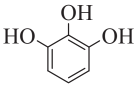
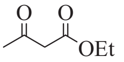
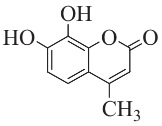
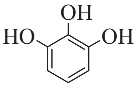
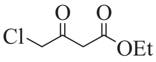
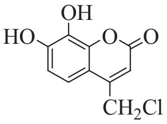
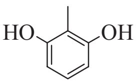
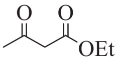
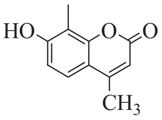
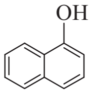
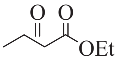
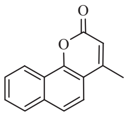
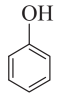
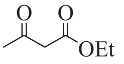
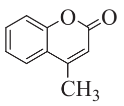
Table 1 $CoPy_2Cl_2$ catalysed synthesis of coumarins

Entry	Phenol	Ester	Coumarin	Method-A		Method-B		M.p./°C
				Time/min	Yield/%[a]	Time/min	Yield/%[a]	
1				2	97	1.5	94	185[19]
2				2	95	2	93	180[21]
3				2.5	96	3	92	257[20]
4				1	96	1.5	94	280[19]
5				1.5	95	2	93	187[22]
6				2	96	2	94	242[19]
7				3	95	2.5	94	134[22]
8				2	97	2.5	96	137[29]
9				3	96	3	94	153[20]
10				3	67	3	58	81[29]

[a]Yields refer to pure products and all products were characterised by comparison of their physical data and in 1H NMR, IR, and mass spectral data with those authentic samples.

After filtration, the filtrate (water) containing the catalyst was evaporated under reduced pressure to give a violet solid. The recovered catalyst was washed with ether, dried at 85°C for 2 h under high-pressure prior to use in a further reaction.

Spectral data

(1) *(Entry 1)*: M.p. 185°C. IR (KBr, cm^{-1}): 3400, 1725, 1530; ^{1}H NMR ($CDCl_3$): δ 10.12 (s, 1H, OH), 7.45 (d, 1H, ArH), 6.88 (d, 1H, ArH), 6.56 (s, 1H, ArH). 6.15 (s, 1H, C-3H), 2.15 (s, 3H, CH_3): ^{13}C NMR ($CDCl_3$): δ = 161.7, 159.6, 152.6, 151.80, 128.9, 113.9, 112.5, 111.5, 109.7, 22.0; EIMS, 70Ev, *m/z*: 176 (M^+).

(2) *(Entry 2)*: M.p. 180°C. IR (KBr, cm^{-1}): 3389, 1705, 1522; ^{1}H NMR ($CDCl_3$): δ 10.09 (s, 1H, OH), 7.43 (d, 1H, ArH), 6.81 (d, 1H, ArH), 6.50 (s, 1H, ArH). 6.14 (s,1H, C-3H), 3.72 (s, 2H, CH_2): EIMS, 70Ev, *m/z*: 210 (M^+).

(3) *(Entry 3)*: M.p. 257°C. IR (KBr, cm^{-1}): 3395, 1717, 1545; ^{1}H NMR (DMSO-d_6): δ 10.32 (s, 1H, OH), 7.14–7.41 (m, 5H, ArH), 6.95 (d, 2H, ArH), 6.82 (s, 1H, ArH). 6.31 (s,1H, C-3H): ^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.7,157.3, 155.1, 151.7, 129.2, 128.7, 126.3, 125.8, 123.1, 122.7, 115.9, 114.2, 109.8; EIMS, 70Ev, *m/z*: 238 (M^+)

(4) *(Entry 4):* M.p. 280°C IR (KBr, cm^{-1}): 3400, 3385, 1718, 1530: ^{1}H NMR (DMSO-d_6): δ 10.20 (s, 1H, OH), 9.89 (s, 1H, OH), 7.23 (s,1H, ArH), 6.98 (s, 1H, ArH),6.12 (s,1H, C-3H), 2.21 (s, 3H, CH_3).^{13}C NMR (DMSO-d_6): δ162.7, 160.1, 159.3, 152.6, 151.31, 112.9, 111.0, 105.5, 101.5, 22.5. EIMS, 70Ev: *m/z*: 192 (M^+).

(5) *(Entry 5):* M.p. 187°C IR (KBr, cm^{-1}): 3419, 3373, 1725, 1565: ^{1}H NMR (DMSO-d_6): δ 10.30 (s, 1H, OH), 10.05 (s, 1H, OH), 7.41 (s,1H, ArH), 6.95 (s, 1H, ArH), 6.32(s,1H, C-3H), 4.05 (s, 2H, CH_2).^{13}C NMR (DMSO-d_6): δ162.1, 160.7, 159.9, 153.7, 151.31, 118.9, 111.0, 108.5, 101.5, 43.5: EIMS, 70Ev: *m/z*: 226 (M^+).

(6) *(Entry 6):* M.p. 242°C IR (KBr cm$^-$): 3410, 3228, 1647, 1583: ^{1}H NMR (DMSO-d_6): δ 10.10 (s, 1H, OH), 9.51 (s, 1H, OH), 7.35 (d, 1H, ArH), 6.85 (d, 1H, ArH),6.15 (s,1H, C-3H), 2.20 (s, 3H, CH_3).^{13}C NMR (DMSO-d_6): δ161.7, 155.5, 153.3, 149.6, 145.21, 122.3, 114.2, 112.5, 110.3, 22.5. EIMS, 70Ev: *m/z*: 192 (M^+).

(7) *(Entry 7):* M.p. 134°C IR (KBr, cm^{-1}): 3421, 3275, 1565: ^{1}H NMR (DMSO-d_6): δ 10.31 (s, 1H, OH), 9.95 (s, 1H, OH), 7.31 (d,1H, ArH), 7.15 (d, 1H, ArH),6.21 (s,1H, C-3H), 3.92 (s, 2H,

CH_2).^{13}C NMR (DMSO-d_6): δ161.7, 159.1, 149.3, 148.5, 147.31, 119.9, 115.7,114.1, 112.5, 42.8. EIMS, 70Ev: *m/z*: 226 (M^+).

(8) *(Entry 8):* M.p. 137°C IR (KBr, cm^{-1}) 3420, 1720,1530: ^{1}H NMR (DMSO-d_6): δ 10.42 (s, 1H, OH), 7.42 (d, 1H, ArH), 6.85 (d,1H, ArH),6.11 (s,1H, C-3H), 2.36 (s, 3H, CH_3), 2.15 (s, 3H, CH_3): ^{13}C NMR (DMSO-d_6): δ 161.3, 159.7, 154.6, 153.6, 123.9, 112.8, 112.5, 111.5, 110.7, 19.0, 8.9: EIMS, 70Ev: *m/z*: 190 (M^+).

(9) *(Entry 9):* M.p: 153°C.IR (KBr, cm^{-1}): 1720,1530: ^{1}H NMR (DMSO-d_6): δ 7.25–7.50 (m, 6H, ArH), 6.11 (s, 1H, C-3H), 2.15(s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 160.3, 156.7, 154.6, 143.6, 128.9, 127.8, 126.5, 126.3, 124.6, 122.7, 122.4, 121.5, 112.1, 22.9: EIMS, 70Ev: *m/z*: 210 (M^+).

(10) *(Entry 10):* M.p: 81°C IR (KBr, cm^{-1}):1720, 1530: ^{1}H NMR (DMSO-d_6): δ 7.02–7.37 (m, 4H, ArH), 6.10 (s,1H, C-3H), 2.20 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ160.7, 152.6, 150.6, 128.9, 125.9, 125.6, 121.5, 111.5, 110.7, 22.0: EIMS, 70Ev: *m/z*: 160 (M^+).

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