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ARTICLE TYPE

In water one-pot three-component Mannich reaction catalyzed by eco-friendly, hydrophobic and recyclable sulfonic acid based nanosilica (SBA-15-Ph-PrSO₃H)

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A mild, effective and green method for Mannich reaction of aromatic aldehydes, aromatic amines and ketones has been accomplished in good to excellent yields using hydrophobic SBA-15-Ph-PrSO₃H in water at room temperature. This new method consistently has the advantages of excellent yields, short reaction times, and non-toxic nature and reusability of the catalyst. Additionally, utilization of water as green solvent, simple reaction conditions, isolation, and purification makes this manipulation interesting from environmental perspective.

Introduction

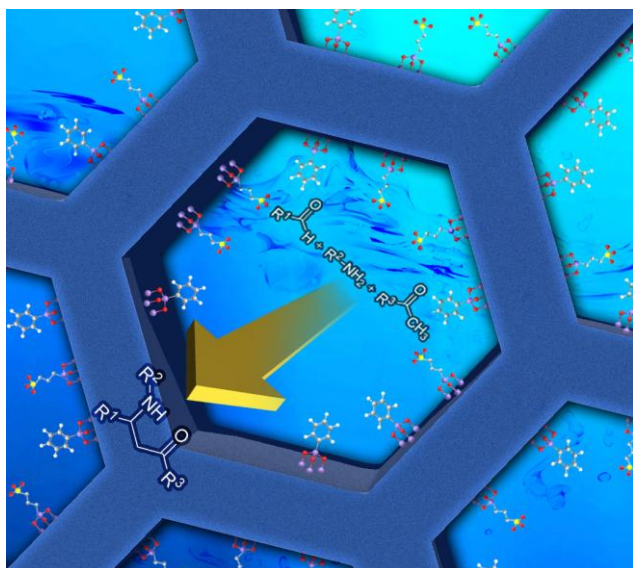
Mannich reaction is one of the most important carbon-carbon bond forming reactions widely used in the synthesis of various β-amino ketones, which are versatile synthetic building blocks for the preparation of amino alcohols, peptides, lactams and as precursors to synthesize amino acids and many nitrogen-containing biologically important compounds.¹⁻³ The Mannich reaction relies on two as well as three component systems, but the more desirable route is the use of a one-pot three-component setup.⁴⁻⁶ Accordingly, the development of new catalytic methods for one-pot three-component Mannich reaction is of prime importance in organic synthesis. Mannich reactions of aldehydes, ketones and amines have been realized via Lewis acids,⁷⁻¹⁶ Lewis base,¹⁷ Brønsted acids¹⁸⁻²³ and transition metal salts²⁴⁻²⁶ approaches. Despite the merits of these methodologies, problems recycling and reusing of the catalysts, toxic reagents and solvents, harsh reaction conditions, toxicity or difficulty in product separation remain concerns. Therefore, the search for new green methods is still being actively pursued.

On the other hand, because of increasing concerns about environmental effects, carrying out organic reactions in water has become highly desirable in recent years.²⁷⁻³³ Apart from being environmentally friendly, water possesses some unique properties (such as being non-toxic, available in large quantities, cheap, non-flammable and non-hazardous) that are different from other solvents, thus making it a very good reaction medium for organic synthesis. The main catalysts reported for Mannich reaction in water include Lewis acids such as triflates^{34,35} and chlorides,³⁶ Brønsted acids,^{19,37-41} hydrochloric acid,²¹ heteropoly acids^{42,43} and functionalized ionic liquid.⁴⁴ However, despite the diverse

synthetic routes so far developed for the Mannich reaction, a few one-pot procedures on the use of unmodified aldehydes or ketones in water have been reported in the literature. Furthermore, most of the reported Mannich reactions in water have been carried out using silyl enol ether as precursor,³⁴⁻³⁹ or performed in the presence of surfactants such as sodium dodecyl sulfate.^{21,38-40} Unfortunately, normal-phase separation is difficult during workup due to the formation of emulsions because of the sodium dodecyl sulfate.

Additionally, it is very well known that green chemistry not only requires the use of environmentally benign reagents and solvents, but also the recovery and reuse of the catalyst. In this regard, SBA is highly ordered mesoporous silica structured materials (20-500 Å). The unique physical properties of SBA and SBA-based materials have made them highly desirable for their applications. The large pore size allows for fixation of large active complexes, reduces diffusional restriction of reactants, and enables reactions involving bulky molecules to take place. The thicker pore walls make them more thermally and hydrothermally stable. Additionally, mesoporous materials containing sulfonic groups which combine a relatively high acid strength with a large surface area and reactant accessibility, are promising acid catalysts.⁴⁵⁻⁴⁸

As a continuation of our research work in using SBA-15-Ph-PrSO₃H as a heterogeneous, hydrophobic, and easily recyclable catalyst in organic synthesis,⁴⁹⁻⁵² and due to the numerous advantages of using water as a solvent in organic reactions, herein we wish to report an efficient and green procedure for the synthesis of β-amino carbonyl compounds in water using SBA-15-Ph-PrSO₃H (Scheme 1).



Scheme 1: One-pot Mannich reaction of aldehydes, ketones and amines catalyzed by SBA-15-Ph-PrSO₃H in water at room temperature.

5 Results and discussion

On the basis of the information obtained from our previous studies,⁴⁹⁻⁵² we anticipated that SBA-15-Ph-PrSO₃H can be used as an efficient catalyst for the promotion of the reactions which need the use of an acidic catalyst to speed up. Additionally, as a clean and cheap solvent, it is important to carry out Mannich-type reaction in water for the environmental and economic reasons. So, since the reactants were insoluble in water, we were interested to investigate the applicability of this hydrophobic catalyst in the Mannich reaction in water. Notably, introduction of organosulfonic acid and hydrophobic phenyl groups into the channels of SBA-15-Ph-PrSO₃H was interesting since the combination of both functionalities (acidic and hydrophobic) allows the effectual reaction of organic substrates within the hydrophobic channels of catalyst in water.

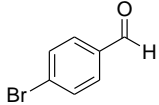
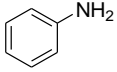
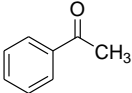
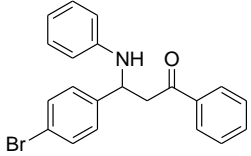
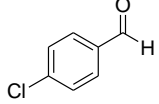
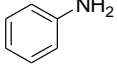
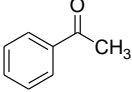
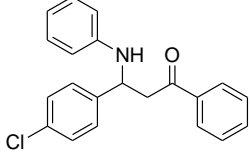
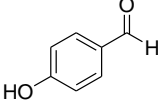
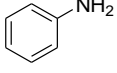
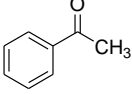
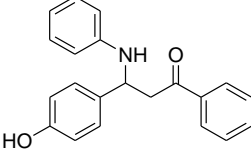
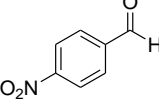
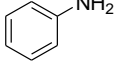
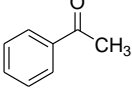
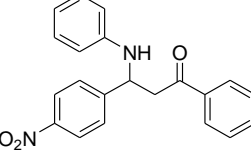
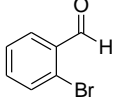
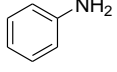
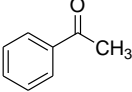
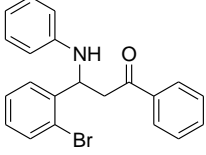
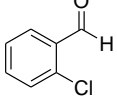
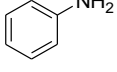
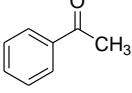
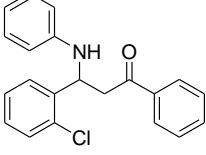
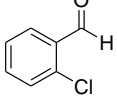
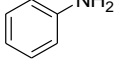
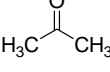
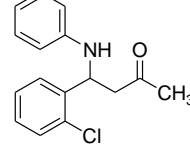
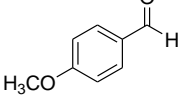
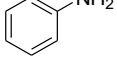
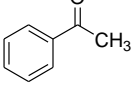
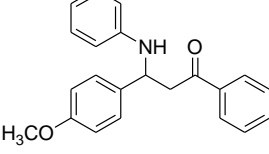
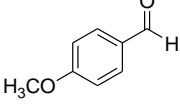
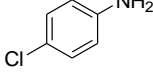
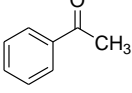
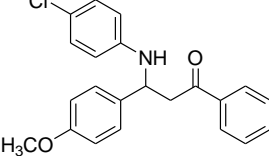
At the outset, for obtaining the optimum reaction conditions, in the initial catalytic activity experiment, a reaction was carried out using 1mmol benzaldehyde, 1mmol aniline, 1mmol acetophenone and 1mol% catalyst. These were stirred at ambient temperature in water. Interestingly, 35% of the related β-amino

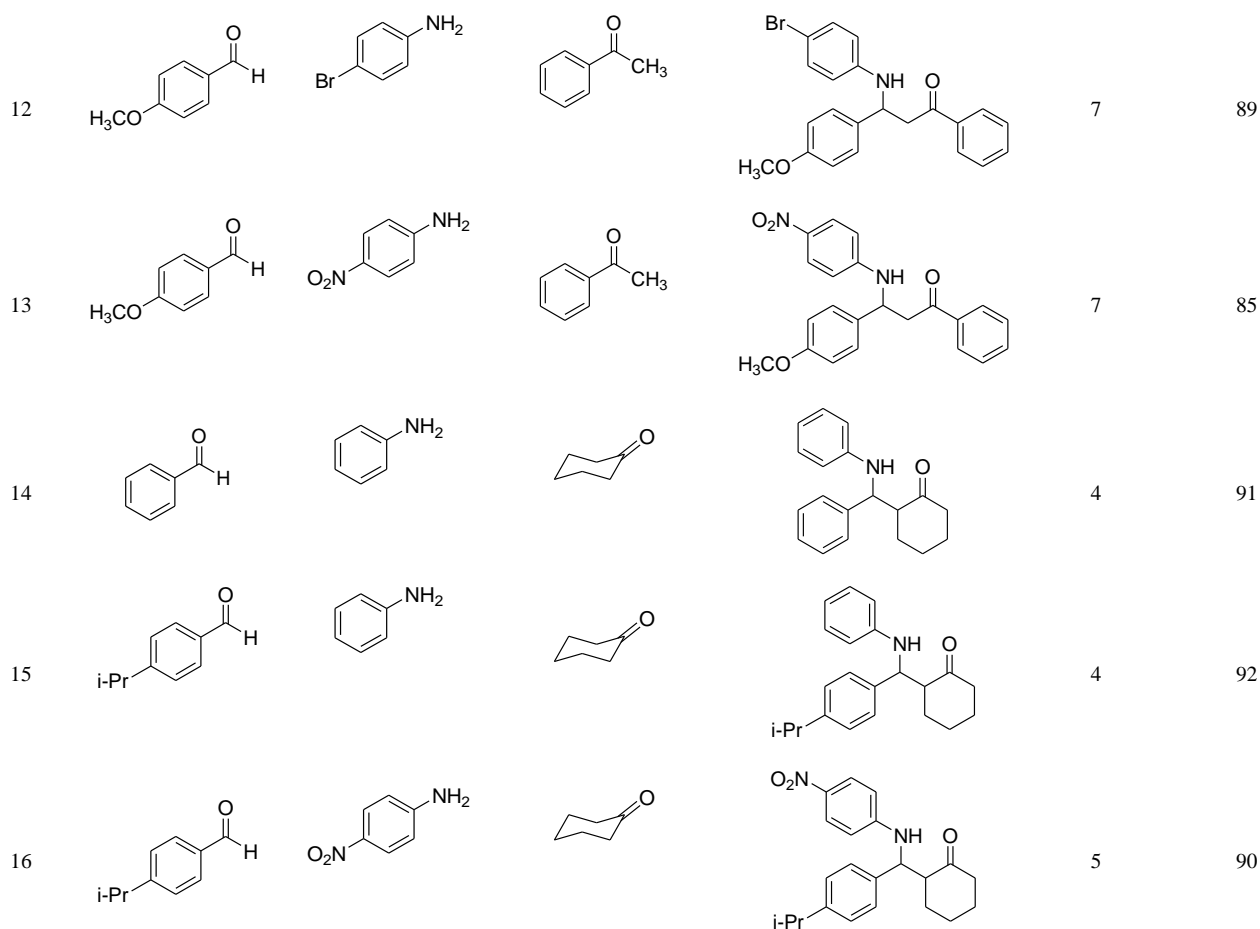
carbonyl compound was obtained after 8h. Considerable improvement was observed in the yield of the related product when amount of catalyst increased to 3mol% (68% yield after 6h) and 5mol% (92% yield after 4h). Besides, increasing the quantity of catalyst to 7mol% did not improve the result to a greater extent. To illustrate the efficiency of the catalyst, the same reaction was also carried out in the absence of the catalyst. The reaction was not performed after a long reaction time. These results indicate that the presence of 5 mol% of this hydrophobic catalyst is necessary to produce the β-amino carbonyl compounds in good yields. Then, in order to show the effect of surface hydrophobicity of the catalyst, we compared the results of Mannich reaction using hydrophilic catalyst SBA-15-PrSO₃H in water. To test the catalytic capabilities of SBA-15-PrSO₃H, the reaction of benzaldehyde, aniline and acetophenone was studied in the presence of 5 mol% SBA-15-PrSO₃H in water. As we expect, SBA-15-PrSO₃H appeared to be much less active than SBA-15-Ph-PrSO₃H, affording 5% yield of the desired β-aminocarbonyl compound after 4h, while SBA-15-Ph-PrSO₃H gave 92% yield of the same product in 4 h. The greater reactivity of SBA-15-Ph-PrSO₃H is probably due to a synergistic effect between sufficient hydrophobicity and acidity of siliceous network. Furthermore, Mannich reaction is very sensitive to reaction temperature. Although the high temperature could improve the reaction rate and shorten the reaction time, but favor side reactions. It was found that the room temperature was an appropriate condition for Mannich reaction catalyzed using SBA-15-Ph-PrSO₃H.

Subsequently, on the basis of the optimization dosage of the catalyst, studies focused on the application of SBA-15-Ph-PrSO₃H for different Mannich reactions of various electron-rich and electron-poor benzaldehydes with different ketones and amines in water at room temperature. As shown in Table 1, the results reveal that the SBA-15-Ph-PrSO₃H catalysis generally results in good yields with aromatic aldehydes including those carrying electron donating- or withdrawing substituents (Table 1, entries 1-6), even when moderately hindered aldehydes were used (Table 1, entries 7-9), with the advantages of mild reaction conditions and minimal environmental impact. The reaction conditions were mild enough not to induce any damage to moieties like methoxy group (Table 1, entries 10-13) which often undergo cleavage in the presence of strong acids or certain Lewis acids. From the entries 14-16, it could be inferred that, besides the aromatic ketones, aliphatic ketones could also be employed to give good yields under the identical reaction condition.

Table 1: Synthesis of different β-aminocarbonyl compounds in water at room temperature using SBA-15-Ph-PrSO₃H as catalyst

Entry	Aldehyde (R ¹)	Amine (R ²)	Ketone (R ³)	Product	Time (h)	Yield ^a (%)
1					4	92
2					3.5	92

3					4	90
4					4	89
5					4	90
6					6	90
7					6	88
8					6	90
9					6	83
10					3.5	94
11					7	90



^a Isolated Yields.

To show whether the reaction is actually proceeding in a heterogeneous pathway or whether it is conducting through a homogeneous manner, another reaction was performed, in which the reactions of benzaldehyde, aniline and acetophenone in the presence of SBA-15-Ph-PrSO₃H was quenched after 90 min and filtered off (~56% conversion). Then the residue was then subjected to further reaction after addition of water. We found that no further catalytic activity was observed after 3 h, thus supporting the heterogeneous nature of the reaction.

Having established the viability of this reaction, it was then decided to investigate reusability of the catalyst in the synthesis of β-amino carbonyl from benzaldehyde, aniline and acetophenone. Upon completion of the reaction, hot ethanol (30 mL) was added to the reaction mixture. After decantation of solvents, the fresh substrates and water were added. As shown in Figure 1, the recovered SBA-15-Ph-PrSO₃H could be directly reused in seven successive runs without significant loss of activity which clearly demonstrates the practical recyclability of this catalyst. Moreover, the uniformity of highly ordered structure of SBA-15 after seven times recovery is confirmed by TEM images (Figure 2).

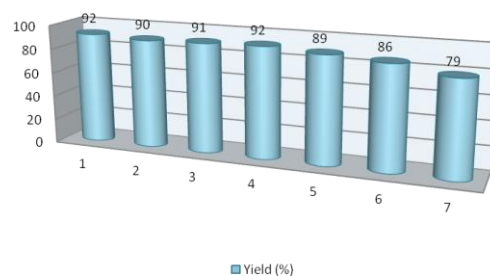


Figure 1: Recyclability of the catalyst SBA-15-Ph-PrSO₃H for the Mannich reaction of benzaldehyde, aniline and acetophenone after 4h

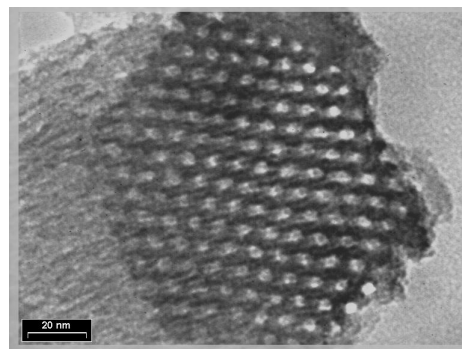


Figure 2: TEM images of the SBA-15-Ph-PrSO₃H after the 7th reaction cycle

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Experimental section

General procedure for the preparation of β -amino carbonyl compounds: To the mixture of aldehyde (1 mmol), ketone (1 mmol) and amine (1 mmol) in 3mL of water, SBA-15-Ph- PrSO_3H (0.03 g, 5 mol%) was added. The mixture was stirred at room temperature for appropriate time indicated in Table 1 until the reaction was completed as monitored by thin-layer chromatography. The resulting mixture was filtered to recover the catalyst, and the filtrate was evaporated off the solvent to give the crude product. The analytical sample was obtained by recrystallization of crude product from ethanol. Spectroscopic data for selected examples listed below.

(Entry 2): ^1H NMR (400 MHz; CDCl_3): $\delta_{\text{H}} = 2.34$ (s, 3H), 3.48–3.60 (m, 2H), 5.01 (t, $^3\text{J} = 8$ Hz, 1H), 6.64–6.66 (d, $^3\text{J} = 8$ Hz, 2H), 6.73 (t, $^3\text{J} = 8$ Hz, 1H), 7.11–7.20 (m, 3H), 7.35–7.37 (d, $^3\text{J} = 8.4$ Hz, 2H), 7.45–7.49 (t, 2H), 7.57–7.61 (m, 1H), 7.93–7.99 (d, $^3\text{J} = 8.4$ Hz, 2H).

(Entry 3): ^1H NMR (400 MHz; CDCl_3): $\delta_{\text{H}} = 3.46$ –3.57 (m, 2H), 5.00 (t, $^3\text{J} = 6.4$ Hz, 1H), 6.60–6.62 (d, $^3\text{J} = 8$ Hz, 2H), 6.73–6.75 (t, $^3\text{J} = 8$ Hz, 1H), 7.12–7.16 (t, $^3\text{J} = 8$ Hz, 2H), 7.36–7.38 (d, $^3\text{J} = 8.4$ Hz, 2H), 7.46–7.53 (m, 4H), 7.59–7.62 (t, $^3\text{J} = 7.2$ Hz, 1H), 7.92–7.96 (t, $^3\text{J} = 7.2$ Hz, 2H), ^{13}C NMR (100 MHz, CDCl_3): $\delta_{\text{C}} = 45.8, 54.8, 114.4, 118.7, 121.2, 128.2, 128.4, 128.8, 129.2, 131.9, 133.6, 136.5, 141.6, 197.8$.

(Entry 4): ^1H NMR (400 MHz; CDCl_3): $\delta_{\text{H}} = 3.44$ –3.56 (m, 2H), 5.00–5.03 (t, $^3\text{J} = 6.8$ Hz, 1H), 6.58–6.61 (d of d, $^3\text{J} = 0.8$ Hz, $^3\text{J} = 10$ Hz, 2H), 6.71 (t, $^3\text{J} = 10$ Hz, 1H), 7.11–7.16 (m, 2H), 7.30–7.33 (m, 2H), 7.41–7.44 (m, 2H), 7.47–7.51 (m, 2H), 7.59–7.63 (m, 1H), 7.92–7.95 (m, 2H), ^{13}C NMR (100 MHz, CDCl_3): $\delta_{\text{C}} = 46.0, 54.4, 114.1, 118.4, 127.9, 128.2, 128.8, 129.0, 129.2, 133.1, 133.6, 136.6, 141.3, 146.4, 197.9$.

(Entry 10): ^1H NMR (400 MHz; CDCl_3): $\delta_{\text{H}} = 3.50$ –3.58 (m, 2H), 3.80 (s, 3H), 5.00 (t, $^3\text{J} = 6.4$ Hz, 1H), 6.62–6.64 (d, $^3\text{J} = 8$ Hz, 2H), 6.72 (t, $^3\text{J} = 7.6$ Hz, 1H), 6.87–6.89 (d, $^3\text{J} = 8.4$ Hz, 2H), 7.11–7.15 (m, 2H), 7.38–7.40 (d, $^3\text{J} = 8.4$ Hz, 2H), 7.45–7.49 (t, $^3\text{J} = 7.2$ Hz, 2H), 7.57–7.61 (t, $^3\text{J} = 7.2$ Hz, 1H), 7.92–7.94 (t, $^3\text{J} = 7.2$ Hz, 2H), ^{13}C NMR (100 MHz, CDCl_3): $\delta_{\text{C}} = 46.1, 54.8, 55.3, 114.2, 114.4, 118.4, 127.7, 128.2, 128.5, 128.7, 129.2, 133.5, 134.4, 136.7, 158.9, 198.4$.

(Entry 11): ^1H NMR (400 MHz; CDCl_3): $\delta_{\text{H}} = 3.38$ –3.52 (m, 2H), 3.80 (s, 3H), 4.59 (brs, 1H), 4.92–4.94 (t, $^3\text{J} = 6.8$ Hz, 1H), 6.48–6.51 (d of d, $^3\text{J} = 4$ Hz, 2H), 6.86–6.89 (m, 2H), 7.03–7.06 (m, 2H), 7.28–7.35 (m, 2H), 7.45–7.49 (m, 2H), 7.57–7.61 (m, 1H), 7.91–7.93 (m, 2H), ^{13}C NMR (100 MHz, CDCl_3): $\delta_{\text{C}} = 46.3, 54.3, 55.3, 114.3, 115.0, 122.4, 127.4, 128.2, 128.7, 128.9, 133.5, 134.4, 136.6, 145.6, 158.8, 198.3$.

Conclusions

In conclusion, at room temperature, the direct Mannich reaction of a variety of aromatic aldehydes, anilines and ketones in a three-component reaction in aqueous media was efficiently catalyzed by SBA-15-Ph-Pr- SO_3H with dual functionality comprised of both hydrophobicity and acidity properties. The high yield, reusability of catalyst, operational simplicity and using water make the present method as potentially green and useful method in organic synthesis.

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Notes and references

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