

Synthesis of β -Amino Carbonyl Compounds via Mannich reaction using sulfated MCM-41

Pullar Vadivel, Cinnathambi Subramani Maheswari, Appaswami Lalitha

Abstract-One-pot three-component reaction of anilines with ketone and aldehyde leads to the formation of β -amino carbonyl compounds in the presence of sulfated MCM-41 as a recyclable solid acid catalyst. This method has several advantages like simple and easy work-up procedures with shorter reaction time and high yields of Mannich products.

Index Terms: β -amino carbonyl compounds, Sulfated MCM-41, solid acid catalyst, Mannich products.

I. INTRODUCTION

The formation of carbon-carbon bonds is crucial to the development of organic molecules such as medicines, biodegradable plastics and natural products and a great deal of research has been focused in this area recently. Mannich reaction plays a vital role in the construction of variety of organic molecules [1]. The products of the Mannich reaction are used for the synthesis of amino alcohols, peptides and lactams and as precursors to synthesize amino acids. In this regard, we have synthesized β -amino ketones as products of three component Mannich reaction in the presence of sulfated MCM-41 as a reusable heterogeneous catalyst. The good yields under mild reaction conditions with low catalyst loading make this protocol an attractive one. Moreover there is no formation of by-products making this protocol an important addition to the methods of synthesis of natural products. Many natural products have been discovered to have medicinal values including anti-bacterial, anti-tumor, and anti-cancer properties. Aspirin, for example, was originally found in tree bark and used medicinally by the Greeks and Romans before being synthetically produced in 1899 [2].

The conventional catalysts for classical Mannich reaction of aldehydes, ketones and amines involve mainly organic or mineral acids. A vast literature available for the synthesis of β -amino carbonyl compounds using Mannich reaction includes catalysts such as $\text{HClO}_4\text{-SiO}_2$ [3], bromo dimethylsulfonium bromide (BDMS) [4], TMSCl [5], *p*-TSA [6], SmCl_3 [7], Amberlyst-15 [8], $\text{AuCl}_3\text{-PPh}_3$ [9], silica supported sulfuric acid [10], carbon-based solid acid [11], InCl_3 [12], NbCl_5 [13], sulfamic acid [14], Fe_3O_4 -cysteine MNP [15], ionic liquid [16], Bismuth(III) chloride

[17], sucrose char sulfonic acid [18], boric acid [19] and $\text{Zn}(\text{OTf})_2$ [20]. Herein we report the synthesis of β -amino carbonyl compounds in presence of sulfated MCM-41 as a catalyst with good yield.

II. EXPERIMENTAL METHODS

General Method

Materials used such as, CTAB, TEOS, aromatic amine, aromatic aldehydes, aromatic ketones and cyclohexanone are commercially available and were purchased and used without further purification. Solvents were purified by the standard procedures. Melting points of the products were determined in open capillaries and are uncorrected. ^1H NMR spectra were recorded on 500 MHz NMR Bruker spectrometer using CDCl_3 as solvent. Chemical shifts are mentioned in ppm. IR spectra were recorded in Nicolet FT-IR spectrometer $400\text{-}4000\text{ cm}^{-1}$.

Synthesis of MCM-41

About 1.988g of cetyl trimethyl ammonium bromide (CTAB, 98%) was dissolved in 120ml of water at room temperature. After complete dissolution, 8ml of aqueous ammonia (32% in water) was added and then, 10ml of tetraethyl orthosilicate (TEOS, 99%) was added with vigorous stirring (300 rpm). The hydrolysis of TEOS happened during the first 2 min at room temperature (the solution becomes milky and slurry forms) and the condensation of the mesostructured hybrid material was achieved after 2 h of reaction. The material was then filtered and allowed to dry under static air at $80\text{ }^\circ\text{C}$ for 12 h. The mesoporous material was finally obtained by calcinating the hybrid structure at $550\text{ }^\circ\text{C}$ for 5h.

Synthesis of sulfated MCM-41 [21]

The sulfated MCM-41 sample was prepared by wet impregnation method. The sulfate ion was impregnated in the form of H_2SO_4 . About 1 g of the calcined sample of MCM-41 was treated with required amount of 0.25M H_2SO_4 at room temperature for 2 h and heated at $70\text{ }^\circ\text{C}$ to get a dry solid. Then the sample was dried at $110\text{ }^\circ\text{C}$ for 10 hr, in an air oven and subsequently calcinated at $550\text{ }^\circ\text{C}$ for 5 h in a muffle furnace.

Typical general procedure for Mannich reaction

A mixture of an aromatic aldehyde (1eq.), aniline (1eq.) and aromatic ketone or cyclohexanone or diethylmalonate (1eq.) in ethanol (5 mL) and sulphated MCM-41(100mg) was refluxed and the reaction was monitored by thin-layer chromatography (TLC). After completion, the mixture was filtered, and the catalyst was recovered by washing with ethanol.

Manuscript published on 30 April 2013.

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III. RESULTS AND DISCUSSION

One pot three component condensation reaction of aromatic aldehyde, aromatic ketone or cyclohexanone or diethyl melonate with aromatic amine to provide β -amino carbonyl compounds would be an ideal Mannich type reaction and can be considered as one of the convenient C-C bond forming reaction. We have performed the cyclo condensation in the presence sulfated MCM-41 as a catalyst to get good yields of the corresponding products.

MCM-41, a member of the M41S family, possesses a regular hexagonal array of uniform pore openings with a broad spectrum of pore diameters between 15 and 100 Å [22]. The mesoporous structure can be controlled by the choice of templates (surfactants) and changing the reaction parameters like temperature, compositions, etc., The pores of these novel materials are nearly as regular as those present in crystalline microporous materials like zeolites, offering newer opportunities for applications to catalysis with added advantages of larger pore size. Synthetic organic chemists face an increasing obligation to optimize their synthetic methods in order to produce the desired product in high yields and selectivity via a safe and environmentally acceptable process. By taking this as a challenge, we intend to replace the existing catalysts by MCM-41 which is having advantages such as, adjustable acid strength, hydrophilic and hydrophobic properties, and easier to separate from the product there by providing catalyst reusability.

The silanol groups present in the MCM-41 was found to be mild acidic in nature, resulting in longer reaction time with low yield of β -amino carbonyl compounds. In order to improve the acidity, MCM-41 was impregnated with 0.25M H₂SO₄ and the resulting sulfated MCM-41 was characterized by scanning electron microscopy, X-ray diffraction and IR spectroscopy. As a continuation of our efforts for the development of greener synthetic methodologies using MCM-41 materials [23], we are reporting the synthesis of substituted β -amino carbonyl compounds using sulfated MCM-41 as catalyst. The catalytic activity of the sulfated MCM-41 was tested for the reaction of acetophenone (1eq.), benzaldehyde (1eq.) and 4-chloroaniline (1eq.) in ethanol yielding the corresponding β -amino ketone (**Scheme 1**).

The solvents played an important role in the Mannich reaction catalyzed by sulfated MCM-41. Different solvents like EtOH, CH₃CN, CH₂Cl₂, H₂O, CHCl₃, Et₂O, and toluene were tested for the reaction in which the reaction in EtOH afforded products in high selectivity with nearly complete conversion (**Table 1**). Therefore, EtOH was selected as the solvent in further investigations.

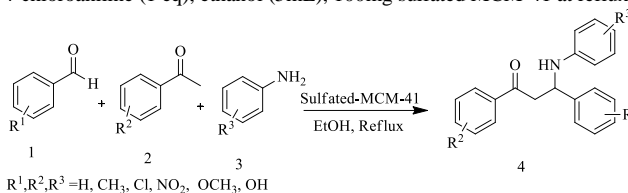
After optimizing the dosage of the catalyst, studies have been focused on the application of sulfated MCM-41 for Mannich reactions with different aldehydes and the results are given in **Table 2**. All the reactions were completed within the periods ranging from 5 to 8 h to provide good yields of β -amino carbonyl compounds.

Table 1. Mannich reactions of benzaldehyde (1eq.), 4-chloroaniline (1eq.), and acetophenone (1eq.) using different solvents

Entry	Solvent	Isolated product ^a (%)
1	EtOH	93
2	CH ₃ CN	65
3	CHCl ₃	55

4	Toluene	-
5	H ₂ O	-
6	CH ₂ Cl ₂	trace
7	Et ₂ O	-

^aReaction conditions: acetophenone (1 eq), benzaldehyde (1 eq), 4-chloroaniline (1 eq), ethanol (5mL), 100mg sulfated MCM-41 at reflux.



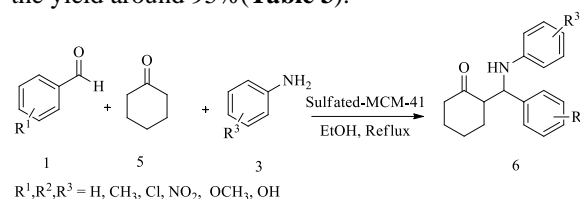
Scheme: 1 Three-component Mannich reaction of benzaldehyde with aniline and acetophenones

Table: 2 Three-component Mannich reaction of benzaldehyde with aniline and acetophenone.^a

Entry	Product ^b	R ₁	R ₂	R ₃	Time(h)	Yield ^c
1	4a	H	H	H	6	95
2	4b	H	H	4-Cl	5	92
3	4c	4-OH	H	H	5	95
4	4d	H	4-NO ₂	H	7	89
5	4e	4-OCH ₃	H	H	7	85
7	4g	4-NO ₂	H	H	6	80
8	4h	H	4-Cl	H	7	84
9	4i	4-Cl	H	H	8	82
10	4j	4-Cl	H	4-Cl	8	83

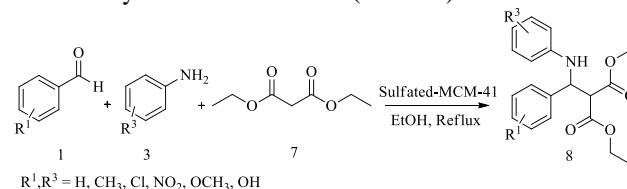
^aReaction conditions: acetophenone (1 eq), benzaldehyde (1 eq), aniline (1 eq), ethanol (5mL), 100mg sulfated MCM-41 at reflux. ^bProducts were characterized by melting point, IR, ¹H NMR and comparison with literature. ^cIsolated yield

Due to the observed conversions, the above reaction was also carried out using some other active methylenic compounds. Mannich reaction of benzaldehyde and anilines with cyclohexanone in the above experimental manner gives the yield around 95% (**Table 3**).



Scheme: 2 Three-component Mannich reaction of benzaldehyde with aniline and cyclohexanone

Similarly, the Mannich reaction of benzaldehyde and anilines with diethyl melonate was also investigated in which the yield was about 93% (**Table 4**).



Scheme: 3 Three-component Mannich reaction of benzaldehyde with aniline and diethyl melonate

Table: 3 Three-component Mannich reaction^a of benzaldehyde with aniline and cyclohexanone

Entry	Product ^b	R ₁	R ₃	Time(h)	Yield ^c
1	6a	H	H	6	95
2	6b	H	4-Cl	5	92
3	6c	2-Cl	H	4	95
4	6d	4-Cl	4-Cl	7	89
5	6e	4-OCH ₃	H	7	85
6	6f	2-Cl	4-Cl	7	83
7	6g	H	4-Cl	6	83

^aReaction conditions: cyclohexanone (1 eq), benzaldehyde (1 eq), aniline (1 eq), ethanol (5mL), 100mg sulfated MCM-41 at reflux.

^bProducts were characterized by melting point, IR, ¹H NMR and comparison with literature. ^cIsolated yield

Table: 4 Three-component Mannich reaction^a of benzaldehyde with aniline and diethyl melonate

Entry	Product ^b	R ₁	R ₃	Time(h)	Yield ^c
1	8a	H	H	8	93
2	8b	H	4-Cl	9	92
3	8c	4-OH	H	8	91
4	8d	4-NO ₂	H	7	89
5	8e	4-OCH ₃	H	8	85
6	8f	4-Cl	4-Cl	9	83
7	8g	2-Cl	4-Br	9	85

^aReaction conditions: Diethyl melonate (1.2 eq), benzaldehyde (1 eq), aniline (1 eq), ethanol (5mL), 100mg sulfated MCM-41 at reflux.

^bProducts were characterized by melting point, IR, ¹H NMR and comparison with literature. ^cIsolated yield

Reusability of MCM-41

Additionally, we have investigated the reusability of sulfated MCM-41. At the end of the reaction, the catalyst that could be recovered by simple filtration has been washed with methanol and subjected to a second run of the reaction process. In **Table 5**, the comparison of efficiency of sulfated MCM-41 in the synthesis of **4b** for four consecutive cycles is reported. As shown in **Table 5**, the first reaction using recovered sulfated MCM-41 afforded the yield similar to that obtained in the first run. In the second, third, and fourth runs, the yields were gradually decreased.

Table 5 Reusability of the MCM-41 for Synthesis of β-amino carbonyl compound **4b**.

Entry	Time (h)	Isolated Yield (%)
1	5	95
2	6	93
3	6	88
4	6	84
5	7	70

Spectral Data

1,3-Diphenyl-3-(phenylamino)propan-1-one (4a): ¹H NMR (500 MHz, TMS, CDCl₃), δ 3.44 (d, J = 6.2 Hz, 1H), 3.50 (d, J = 6.2 Hz, 1H), 5.03 (m, 1H), 6.54 (d, J = 7.8 Hz, 2H), 6.62-6.68 (m, 1H), 7.05-7.09 (m, 2H), 7.23 (d, J = 6.4 Hz, 1H), 7.29-7.34 (m, 2H), 7.42-7.55 (m, 5H), 7.89 (d, J = 7.8 Hz, 2H).

3-(4-Nitrophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4g): ¹H NMR (500 MHz, TMS, CDCl₃), δ 3.54 (d, J = 6.1 Hz, 2H), 5.17 (t, J = 6.1 Hz, 1H), 6.77 (d, J = 6.9 Hz, 2H), 6.92 (t, J = 6.8 Hz, 1H), 7.15 (t, J = 7.8 Hz, 2H), 7.47 (t, J =

7.4 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.69 (t, J = 8.5 Hz, 2H), 7.91 (d, J = 7.8 Hz, 2H), 8.20 (d, J = 8.5 Hz, 2H).

3-(4-Chlorophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4i): ¹H NMR (500 MHz, TMS, CDCl₃), δ 3.41-3.53 (m, 2H), 4.59 (br, 1H), 5.01 (t, J = 5.6 Hz, 1H), 6.34 (t, J = 7.6 Hz, 2H), 6.55 (d, J = 7.6 Hz, 2H), 6.92 (t, J = 6.8 Hz, 2H), 7.06 (t, J = 8.4 Hz, 2H), 7.39-7.52 (m, 2H), 7.61 (t, J = 7.6 Hz, 2H), 7.95 (d, J = 8.0 Hz, 2H).

2-(Phenyl (phenylamino) methyl) cyclohexanone (6a):

¹H NMR (500 MHz, CDCl₃): δ 7.37-7.34 (m, 2 H), 7.30-7.26 (m, 2 H), 7.22-7.17 (m, 1 H), 7.06-7.03 (m, 2 H), 6.62-6.59 (m, 1 H), 6.53-6.51 (m, 2 H), 4.73 (s, br, 1 H), 4.62 (d, J = 7.1 Hz, 1H), 2.75-2.73 (m, 1 H), 2.41-2.30 (m, 2 H), 1.90-1.80 (m, 4 H), 1.70-1.65 (m, 2 H)

2-(2-Chlorophenyl(4-chlorophenylamino)methyl) cyclohexanone (6f):

¹H NMR (500 MHz, CDCl₃): δ 7.51 (d, J = 9.4 Hz, 1 H), 7.33 (d, J = 9.4 Hz, 1 H), 7.18-7.13 (m, 2 H), 7.02-7.00 (m, 2 H), 6.43-6.40 (m, 2 H), 5.31 (d, J = 7.0 Hz, 1 H), 4.83 (d, J = 4.7 Hz, 1 H), 2.93-2.89 (m, 1 H), 2.35-2.29 (m, 2 H), 2.08-2.00 (m, 2 H), 1.97-1.93 (m, 2 H), 1.77-1.73 (m, 2 H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 213.4, 145.8, 138.9, 133.5, 129.6, 129.2, 129.1, 128.6, 127.3, 122.3, 114.7, 55.8, 55.4, 43.1, 33.0, 28.4, 25.1 ppm.

2-(Phenyl (4-Chlorophenylamino) methyl) diethyl malonate (8b): ¹H NMR (500MHz, CDCl₃): δ 7.43-7.35 (m, 5H), 7.15-7.12 (m, 2H), 6.63-6.60 (m, 2H), 5.37 (br, 1H), 5.12 (d, 1H), 4.21-4.37 (m, 4H), 3.85(d, 1H), 1.35 (t, 3H), 1.23 (t, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 168.7, 167.8, 145.3, 139.3, 129.2, 129.0, 128.1, 126.8, 122.8, 115.2, 62.9, 62.3, 58.3, 57.8, 15.1, 14.9 ppm

2-(4-Chlorophenyl (4-Chlorophenylamino)methyl) diethyl malonate (8k): ¹H NMR (500 MHz, CDCl₃): δ 7.25-7.20 (m, 4H), 6.92 (d, 2H), 6.45 (d, 2H), 5.5 (br, 1H), 5.1 (d, 1H), 4.17-4.10 (m, 4H), 3.75 (d, 1H), 1.17 (t, 3H), 1.13 (t, 3H). ¹³C NMR (125MHz, CDCl₃): δ 168.3, 167.3, 144.7, 137.6, 133.7, 129.0, 128.9, 128.1, 122.9, 114.9, 62.2, 61.9, 57.8, 56.8, 14.4, 14.3 ppm.

IV. CONCLUSION

Sulphated MCM-41, as a heterogeneous catalyst showed effective catalytic activity in the synthesis of β-amino ketones via three component Mannich reaction. The good yields, mild conditions, low catalyst loading and convenient operations as well as no formation of by-products made it to be considered that this protocol would play important role in the synthesis of natural products.

ACKNOWLEDGEMENTS

PV gratefully acknowledges the financial support from UGC Minor Research Project; F.No: MRP/SERO/3817/11, Hyderabad, India.

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