A magnetic solid sulfonic acid modified with hydrophobic regulators: An efficient recyclable heterogeneous catalyst for one-pot aza-Michael-type and Mannich-type reactions of aldehydes, ketones and amines

Barahman Movassagh, Leili Tahershamsi, Akbar Mobaraki

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Graphical Abstract

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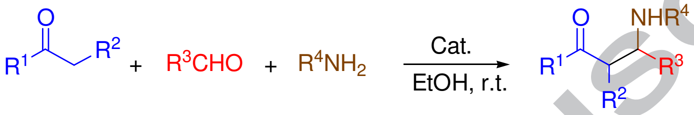

Cat. = $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$

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A magnetic solid sulfonic acid modified with hydrophobic regulators: An efficient recyclable heterogeneous catalyst for one-pot aza-Michael-type and Mannich-type reactions of aldehydes, ketones and amines

Barahman Movassagh,* Leili Tahershamsi, Akbar Mobaraki

Department of Chemistry, K. N. Toosi University of Technology, P. O. Box 16315-1618, Tehran, Iran

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ABSTRACT

Two convenient green protocols for the synthesis of β-amino ketones have been developed which involve one-pot aza-Michael-type and Mannich-type reactions of a series of aldehydes, ketones and amines in the presence of a catalytic amount of the magnetic solid sulfonic acid catalyst, Fe_3O_4@SiO_2@Me&Et-$PhSO_3H$, at room temperature. The catalyst can be reused four times without loss of activity.

The construction of carbon-nitrogen bonds, especially under green and safe conditions, is an important transformation in organic synthesis. The development of novel synthetic routes leading to β-aminocarbonyl compounds has received considerable interest due to their occurrence in a wide variety of biologically active natural products;[1] they also serve as key intermediates for the synthesis of important nitrogen-containing compounds such as β-lactams, β-amino acids, and β-amino alcohols.[2] One-pot Mannich reactions of aldehydes, ketones and amines using a variety of Lewis acids,[3] Brønsted acids,[4] and Lewis base[5] catalysts have been reported. However, many of these suffer from drawbacks such as long reaction times, toxicity, and difficult separations after the reaction.

Another approach for preparing β-amino carbonyl compounds is based on the addition of amines to α,β-unsaturated carbonyl compounds (aza-Michael reaction). This method has a prominent advantage over the Mannich reaction in that it covers a wide range of nitrogen nucleophiles including amides, carbamates, and sulfonamides, which can rarely be utilized using the conventional Mannich condensation. A number of Lewis acid catalysts, solid acids, and Brønsted acids,[6] as well as basic catalysts[7] have been employed. Unfortunately, several drawbacks such as high costs, harsh reaction conditions, long reaction times, the requirements for large excesses of reagents or catalysts, and the use of toxic solvents are associated with the above methods. Also, some of the reported procedures were only applicable to aliphatic amines and failed to work with aromatic amines.[6h,7b] Although recent protocols have made this route more attractive, the development of simple, recyclable, and environmentally friendly approaches that can be performed at ambient temperature for both aza-Michael and Mannich reactions are desirable.

Significant attention has been paid to solid acid catalysts due to their potential applications for replacing liquid mineral acids in industry;[8] they exhibit advantages of easy separation of the catalyst from the liquid reaction medium, minimal corrosion, good recyclability, green chemical processes, and enhanced product selectivity.[9] In many reactions catalyzed by solid sulfonic acids involving hydrophobic and hydrophilic substrates, the water produced as a by-product is co-adsorbed by the catalyst poisoning the surface and producing a more hydrophilic environment, resulting in reduced catalytic activity.[10] On the other hand, the polarities of the reactants and products, the acidity of the catalyst, and hydrophobic-hydrophilic balance on the catalyst surface have significant effects on the progress of the reaction. Further studies have addressed the design, synthesis and catalytic applications of surface-modified SO_3H solid materials in order to optimize these properties, and the overall performance of the catalysts.[10d,11] Recently, among solid acid catalysts, special attention has been paid to the preparation, characterization, and catalytic investigation of magnetic sulfonic acids.[12]

In continuation of our investigations on the hydrophobic, organosulfonic acid functionalized silica-coated magnetic nanoparticle catalyst, Fe_3O_4@SiO_2@Me&Et-$PhSO_3H$ (Figure 1),[12a,b] in this paper, we report the synthesis of β-amino ketones by two one-pot approaches: aza-Michael-type (pathway a) and Mannich-type (pathway b) reactions of aryl aldehydes, ketones and amines in EtOH at room temperature employing this reusable catalyst (Scheme 1).

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[*] Corresponding author. Tel.:+98 21 8802 5459; fax:+98 21 2285 3650. E-mail: bmovass1178@yahoo.com (B. Movassagh).

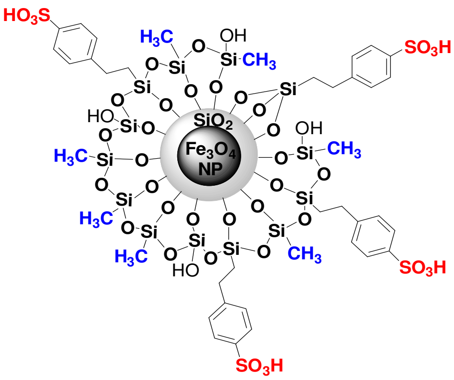
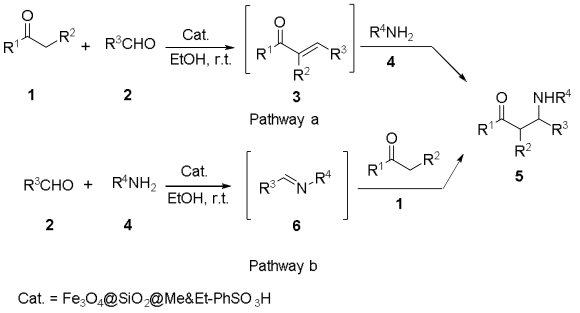


Figure 1. The hydrophobic magnetic solid sulfonic acid catalyst, $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$.



Scheme 1. Two approaches for the synthesis of β-amino ketones.

Table 1

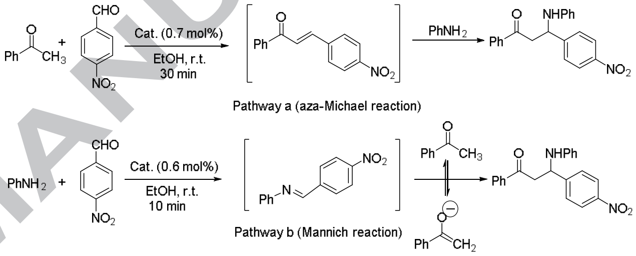
Optimization of the $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$-catalyzed one-pot reaction of cyclohexanone, benzaldehyde, and aniline[a]

Entry	Solvent	T (°C)	Catalyst (mol%)	Yield (%)[b]	
				Aza-Michael	Mannich
1	EtOH	25	0.3	–	86
2	EtOH	50	0.3	62[c]	51[c]
3	EtOH	80	0.3	–	25[c]
4	H_2O	25	0.6	45	68
5	THF	25	0.6	–	56
6	–	25	0.6	85	80
7	EtOH	25	0.4	–	87
8	EtOH	25	0.6	87	99
9	EtOH	25	0.7	96	99
10	EtOH	25	0.9	96	–
11	MeOH	25	0.9	95	–
12	CH_3CN	80	0.9	N.R.	N.R.
13	CH_2Cl_2	25	0.9	15	–

[a] Reaction conditions: cyclohexanone (3.0 mmol), benzaldehyde (2.0 mmol), aniline (2.0 mmol), catalyst, solvent (4 mL), 2 h.

[b] Isolated yield. N.R = no reaction.

[c] Several by-products were detected.



Scheme 2. Two possible pathways for the formation of 3-(4-nitrophenyl)-1-phenyl-3-(phenylamino)propan-1-one in the presence of $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$.

To find the optimum conditions which suit the two approaches, the reaction of cyclohexanone, benzaldehyde and aniline, via different sequences of addition, was examined under various conditions catalyzed by $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$ (Table 1).

The effect of different molar ratios of the reactants, the amount of catalyst, the solvent, and temperature on the yield, was studied. The best results (96% for aza-Michael and 99% for Mannich reactions) were obtained by carrying out the reaction with a 1.5:1:1 molar ratio of cyclohexanone, benzaldehyde, and aniline at room temperature in the presence of 0.7 and 0.6 mol% (based on benzaldehyde) of the catalyst for the aza-Michael and Mannich reactions, respectively, in 4 mL of absolute EtOH for two hours (Table 1, entries 9 and 8, respectively). We observed that 0.7 and 0.6 mol% of the catalyst could catalyze the aza-Michael and Mannich reactions efficiently; increasing or decreasing the amount of the catalyst did not lead to any improvement in the yields. To investigate the aza-Michael addition reaction of amines with α,β-unsaturated carbonyl compounds (pathway a), and the reaction of enolates with imines (Mannich reaction, pathway b), we performed two experiments as shown in Scheme 2.

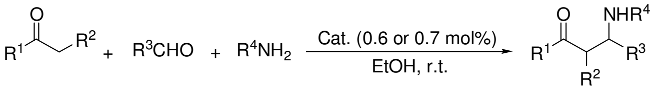
In the first experiment (pathway a), an ethanolic mixture of acetophenone and 4-nitrobenzaldehyde was stirred at room temperature in the presence of the catalyst (0.7 mol%); after 30 minutes, the corresponding chalcone was separated as a light orange solid [mp 157-158 °C, Lit.[13] mp 158-160 °C; IR (KBr): ν_{max} =1677 and 1596 cm^{-1}]. The reaction of this intermediate with aniline, after 1.5 hours, led to the corresponding β-amino ketone. In another experiment (pathway b), aniline and 4-nitrobenzaldehyde were stirred in the presence of the catalyst (0.6 mol%). The corresponding imine was formed in 10 minutes and was separated as a yellow solid [mp 86-88 °C, Lit.[14] mp 88-90 °C; IR (KBr): ν_{max} = 1597 and 1517 cm^{-1}]. The addition of acetophenone to this intermediate gave the corresponding β-amino ketone after one hour.

This catalyst is composed of Brønsted acidic groups and hydrophobic methyl moieties. The aza-Michael reaction (pathway a) proceeds through the formation of intermediate **3** (Scheme 1) followed by nucleophilic attack by the amine. The $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$-catalyzed Mannich reaction of the aldehyde and amine proceeds through imine formation (**6**) with subsequent attack of the enol derived from the ketone on the protonated imine (pathway b, Scheme 1). The characteristic feature of both reactions is the formation of water as a by-product in the first step.

Using the optimized reaction conditions, the one-pot aza-Michael and Mannich reactions of various aromatic ketones, aldehydes and amines were investigated and the results are shown in Table 2.[15] It was found that the reaction of various aromatic aldehydes with aromatic amines and acetophenones bearing electron-withdrawing and electron-donating groups proceeded smoothly using both approaches, and gave the corresponding β-amino ketones in high to excellent yields (Table 2, entries 1-20). Amines with electron-withdrawing groups, such as 4-nitroaniline and 4-chloroaniline gave the desired products in good to excellent yields (Table 2, entries 3, 5, 6 and 11). The aliphatic amine, benzylamine was also studied, and was found to give the corresponding products in high yields (Table 2, entries

Table 2

Fe_3O_4@SiO_2@Me&Et-$PhSO_3H$-catalyzed one-pot aza-Michael-type and Mannich reactions of various aldehydes, ketones and amines



Entry	Ketone		Aldehyde	Amine	Yield (%)[a]/ Time (h)[b]	
	R^1	R^2	R^3	R^4	Pathway a	Pathway b
1	Ph	H	Ph	Ph	95/2[7e]	91/1.5
2	Ph	H	Ph	4-$MeOC_6H_4$	96/1.5[7e]	90/1
3	Ph	H	Ph	4-$O_2NC_6H_4$	–	95/1[7e]
4	Ph	H	Ph	4-MeC_6H_4	–	93/2[16a]
5	Ph	H	Ph	4-ClC_6H_4	–	98/1[7e]
6	Ph	H	4-ClC_6H_4	4-ClC_6H_4	–	92/1.5[7e]
7	Ph	H	4-ClC_6H_4	Ph	96/2[7e]	91/2
8	Ph	H	4-MeC_6H_4	4-MeC_6H_4	90/4[16b]	90/3
9	Ph	H	4-HOC_6H_4	4-MeC_6H_4	–	90/3[16b]
10	Ph	H	4-$O_2NC_6H_4$	Ph	99/1.5[7e]	99/1
11	Ph	H	4-$MeOC_6H_4$	4-ClC_6H_4	90/2[7e]	89/1.5
12	Ph	H	4-MeC_6H_4	Ph	–	92/2[7e]
13	Ph	H	4-$MeOC_6H_4$	Ph	90/2[7e]	–
14	Ph	H	4-ClC_6H_4	4-$MeOC_6H_4$	90/2[7e]	–
15	Ph	H	2-$MeOC_6H_4$	Ph	87/3[16c]	–
16	Ph	H	3-pyridyl	Ph	86/2[16d]	90/1
17	Ph	H	2-thienyl	Ph	85/2[16e]	92/1
18	4-ClC_6H_4	H	Ph	Ph	–	98/1.5[7e]
19	4-$MeOC_6H_4$	H	Ph	Ph	–	93/1.5[7e]
20	4-MeC_6H_4	H	Ph	Ph	92/1.5[7e]	90/1
21	Ph	H	4-ClC_6H_4	CH_2Ph	85/4[7e]	86/3
22	Ph	H	4-MeC_6H_4	CH_2Ph	88/4[16f]	90/3
23	cyclohexanone		Ph	Ph	96/1[16a]	99/1.5
24	cyclohexanone		4-$O_2NC_6H_4$	Ph	94/1[16g]	99/0.5
25	cyclohexanone		4-$MeOC_6H_4$	Ph	90/1[16h]	92/1

[a] Isolated yields.

[b] References are provided for known compounds.

21 and 22). The successful results obtained with these protocols prompted us to use cyclohexanone under these conditions (Table 2, entries 23-25). The results indicated that cyclohexanone was more active than acetophenones (Table 2, entries 1, 10 and 13), because formation of its enol was much faster than that of the acetophenones.

The catalytic activity and the reusability of this hydrophobic magnetic solid acid catalyst were also studied for the Mannich and aza-Michael reactions of 4-nitrobenzaldehyde (2.0 mmol), acetophenone (3.0 mmol), and aniline (2.0 mmol) in the presence of 0.6 and 0.7 mol%, respectively, of the catalyst in absolute EtOH at room temperature. Upon completion of each reaction, the catalyst was easily separated and recovered by applying an external magnet. The catalyst was washed with EtOH and finally dried at 100 °C for 30 minutes prior to the next run. The crude product was recrystallized from EtOH. During the recycling experiment with fresh reactants, under the same reaction conditions, no considerable change was observed in the activity of the catalyst over four successive runs (Table 3).

In conclusion, we have successfully developed a magnetic solid sulfonic acid modified with hydrophobic regulators,

Table 3

Recycling of catalyst for the reaction of 4-nitrobenzaldehyde, acetophenone, and aniline[a]

Entry	Cycle	Aza-Michael yield (%)[b]	Mannich yield (%)[b]
1	1	99	99
2	2	97	93
3	3	95	91
4	4	90	88

[a] Reaction conditions were the same as that of entry 10, Table 2 for both reactions.

[b] Isolated yields.

$Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$, which was used efficiently as a heterogeneous catalyst in one-pot aza-Michael and Mannich reactions for the synthesis of β-amino carbonyl compounds under mild conditions. The high reactivity of the catalyst is probably due to synergistic effects between sufficient hydrophobicity and acidity of siliceous networks, which in turn results in: (a) remarkable shielding effects against polar molecules, good accessibility of the active sites and easier diffusion of reaction partners within the network resulting from the presence of organic methyl groups on the surface of catalyst, and (b) mild acidic conditions for the preparation of β-amino ketones.[10,11,12b] The catalyst can be recovered and reused, thus making these procedures more environmentally acceptable.

Acknowledgments

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15. *General procedure for the one pot aza-Michael-type reaction:* A mixture of aldehyde (2.0 mmol), ketone (3.0 mmol) in absolute EtOH (4 mL) was placed in a flask. While stirring magnetically at room temperature, $Fe_3O_4@SiO_2@Me\&Et\text{-}PhSO_3H$ (0.1 g, 0.72 mol%) was added to the above mixture and stirring was continued for 30-60 min. The course of the reaction was monitored by TLC until the starting materials had completely disappeared, and the corresponding chalcone had formed. Next, the amine (2 mmol) was added, and the mixture was stirred for the appropriate amount of time (Table 2). After the completion of the reaction (TLC), the catalyst was separated by magnetic decantation, followed by evaporation of the solvent. The crude product was either recrystallized from EtOH or subjected to preparative TLC (silica gel, eluent EtOAc/pet. ether = 1:4). All the products were characterized by IR, ^1H and ^{13}C NMR spectroscopy.

   General procedure for the one-pot Mannich-type reaction: To a mixture of aldehyde (2.0 mmol) and amine (2.0 mmol) in absolute EtOH (4 mL), was added the catalyst (0.06 g, 0.6 mol%). The mixture was stirred at room temperature for 10-15 min until the starting materials had almost disappeared (TLC). The ketone (3.0 mmol) was then added, and the mixture was stirred for the appropriate amount of time (Table 2) until the reaction was complete as monitored by TLC. An analytical sample was obtained by the same method described for the aza-Michael-type reaction.
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