

*Full Length Research Paper*

# Synthesis and characterization of a novel ionic liquid (TBA-AMPS) and its applications in Mannich condensation reactions under solvent free conditions

A. Rajendran\* and M. Priyadarshini

Department of Chemistry, Sir Theagaraya College, Chennai-600 021, Tamilnadu, India.

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**This paper deals with the synthesis and characterization of a novel ionic liquid using green chemicals such as *tetra*-butyl ammonium chloride (TBA) and 2-acrylamido-2-methylpropanesulphonate (AMPS) via an anion metathesis reaction and characterization by <sup>1</sup>H-NMR technique. Also, this ionic liquid was used to catalyze Mannich reactions under solvent free conditions to afford the corresponding β- amino carbonyl compound (Mannich base) in excellent yields in shorter span of time than those of the conventional methods. This work has proven to be a very efficient and selective protocol for Mannich condensation reactions as it involves a simple work-up procedure, absence of by-products, recyclability of the catalyst and using greener chemicals that are environmentally and ecologically benign.**

**Key words:** Ionic liquid, TBA-AMPS, Mannich base, condensation reaction, metathesis reaction, solvent free condition.

## INTRODUCTION

Optimizing yield is important in traditional chemical synthesis but other issues need to be addressed, including minimizing the number of steps, simplicity, waste, atom efficiency, energy usage, safety and whether the chemistry is environmentally acceptable (Rajendran, 2010). Reducing the use of organic solvents can minimize the generation of waste, which is a requirement of one of the principles of green chemistry (Zhang et al., 2005). Organic solvents are conventionally used in chemical synthesis in R & D and in industrial processes on a large scale for heat transfer and controlling chemical reactivity. However, there are serious safety issues (fire, explosion and toxicity) and costly technologically challenging demands associated with containing volatile material (Shelton, Arends and Hanefeld, 2009).

Greening of chemical synthesis is a formidable challenge and often requires a multidisciplinary approach (Larock, 1999). Alternative media to organic solvents include ionic liquids, liquid and supercritical CO<sub>2</sub>, water

(including at high temperature under micro-wave irradiation) and polyethylene and propylene glycol (Kumar, 2009). There is also the possibility of avoiding the use of any reaction medium as solventless reactions, which is the main theme of this article. The choice of reaction medium of solventless condition depends on the reaction; no single medium or choice of solventless conditions will apply to all reactions, or even classes of reactions. The advantages of solventless reactions include (i) the possibility of direct formation of high purity of compounds, (ii) the possibility of sequential reactions, (iii) fast kinetics, (iv) lower energy usage, (v) minimal need for preformed salts and metal-metalloid complexes, (vi) simplicity and low equipment cost, and (vii) the possibility of avoiding functional group protection – deprotection (Kumar, 2009). These ionic liquid molecules typically contain an organic cation with delocalized charge and a bulky inorganic anion (Ganeshpure et al., 2007). Interest in RTILs continues to grow because of their potential as greener solvent alternatives to conventional environmentally damaging organic solvents. In addition, they have unique properties such as lack of measurable vapor pressure, high thermal stability and recyclability. Such environmental-friendly properties make

\*Corresponding author. E-mail: [annamalai\\_rajendran2000@yahoo.com](mailto:annamalai_rajendran2000@yahoo.com). Tel: 944 3765051.

ILs relatively benign solvents for chemical industries (Shelke et al., 2009). Mannich reaction is one of the most important C-C bond forming reactions in organic chemistry for the synthesis of secondary and tertiary amine derivatives (Sahoo et al., 2006). Trissa Joseph and his co-workers have reported a remarkable contribution using 1-methylimidazole and triphenyl phosphine with 1,4-butane sultone, inorganic anions p-toluene sulphonic acid (PTSA) and trifluoroacetic acid (TFA). Following our interest to develop new simple, ecoefficient and environmentally friendly procedures for the synthesis of biologically and pharmaceutically important molecules, including grammine, we explored the newly synthesized ionic liquid [TBA] AMPS. The newly synthesized IL was used to catalyze Mannich reactions using different aldehydes, ketones and amines Scheme 1.

## EXPERIMENTAL

### Materials and reagents

All chemicals were of AR grade and used without further purification unless otherwise stated. All aldehydes, ketones, amines were obtained from S.D. fine chemicals, Mumbai. TBA and AMPS were obtained from Aldrich chemicals, USA and used as received.

### Synthesis of ionic liquid

2-Acrylamido-2-methylpropanesulphonic acid (AMPS) (1 equiv., 0.001 mol, 0.2073 g) was treated with NaOH (1 equiv., 0.4 g) to afford the organic anion. To this anion, tetrabutylammonium chloride (1 equiv., 0.2073 g) was added. The white solid separated was recrystallized from ethanol. The ionic liquid was formed quantitatively and in high purity as assessed by NMR (Wang et al., 2006).

### Mannich reaction: a typical procedure

In a typical reaction, formaldehyde (1 equiv., 0.5 g), aniline (1 equiv., 0.45 g), cyclohexanone (1 equiv., 0.6 g), and ionic liquid (1 equiv., 0.6 g) as catalyst and solvent were stirred at room temperature (30°C) in a round-bottomed flask fitted with a condenser. At this stage the time was noted and the ionic liquid was separated from the reaction mixture by extraction with copious amount of water. The ionic liquid being soluble in water comes in the water layer. The solid was separated by filtration and the product was recrystallized from ethanol and dried in vacuum for 5 h. The product was identified using <sup>1</sup>H NMR in CDCl<sub>3</sub> with TMS as reference (200 MHz). The ionic liquid in the filtrate was separated from the unreacted starting materials by extracting the filtrate with ether.

## RESULTS AND DISCUSSION

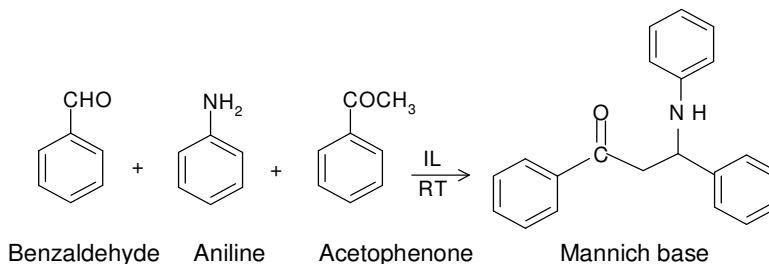
Different types of amines with either electron pumping or electron withdrawing groups were subjected to Mannich condensation reactions with various ketones (aromatic and alicyclic) and various aldehydes (aromatic and

alicyclic) with either electron pumping or electron withdrawing substituents, in the presence of ionic liquid [TBA] AMPS under solvent free conditions at room temperature (30°C). Under these conditions, no self condensation of the starting materials was observed.

The conditions for the Mannich reaction were optimized with various aldehydes, amines and ketones as substrates in the presence of the proposed IL and the results are displayed in Table 1 (Smith and March, 2001). Use of various aldehydes, amines and ketones in 1:1:1 equivalent ratio with the proposed ionic liquid [TBA] AMPS (0.65g) at 30°C (Room Temperature (RT)) gave their respective Mannich bases ( $\beta$  - amino carbonyl compound) in 90 – 96% yield (% yield of the product was ascertained based on the amount of aldehyde taken initially) with no appreciable amount of by-products in just 1 to 1.5 h. The greater yield in all these reactions is in accordance with atom economy concept. Extending the time beyond 1.5 h had practically no effect on the yield indicating that the reaction is complete in just 1.5 h. Increase of reaction temperature above 30°C or use of double amount of the proposed IL had only marginal effect on the yield of Mannich base. The promoting effect of the ionic liquid was proved by performing certain reactions in the absence of IL (Table 2). When the same set of reactions was carried out with the same amount of reactants but without the IL, it was noted that the yield was only 83 to 92% (with the appreciable amount of by-products) at 30°C in the time range of 1.5 to 2.5 h. But when the temperature and time were slightly increased beyond 30°C and 2.5 h respectively, the % yield of the product was remarkably increased. From these observations, it is apparently demonstrated that the IL procures more product in less time and utilizing less thermal energy with the minimal wastes of the reactants (production of less side products) than the conventional reactions (reactions carried out without IL). The greater yield in reactions using this IL may be because of the fact that this IL provides more active centers for more number of reactants to come and sit over the surface of the IL and thereby reacting more effectively in less time consuming less thermal energy (Ganeshpure et al., 2007). Another greatest advantage is that, the reactions using this IL do not require any solvent as all the substrates are highly soluble in IL. The reusability of the ionic liquid catalyst was demonstrated by carrying out the reaction for 6 runs and the results are documented in Table 3. It is interesting to note that the efficiency of the proposed ionic liquid in this work is not significantly altered.

% Yield<sup>a</sup> was determined with respect to starting aldehyde.

In the experiments where IL was employed, after the reactions were over, the products were isolated and the remaining ionic liquid catalyst was washed with water and reloaded with fresh substrates for further runs. Same amount of IL was used after recycling for further runs. No



**Scheme 1.** An example for Mannich reaction (a representative reaction).

**Table 1.** Results of Mannich reaction with the proposed IL.

Entry	Aldehyde	Amine	Ketone	Time (h)	% Yield <sup>a</sup>
1	3-Bromobenzaldehyde	Aniline	Acetophenone	1.5	95
2.	3-Chlorobenzaldehyde	Aniline	Cyclohexanone	1.5	90
3.	3-Bromobenzaldehyde	Aniline	Cyclohexanone	1.5	92
4.	Benzaldehyde	Aniline	Acetophenone	1.0	90
5.	Benzaldehyde	Aniline	Cyclohexanone	1.0	92
6.	3-Chlorobenzaldehyde	Aniline	Acetophenone	1.5	93
7.	Benzaldehyde	4-Bromoaniline	Acetophenone	1.0	95
8.	Benzaldehyde	N-Methylaniline	Acetophenone	1.0	96
9.	Benzaldehyde	N-Methylaniline	Cyclohexanone	1.0	95
10.	Benzaldehyde	4-Bromoaniline	Cyclohexanone	1.0	93

% Yield<sup>a</sup> was determined with respect to starting aldehyde.

**Table 2.** Results of Mannich reaction without the proposed IL.

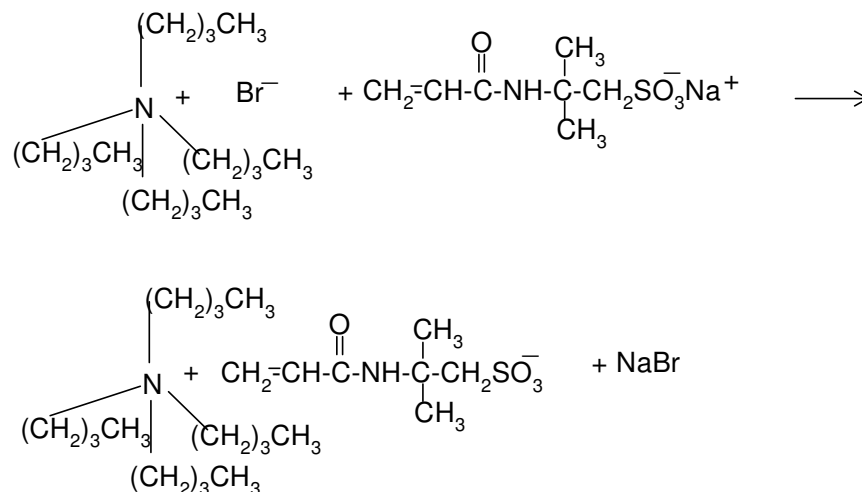
Entry	Aldehyde	Amine	Ketone	Time (h)	% Yield <sup>a</sup>
1	3-Bromobenzaldehyde	Aniline	Acetophenone	2.0	90
2.	3-Chlorobenzaldehyde	Aniline	Cyclohexanone	2.5	83
3.	3-Bromobenzaldehyde	Aniline	Cyclohexanone	2.0	90
4.	Benzaldehyde	Aniline	Acetophenone	1.5	87
5.	Benzaldehyde	Aniline	Cyclohexanone	2.0	89
6.	3-Chlorobenzaldehyde	Aniline	Acetophenone	2.0	90
7.	Benzaldehyde	4-Bromoaniline	Acetophenone	2.0	90
8.	Benzaldehyde	N-Methylaniline	Acetophenone	2.0	92
9.	Benzaldehyde	N-Methylaniline	Cyclohexanone	2.5	90
10.	Benzaldehyde	4-Bromoaniline	Cyclohexanone	2.0	89

% Yield<sup>a</sup> was determined with respect to starting aldehyde.

**Table 3.** Reusability of ionic liquid for Mannich reactions.

Entry	Cycle	% Yield
1.	I	90
2.	II	90
3.	III	88
4.	IV	88
5.	V	88
6.	VI	85

Reaction condition: Benzaldehyde: Aniline: Acetophenone, 1:1:1 (equiv. ratio), ionic liquid= [TBA] AMPS (0.65g), temperature=30°C.



**Scheme 2.** Synthesis of a novel ionic liquid [TBA-AMPS].

significant decrease in the yield of the products was noticed demonstrating that the ionic liquid can be reused in Mannich condensation reactions without any environmental discharge (Ahluwalia and Aggarwal, 2006).

## Conclusion

In the present investigation, a novel tetrabutylammonium-2-acrylamido-2-methylpropanesulphonate (TBA-AMPS) was synthesized and characterized by NMR techniques. The synthesis of this new ionic liquid was accomplished via an anion metathesis reaction between commercially available tetrabutyl ammonium (TBA) chloride and its counter ion 2-acrylamido-2-methylpropanesulphonate (AMPS) Scheme 2. This ionic liquid was used to catalyze Mannich reactions under solvent free conditions to afford the corresponding  $\beta$ - amino carbonyl compound (Mannich base) in excellent yields in less time. The ionic liquid was easily separated from its reaction mixture by extraction with water. The ionic liquid is reusable for several times without any significant loss in its potentiality. In conclusion, the present method is a very efficient and selective protocol for Mannich condensation reactions of various aldehydes, amines and ketones in the presence of reusable and environmentally benign catalyst. This study evaluates the effect of very small amount of ionic liquid [TBA] AMPS and shows that the yields are much improved and the reaction is much faster in this IL than other conventional catalyst. The recovery of the ionic liquid from the reaction mixture is possible by simple extraction with water. Simple work-up procedure, including washing the reaction followed by evaporation of the solvent is another advantage of this method. The most attractive part of this work is that only a very small amount of IL can catalyze this reaction in less time without degrading the environment.

## ACKNOWLEDGEMENTS

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**Appendix A. Spectral data for the Mannich products**

- 3-(N-Phenylamino)-3-(3-Bromophenyl)-1-phenylacetone:  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ): 3.42 (2H,m), 4.93 (1H,m), 6.50 (2H,d,J=7.95Hz), 7.35 (3H, d,J=7.95Hz), 7.49 (2H,m), 7.82-7.86(2H,d,J=7.8Hz); FT IR (cm-1): 3399,3024,2974,1672,1598,1515,1295,1221,1080,1026,1001,860,693,512.
- 2-[1-(N-Phenylamino)-1-(3-Chlorophenyl)methylcyclohexanone:  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ): 1.65 (2H,m), 1.82-1.93 (4H,m), 2.33-2.44 (2H,m), 2.73-2.77 (1H,m), 4.61-4.65 (1H,d, J=7.09Hz), 6.53-6.56(2H,d,J=7.90Hz), 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=7.9Hz); FT IR (cm-1): 3399,3011,2923,2811,1674,1598,1505,1310,1114,1047,860,693,522.
- 2-[1-(N-Phenylamino)-1-(3-Bromophenyl)methylcyclohexanone:  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ): 1.65 (2H,m), 1.82-1.93 (4H,m), 2.33-2.44 (2H,m), 2.73-2.77 (1H,m), 4.61-4.65 (1H,d, J=7.09Hz), 6.53-6.56(2H,d,J=7.90Hz), 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=7.9Hz); FT IR (cm-1): 3399,3011,2923,2811,1674,1598,1505,1310,1114,1047,860,693,522.
- 3-(N-Phenylamino)-1,3-diphenyl-1-acetone:  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ): 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); FT IR (cm-1): 3399,3024,2974,1672,1598,1515,1295,1221,1080,1026,1001,860,693,512.
- 2-[1-(N-Phenylamino)-1-phenyl]methylcyclohexanone:  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ): 1.65 (2H,m), 1.82-1.93 (4H,m), 2.33-2.44 (2H,m), 2.73-2.77 (1H,m), 4.61-4.65 (1H,d, J=7.09Hz), 6.53-6.56(2H,d,J=7.90Hz), 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=7.9Hz); FT IR (cm-1): 3399,3011,2923,2811,1674,1598,1505,1310,1114,1047,860,693,522.
- 3-(N-*p*-Bromophenylamino)-1-phenyl]methylcyclohexanone:  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ): 1.65 (2H,m), 1.82-1.93 (4H,m), 2.33-2.44 (2H,m), 2.73-2.77 (1H,m), 4.61-4.65 (1H,d, J=7.09Hz), 6.53-6.56(2H,d,J=7.90Hz), 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=7.9Hz); FT IR (cm-1): 3399,3011,2923,2811,1674,1598,1505,1310,1114,1047,860,693,522.
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- 3-(N-*p*-Bromophenylamino)-1,3-diphenyl-1-acetone:  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ): 3.40 (2H,m), 4.87 (1H,m), 6.35-6.38 (2H,d,J=7.9Hz), 7.06-7.10 (2H,d,J=8.26Hz), 7.15-7.25 (3H,m), 7.28-7.35(2H,d,J=9Hz), 7.37-7.41 (2H,m), 7.47-7.50 (1H,m), 7.80-7.85 (2H,d,J=7.95Hz); FT IR (cm-1): 3399,3020,2934,1675,1508,1485,1367,1308,1273,1119,1071,860,753,683,516.
- 3-(N-Methyl-N-Phenylamino)-1,3-diphenyl-1-acetone:  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ): 3.41 (2H,d), 4.93 (1H,m), 6.48 (2H,d), 6.59 (1H,m), 7.01 (2H,m), 4.18(3H,s), 7.24 (2H,m), 7.35 (5H,m), 7.85 (2H,d); FT IR (cm-1): 3399,3024,2974,1672,1598,1515,1295,1221,1080,1026,1001,860,693,512.
- 2-[1-(N-Methyl-N-Phenylamino)-1-phenyl]methylcyclohexanone:  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ): 1.65 (2H,m), 1.82-1.93 (4H,m), 2.44 (2H,d), 2.77 (1H,t), 4.65 (3H,s), 6.53-6.56(2H,d,J=7.90Hz), 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=7.9Hz); FT IR (cm-1): 3399,3011,2923,2811,1674,1598,1505,1310,1114,1047,860,693,522.
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