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MoO_3/Al_2O_3: AN EFFICIENT AND REUSABLE HETEROGENEOUS CATALYST FOR SOLVENT-FREE SYNTHESIS OF COUMARINS *VIA* PECHMANN CONDENSATION

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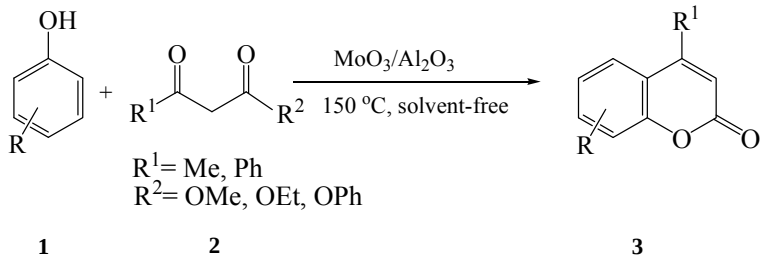
Abstract – 16 wt % alumina supported MoO_3 has been found to be an efficient catalyst for the synthesis of various substituted coumarins *via* Pechmann condensation. This method offers several advantages like high yields, facile recovery and reusability of the catalyst without loss in activity, nearly neutral and solvent free condition**.**

INTRODUCTION

In the recent years, development of greener and more sustainable technologies in chemical industry has become a pressing need due to the stringent environmental and economical regulations. In this context, use of heterogeneous catalyst under solvent free condition is gaining ever-increasing interest due to the facile recovery and reusability of the expensive catalyst. Further solvent-less synthetic methods are valuable not only for green chemistry reason but also for simplicity in procedure and high yields of the products.[1] Coumarin and its derivatives represent an important class of compounds due to their widespread application as additives in food, perfumes, cosmetics, pharmaceuticals, insecticides, optical brightening agents and laser dyes.[2] These compounds are well known to have diverse biological activities including anti-HIV, antiviral, antitumour, antibiotic, anti-inflammatory and antioxidant. Therefore, synthesis of coumarin and its derivatives has become an area of tremendous importance in recent years. Among the various approaches known, Pechmann condensation,[3] which involves the reaction of a phenol with β-ketoester in presence of acid, is particularly useful as it proceeds with simple substrates and affords good yields of the products. However one of the major limitations of this method is the use of strong acid like H_2SO_4, which is difficult to handle and causes environmental hazards.

Consequently, several alternative methods using polyphosphoric acid, trifluroacetic acid,[4] solid superacid,[5] $ZnCl_2$, $POCl_3$, $AlCl_3$,[6] P_2O_5,[7] ion exchange resins,[8] zeolite H-BEA, Nafion-H,[9]

Montmorillonite-K,[10] silica sulfuric acid,[11] alumina supported $MeSO_3H$[12] as catalysts have been explored for synthesis of coumarins *via* Pechmann condensation. The Pechmann condensation has also been attempted using microwave irradiation[13] and in ionic liquids[14] as alternatives to conventional methods. However limitations associated with most of these methods such as requirement of stoichiometric amount of catalyst, tedious purification process, expensive reagents, toxic/volatile organic solvents, longer reaction times and low selectivity leave scope for further development of an efficient, facile and versatile catalytic system for Pechmann condensation. Use of supported reagents helps in meeting the requirement of green synthesis due to their several inherent properties such as improved activity and selectivity of a reagent dispersed on support, high thermal and mechanical stability, non-corrosive nature, easy separation of catalyst from the reaction mixture and reusability. In view of this, herein we reveal the first time use of 16 wt % MoO_3 supported on alumina[15] as a recyclable catalytic system for the synthesis of coumarins via Pechmann condensation under solvent free conditions. (Scheme 1).



Scheme 1

RESULTS AND DISCUSSION

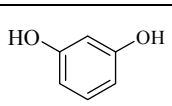
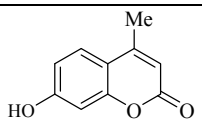
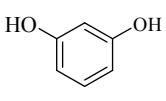
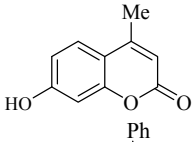
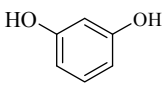
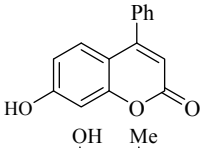
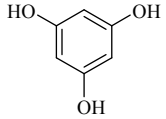
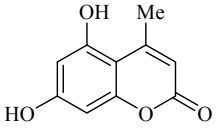
16 wt % MoO_3/Al_2O_3 catalyst was prepared on γ-Al_2O_3 support by incipient wet impregnation method using ammonium heptamolybdate [$(NH_4)_6Mo_7O_{24}$ $4H_2O$] salt. The catalyst was dried at 110 °C (overnight) and finally calcined at 550 °C for 6 h.[16]

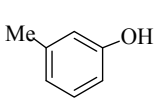
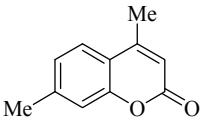
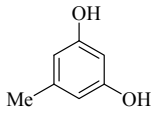
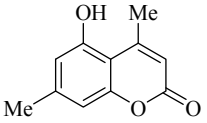
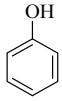
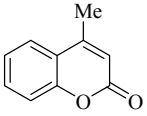
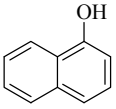
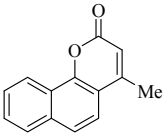
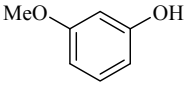
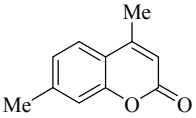
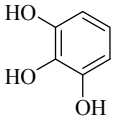
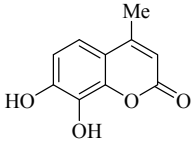
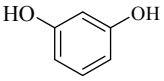
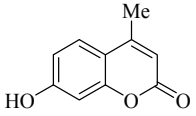
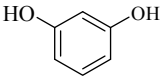
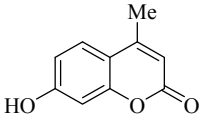
Mo content of the prepared catalyst was estimated by ICP-AES (Inductively Coupled Plasma Atomic Emission Spectroscopy) analysis and was found to be 16 %. X-Ray diffraction pattern of the catalyst showed the amorphous nature and did not show any characteristic peak of MoO_3 indicating that MoO_3 is finely dispersed over Al_2O_3 surface. BET surface area of the catalyst was determined by N_2 adsorption-desorption isotherm at liquid nitrogen temperature (-195 °C) and found to be SBET 248.9 m^2/g and total pore volume 0.394 mL/g, with pore size distribution <10 (15.14 %), 10-20 Å (8.04 %), 20-100 Å (48.85 %), 100-200 Å (25.71 %), 200-500 Å (1.49 %), > 500 Å (0.77 %).

Initially, we carried out the cyclocondensation of resorcinol and ethyl acetoacetate in presence of catalytic amount of 16 % MoO_3 supported on alumina (5 mol %) at 150 °C under solvent free reaction conditions. The reaction mixture got solidified within 30 min. The resulting solid mixture was diluted with ethyl acetate and catalyst was separated by filtration. The filtrate obtained was washed with water, dried over

anhydrous $MgSO_4$ and concentrated under reduced pressure to yield crude product, which was further purified by recrystallization with EtOH to yield pure 7-hydroxy-4-methylcoumarin in 97% yield. Similarly resorcinol was reacted with methyl acetoacetate, phenyl acetoacetate and ethyl benzoylacetate to afford corresponding coumarin under similar reaction condition. These results are presented in Table 1 (entries 1-3). A variety of substituted phenols were efficiently reacted with β-ketoesters to afford corresponding coumarins in high yields using catalytic amounts of 16 % MoO_3 supported on alumina (5 mol %) under similar reaction conditions. These results are summarized in Table 1. Polyhydric alcohols such as resorcinol, pyrogallol and phloroglucinol were found to be more reactive. Phenol reacted sluggishly and yielded coumarin in moderate yield (Table 1, entry 7). 1-Naphthol afforded corresponding coumarin in good yield but requires longer reaction time (Table 1, entry 8). Condensation of 3-methoxyphenol with ethyl acetoacetate under described reaction conditions yielded coumarin selectively without any evidence for the formation of demethylated product as mentioned in various conventional methods[14] (Table 1, entry 9). In a controlled blank experiment, Pechmann condensation of resorcinol and ethyl acetoacetate did not proceed in the absence of catalyst, establishing the MoO_3 supported on alumina to be the main promoter for this reaction. Similarly no reaction between resorcinol and ethyl acetoacetate was observed in the presence of pure thermally treated alumina under similar reaction conditions. Further we studied the condensation of resorcinol and ethyl acetoacetate in presence of pure thermally treated MoO_3 (Aldrich) under similar reaction conditions. The reaction was found to be slow and gave poor yield of desired product (Table 1, entry 11). The high catalytic activity of 16 % MoO_3/Al_2O_3 in this reaction is presumably due to increased Lewis acidity of Mo oxide dispersed on alumina support. Further the use of 8 wt % MoO_3/Al_2O_3 in place of 16 wt % MoO_3/Al_2O_3 resulted in decreasing yield of desired product (Table 1, entry 12).

Table 1. Alumina supported MoO_3 catalyzed cyclocondensation of phenols and β-ketoesters[a]

Entry	Substrate	Coumarin	Reaction Time (h)	Yield (%)[b]	Melting Point °C	
					Found	Reported
1			0.5	97[c], 97[d]	182-186	185[8]
2			1.0	92[e]	182-186	185
3			1.5	89[f]	240-242	244[17]
4			0.75	93[c], 91[d]	281-283	282-284[18]

5			3.0	90[c], 88[d]	130-132	131.5-132[10]
6			2.5	91[c], 89[d]	246-249	248-250[19]
7			4.0	65[g c], 63[g d]	79-81	82[20]
8			5.0	88[c], 87[d]	152-155	155[21]
9			1.5	92[c], 89[d]	160-161	158-159[20]
10			0.75	89[c]	232-244	235[17]
11			2.5	60[h, c]	182-186	185
12			1.5	75[i, c]	182-186	185

[a]: Reaction condition: Substrate **1** (1 mmol), β-ketoester **2** (1 mmol), 16 wt % MoO_3/Al_2O_3 (5 mol %) at 150 ^oC. [b]: Isolated Yields. [c]: Experiments carried out with ethyl acetoacetate. [d]: Experiments carried out with methyl acetoacetate. [e]: Experiments carried with phenyl acetoacetate. [f]: Experiments carried with ethyl benzoylacetate. [g]: Reaction was carried out at 120 ^oC. [h]: Reaction was carried out using pure MoO_3. [i]: Reaction was carried out using 8 wt % MoO_3/Al_2O_3 as a catalyst.

To evaluate the effect of solvent, we studied the Pechmann condensation of resorcinol and ethyl acetoacetate using 5 mol % of 16 % MoO_3 supported on alumina as catalyst in various organic solvents like toluene, nitrobenzene and acetonitrile at their refluxing temperatures under similar reaction conditions (Table 2). Among the various solvents studied, toluene was found to be efficient but solvent free conditions remained best both from yield and reaction time points of view. To evaluate the effect of reaction temperature, condensation of resorcinol and ethyl acetoacetate in presence of catalytic amount of 16 wt % MoO_3/Al_2O_3 was carried out at different temperatures under similar reaction conditions. The reaction rate was found to be very slow at room temperature, while it increased with increase in temperature as shown in Table 2. At 150 ^oC reaction rate was found to be maximum and further increase in temperature did not show any enhancements. When condensation of resorcinol and ethyl acetoacetate was carried out in presence of 16 wt % MoO_3/Al_2O_3 under microwave irradiation, coumarin (**1a**) was obtained in 92 % yield.

Table 2: Results of reaction of resorcinol and ethyl acetoacetate under different reaction conditions.[a]

Entry	Solvent	Temperature	Time (h)	Yield (%)[b]
1	toluene	110 ^{o}C	3.0	55
2	nitrobenzene	110 ^{o}C	3.0	40
3	acetonitrile	80 ^{o}C	5.0	25
4	-	room temp.	5.0	20
5		80 ^{o}C	4.5	40
6	-	110 ^{o}C	2.5	70
7	-	150 ^{o}C	.5	97

[a]: Resorcinol (1 mmol), ethyl acetoacetate (1 mmol), 16 wt % MoO_3/Al_2O_3 (5 mol %).
[b]: Isolated yields.

The recyclabitity of the catalyst was established by carrying out condensation of resorcinol with ethyl acetoacetate using recovered catalyst under similar reaction conditions. After completion of reaction, the reaction mixture was diluted with ethyl acetate and catalyst was recovered from reaction mixture by filtration. The recovered catalyst was reused as such for subsequent experiments (3 times). The observed fact that yields of coumarin and reaction times remained almost same in these experiments established the recyclability/reusability of the catalyst (Table 3). There was no catalyst leaching as ascertained by ICP-AES analysis of Mo content of recovered and fresh MoO_3/Al_2O_3 catalyst.

Table 3. Results of recyclability of the catalyst MoO_3/Al_2O_3 in cyclocondensation of resorcinol and ethyl acetoacetate.

Run	Catalyst (mol %)	Reaction Time (h)	Yield (%)[a]
1[b]	-	5.0	0
1[c]	5	0.5	97
2[c]	5	0.5	96
3[c]	5	0.5	95

[a]: Isolated yields. [b]: Blank experiment without using catalyst. [c]: Reaction conditions same as per Table 1 entry 1.

In conclusion, we have developed an environmentally acceptable improved protocol for synthesis of various substituted coumarins using 16 wt % MoO_3/Al_2O_3 as a recyclable heterogeneous catalyst under solvent free conditions. The key advantages of the developed method are (i) green synthesis as it reduces the environmental pollution causing by the use of homogeneous metal complexes and volatile organic solvents (ii) easy work-up (iii) recyclability and reusability of catalyst with consistent activity.

EXPERIMENTAL

All the reactions were carried out without any special precautions in an atmosphere of air. All the phenols and β-ketoesters used were purchased from Aldrich. Melting points were determined in open capillaries in Büchi apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on Bruker 300 MHz spectrometer and the chemical shifts are expressed in δ parts per million relative to tetramethylsilane (TMS) as internal standard. The IR spectra were recorded on a Perkin Elmer FTIR X 1760 instrument.

Typical Experimental Procedure: To a stirred mixture of phenol (1 mmol) and β-ketoester (1 mmol) in a 25 mL round bottom flask, was added 16 wt % MoO_3/Al_2O_3 (5 mol %) at 150 ^oC under solvent free condition. The temperature of the reaction vessel was maintained using an oil bath. Progress of the reaction was monitored by TLC (SiO_2). At the end of reaction, reaction mixture got solified. The resulting solid mixture was cooled to rt and diluted with EtOAc (5 mL) to recover catalyst by filtration. The filtrate obtained was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield crude product. The crude product was further purified either by recrystalization with EtOH or flash chromatography using EtOAc:hexane (4:6) as eluent to afford pure coumarin.

Product 1a (Table 1, entry 1): ^{1}H NMR ($CDCl_3$) δ ppm 2.35 (s, 3H), 6.10 (s, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 6.90 (s, 1H), 7.44 (d, *J* = 8.7 Hz, 1H). IR (KBr) 3200-3000, 1690.

Product 3a (Table 1, entry 3): ^{1}H NMR ($CDCl_3$) δ ppm 6.12 (s, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.90 (s, 1H), 7.30-7.40 (m, 5H), 7.49 (d, *J* = 8.7 Hz, 1H). IR (KBr) 3200, 3390, 2890, 1690, 1545.

Product 4a (Table 1, entry 4): ^{1}H NMR (DMSO-d_6) δ ppm 2.50 (s, 3H), 5.84 (s, 1H), 6.20 (s, 1H), 6.30 (s, 1H). IR (KBr) 3473, 3200, 1670, 1610.

Product 5a (Table 1, entry 5): ^{1}H NMR ($CDCl_3$) δ ppm 2.42 (s, 3H), 3.85 (s, 3H), 6.14 (s, 1H), 6.80 (s, 1H), 6.88 (d, *J*= 8.7 Hz, 1H), 7.49 (d, *J*= 8.7 Hz, 1H). IR (KBr) 3009, 2925, 1680.

Product 6a (Table 1, entry 6): ^{1}H NMR ($CDCl_3$) δ ppm 2.44 (s, 3H), 3.90 (s, 3H), 6.12 (s, 1H), 6.78 (s, 1H), 7.10 (s, 1H). IR (KBr) 3210-3009, 2925, 1680.

Product 7a (Table 1, entry 7): ^{1}H NMR ($CDCl_3$) δ ppm 2.42 (s, 3H), 6.17 (s, 1H), 7.15-7.44 (m, 3H), 7.49(d, *J*= 6.0 Hz, 1H). IR (KBr) 3010, 2925, 1669, 1140.

Product 8a (Table 1, entry 8): ^{1}HNMR ($CDCl_3$) δ ppm 2.47 (s, 3H), 6.39 (s, 1H), 7.50 (d, *J* = 9.0 Hz, 1H) 7.55-7.70 (m, 2H), 7.91 (d, *J* = 8.7 Hz, 1H), 8.00 (d, *J* = 9.0 Hz, 1H) 8.63 (d, *J* = 8.7 Hz, 1H). IR (KBr) 3067, 3020, 2860, 1716, 1081.

Product 9a (Table 1, entry 9): ^{1}H NMR ($CDCl_3$) δ ppm 2.35 (s, 3H), 3.75 (s, 3H), 6.19 (s, 1H), 6.84 (s, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 1H). IR (KBr) 3067, 2970, 1742, 1625.

Product 10a (Table 1, entry 10): ^{1}H NMR ($CDCl_3$) δ ppm 2.32 (s, 3H), 6.10 (s, 1H), 6.80 (d, 1H, *J*=8.7 Hz), 7.09 (d, *J* = 8.7 Hz, 1H), 9.28 (s, 1H), 10.05 (s, 1H). IR (KBr) 3417, 3237, 2965, 2956, 1655, 1604.

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