

Mannich reaction in Brønsted acidic ionic liquid: A facile synthesis of β -amino carbonyl compounds

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Abstract

Brønsted acidic ionic liquid containing nucleophile 1-methylimidazole and triphenylphosphine with 1,4-butane sultone and inorganic anions *p*-toluenesulfonic acid (PTSA) and trifluoroacetic acid (TFA) catalyzed Mannich reaction smoothly to afford β -amino carbonyl compounds in excellent yield and less time. Effect of addition of two drops of water on the product yield and effect of anions and cations of the ionic liquid on the reaction rate have been investigated. The ionic liquid was easily separated from the reaction mixture by water extraction and was recycled four times without any loss in activity.

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1. Introduction

Mannich reaction is one of the most important C–C bond forming reactions in organic synthesis for the preparation of secondary and tertiary amine derivatives [1]. These amines are further used for the synthesis of many intermediates, biologically active and natural products such as alkaloids and polyketides. The products of Mannich reaction are mainly β -amino carbonyl compounds and its derivatives that are used for the synthesis of amino alcohols, peptides, lactams and as precursors to optically active amino acids. The conventional catalysts for classical Mannich reaction of aldehydes, ketones and amines involve mainly organic and mineral acids like proline [2–4], acetic acid [5], *p*-dodecylbenzenesulfonic acid [6] and some Lewis acids [7,8]. They often suffer from the drawbacks of long reaction times and harsh reaction conditions, toxicity and difficulty in product separation, which limit its use in the synthesis of complex molecules. The most frequently used promoters like Lewis acid catalysts [9], Brønsted acid catalysts [10,11] and Lewis base catalysts [12] have been reported to catalyze Mannich reaction. Scandium triflate, copper triflate, scandium tris(dodecylsulfate) and scandium tris(dodecanesulfonate) [13], InCl_3 [14] and HBF_4 [10,15]

have also been known to catalyze these reactions in good yields with the aid of surfactant only. Lanthanide triflate in solvents like dichloromethane and acetonitrile have also been known to catalyze Mannich reaction [16,17].

As there is a growing demand for the development of organic reactions in environment friendly media, synthetic manipulations have to be made to minimize the use of hazardous chemicals like replacing the traditional organic solvents in reactions and their subsequent workup with other non-toxic solvents like water or super critical CO_2 . In this context Akiyama et al. [10,11] have reported Mannich type reactions in aqueous media.

Ionic liquids have attracted extensive research interest in recent years as environmentally benign solvents due to their favorable properties like non-inflammability, negligible vapour pressure, reusability and high thermal stability [18,19]. They have also been referred to as ‘designer solvents’ as their physical and chemical properties could be adjusted by a careful choice of cation and anion. Apart from this they exhibit acidic properties. Combining these unique properties of ionic liquids they are emerging as a ‘green reaction media’ (catalyst + solvent). The use of ionic liquids as reaction medium may offer a convenient solution to both the solvent emission and catalytic recycling problem [18,20–22].

Among the different Mannich type reactions reported, the reaction of silyl enolates with aldimines have been reported in ionic liquids [23]. Ruthenium complexes and ytterbium(III)

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triflate catalyzed Mannich reaction in BMIM[PF6] have been reported [24,25]. Mannich reaction using Brønsted acid ionic liquids as catalysts and solvent have also been reported [26].

Our recent interest has been in the development of new synthetic methods on using ionic liquids as reaction media [27]. Herein as a part of the program to investigate the different organic reactions feasible in Brønsted acid ionic liquids, we report a simple and fast reaction of different aldehydes, ketones and amines to afford corresponding β -amino carbonyl compounds. To the best of our knowledge in the open literature, Mannich reaction involving catalytic amount of ionic liquids bearing triphenyl phosphonium sultone/imidazolium sultone as cation and TFA/PTSA as anion are unprecedented. The reaction proceeded very fast with high yield of the desired Mannich base using catalytic amount of ionic liquid. The effect of anions and cations of the ionic liquid on the reaction rate has also been investigated.

2. Experimental

2.1. Chemicals

All the aldehydes, ketones, amines, were obtained from S.D. Fine Chemicals, Mumbai. 1-Methylimidazole and 1,4-sultone were obtained from Lancaster (UK), and were used as received. Triphenylphosphine was obtained from Aldrich Chemicals, USA. Trifluoroacetic acid (TFA) was obtained from Fluka Chemicals and *p*-toluene sulfonic acid (PTSA) was obtained from Loba Chemie, India.

2.2. Synthesis of ionic liquids

The synthesis of these ionic liquids has been carried out using a similar method reported in the literature [28]. The method involves the reaction of neutral nucleophiles triphenylphosphine and *N*-methyl imidazole with 1,4-butane sultone in equimolar ratio to afford the zwitterions that is further converted into ionic liquid by acidification with PTSA and TFA (Scheme 1). The ionic liquid was formed quantitatively and in high purity as assessed by NMR.

2.3. Mannich reaction: a typical procedure

In a typical reaction, benzaldehyde (1 equiv., 0.5 g), aniline (1 equiv., 0.45 g), acetophenone (1 equiv., 0.6 g), and ionic liquids (0.65 g) as catalysts and solvent were stirred at room temper-

ature (25 °C) in a round-bottomed flask fitted with a condenser. After a certain time the reaction mixture became viscous and solidified. At this stage the time was noted and the ionic liquid was separated from the reaction mixture by extraction with copious amount water (5 × 3 ml). The ionic liquid being soluble in water comes in the water layer. The solid was separated by filtration and product was recrystallized from ethanol and vacuum dried for 5 h. The product was identified using ¹H NMR in CDCl₃ with TMS as reference (300 MHz) and by FTIR on a Shimadzu (model 8201 PC) spectro-photometer using KBr plates in a frequency range. The ionic liquid in the filtrate was separated from the unreacted starting materials by extracting the filtrate with ether. Then the water layer containing ionic liquid was vacuum dried at 70 °C for 5 h to remove water and the ionic liquid was reused.

3. Results and discussion

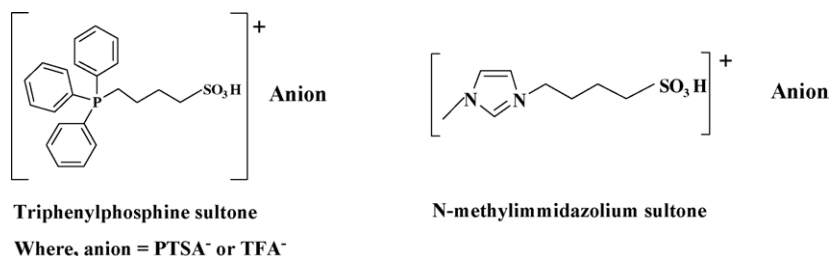
The Mannich reaction of aldehydes, ketones and amines in presence of Brønsted acidic ionic liquids is conducted at room temperature and the results are summarized in Table 1. No Mannich base is observed in the absence of ionic liquids (Table 1,

Table 1
Results of Mannich reaction with different ionic liquids

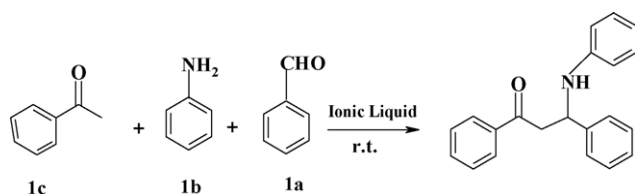
Entry	Aldehyde	Amine	Ketone	Ionic liquid (g)	Time (h)	% Yield
1	1a	1b	1c	Nil	10	0
2	1a	1b	1c	PTSA ^a (0.1)	4	55
3	1a	1b	1c	TFA ^a (0.06)	4	57
4	1a	1b	1c	MIM-TFA (0.5)	2	70
5	1a	1b	1c	MIM-PTSA (0.65)	2	70
6	1a	1b	1c	PS-TFA (0.65)	45 min	96.7
7	1a	1b	1c	PS-PTSA (0.65)	45 min	85
8	1a	1b	1c	PS-PTSA ^a (0.5)	45 min	77
9	1a	1b	1c	PS-PTSA ^a (0.65)	45 min	80
10	2a	1b	1c	PS-PTSA (0.65)	2	84
11	1a	2b	1c	PS-PTSA (0.65)	12	0
12	1a	3b	1c	PS-PTSA (0.65)	12	0
13	1a	4b	1c	PS-PTSA (0.65)	2	76
14	1a	5b	1c	PS-PTSA (0.65)	12	0
15	1a	1b	2c	PS-PTSA (0.65)	2	35

Reaction condition: aldehyde:amine:ketone, 1:1:1 (mole ratio); temperature = 25 °C. Two drops of water (0.06 g) was added to the ionic liquid to allow proper mixing. 1a = benzaldehyde, 1b = aniline, 1c = acetophenone, 2a = chloro benzaldehyde, 2b = 2,4-xylidene, 2c = cyclohexanone, 3b = cyclohexyl amine, 4b = 4-bromo aniline, 5b = *N*-methyl aniline.

^a No water added. Reaction with PTSA and TFA was carried out using 2.5 g of ethanol.



Scheme 1. Schematic diagram of ionic liquid.



Scheme 2. Reaction scheme for Mannich reaction of acetophenone, aniline and benzaldehyde.

Table 2
Catalyst recycling of ionic liquid for Mannich reaction

Entry	Cycle	Mannich base, % yield
1	Fresh	87
2	1st recycle	86
3	2nd recycle	85
4	3rd recycle	85
5	4th recycle	85

Reaction condition: benzaldehyde:aniline:acetophenone, 1:1:1 (mole ratio), ionic liquid = PS-PTSA (0.65 g), temperature = 25 °C. Two drops of water (0.06 g) was added to the ionic liquid.

entry 1). Mannich reaction with TFA and PTSA in ethanol (2.5 g) gave a yield of 57 and 55% (Table 1, entries 2, 3). The study shows that catalytic amount of ionic liquids bearing triphenyl phosphonium sultone/imidazolium sultone as cation and TFA/PTSA as anion catalyzes Mannich reaction in very less time and gives high isolated yield. All the above ionic liquids are suitable for Mannich reaction, however, catalytic amount of triphenyl phosphonium sultone TFA⁻, a solid at room temperature (PS-TFA), gave the highest yield in very less time compared to other ionic liquids studied (Table 1, entry 6). On comparing the results obtained on using imidazolium sultone as cation and PTSA as anion (MIM-PTSA), it is observed that triphenyl phosphonium sultone PTSA (PS-PTSA) gave higher yield (Table 1, entries 5, 7). This could be because strongly acidic H⁺ bind with amines and reduce the formation of Mannich base. Reaction of *o*-benzaldehyde with aniline and acetophenone gave a yield of 84% over a period of 2 h (Table 1, entry 10). 4-Bromo aniline gave a yield of 76% over a period of 2 h (Table 1, entry 13) and cyclohexanone gave a yield of 35% (Table 1, entry 15). No Mannich base was obtained on using 2,4-xylidene, and *N*-methyl aniline which could be because of space hindrance (Table 1, entries 11, 14). In case of cyclohexyl amine also no Mannich product was obtained (Table 1, entry 12).

To optimize the reaction conditions, Mannich reaction was carried out with benzaldehyde, aniline and acetophenone (Scheme 2) using PS-PTSA (0.5 g, a sticky solid at room temperature), which gave a yield of 77% (Table 1, entry 8). However, on increasing the amount of PS-PTSA (0.65 g), the yield increased to 80% only (Table 1, entry 9). On reusing PS-PTSA (a viscous liquid and not a sticky solid), it was observed that the yield increased to 87% (Table 2, entry 2) even though some loss of PS-PTSA cannot be ruled out during handling. This could be because of the thorough mixing of the ionic liquid in the reaction medium due to the presence of water in ionic liquid, which lead to higher yield. This was not the case with first reaction

of PS-PTSA (0.65 g) (Table 1, entry 9). It suffered from the drawback of poor mixing and hence low yield. Hence addition of small amount of water to the solid ionic liquid will lead to higher yield. To study the effect of water on the 1st reaction, we deliberately added 1 ml of de-ionized water to the ionic liquid and carried out the reaction but a decrease in the yield was obtained. Hence, large amount of water is not favorable for the reaction. Similar trend was also observed on varying the substrates as well as the ionic liquids. In our further studies, we added two drops of water to the ionic liquid in each reaction.

All the ionic liquids were easily recyclable after removing starting materials and water. PS-PTSA was recycled four times for the reaction of benzaldehyde, aniline and acetophenone (Table 2). Even after four recycles, product was obtained with similar yield and purity of those obtained in the first recycle. The ionic liquid retained its structure even after four recycles as confirmed by NMR.

4. Conclusions

In summary, this study evaluates the effect of very small amount of sultone-based ionic liquids as potential catalysts for Mannich reaction of aldehyde, amine and ketone. This work shows that the yields are much improved and the reaction is much faster in this particular ionic liquid which we have used and recovery of the ionic liquid from the reaction mixture is possible by simple extraction with water. This method avoids the use of acid catalysts and environmentally unfavorable volatile organic solvents. The most attractive part of this work is that only small amount of ionic liquid can catalyze this reaction in less time. The simple experimental procedure, fast reaction, easy product separation and reuse of ionic liquids makes the use of the above ionic liquid a greener and economically viable catalyst for the synthesis of β -amino carbonyl compounds compared with the traditional protocols.

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Appendix A. Spectral data for the Mannich products

3-(*N*-Phenylamino)-1,3-diphenyl-1-acetone: ¹H NMR (200 MHz, CDCl₃): 3.41 (2H, d), 4.93 (1H, m), 6.48 (2H, d), 6.59 (1H, m), 7.01 (2H, m), 7.18 (1H, d), 7.24 (2H, m), 7.35 (5H, m), 7.85 (2H, d); IR (cm⁻¹): 3399, 3024, 2974, 1672, 1598, 1515, 1295, 1221, 1080, 1026, 1001, 860, 693, 512.

3-(*N*-Phenylamino)-3-(3-chlorophenyl)-1-phenylacetone: ¹H NMR (200 MHz, CDCl₃): 3.42 (2H, m), 4.93 (1H, m), 6.52 (2H, d, *J* = 7.95 Hz), 6.60 (2H, m), 7.01 (2H, m), 7.18 (2H, m), 7.24 (1H, d, *J* = 7.05 Hz), 7.36 (3H, d, *J* = 7.9 Hz), 7.49 (1H, m), 7.82–7.85 (2H, d, *J* = 7.8 Hz); IR (cm⁻¹): 3390, 3035, 1674, 1596, 1515, 1377, 1292, 1222, 1080, 1002, 929, 860, 749, 690, 621, 516.

3-(*N*-*P*-Bromophenylamino)-1,3-diphenyl-1-acetone: ¹H NMR (200 MHz, CDCl₃): 3.39 (2H, m), 4.87 (1H, m),

6.34–6.38 (2H, d, $J=7.9$ Hz), 7.06–7.10 (2H, d, $J=8.25$ Hz), 7.16–7.25 (3H, m), 7.29–7.34 (2H, d, $J=9$ Hz), 7.37–7.41 (2H, m), 7.47–7.50 (1H, m), 7.80–7.85 (2H, d, $J=7.95$ Hz); IR (cm^{-1}): 3339, 3020, 2937, 1675, 1509, 1485, 1367, 1308, 1273, 1119, 1072, 859, 753, 683, 518.

2-[1-(*N*-Phenylamino)-1-phenyl]methylcyclohexanone: ^1H NMR (200 MHz, CDCl_3): 1.65 (2H, m), 1.81–1.92 (4H, m), 2.32–2.43 (2H, m), 2.74–2.77 (1H, m), 4.62–4.64 (1H, d, $J=7.09$ Hz), 6.53–6.56 (2H, d, $J=7.88$ Hz), 6.63–6.65 (1H, m), 7.03–7.07 (2H, m), 7.22–7.27 (1H, m), 7.30–7.34 (2H, m), 7.38–7.40 (2H, m), 7.41–7.44 (2H, d, $J=7.9$ Hz); IR (cm^{-1}): 3339, 3011, 2923, 2811, 1674, 1592, 1507, 1310, 1114, 1047, 862, 699, 521.

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