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An Efficient Protocol for Aza-Michael Addition Reactions Under Solvent-Free Condition Employing Sulfated Zirconia Catalyst

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Abstract The aza-Michael addition reactions of amines with α,β-unsaturated carbonyl compounds were efficiently carried out at room temperature under solvent-free condition employing sulfated zirconia as a reusable heterogeneous catalyst. The desired products were formed in short reaction times and in high yields. The bulk and surface properties of the synthesized catalyst was examined by X-ray powder diffraction, BET surface area, temperature programmed desorption of ammonia, scanning electron microscopy and thermogravimetric techniques. Characterization results reveal the super acidic nature of the catalyst.

Keywords Aza-Michael addition · Amines · β-Amino ketones · α,β-Unsaturated carbonyl compounds · Sulfated zirconia · Solvent-free · Solid acid catalyst

1 Introduction

The aza-Michael addition is one of the most important reactions in organic chemistry especially for the synthesis of C–N heterocycles containing β-amino carbonyl functionality [1, 2]. Such functionality not only constitutes a component of biologically active natural product but also serves as an essential intermediate in the synthesis of β-amino ketones, β-amino acids and β-lactam antibiotics. Additionally, it is extensively used in the fine chemicals and pharmaceutical sectors [3, 4]. Because of the intrinsic importance of β-amino carbonyl compounds that attracted sustained attention in organic synthesis, and the methods of construction of the functionality have undergone a metamorphosis from the classic Mannich-type reaction to the more widely used conjugated addition of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds, which is commonly known as the aza-Michael reaction [5]. The classical Mannich-type reactions are certainly very powerful but need quite severe reaction conditions. Further, they are rather sluggish thereby limiting their use in practice [6]. The conjugated addition reactions are, in contrast, atom economic and quite easy to operate. However, these reactions require either basic conditions [7] or acidic catalysts [8], which are detrimental to the desired synthesis. In order to overcome some of these disadvantages, a good number of alternative procedures were reported over the past few years using $Yb(OTf)_3$ [9], $InCl_3$ [10], $ZrCl_4$ [11], $CeCl_3 \cdot 7H_2O$ [12], $Bi(NO)_3$ [13], $Cu(OTf)_2$ [14], $Y(NO_3)3 \cdot 6H_2O$[15], $FeCl_3 \cdot 7H_2O/Co(OAc)_2$ [16], $LiClO_4$ [17], solid acids [18] and ionic liquids [19]. Recently, basic ionic liquids [20], polyaniline supported indium chloride [21] and amberlyst-15 [22] have also been reported to efficiently catalyze the aza-Michael reaction. However, the need for an environmentally benign and facile protocol still exists. Among various solid acid catalysts, the sulfate-ion promoted zirconia received much attention recently due to its high thermal stability, large specific surface area, easy recovery and reusability, and ability to perform organic reactions at much lower temperatures [23–28]. Also in recent times, inorganic solid acid catalyzed organic reactions are gaining much attention due to the proven advantage of heterogeneous catalysts such as simplified product isolation, mild reaction conditions, high selectivity, ease in recovery and reuse of the catalysts, and reduction in the generation of wasteful products [29–31]. Sulfated zirconia has been reported to be an excellent catalyst for various organic synthesis and transformation reactions [28, 32–37] of

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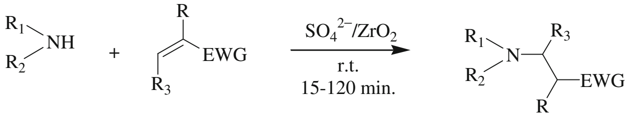


Scheme 1

industrial significance [26]. Herein, we report the aza-Michael addition reaction of amines with α,*β*-unsaturated carbonyl compounds to produce the corresponding *β*-amino ketones in high yields (Scheme 1) employing sulfated zirconia (SO_4^{2-}/ZrO_2) catalyst under solvent-free conditions and at ambient temperature. We initially carried out several experiments by using morpholine and catalytic amounts of sulfated zirconia under solvent-free conditions to optimize the reaction conditions. Interestingly, insignificant catalytic activities were observed with solvents such as CH_2Cl_2 and CH_3CN. Therefore, the reported reactions were conducted under solvent-free conditions.

The solvent-free or utilization of environmentally benign solvents represent an ideal green chemical technology procedure from both economical and environmental point of view. To the best of our knowledge, this will be one of the promising approaches for the aza-Michael addition reactions of amines with α,*β*-unsaturated carbonyl compounds catalyzed by a simple and inexpensive solid acid catalyst, sulfated zirconia, under solvent-free conditions at ambient temperature.

2 Experimental

2.1 Catalyst Preparation

About 25 g of $ZrOCl_2 \cdot 8H_2O$ (Fluka, GR grade) was dissolved in doubly distilled water. To this clear solution, dilute aqueous ammonia was added drop-wise from a burette with vigorous stirring until the pH of the solution reached 8. The obtained precipitate was washed thoroughly with distilled water until free from chloride ions and dried at 393 K for 16 h. To prepare sulfated ZrO_2 catalyst, a portion of the obtained hydrous zirconia sample was ground to fine powder and immersed in 15 cm^3/g of 0.5 M H_2SO_4 solution for 30 min. Excess water was evaporated on a water-bath and the resulting sample was oven-dried at 393 K for 12 h. It was finally calcined at 923 K for 5 h in air atmosphere and stored in a vacuum desiccator. The stored sample was activated at 623 K for 5 h in vacuum before catalytic runs.

2.2 Typical Reaction Procedure

A mixture of SO_4^{2-}/ZrO_2 catalyst (50 mg), amine (1 mmol) and α,*β*-unsaturated compound (1.2 mmol) were stirred at room temperature for an appropriate time (Table 1). After completion of the reaction, as confirmed by TLC, the product was extracted with ethyl acetate (3 × 10 mL). The combined ethyl acetate extracts were concentrated under vacuum and the resulting product was purified by column chromatography on a silica gel column with ethyl acetate and *n*-hexane as eluent to afford the pure *β*-amino product. The recovered products were confirmed by comparison of their NMR, IR and mass spectral data with those of authentic samples.

3 Results and Discussion

The synthesized catalyst was characterized using various techniques, including XRD, BET surface area, TPD of ammonia, Raman spectroscopy, SEM and TGA/DTA. All characterization results revealed that the incorporated sulfate-ions show a strong influence on the surface and bulk properties of the ZrO_2 [32]. In particular, the impregnated sulfate-ions stabilized the metastable zirconia tetragonal phase at ambient conditions and enhanced the total number and strength of acid sites. The BET surface area, amount of NH_3 desorbed, crystallite size and phase composition of unpromoted and sulfate-ion promoted ZrO_2 samples are shown in Table 2. As can be noted from this table, the sulfate-ion impregnated sample exhibits more specific surface area (100 $m^2 g^{-1}$) than the unpromoted ZrO_2 (42 $m^2 g^{-1}$) sample. To understand the surface topography and to assess the surface dispersion of sulfate-ions over the zirconia support, we performed SEM investigations on $Zr(OH)_4$ and sulfate-ion promoted $Zr(OH)_4$ samples calcined at 923 K. As shown in Fig. 1, the micrograph of $Zr(OH)_4$ calcined at 923 K reveals some crystallinity with less porosity. There are certain cracks on the surface, which may be attributed to the loss of water molecules during calcination. As can be noted from the micrograph of the SO_4^{2-}/ZrO_2 sample, the sulfate-ions strongly interacted with the zirconia and equally spread on the surface of the support generating porosity. Most importantly, the TGA/DTA results (Fig. 2) suggest that the optimum temperature for calcination of SO_4^{2-}/ZrO_2 samples is 873–923 K where no loss of sulfate species could be observed. The TGA profile revealed two broad peaks. The first broad peak at around 473 K is due to desorption of water molecules adsorbed on the surface and the broadness up to ~673 K indicates heterogeneity of strong acid sites. The second peak centered at ~1053 K could be ascribed to decomposition of the sulfate species on the surface.

A variety of α,*β*-unsaturated carbonyl compounds namely, methyl vinyl ketone, methyl acrylate, ethyl acrylate and cyclohexenone underwent 1,4-addition with a wide range of aliphatic, aromatic, heterocyclic amines and primary as well as secondary amines in the presence of

Table 1 Sulfated zirconia catalyzed aza-Michael reaction of amines with α,β-unsaturated carbonyl compounds

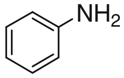
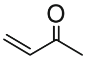
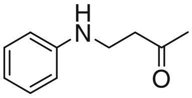
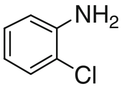
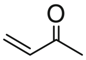
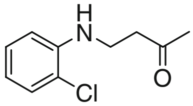
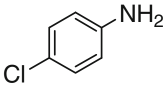
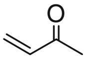
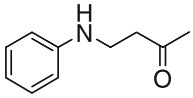
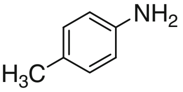
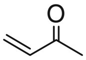
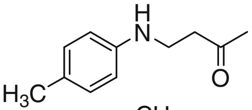
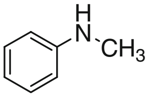
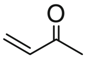
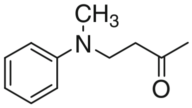
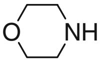
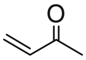
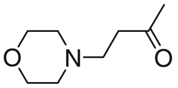
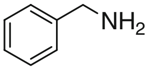
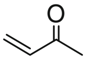
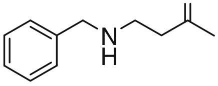
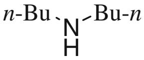
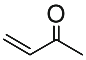
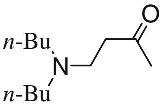
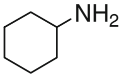
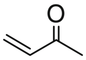
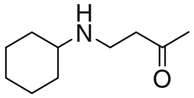
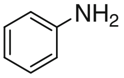
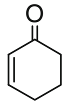
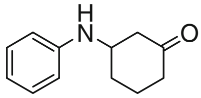
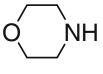
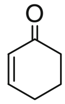
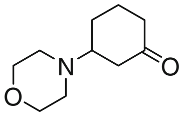
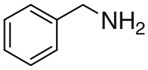
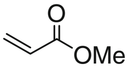
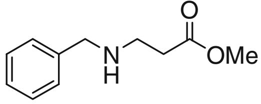
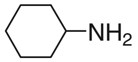
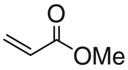
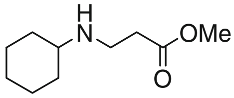
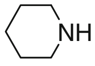
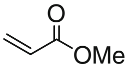
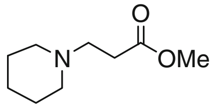
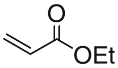
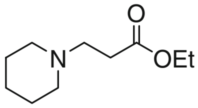
Entry	Amine	α,β-Unsaturated compounds	Product	Time [min]	Yield [%]
1.				75	95
2.				120	85
3.				30	92
4.				45	95
5.				120	92
6.				45	90
7.				45	95
8.				45	85
9.				60	85
10.				45	70
11.				30	90
12.				15	84
13.				60	80
14				90	95
15.				75	93

Table 2 BET surface area, XRD phases, crystallite size and ammonia desorption amount pertaining to unpromoted and sulfate-ion promoted ZrO_2 samples

Sample	BET SA ($m^2\ g^{-1}$)	XRD phases				Total NH_3 desorbed (mL g^{-1})
		Monoclinic		Tetragonal		
		Amount (%)	Size (nm)	Amount (%)	Size (nm)	
ZrO_2	42	76	11.2	24	13	5
SO_4^{2-}/ZrO_2	100	20	7.3	80	12.3	16

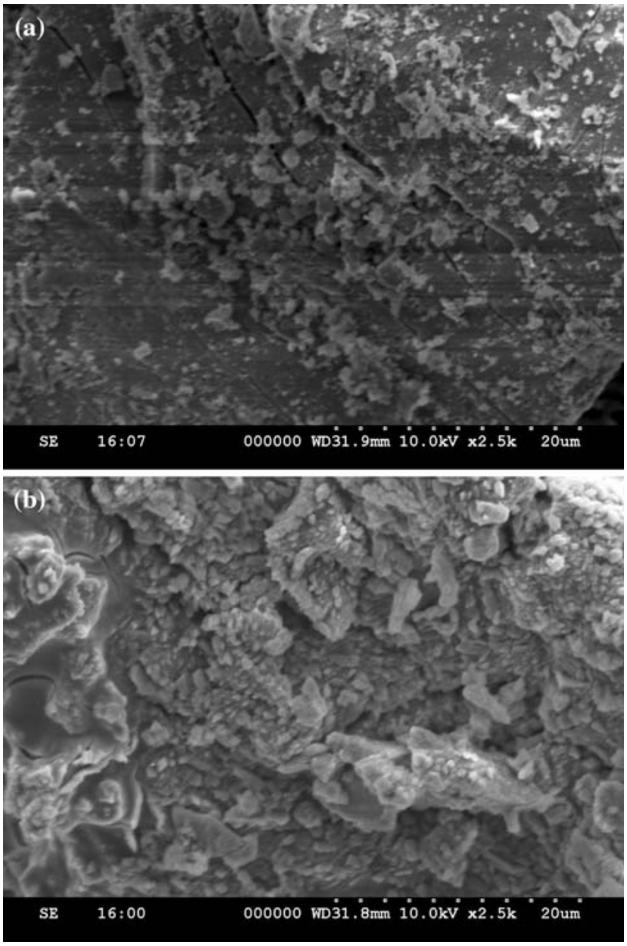


Fig. 1 SEM micrographs of **a** ZrO_2, **b** SO_4^{2-}/ZrO_2 calcined at 923 K

sulfated zirconia catalyst under solvent-free conditions at ambient temperature to provide the corresponding β-amino compounds in high yields in short reaction times. These results are summarized in Table 1. In general, all the reactions were completed within 15–120 min and the obtained yields are good to excellent (70–95%) as can be noted from Table 1. After the reaction, the solid catalyst was conveniently removed by simple filtration from the reaction mixture. The wet catalyst was reused for the reaction and there was no big change in the catalytic activity.

The cyclic α,β-unsaturated ketones such as cyclohexenone reacted rapidly with morpholine (Table 1, Entry 11) to offer the corresponding 1,4-adducts in high yields. The cyclohexenone reacted relatively slowly with aromatic amine (Table 1, Entry 10) as compared to that of the reaction of methyl vinyl ketone. In the case of aliphatic primary amines, 8–15% of bis-adducts were also formed due to that the yield of the products is less (Table 1, Entry 12, 13). When a mixture (1:1) of morpholine and aniline was treated with an excess methyl vinyl ketone in the presence of sulfated zirconia, only the morpholine adduct was formed as the sole product (Scheme 2). The spectral data for some of the selected representative compounds are given below:

3.1 4-Phenylamino-butan-2-one (Table 1, Entry 1)

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.104$ (t, 2H), 6.645 (t, 1H), 6.528 (d, 2H), 3.390 (t, 2H), 2.706 (t, 2H), 2.142 (S, 3H) ppm. IR (neat): $\upsilon = 2923.14$, 1708.40, 1169.43, 752.18 cm^{-1}; ESIMS: (M +1) 164 *m/z*.

3.2 4-(2-Chloro-phenylamino)-butan-2-one (Table 1, Entry 2)

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.196$ (q, 1H), 7.077 (m, 1H), 6.551–6.627 (m, 2H), 4.503 (bs, 1H), 3.452 (q, 2H), 2.743 (t, 2H), 2.162(S, 3H) ppm. IR (neat): $\upsilon = 2{,}922.51$, 1,711.59, 1,166.40, 742.35 cm^{-1}. ESIMS: (M +1) 198 *m/z*.

3.3 4-(4-Chloro-phenylamino)-butan-2-one (Table 1, Entry 3):

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.063$ (d, 2H), 6.462 (d, 2H), 3.351 (t, 2H), 2.687 (t, 2H), 2.142(S, 3H) ppm. IR (neat): $\upsilon = 2{,}924.02$, 1,706.34, 1,167.88, 754.61 cm^{-1}. ESIMS: (M +1) 198 *m/z*.

3.4 4-Morpholin-4-yl-butan-2-one (Table 1, Entry 6)

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.641$(t, 4H), 2.633–2.538 (m, 4H), 2.404 (t, 4H), 2.154 (s, 3H) ppm. IR (neat):

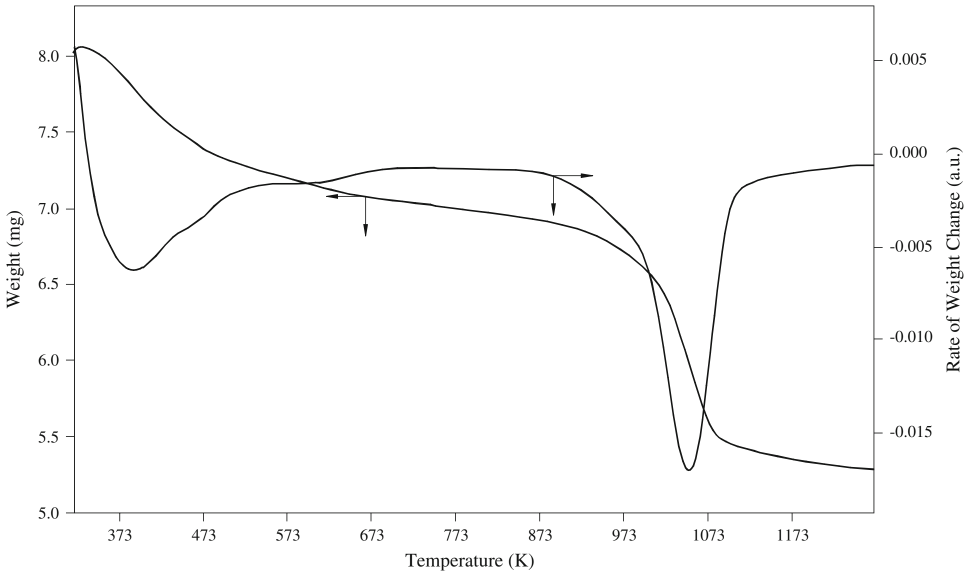
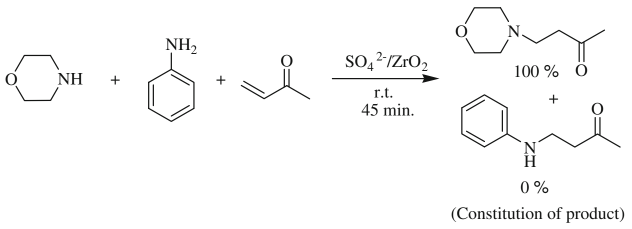


Fig. 2 TGA and DTG profiles of SO_4^{2-}/ZrO_2 catalyst



Scheme 2

$\upsilon = 2{,}923.87$, 1,712.31, 1,116.05 cm^{-1}. ESIMS: (M +1) 158 *m/z*.

3.5 3-Cyclohexylamino-propionic Acid Methyl Ester (Table 1, Entry 13)

^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.665$(s, 3H), 2.868 (t, 2H), 2.473(m, 2H), 2.387(m, 1H) 0.883–1.922 (m, 10H) ppm. IR (neat): $\upsilon = 2{,}931.88$, 1,737.88, 1,207.52 cm^{-1}. ESIMS: (M +1) 186 *m/z*.

3.6 3-Piperidin-1-yl-propionic Acid Methyl Ester (Table 1, Entry 14)

^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.672$(s, 3H), 2.821 (t, 2H), 2.560–2.660 (m, 6H), 1.671 (m, 4H), 1.430–1.548 (m, 2H) ppm. IR (neat): $\upsilon = 2{,}934.62$, 1,737.16, 1,117.30 cm^{-1}. ESIMS: (M +1) 172 *m/z*.

3.7 3-Piperidin-1-yl-propionic Acid Ethyl Ester (Table 1, Entry 15)

^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.117$(q, 2H), 2.731 (t, 2H), 2.522 (m, 2H), 1.412–1.709 (m, 10H), 1.263 (t, 3H) ppm. IR (neat): $\upsilon = 2{,}933.19$, 1,731.08, 1,117.78 cm^{-1}. ESIMS: (M +1) 186 *m/z*.

4 Conclusions

In conclusion, a very simple and convenient methodology for the synthesis of β-amino ketones has been developed employing catalytic amounts of sulfated zirconia under solvent-free conditions. The experimental simplicity, mild reaction conditions, inexpensive catalyst, reusability of the catalyst, eco-friendliness of the process (solvent-less) and a high yield of the products make this a very useful and very important addition to the existing methodologies for the title reaction.

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