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ORIGINAL PAPER

Brønsted-acidic ionic liquid $[HO_3S(CH_2)_4MIM][HSO_4]$ as efficient and reusable catalyst for one-pot synthesis of β-acetamido ketones

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Abstract Efficient and convenient synthesis of *β*-acetamido ketones has been achieved by one-pot reaction of acetophenone, aryl aldehydes, acetyl chloride, and acetonitrile in the presence of 3-methyl-1-(4-sulfonylbutyl) imidazolium hydrogensulfate $[HO_3S(CH_2)_4MIM][HSO_4]$, a Brønsted-acidic ionic liquid, as a green and reusable catalyst in solvent-free media at room temperature. The catalyst could be recycled and reused without noticeable decrease in catalytic activity.

Keywords Brønsted-acidic ionic liquids · Multi-component reactions · One-pot synthesis · *β*-Acetamido ketones · Solvent-free conditions

Introduction

Multicomponent reactions (MCRs) are among the most important procedures in organic synthesis and medicinal chemistry [1–3]. These processes consist of two or more synthetic steps, which are performed without isolation of any intermediates [4, 5]. The diversity, efficiency, and rapid access to small and highly functionalized organic molecules make this approach of central interest in the construction of combinatorial libraries and optimization of drug-discovery processes [6, 7]. For this reason, the discovery of novel MCRs and improving known MCRs are popular areas of research in current organic chemistry.

β-Acetamido ketones are versatile intermediates because their skeletons exist in a number of biologically important compounds [8, 9]. They are usually prepared by acylation of *β*-amino ketones [10], Michael addition to *α*,*β*-unsaturated ketones [11], or photoisomerization of phthalimides [12]. The best known route for the synthesis of acetamido ketones is the Dakin–West reaction [13], which involves the condensation of an amino acid with acetic anhydride in the presence of a base via an azalactone intermediate [14]. Iqbal et al. proposed another procedure for the formation of these compounds through the MCR of an aryl aldehyde, acetophenone, and acetyl chloride in acetonitrile in the presence of $CoCl_2$ [15] or montmorillonite K-10 clay [16].

β-Acetamido ketones have also been synthesized using $Cu(OTf)_2$ [17], silica-supported sulfuric acid [18], BiOCl [19], $ZrOCl_2 \cdot 8H_2O$ [20], NH_2SO_3H [21], $H_3PW_{12}O_{40}$ [22], $FeCl_3 \cdot 6H_2O$ [23], and $SnCl_2 \cdot 2H_2O$ [24] as catalysts. Although these methods are quite useful, most have limitations, for example requirement of expensive catalysts, long reaction time, and harsh reaction conditions. Therefore, the development of simple, efficient, clean, high-yielding, and environmentally friendly approaches using new catalysts for synthesis of these compounds is an important task for organic chemists.

Ionic liquids (ILs), recognized as environmentally benign media, have been widely applied in many reactions as catalysts or as dual catalyst–solvent because of their low vapor pressure, reusability, and high thermal and chemical stability [25, 26]. The introduction of Brønsted-acidic functional groups into cations or anions of the ILs, especially the SO_3H functional group, obviously enhanced their acidities and water solubilities [27–30]. Therefore, Brønsted-acidic ILs

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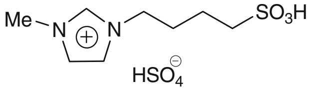
can be used as highly efficient acid catalysts. Moreover their polar nature makes them useful for use under solvent-free conditions. In fact, use of Brønsted-acidic ILs as catalysts is an area of ongoing activity. However, development and exploration of these catalysts are currently in the preliminary stage.

In continuation of our previous work on the applications of reusable acid catalysts in the synthesis of heterocyclic compounds [31–33] here we wish to report the green synthesis of *β*-acetamido ketones **3a**–**3l** by use of 3-methyl-1-(4-sulfonylbutyl)imidazolium hydrogensulfate [$HO_3S(CH_2)_4MIM$][HSO_4] (Scheme 1), a Brønsted-acidic IL, using one-pot condensation of acetophenone (**1**), aryl aldehydes **2a**–**2l**, acetyl chloride, and acetonitrile under solvent-free conditions (Scheme 2).

Results and discussion

To find the optimum conditions, synthesis of *β*-acetamido-*β*-phenylpropiophenone (**3a**) was used as model reaction. A mixture of acetophenone (4 mmol), benzaldehyde (4 mmol), acetyl chloride (1.2 cm^3), and acetonitrile (12 cm^3) was stirred under various reaction conditions (Table 1). In the absence of the catalyst, *β*-acetamido-*β*-phenylpropiophenone (**3a**) was obtained in trace amounts after 180 min, whereas good results were obtained in the presence of [$HO_3S(CH_2)_4MIM$][HSO_4] after 25–120 min (entries 2–7). The optimum amount of [$HO_3S(CH_2)_4MIM$][HSO_4] was 65 mol% (entry 6). A greater amount of the catalyst was found to have an inhibitory effect on formation of the product (entry 7).

Also, the reaction was carried out in various solvents and also under solvent-free conditions. As shown in Table 2, in comparison with conventional methods the yields of the reaction under solvent-free conditions are higher and the reaction time is shorter. Subsequently, therefore, all reactions were carried out at room temperature in the presence of 65 mol% $HO_3S(CH_2)_4MIM$[HSO_4] under solvent-free conditions.



[$HO_3S(CH_2)_4MIM$][HSO_4]

Scheme 1

To extend the preparative utility and generality of this multicomponent reaction, a variety of aromatic aldehydes containing both electron-donating and withdrawing substituents were used to obtain the corresponding *β*-acetamido ketones in good yields under the optimized reaction conditions (Table 3).

In conclusion, we have developed a mild and simple method for synthesis of *β*-acetamido ketones using [$HO_3S(CH_2)_4MIM$][HSO_4], a Brønsted-acidic IL. The catalyst can be reused after simple work-up, with a gradual decline of its activity being observed. Good yields, short reaction times, simplicity of operation, and easy work-up are some advantages of this procedure.

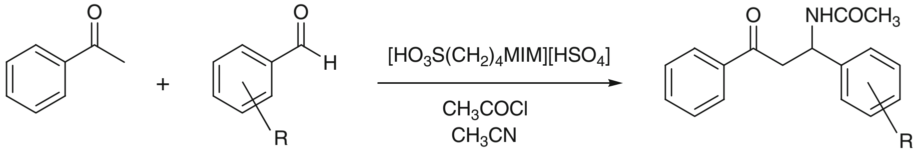
Experimental

All chemicals were commercially available and used without further purification. The Brønsted-acidic ionic liquid [$HO_3S(CH_2)_4MIM$][HSO_4] was synthesized according to Ref. [34]. Melting points were recorded on an electrothermal type 9,100 melting point apparatus. The IR spectra were obtained on a Shimadzu 4300 spectrophotometer as KBr disks. The ^1H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer.

*General procedure for the synthesis of β-acetamido ketones **3a**–**3l***

To a solution of 4 mmol acetophenone, 4 mmol aryl aldehyde **2a**–**2l**, 1.2 cm^3 acetyl chloride, 12 cm^3 acetonitrile, and 0.83 g [$HO_3S(CH_2)_4MIM$][HSO_4] (2.6 mmol, 65 mol%) were added. The reaction mixture was stirred at room temperature for the appropriate time. The progress of the reaction was monitored by TLC. After completion of

Scheme 2



1 **2a-2l** **3a-3l**

a: R = H
b: R = 3-Cl
c: R = 4-Cl
d: R = 3-Br
e: R = 2-NO_2
f: R = 3-NO_2
g: R = 4-NO_2
h: R = 3-Me
i: R = 4-Me
j: R = 3-OH
k: R = 4-OH
l: R = 4-OMe

Table 1 Effect of the amounts of $[HO_3S(CH_2)_4MIM][HSO_4]$ on the reaction

Entry	Catalyst (mol%)	Time (min)	Yield (%)[a]
1	None	180	Trace
2	25	120	51
3	30	90	55
4	40	45	57
5	55	25	63
6	65	25	76
7	70	45	58

4 mmol acetophenone, 4 mmol benzaldehyde, 1.2 cm^3 acetyl chloride, and 12 cm^3 acetonitrile at r.t.

[a] Isolated yields

Table 2 Synthesis of β-acetamido-β-phenylpropiophenone (**3a**) in the presence of 65 mol% $[HO_3S(CH_2)_4MIM][HSO_4]$ in different solvents at r.t.

Entry	Solvent	Time (min)	Yield (%)[a]
1	EtOH	90	Trace
2	CH_2Cl_2	30	35
3	$CHCl_3$	30	47
4	Solvent-free	25	76

[a] Isolated yields

Table 3 Synthesis of β-acetamido ketones **3a**–**3l** using $[HO_3S(CH_2)_4MIM][HSO_4]$ (65 mol%) as catalyst at room temperature under solvent-free conditions

Entry	Products[a]	R	Time (min)	Yield (%)[b]	Mp (°C)
1	**3a**	H	25	76	103–105
2	**3b**	3-Cl	25	86	105–108
3	**3c**	4-Cl	20	94	145–147
4	**3d**	3-Br	45	68	100–103
5	**3e**	2-NO_2	30	78	181–183
6	**3f**	3-NO_2	30	74	138–140
7	**3g**	4-NO_2	30	90	147–149
8	**3h**	3-Me	20	76	80–82
9	**3i**	4-Me	20	91	108–110
10	**3j**	3-OH	30	72	135–137
11	**3k**	4-OH	25	69	182–184
12	**3l**	4-OMe	25	80	105–107

[a] All products were characterized by ^{1}H NMR and IR spectroscopy and comparison with authentic samples [17–24]

[b] Isolated yields

the reaction, the mixture was poured into ice-cold water and stirred thoroughly, which resulted in precipitation of the desired β-acetamido ketones. The precipitated solid was isolated by filtration and washed with diethyl ether. The pure product was obtained by recrystallization from ethyl acetate–*n*-hexane. The structure of the products was confirmed by ^{1}H NMR and IR spectroscopy, and comparison with authentic samples prepared by reported methods [17–24].

Recycling and reuse of the catalyst

The catalyst is soluble in water and could therefore be recycled as the filtrate. The catalyst was recovered by evaporation of the water, washed with diethyl ether, dried at 50 °C under vacuum for 1 h and reused in another reaction without appreciable reduction in the catalytic activity. This procedure applied for **3a** in a second run resulted in 74% yield.

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