One-pot synthesis of β-amido ketones using Brønsted acidic ionic liquid as an efficient and reusable catalyst

Krishna M. Deshmukh, Ziyauddin S. Qureshi, Nitin S. Nandurkar, and Bhalchandra M. Bhanage

Abstract: An efficient protocol was developed for one-pot condensation of an aldehyde, ketone, acetyl chloride, and nitriles catalyzed by a stable and reusable 1-methyl-imidazolium hydrogen sulfate ([Hmim][HSO_4]) as a Brønsted acidic ionic liquid. The system tolerated a variety of functional groups affording the corresponding β-amido ketones in moderate to good yields under milder operating conditions.

Key words: ionic liquids, multicomponent reactions, β-amido ketones, one-pot synthesis.

Résumé : On a développé un protocole efficace pour la condensation monotope d'un aldéhyde, d'une cétone, du chlorure d'acétyle et de nitriles, catalysée par un liquide ionique stable et réutilisable, le sulfate acide de 1-méthyl-imidazolium [Hmim][HSO_4] qui agit comme acide de Brønsted. Le système tolère une grande variété de groupements fonctionnels conduisant à la formation des β-amidocétones correspondantes avec des rendements allant de modérés à bons, dans les conditions d'opération les plus douces.

Mots-clés : liquides ioniques, réactions à plusieurs composantes, β-amidocétones, synthèse monotope.

[Traduit par la Rédaction]

Introduction

β-Amido ketones constitute an important class of compounds having biological and medicinal properties.[1,2] They are used as precursors for the synthesis of 1,3-amino alcohol present in antibiotic drug such as nikkomycines or neopolyoxines.[3,4] Traditionally, these compounds are synthesized by a Dakin–West reaction, which involves the condensation of an α-amino acid with acetic anhydride in the presence of a base.[5] Iqbal and co-workers proposed a multicomponent route for the synthesis of β-acetamido ketones via condensation of an aldehyde, enolizable ketones, acetyl chloride, and acetonitrile using $CoCl_2$[6] and Montmorillonite K10[7] as the catalysts. Subsequently, other groups extended these methodologies by exploring various Lewis or Brønsted acid catalysts such as $FeCl_3{\cdot}6H_2O$,[8] $ZrOCl_2{\cdot}8H_2O$,[9] silica sulfuric acid,[10,11]$SiCl_4$-$ZnCl_2$,[12] heteropoly acid,[13] ZnO,[14] and $BiCl_3$ generated from BiOCl.[15] Inspite of their potential applications, these methodologies face disadvantages like the requirement of harsh reaction conditions, use of expensive and moisture sensitive Lewis acid catalysts, and elevated temperatures.

In recent years, application of ionic liquids have gained considerable interest in the context of green synthesis. Although ionic liquids were initially introduced as an alternative green reaction media, today they have marched far beyond this border for their significant role in controlling the reaction as a catalyst. Among various ionic liquids developed to date, Brønsted acidic ionic liquids have emerged as a most promising alternative for a wide variety of acid catalyzed reactions.[16–24]

Results and discussion

We herein report an efficient protocol for one-pot condensation of an aldehyde, ketone, acetyl chloride, and nitriles catalyzed by a stable and reusable Brønsted acidic ionic liquid, 1-methyl-imidazolium hydrogen sulfate ([Hmim][HSO_4]). The system tolerated a variety of functional groups affording corresponding β-amido ketones in moderate to good yields under milder operation conditions (Scheme 1).

Initially, condensation of benzaldehyde, acetophenone, acetyl chloride, and acetonitrile were chosen as model reaction and the role of the different ionic liquids as a catalyst and it's loading on the reaction system was investigated (Table 1, entries 1–4). The influence of various 1-methylimidazolium based ionic liquids, such as 1-butyl-3-methylimidazolium hydrogen sulfate ([C_4mim][HSO_4]), 1-methylimidazolium hydrogen sulfate ([Hmim][HSO_4]), 1-methylimidazolium tetraflouroacetate ([Hmim][Tfa]), and 1-methyl-imidazolium nitrate ([Hmim][NO_3]), were studied. Out of various ionic liquids screened, the [Hmim][HSO_4] ionic liquid was found to be the most effective, providing good yield of the desired product. The effect of catalyst

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Scheme 1. Synthesis of β-amido ketones using ionic liquid as catalyst.

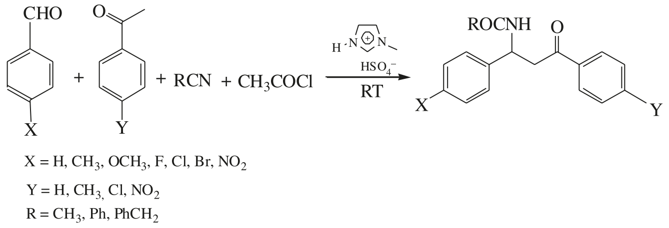


Table 1. Effect of catalysts and catalyst loading on the condensation of benzaldehyde, acetophenone, acetyl chloride, and acetonitrile.

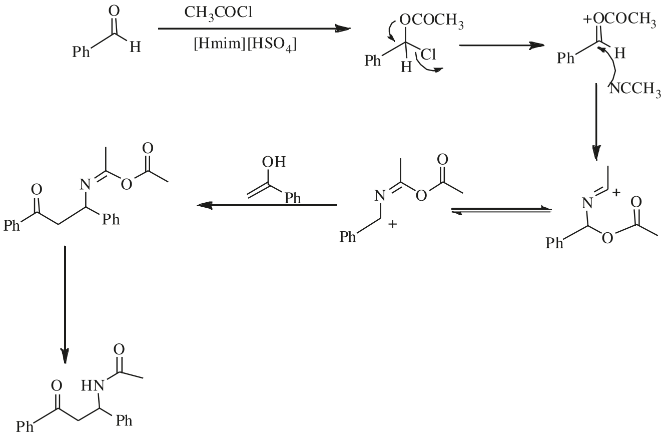
Entry	Catalyst	Catalyst loading (mol %)	Yield (%)[a]
1	[C_4mim][HSO_4]	40	60
2[b]	[Hmim][HSO_4]	40	75, 73, 71
3	[Hmim][Tfa]	40	66
4	[Hmim][NO_3]	40	36
5	[Hmim][HSO_4]	10	50
6	[Hmim][HSO_4]	20	54
7	[Hmim]HSO_4]	30	63
8	[Hmim][HSO_4]	50	72
9	[Hmim][HSO_4]	60	70
10	[Hmim][HSO_4]	100	62

Note: Reaction conditions: benzaldehyde (1 mmol); acetophenone (1 mmol); acetyl chloride (0.3 mL); acetonitrile (4 mL); reaction time: 10 h at RT.

[a]Isolated yields.

[b]Recyclability of the catalyst tested up to three cycles.

Scheme 2. Mechanism for the synthesis of β-amido ketones.



loading on the reaction system was also investigated and 40 mol% [Hmim][HSO_4] was found to be the most effective in providing a higher yield. (Table 1, entries 5–10).

Since [Hmim][HSO_4] was one of the most effective functional ionic liquids, it was selected to investigate the possibility of recyclability. After the completion of the reaction, the reaction mixture was evaporated under reduced pressure to obtain a residue. The residue was dissolved in ethyl acetate to obtain two phases; the ionic liquid phase was separated by decantation of ethyl acetate. The ionic liquid phase was then washed with diethyl ether (3 × 5 mL) and was evaporated under reduced pressure at 80 °C for 1 h to remove the redundant mixed solvent and it was then used for further recyclability test.

It can be seen from Table 1, entry 2, that there was no obvious change on the recovered catalyst (88%–95%) and excellent yield was obtained. After recycling three times, [Hmim][HSO_4] was still stable enough and had less impact on the catalytic activity. The purity of the recycled ionic liquid was confirmed using ^1H NMR and it was the same as that used for the first run. This indicated that [Hmim][HSO_4] was a highly efficient and recyclable catalyst for synthesis of β-amido ketones.

Thus, using [Hmim][HSO_4] as the best catalyst, the condensation of various aldehydes, ketones, and nitriles with different steric and electronic properties were investigated (Table 2, entries 1–22). The condensation of benzaldehyde, acetophenone, acetyl chloride, and nitriles provided a 75% yield of the desired product. Aldehydes with electron-donating (CH_3, OCH_3) and electron-withdrawing substituents (NO_2, Cl, Br, F) were also investigated and found to provide good yields (50%–84%) under the present conditions. Substituted acetophenones having activating and deactivating groups were found to be compatible and provided good yields of the desired products (Table 2, entries 2–4, 10–13, 16, 17, 21, 22). To show the generality of the protocol, the effect of aliphatic and aromatic nitriles, such as acetonitrile, benzonitrile, and phenylacetonitrile were also investigated. The reaction of benzonitrile require longer reaction times, up to 24 h and the probable reason for this may be the steric factor as well as low nucleophilicity of benzonitrile (Table 2, entries 14–17).

The reaction of acetonitrile and phenylacetonitrile were found to proceed smoothly under the present conditions, providing good yields of the desired products. Thus, the protocol is general in nature and tolerates a wide range of functional groups. A plausible reaction mechanism for the present reaction may proceed as depicted in Scheme 2. The yield of β-amido ketones depends upon the ionic liquid chosen, as shown in Table 1. It can be seen that [Hmim][NO_3] gives a lower yield of the product as compared to [Hmim][HSO_4] and [C_4mim][HSO_4], which suggests that the counter anion also plays a catalytic role in the reaction (Scheme 2). The counter anion protonates the ketone by a donating proton.

In summary, [Hmim][HSO_4] is a reusable and moisture stable Brønsted acidic ionic liquid, reported as an efficient catalyst for the synthesis of a wide range of β-amido ketone under mild operating conditions. The system tolerates a wide range of functional groups affording the desired products in good to excellent yields. Further work is in progress to broaden the scope of ionic liquids to various other organic transformations.

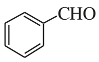
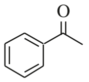
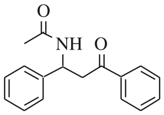
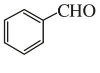
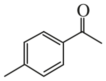
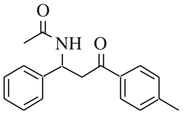
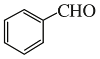
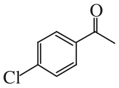
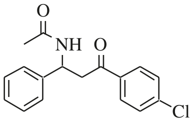
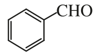
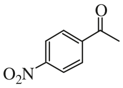
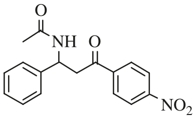
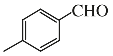
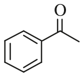
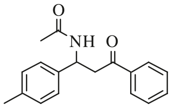
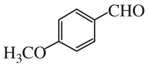
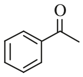
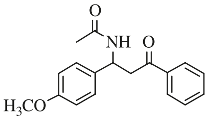
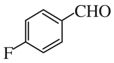
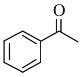
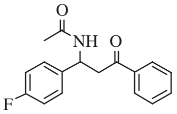
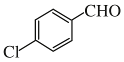
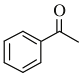
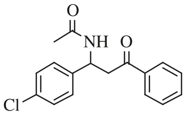
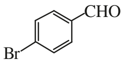
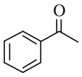
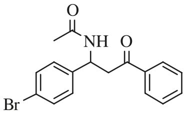
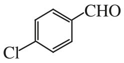
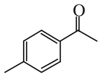
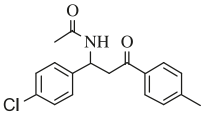
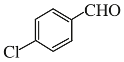
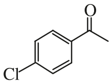
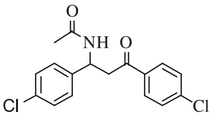
Experimental section

The chemicals and solvents were supplied by Sigma-Aldrich, Fluka, and S.D. Fine-chem Ltd. companies and used without further purification

Synthesis of ionic liquids

In this study, the ionic liquids used were synthesized according to the procedure reported in the literature[22–24] and were characterized by ^1H NMR.

Table 2. One-pot condensation of aldehyde, ketone, acetyl chloride, and nitriles to give the corresponding β-amido ketone catalyzed by [Hmim][HSO_4].

Entry	Aldehyde	Ketone	Product	Yield (%)[a]	Mp found (°C)	Mp reported (°C), Ref.
1				75	100–102	101–103, 13
2				64	120–121	121–123, 11
3				77	112–114	114–115, 11
4				65	76–78	74–76, 13
5				68	111–114	112, 6
6				84	112–115	115–117, 13
7				76	109–111	109–111, 11
8				61	143–145	144–146, 13
9				66	148–150	148–150, 8
10				72	143–145	14
11				53	140–142	141–143, 10

Synthesis of β-amido ketones using [Hmim][HSO_4] as the catalyst

To a stirred suspension of [Hmim] [HSO_4] (40 mol %) in acetonitrile (4 mL) were added benzaldehyde (1 mmol), acetophenone (1 mmol), and acetyl chloride (0.3 mL). The reaction mixture was stirred at ambient temperature for 10 h. After the completion of the reaction, crushed ice (30 mL) was added to the reaction mixture and stirred thoroughly. On solidification, the products were filtered off and dried to get the corresponding β-amido ketone. The solid product obtained was recrystallized from the mixture of solvents (ethyl acetate–hexane) to get the pure product. All compounds are known compounds and were characterized by using IR and ^1H NMR.

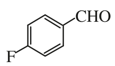
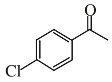
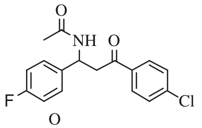
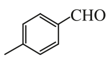
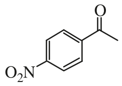
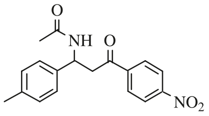
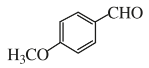
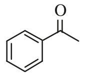
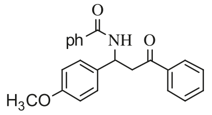
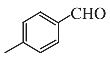
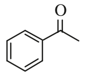
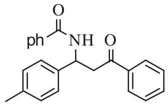
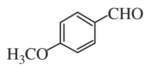
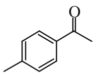
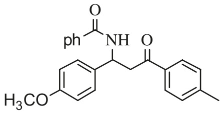
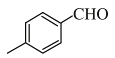
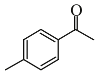
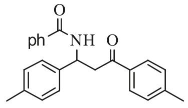
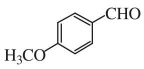
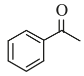
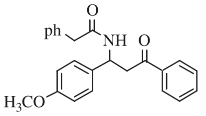
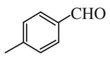
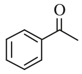
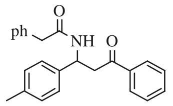
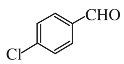
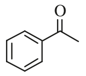
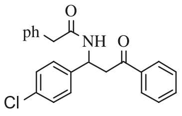
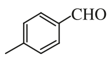
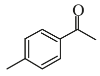
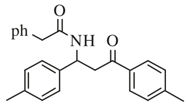
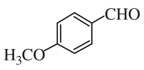
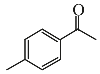
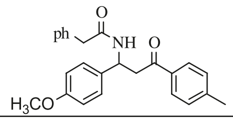
Selected spectroscopic data

Characterization of ionic liquids using ^1H NMR

1-Butyl-3-methyl-imidazolium hydrogen sulfate ([C_4mim][HSO_4])

^1H NMR (400 MHz, $CDCl_3$, ppm) δ: 0.91 (t, J = 7.5 Hz,

Table 2 (*concluded*).

Entry	Aldehyde	Ketone	Product	Yield (%)[a]	Mp found (°C)	Mp reported (°C), Ref.
12				57	109–111	108–110, 11
13				53	84–86	83–85, 13
14[b]				60	175–177	12
15[b]				62	169–170	172–173, 12
16[b]				63	178–180	12
17[b]				66	176–177	12
18				67	128–130	131–132, 12
19				64	127–129	12
20				50	143–145	12
21				56	129–131	12
22				65	133–134	12

Note: Reaction conditions: aldehyde (1mmol), ketone (1mmol), acetyl chloride (0.3mL), nitriles (4 mL), [Hmim] [HSO_4] (40%), and reaction time 10 h at ambient temperature.
[a] Isolated yield.
[b] Reaction time 24 h.

3H), 1.25 (m, $J = 7.4$ Hz, 2H), 1.75 (m, $J = 7.4$ Hz, 2H), 2.5 (s, 3H), 4.18 (t, $J = 7.0$ Hz, 2H), 7.70 (m, 2H), 7.79 (s, 1H), 9.25 (s, 1H).

1-Methyl-imidazolium hydrogen sulfate ([Hmim][HSO$_4$])

IR (KBr, cm^{-1}) ν: 3265, 3145, 2846, 1550, 1480, 1186, 1058, 883, 618. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 3.86 (s, 3H), 7.67 (m, 3H), 9.07 (s, 1H), 14.5 (br, s, 1H).

Characterization of β-amido ketones using ^{1}H NMR and FT-IR

N-*[3-Oxo-1,3-diphenyl-propyl] acetamide (Table 2, entry 1)*

IR (KBr, cm^{-1}) ν: 3284, 3058, 2925, 1690, 1646, 1540, 1225, 988, 618. ^{1}H NMR (200 MHz, $CDCl_3$, ppm) δ: 2.03 (s, 3H), 3.40 (dd, $J = 6.0$, 16.9 Hz, 1H), 3.76 (dd, $J = 6.0$, 16.9 Hz, 1H), 5.57 (m, 1H), 6.70 (br d, $J = 7.5$ Hz, 1H), 7.22–7.61 (m, 8H), 7.91 (d, $J = 7.5$ Hz, 2H).

N-*[1-(4-Fluorophenyl)-3-oxo-3-phenyl-propyl] acetamide (Table 2, entry 7)*

IR (KBr, cm^{-1}) ν: 3283, 3083, 1686, 1635, 1574, 1372, 1298, 990, 895. ^1H NMR (200 MHz, $CDCl_3$, ppm) δ: 2.01 (s, 3H), 3.45 (dd, J = 6.0, 16.9 Hz, 1H), 3.75 (dd, J = 6.0, 16.9 Hz, 1H), 5.50 (m, 1H), 6.72 (brs, 1H), 7.01 (t, 2H), 7.40 (m, 5H), 7.83 (d, J = 7.5 Hz, 2H).

N-*[1-(4-Methoxyphenyl)-3-oxo-3-(4-methylphenyl) propyl]-2-phenylacetamide (Table 2, entry 22)*

IR (KBr, cm^{-1}) ν: 3333, 2955, 1689, 1640, 1515, 1247, 1184, 1032, 822, 733. ^1H NMR (200 MHz, $CDCl_3$, ppm) δ: 2.32 (s, 3H), 3.22 (dd, J = 5.5, 16.6 Hz, 1H), 3.45 (dd, J = 5.5, 16.6 Hz, 1H), 3.51 (s, 2H), 3.68 (s, 3H), 5.39 (m, 1H), 6.49 (brs, 1H), 7.03 (d, J = 7.5 Hz, 2H), 7.13–7.28 (m, 9H), 7.69 (d, J = 7.8 Hz, 2H).

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