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Mesoporous silica nanoparticles (MSNs) as an efficient and reusable nanocatalyst for synthesis of β-amino ketones through one-pot three-component Mannich reactions†

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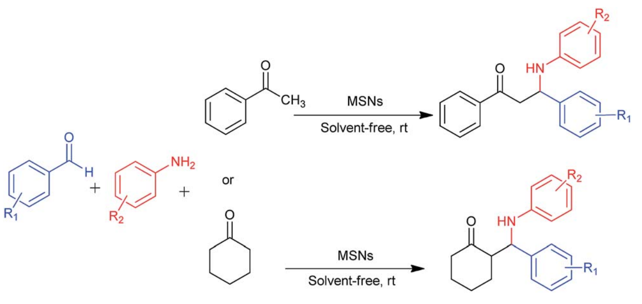
Mesoporous silica nanoparticles (MSNs) proved efficient and reusable in the catalytic synthesis of β-amino ketones, through three-component Mannich reaction of ketones, aromatic aldehydes and aromatic amines under solvent-free conditions. Simple reaction conditions coupled with simple work-ups, makes this methodology a superior option for the synthesis of such β-amino ketones.

Introduction

Synthesis of natural molecules, pharmaceuticals and other nitrogenous biologically active compounds has long been a significant branch of organic chemistry.[1,2] Multicomponent condensation reactions (MCRs) have been discovered to be a powerful tool for the synthesis of organic compounds. The products are formed in a single step and diversity can be achieved by simply varying a single component.[3,4] On the other hand, Mannich reaction is a very useful tool for development and synthesis of several molecules.[5] This reaction is an important carbon–carbon bond forming reaction in organic synthesis. It is used for preparation of various nitrogen-containing natural products and intermediates of significant pharmaceuticals.[6–8] The products of Mannich reaction are mainly β-amino carbonyl compounds and their derivatives. The β-amino carbonyl functionality is not only a segment of biologically active natural products but also serves as a key intermediate for synthesis of important nitrogen containing compounds such as β-amino acids, β-lactams, and β-amino alcohols.[9–13] Therefore, much consideration has been drawn to the development of new synthetic methods to prepare these compounds. The conventional catalysts for classical Mannich reaction of aldehydes, ketones and amines involve mainly organic or mineral acids like proline,[14,15] I_2,[16] *p*-dodecyl benzene sulphonic acid[17] and some Lewis acids.[18] Over the past decades, ionic liquids,[19–22] nanoparticles,[23–25] and enzymes[26] have been investigated. However, these methods suffer from several drawbacks such as low yields, long reaction times, high temperature, tedious work-up procedures, toxic solvents and use of expensive and air sensitive catalysts.

Therefore, the search for the new readily available and green catalysts is still being actively pursued. In recent years, mesoporous materials have attracted much attention because of their many advantageous properties, such as facile synthesis, stable mesostructures, large surface areas, well-defined surface properties, versatile inner and outer surface chemistry, and good biocompatibility.[27–29] Also, because of the availability of a large number of free silanol groups on their surface, they could be applied as catalysts.[30] In continuation of our efforts on the development of green and sustainable methods, we are especially interested in preparation and development of efficient and simple MSNs catalyst.[31] In this study, MSNs is employed as a heterogeneous nanocatalyst in the synthesis of β-amino ketones through the Mannich-type reaction of aldehydes, anilines and ketones, under solvent-free conditions (Scheme 1).



Scheme 1 The Mannich-type reaction catalyzed by mesoporous silica nanoparticles (MSNs).

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Results and discussion

MSNs was prepared (Scheme 2) and characterized by different techniques, including X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), Fourier transforms infrared (FT-IR), nitrogen absorption and desorption analyzes.

X-ray diffraction

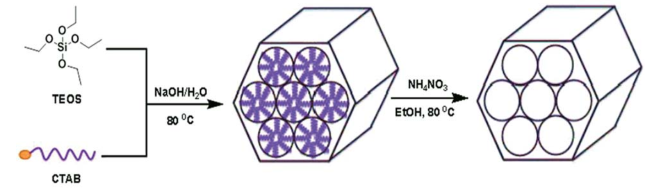
X-ray diffraction (XRD) is conducted to determine the structures of MSNs. The low-angle XRD pattern show three main diffraction peaks due to (1 0 0), (1 1 0), and (2 0 0) planes, respectively, which well correspond to the typical diffraction peaks of hexagonal mesoporous structure (Fig. 1).

SEM and TEM

The SEM image showed that the embedded mesoporous nanoparticles were present as uniform particles with spherical morphology (Fig. 2a). TEM image display rather monodispersed spherical MSNs with a mean diameter of 110 ± 10 nm (Fig. 2b).

FT-IR spectroscopy

Asymmetric and symmetric Si–O–Si stretching vibrations of MSNs appear at 1086 cm^{-1} and 801 cm^{-1} respectively. These are along with that of Si–OH at 962 cm^{-1} and bending Si–O–Si at 461 cm^{-1}. The broad band around 3450 cm^{-1} is due to the surface silanols and adsorbed water molecules and the band at 1635 cm^{-1} is assigned to the H–O–H bending vibrations of the free or absorbed water molecules. Also, in the FT-IR spectrum of MSNs, C–H stretch (2854 cm^{-1} and 2923 cm^{-1}) peaks from CTAB surfactants disappeared after the CTAB removal process, which indicate that no residual CTAB existed in the material (Fig. 3).



Scheme 2 Preparation of mesoporous silica nanoparticles (MSNs).

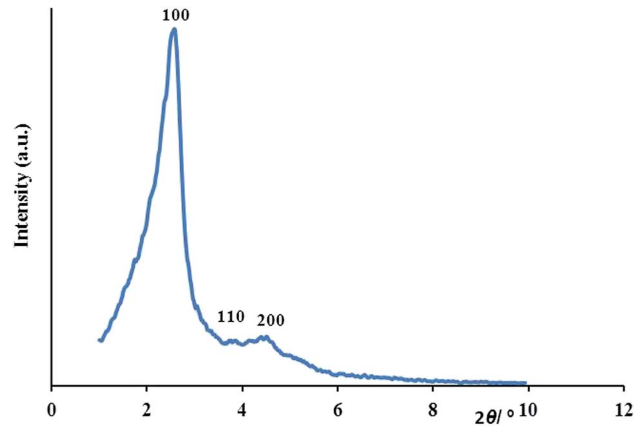


Fig. 1 XRD pattern of MSNs.

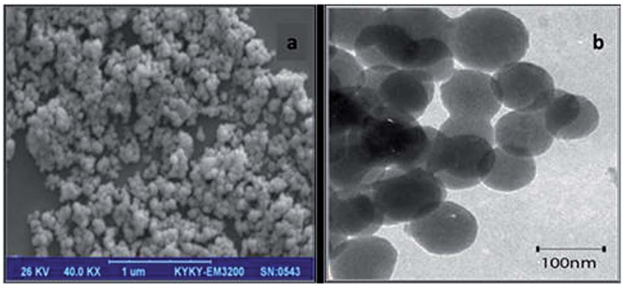


Fig. 2 The SEM image (a) and the TEM image (b) of MSNs.

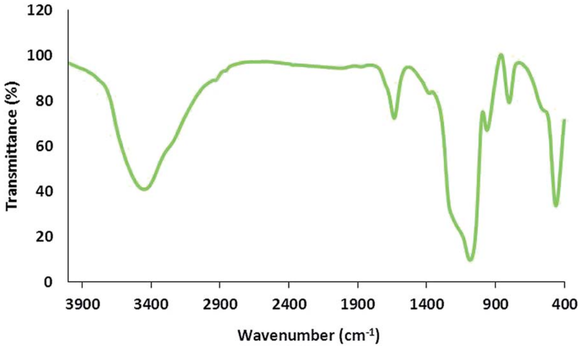


Fig. 3 The FT-IR spectrum of MSNs.

Nitrogen absorption and desorption analyzes

The total surface area and average pore diameter of MSNs were analyzed by the N_2 adsorption and desorption measurements. The Brunauer–Emmett–Teller (BET) isotherm displayed typical IV isotherm according to the IUPAC classification, showing the characteristic of mesopores (Fig. 4). The sharp inflection over a narrow relative pressure ranging from 0.18 to 0.29 indicates that capillary condensation occurs in the mesopores and illustrates that MSNs have uniform pores. The surface area, total pore volume and pore diameter of MSNs determined from the BET equation were 1553 m^2 g^{-1}, 1.10 cm^3 g^{-1} and 2.85 nm, respectively.

After characterization of MSNs, its role as a catalyst was evaluated in synthesis of β-amino ketones. In order to optimize the reaction conditions, three-component Mannich reaction of benzaldehyde, aniline and acetophenone was probed using different amounts of catalyst (5, 10 and 15 mg). The results showed no substantial improvement in the yield with further increase of catalyst at room temperature, under solvent-free conditions. Also, the model reaction was carried out in several solvents (ethanol, acetone, acetonitrile, toluene, and H_2O) and found that reaction under solvent-free conditions was most efficient with respect to reaction time and yield. So, the optimal conditions of the reaction were selected to use no solvent, at

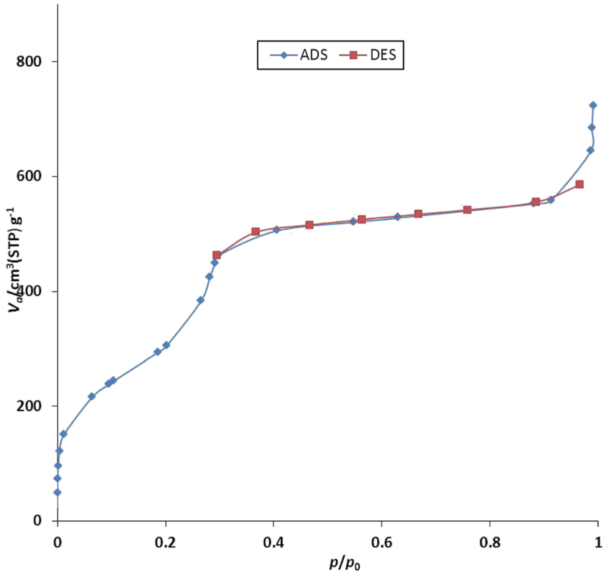


Fig. 4 Nitrogen adsorption and desorption isotherms of MSNs.

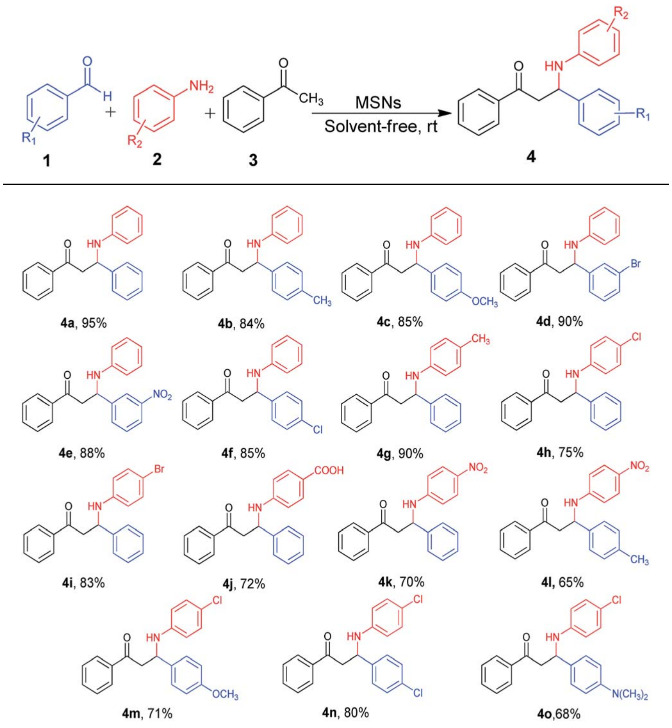
room temperature and in the presence of 15 mg catalyst. With the optimized reaction conditions in hand, different benzaldehydes, anilines and acetophenone gave product (**4**) in moderate to good yields in 6–15 h (Table 1). Aromatic aldehydes and anilines with either electron-withdrawing or electron-donating substituents were all suitable to the reactions. However, with electron-withdrawing substituents in aldehyde and electron-donating substituents in aniline, increased yield of products were obtained and the effect was reversed with strong electron-withdrawing substituents such as $-NO_2$ in aniline.

To further broaden the scope of this protocol, we also investigated three-component Mannich reaction using cyclohexanone under the same reaction conditions. It was found that the corresponding β-amino ketones (**6**) were formed in good to moderate yields (Table 2). The result showed cyclohexanone was more reactive than acetophenone and required shorter reaction times (2–3 h) to give the desired products.

Our suggested probable reaction mechanism for the synthesis of β-amino ketones mediated by MSNs is outlined in Scheme 3. We propose that the aldehyde is activated by hydrogen bonding with free hydroxy groups on surface of MSNs. Then, amine attacks the carbonyl group of the activated aldehyde **I**, and leads to an iminium ion as the intermediate **II**. Next, imine **III** is formed by removing H_2O from **II**. The imine **III** is activated by MSNs to attack of *in situ* generated enolate **IV** and affords the expected β-amino ketone.

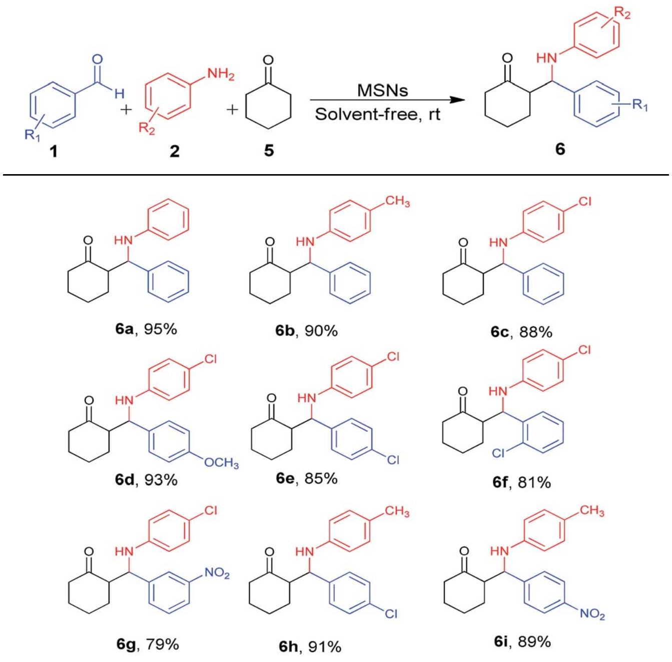
To show the merit of MSNs in comparison with other reported catalysts, we summarized several results for Mannich reaction of aniline and benzaldehyde with acetophenone (Table 3). In comparison with other catalysts used in literature, MSNs showed a much higher catalytic activity in terms of very short reaction time and mild conditions.

Table 1 MSNs catalyzed one-pot three component Mannich reaction of aromatic aldehydes, aromatic amines, and acetophenone[a,b]

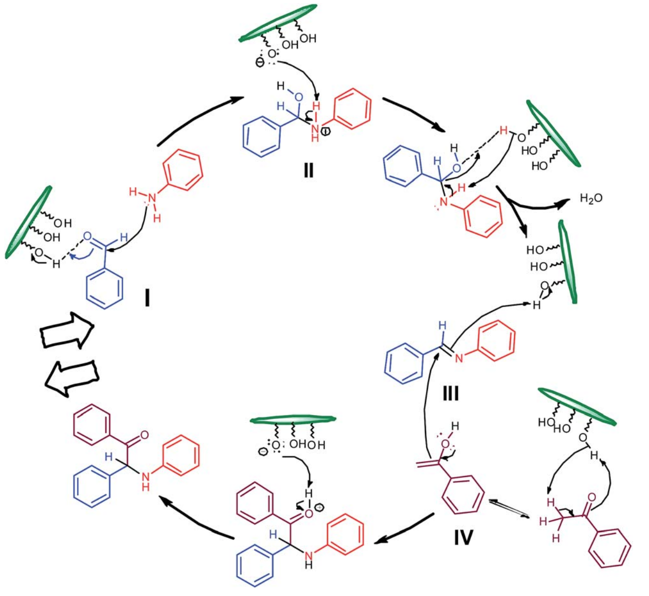


[a] Reaction conditions: aromatic aldehydes (1 mmol), aromatic amines (1 mmol), and acetophenone (1 mmol), all of the reactions were carried out with 15 mg of MSNs at room temperature. [b] Isolated yields.

Table 2 MSNs catalyzed one-pot three component Mannich reaction of aromatic aldehydes, aromatic amines, and cyclohexanone[a,b]



[a] Reaction conditions: aromatic aldehydes (1 mmol), aromatic amines (1 mmol), and cyclohexanone (1 mmol), all of the reactions were carried out with 15 mg of MSNs at room temperature. [b] Isolated yields.



Scheme 3 Plausible reaction mechanism for one-pot three component Mannich reaction of benzaldehyde, aniline, and acetophenone in the presence of MSNs.

Table 3 Comparison of MSNs with other catalysts reported in the literature for Mannich reaction of aniline and benzaldehyde with acetophenone

Entry	Catalyst, condition	Time (h)	Yield (%)	Ref.
1	$CeCl_3 \cdot 7H_2O$, rt, EtOH	10	95	32
2	$Yb(PFO)_3$, rt, EtOH	8	94	33
3	CAN, 45 °C, PEG	9	98	34
4	$HClO_4$–SiO_2, rt, EtOH	12	95	35
5	Saccharose, rt, H_2O/EtOH	9	92	36
6	Cu-NP, MeOH, rt, N_2	8	93	23
7	MSNs, rt, solvent-free	6	95	This work

The recovery and reuse of catalysts are highly valued in a green process. Subsequently, reusability performance of MSNs nanocatalyst was investigated using the Mannich reaction (benzaldehyde, aniline, and cyclohexanone) under the optimal conditions. The catalyst remains insoluble under the present reaction conditions and hence can be easily separated by centrifugation followed by washing. The catalyst was washed with ethanol and dried at 80 °C and used for another Mannich reaction, the recycled catalyst could be reused five times without significant loss of its activity (Fig. 5). As shown by comparison of the FT-IR spectra to that of fresh catalyst and recovered catalyst after five runs had no obvious change in structure (Fig. 6), the recyclability data demonstrates high stability of the catalyst under the reaction conditions.

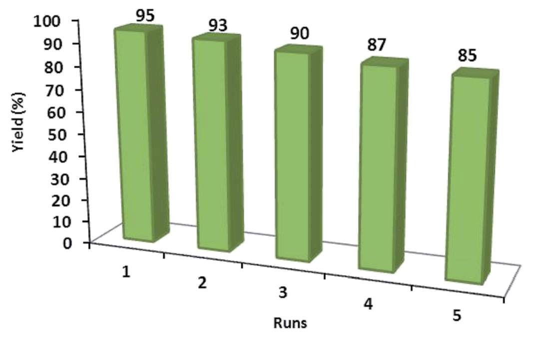


Fig. 5 Reusability of MSNs in the reaction of benzaldehyde (1 mmol), aniline (1 mmol), cyclohexanone (1 mmol) and catalyst (15 mg) under solvent-free conditions.

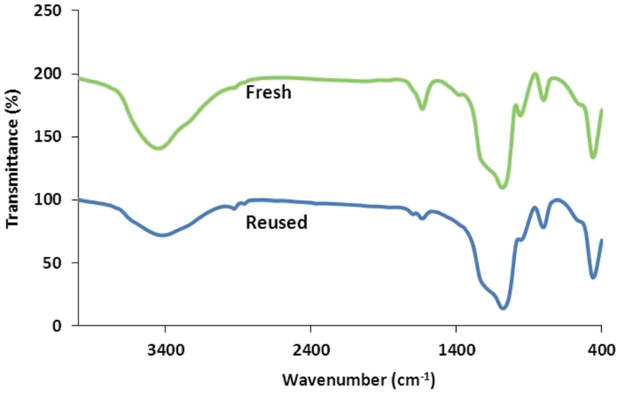


Fig. 6 FT-IR spectra of fresh and recovered catalysts.

Experimental

Chemical reagents in high purity were purchased from Merck and Aldrich and were used without further purification. Fourier transform infrared (FT-IR) spectra were recorded using KBr pellets in the range 400–4000 cm^{-1} on a Nicolet IR-100 infrared spectrometer. The NMR spectra were recorded on a Bruker DRX 500-Avance spectrometer operating at 500 MHz for ^1H NMR in DMSO-d_6 and $CDCl_3$ with TMS as an internal standard. X-ray diffraction (XRD) was performed on Philips XPert 1710 diffractometer. The latter appeared with Co Kα ($\alpha = 1.79285$ Å) voltage: 40 kV. The particle morphology was examined by SEM (KYKY EM3200 – 25 kV) and TEM (Zeiss EM10C 80 kV).

Preparation of mesoporous silica nanoparticle

MSNs was prepared using the sol–gel method.[37] Briefly, 0.5 g of CTAB and 0.14 g of NaOH were mixed in 240 mL deionized water. The solution was stirred vigorously at 80 °C for 2 h, then 2.5 mL of TEOS is added, and the reaction was continued for another 2 h. The as-prepared product (MSNs-CTAB) was washed 3 times with ethanol and redispersed in 200 mL of ethanol containing 2 g of NH_4NO_3, at 80 °C. The remaining mixture was refluxed for 6 h. In this process the CTAB template was removed. The resulting precipitate was collected by centrifugation and washed with ethanol repeatedly. Finally, it was dried under vacuum to give MSNs product as a white powder.

General procedure for the synthesis of β-amino carbonyl compounds

In a typical experiment, to mixture of ketones (1 mmol), aromatic aldehydes (1 mmol) and anilines (1 mmol), MSNs

(15 mg) was added, the mixture was stirred at room temperature for appropriate time, the reaction was monitored by TLC. After completion of the reaction, acetone was added and catalyst was removed by centrifugation, product was recrystallized from EtOH. The catalyst was used in the next run under the same conditions as for the initial run of the catalyst. The purity of these products was ascertained by their melting points and spectral data with those reported in the literatures.

Spectral data for some selected β-amino ketones

3-(3-Bromophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4d). Mp 106–110 °C; IR (KBr): $\nu_{max} = 3392, 1667, 1596, 1509, 1287\ cm^{-1}$; ^1H NMR ($CDCl_3$, 500 MHz) δ ppm: 3.44–3.54 (m, 2H), 4.97 (t, $J = 7.0$ Hz, 1H), 6.59 (d, $J = 8.0$ Hz, 2H), 6.72 (t, $J = 7.5$ Hz, 1H), 7.10–7.13 (t, $J = 7.5$ Hz, 2H), 7.17–7.21 (m, 1H), 7.36–7.41 (m, 2H), 7.44–7.47 (t, $J = 8$ Hz, 2H), 7.55–7.61 (m, 2H), 7.9 (d, $J = 7.5$ Hz, 2H).

1,3-Diphenyl-3(*p*-tolylamino)propan-1-one (4g). Mp 168–170 °C; IR (KBr): $\nu_{max} = 3398, 1677, 1617, 1523, 1291\ cm^{-1}$; ^1H NMR ($CDCl_3$, 500 MHz) δ ppm: 2.19 (s, 3H, CH_3), 3.48–3.53 (m, 2H), 4.98 (t, $J = 6.5$ Hz, 1H), 6.60 (m, 2H), 6.92 (d, $J = 8.0$ Hz, 2H), 7.19–7.23 (m, 1H), 7.29–7.32 (m, 2H), 7.41–7.58 (m, 5H), 7.9 (d, $J = 8.5$ Hz, 2H).

3-(4-Bromophenylamino)-1,3-diphenylpropan-1-one (4i). Mp 175–177 °C; IR (KBr): $\nu_{max} = 3370, 1664, 1594, 1494, 1282\ cm^{-1}$; ^1H NMR ($CDCl_3$, 500 MHz) δ ppm: 3.42–3.53 (m, 2H), 4.95 (t, 1H), 6.46 (d, $J = 9.0$ Hz, 2H), 7.16 (d, $J = 8.5$ Hz, 2H), 7.24 (m, 1H), 7.29–7.34 (t, $J = 7.5$ Hz, 2H), 7.41–7.62 (m, 5H), 7.9 (d, $J = 8$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 45.97, 55.21, 110.08, 115.85, 126.38, 127.59, 128.18, 128.72, 128.91, 131.82, 133.54, 136.57, 142.04, 145.48, 198.05.

2-(Phenyl(phenylamino)methyl)cyclohexanone (6a). Mp 139 °C; IR (KBr): $\nu_{max} = 3327, 1701, 1599, 1495, 1271\ cm^{-1}$; ^1H NMR ($CDCl_3$, 500 MHz) δ ppm: 1.68–172 (m, 2H), 1.79–2.10 (m, 4H), 2.34–2.47 (m, 2H), 2.82–2.97 (m, 1H), 4.58–4.64 (m, 1H), 6.63 (m, 2H), 6.70 (m, 1H), 7.07–7.10 (m, 2H), 7.21–7.24 (m, 1H), 7.29–7.34 (m, 2H), 7.40 (d, $J = 8$ Hz, 2H).

2-(4-Cholorophenyl)amino(phenyl)methyl cyclohexanone (6c). Mp 135–137 °C; IR (KBr): $\nu_{max} = 3379, 1703, 1597, 1497\ cm^{-1}$; ^1H NMR (DMSO-d_6, 500 MHz) δ ppm: 1.22–1.81 (m, 6H), 2.30–2.32 (m, 2H), 2.72–2.73 (m, 1H), 4.68–4.86 (m, 1H), 6.51 (d, 2H), 6.94–6.98 (m, 2H), 7.14–7.18 (m, 1H), 7.23–7.39 (m, 4H).

Conclusions

We have developed a facile, efficient and ecofriendly procedure for the one-pot synthesis of β-amino ketones by a three component Mannich reaction under solvent-free conditions, at room temperature. The notable advantages of this study are high catalytic activity, excellent yields, cleaner reaction profile, low cost, simplicity of product isolation, and mild reaction conditions. These advantages, in general, highlight this protocol as a useful and attractive methodology, among the methods reported in the literature.

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