

## Pyridinium based ionic liquids as promoters for a green and selective synthesis of N-monomethylanilines

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### ABSTRACT

Pyridinium based ionic liquids derived from  $\beta$ -picoline and *n*-alkylbromides were synthesized by a simple procedure at ambient temperature and then characterized. These neutral ionic liquids were investigated for their dual role as the solvent and promoter for the selective synthesis of a series of N-monomethylanilines using dimethylcarbonate as the methylating agent. A solvent free green procedure was developed. Reaction conditions were mild and the product recovery was simple. Excellent selectivity for N-monomethylation, the high yield of the product and recyclability of the ionic liquids are some of the promising features of this protocol.

**Keywords:** Dimethylcarbonate, Pyridinium ionic liquids, Anilines, N-monomethylanilines, Solvent-free reaction.

### 1. Introduction

N-monomethylanilines are an important class of compounds extensively used as precursors for the synthesis of dyes, drugs, pharmaceuticals and explosives [1,2]. N-monoalkylamines were reported to function as  $\beta$ -blockers terminating the synthesis of DNA in cancerous cells [3,4]. Due to their widespread applications, for the synthesis of N-monomethylanilines, using inexpensive and environmentally safe catalyst is a great challenge. Several methods are documented for the synthesis of N-methylanilines notably the use of dimethylcarbonate (DMC) on faujasite and  $\beta$ -alkaline zeolites [5], DMC over Zn-Co-Fe ternary spinal system [6], use of dibenzylcarbonate promoted by zeolites [7], methylation with CO and H<sub>2</sub> using CeO<sub>2</sub> supported Cu-sub nano particles [8], bimetallic alloy Pd/Ga/ TiO<sub>2</sub> [9] and Au nano particles supported on alumina [10], methylation using molecular sieves and metallic copper [11] in addition to others [12-17]. Many of these synthetic protocols suffer from disadvantages such as the use of metal catalysts and poor selectivity of the mono N methylaniline.

In this study, we found that dimethylcarbonate (DMC) can be used as an effective and selective methylating agent for the synthesis of N-monomethyl anilines in the presence of pyridinium based ionic liquids as the catalyst. Ionic liquids (ILs) have low vapour pressure, high thermal and chemical stability and are recognized as environmentally harmless media [18]. Their unique properties coupled with their role in influencing the rate of reactions, selectivity, easy recovery for reuse resulted in their wide applications in many synthetic procedures. Ionic liquids also perform a dual role as catalysts and solvents [19-23]. Among the different ionic liquids, imidazolium based ionic liquids appear to be popular and several procedures for their preparation and synthetic applications have been reported [24,25]. However, the use of imidazolium and based ionic liquids are less attractive due to their high cost and low biodegradability [26]. On the other hand, pyridinium based ionic liquids are easy to prepare and their biodegradability depends on the nature of the aliphatic side chain substituted at the nitrogen [27-30]. The hitherto limited use of pyridinium based ionic liquids, prompted us to explore the possibility of using simple pyridinium based ionic liquids for selective synthesis of N-monomethyl anilines.

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## 2. Experimental

All the chemicals were purchased from Sigma Aldrich and Loba Cheime (India) and were used as received. The compounds synthesized were characterized using  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR recorded in a Bruker 300 MHz Spectrometer using  $\text{CDCl}_3$  as the internal standard and Mass spectra were recorded in a Perkin Elmer Clarus 600 and also by comparing their melting points with those reported in literature. Melting points were recorded in a VMP-D model Melting point apparatus and are uncorrected. TGA experiments were performed using a TGA-DSC1, Mettler Toledo instrument. All products were identified by comparison with authentic samples.

### 2.1. General procedure for the synthesis of ionic liquids

Equimolar mixture of  $\beta$ -picoline and alkyl bromides (*n*-butyl/*n*-octyl) were taken in a round bottom flask and stirred at room temperature for 22-24 hours in the dark. A pale orange coloured viscous liquid was obtained on completion of the reaction. The product obtained was found to be pure and further purification was not necessary. The ionic liquids were hygroscopic and stored in a desiccator for further use.

### 2.2. Procedure for the synthesis of *N*-monomethylanilines

1 mmol of aniline, 1.5 mL dimethylcarbonate and 0.5 equiv. of IL were thoroughly mixed and taken in a round bottom flask fitted with a reflux condenser, and heated to 130 °C in an oil bath with constant stirring for the period 45-70 min. On completion of reaction, as monitored by TLC, the reaction mixture was extracted with diethyl ether, washed with water, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and the crude product was purified by column chromatography on silica gel column using a mixture of ethyl acetate-petroleum ether

(1:5) as the eluent. Low pressure distillation of eluent provided the products which were identified by co-chromatography with authentic sample using ethyl acetate-petroleum ether (1:5) as the eluent.

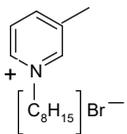
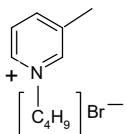
### 2.3. Recycling of catalyst

For reusability of the ionic liquid, after completion of the reaction, the product was extracted with diethyl ether and the precipitated IL was recovered and recycled three times without any perceptible change in activity.

## 3. Results and Discussion

Herein, we wish to report a general procedure for the preparation of pyridinium based ionic liquids derived from  $\beta$ -picoline. Two different ionic liquids (ILs) namely 1-*n*-butyl-3-methylpyridinium bromide and 1-*n*-octyl-3-methylpyridinium bromide were prepared, characterized and used as promoter and also as solvent for the selective synthesis of *N*-monomethyl anilines using DMC as the methylating agent. The ILs were prepared by simply mixing and stirring the equimolecular mixture of  $\beta$ -picoline and the appropriated alkyl halide at room temperature for 20-24 hrs. The yield of the ILs was found to be almost quantitative. These ILs were successfully used for the selective synthesis of *N*-monomethyl anilines. Short reaction time, high yields and excellent selectivity are noteworthy features of the developed protocol. Furthermore, the ILs could be recycled and reused up to three cycles without any significant loss in selectivity and catalytic activity. The pyridinium based ionic liquids were characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, IR and Mass spectrometry. They were further evaluated on the basis of their variation in conductivity on dilution with water. The results obtained from measurement of conductivity are summarized in Table 1.

**Table 1.** Conductometric experiments to determine the variation of conductivity of the two ionic liquids on dilution with deionized water.

Entry	Ionic liquid	Initial conc.	Conductivity (mS/cm) <sup>a</sup>			
			1 mL	2 mL	3 mL	4 mL
1		0.0001 M	1.826	1.95	2.015	2.202
2		0.0001 M	1.665	1.616	1.724	1.818

<sup>a</sup>Variation of conductivity of 5 mL of 0.0001 molar solution of ionic liquid on stepwise addition of 1 mL of deionized water.

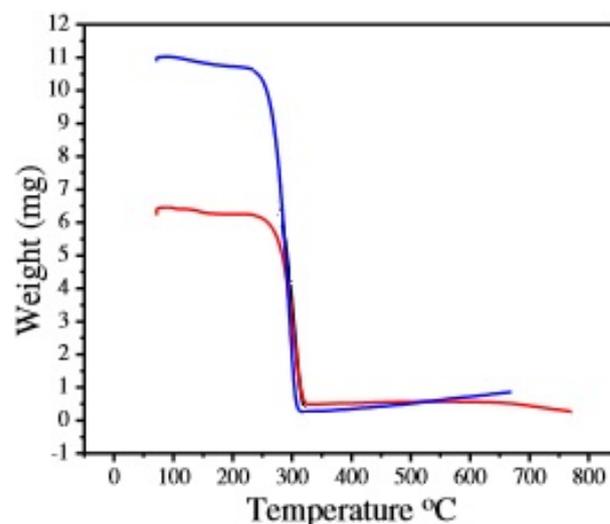
The results indicate that conductivity of aqueous solutions of 0.0001 molar concentration of the ILs falls within the range of 1.0 mS/cm to 10 mS/cm and increases with dilution using water. The results are in agreement with those reported before [30].

The thermogravimetric analysis curves of the two pyridinium based ILs indicated the high thermal decomposition temperature (Fig. 1) which is suitable for carrying out reactions at high reaction temperatures without any perceptible decomposition.

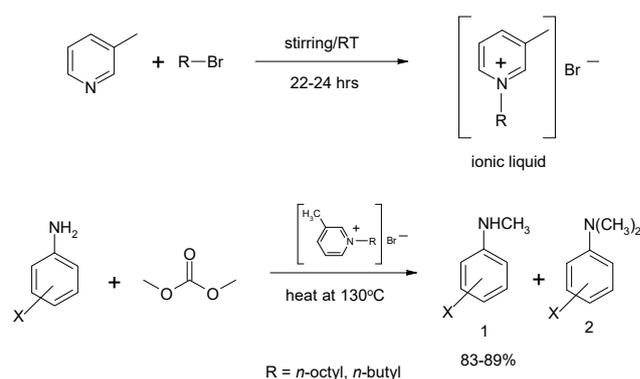
The ILs were investigated for their dual role as the solvent and also a promoter for the selective synthesis of N-monomethylanilines. The reaction carried out is shown in Scheme 1 and generalized for several substituted anilines.

To optimize the reaction conditions for high yield and selectivity, the reaction was investigated with neat ILs and several solvents and was then screened for their suitability. Results summarized in Table 2 indicate that reactions carried out in neat ILs required milder reaction conditions and gave better yield of the desired product.

Further experiments indicated that 1:1 equivalent of ILs and the substrate resulted in poor selectivity as both N-monomethyl and N,N-dimethylanilines were obtained in comparable proportions. However, when the amount of IL was decreased to 0.5 equivalent, N-monomethylanilines were found to be the major product and the N,N-dimethylanilines were obtained in the negligible amount. Further study on the dependence of product yield on reaction temperature revealed that reactions proceeded to near completion at temperatures between 110-130 °C in 30-60 min. It was further observed that the increase in the reaction temperature decreases the selectivity.



**Fig. 1.** Thermogravimetric analysis of data of 1-*n*-butyl-3-methylpyridinium bromide (red) and 1-*n*-octyl-3-methylpyridinium bromide (blue) with the heating rate of 10 °C/min under nitrogen atmosphere.



**Scheme 1.** Selective N-methylation of anilines using DMC catalyzed by ionic liquids.

**Table 2.** Effect of ILs and solvents in the selective synthesis of N-monomethylated aniline.<sup>a</sup>

Entry	Ionic liquid/solvents	Amount/vol	Temp. (°C)	Time (min) <sup>b</sup>	Yield (%) <sup>c</sup>
1		0.5 equiv	130	60	80
2		0.5 equiv	130	60	62
3	CH <sub>3</sub> OH	20 mL	Reflux	60	40
4	DMF	20 mL	Reflux	75	20
5	DMSO	20 mL	Reflux	90	0

<sup>a</sup>Reaction conditions: Aniline (1mmol), DMC (1.5ml), IL/solvent, heat.

<sup>b</sup>For complete conversion.

<sup>c</sup>Isolated yields.

Both the mono and dimethyl anilines were found to be in 1:1 proportion at 160 °C. In an optimized procedure, aniline, DMC and ionic liquid were heated to around 130 °C for 60 min. The reaction was generalized for a variety of anilines with both electron withdrawing and electron releasing groups. The yield of the products was found to be in the range of 83-89 % for all substrates, indicating the negligible influence of electronic effects of groups substituted in the aniline (Table 3).

To establish the superiority of the present procedure over a few procedures reported earlier, the comparison of some methods of synthesis of N-monomethyl anilines is presented in Table 4. Comparison reveals the superiority and higher environmental acceptability of the method reported herein.

#### 4. Conclusions

In conclusion, green, effective and environment friendly catalysts namely 1-*n*-butyl-3-methylpyridinium bromide and 1-*n*-octyl-3-methylpyridinium bromide were used in the selective synthesis of N-monomethyl anilines using dimethylcarbonate in the absence of VOC. The ILs performed the dual role of a catalyst and also a solvent. Results indicate that 1-*n*-butyl-3-methylpyridinium bromide was more effective than the 1-*n*-octyl-3-methylpyridinium bromide in terms of yield obtained (Table 2). This synthetic protocol appears to be highly selective for N-monomethylation of aromatic amines under controlled reaction conditions.

**Table 3.** Selective N-monomethylation of anilines using DMC and 1-*n*-butyl-3-methylpyridinium bromide.

Entry	Substrate	Time (min)	Product	Yield (%)
1	Aniline	60	N-methylaniline	80
2	4-Chloroaniline	45	N-methyl-4-chloroaniline	82
3	2-Bromoaniline	70	N-methyl-2-bromoaniline	86
4	4-Toluidine	50	N-methyl-4-toluidine	81
5	2,4-Dinitroaniline	45	N-methyl-2,4-dinitroaniline	86
6	2,4-Dichloroaniline	60	N-methyl-2,4-dichloroaniline	83
7	4-Chloro-2-nitroaniline	50	N-methyl-4-chloro-2-nitroaniline	85
8	3-Bromoaniline	50	N-methyl-3-bromoaniline	82
9	4-Nitroaniline	60	N-methyl-4-nitroaniline	84
10	4-Bromoaniline	45	N-methyl-4-bromoaniline	85

**Table 4.** Comparison of some methods of synthesis of N-monomethyl anilines.

Entry	Catalyst	Methylating agent	Selectivity for Monomethylation	Reaction condition	Green content	Ref.
1	CeO <sub>2</sub> supported Cu-nano particles	CO <sub>2</sub> , H <sub>2</sub>	70 %	8 h, toluene heat	Low. Use of metal catalyst	[8]
2	Pd/Ge/TiO <sub>2</sub>	(i) CO <sub>2</sub> , H <sub>2</sub> (ii) CH <sub>3</sub> OH (iii) HCOOH	Poor selectivity	10 h at 180 °C	Low. Use of metal catalyst	[9]
3	Au nano particles on alumina	CO <sub>2</sub> , H <sub>2</sub>	Poor selectivity 24- 61%	140 °C, 5 h	Low. VOC used	[10]
4	Molecular sieves- Cu or Al impregnated	CH <sub>3</sub> OH	75% for Al 97% for Cu	170-250 °C	Low. CH <sub>3</sub> OH used	[11]
5	Pyridinium based IL	DMC	81-89 %	130 °C	High. Solvent and metal free	This work

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