ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

Synthesis and Antimocrobial Properties of Imidazolium based Room Temperature Ionic Liquids

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Manuscript Info

Manuscript History:

Received: 12 December 2014
Final Accepted: 26 January 2015
Published Online: February 2015

Key words:

Ionic Liquids, Imidazolium, *B.subtilis, S.aureus, S.epidermidis, M.luteus*

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Abstract

Thirteen imidazolium based Room temperature ionic liquids (RTILs) were synthesized. To tune the solubility of ionic liquids, two different types of cations a) halogen anion b) ortho- and para-substituted benzoates and different alkyl chains to imidazole moiety have been introduced. To investigate the potential of these ionic liquids as antimicrobial agents these have been tested against four bacterial strains, *B.subtilis, S.aureus*, *S.epidermidis*, and *M.luteus*. ILs with dihexyl imidazolium showed positive activity against all four organisms.

INTRODUCTION

One of the most growing topics in the organic chemistry for the last two decades is synthesis and applications of ionic liquids. Ionic liquids are a new class of liquids comprised entirely of cations and anions. According to current definition, a salt melting below the boiling point of water is known as an ionic liquid or by one of many synonyms including low/ambient/room temperature molten salt, ionic fluid, liquid organic salt and neoteric solvent. These unique materials comprise only cation and anion like salts but due to bulky size and 'unsymmetrical' organic cation and weekly coordinating anion they exhibit low melting points and majority exist as liquid at room temperature.

Due to unique properties e.g. high thermal stability, negligibly small vapor pressure, high ionic conductivity, high electrochemical stability, non-flammability, hydrophobicity etc. they have found their applications as solvents in organic reactions (Fischer, et al., 1999; Earle, et al., 1998; Rodriquez, et al., 2003) and catalysis, (Hagiwara,et al., 2004; Ley, et al., 2001) biocatalysis, (Moriguchi, et al., 2000; Hayakawa,et al.,)nano-particle synthesis (Zhou,,et al., 2003) and polymerization, (Dullius,et al., 1998) as electrolyte systems and as a source of redox couple in dye sensitized solar cells (O'regan,et al., 1991; Wang,et al., 2003;)and in separation techniques (Bösmann,et al.,2001; He, et al., 2003).The ballooning number of publications concerning Ionic Liquids demonstrates the vast and deepening interest in this manifold area of science. Not only chemists and engineers, indeed scientists of nearly all fields of R&D are getting completely immersed in this amazing technology (Murugesan,et al., 2005).

While the first generation of Ionic Liquids was used as electrolytes in batteries in the early 1960s, the second generation was originally designed as solvents put into use in organic reactions, also as an alternative media for extracting processes, e.g. for the decontamination of metal-containing or radioactive waste. In this context, the non-volatile character of these so-called "designer-solvents" plays the most important role. Another crucial point is that immiscibility with water (hydrophobicity) can be achieved, provided the right ions are chosen. However, these pioneering Ionic Liquids show some major drawbacks: the hexafluorophosphate anion is known to be quite unstable toward hydrolysis and produces toxic and corrosive HF or fluorides. The toxicity of the imidazolium cation is

difficult to be estimated; an expensive toxicological study is risky. The disposal of these fluorous compounds is expensive and problematic. The synthesis at larger scale is complicated and starting materials are expensive.

However, studies of some groups have demonstrated the toxicity of ionic liquids and raised questions over their greener expect. Since, others have considered toxicity as a tunable property and studied ionic liquids as potential antimicrobial agents have been reported that ionic liquids can be used in antiseptics, disinfectants and anti-fouling reagents (Pernak, et al., 2004; Pernak, et al., 2004; Pernaket al., 2007).The study of different groups also show that activity depends upon structure of ionic liquid like length of alkyl chain type of anion in imidazolium based ionic liquids (Pernak, et al., 2003).

The present work has been designed to synthesize fluorine free ionic liquids and investigate their antimicrobial activity against.

MATERIALS AND METHODS

Chemistry: All chemical were purchased from Sigma-Aldrich Company and verified via TLC and FT-IR techniques. TLC was performed by pre-coated aluminum plates, Kieselgel 60, F254, 0.25mm; e. Merck, Darmstadt, Germany. FT-IR was performed on IRPrestige-21, Fourier Transformed Spectrophotometer by Shimadzu. Chromatograms were detected by UV 254nm and iodine tank. Melting points are taking in conventional paraffin baths. Room temperature was 20 to 30 ºC. Centrifuge process was done with Hettich Centrifuge D-78532.

Synthesis of 1-butyl-3-methylimidazolium bromide($[bmim]^+[Br]^-$)1:

Synthesis of IL **1** was carried out using reported method (Dzyuba,et al., 2001).A flask containing a magnetically stirred solution of 1-methylimidazole 29.4 mmol in 10 mL dichloromethane is cooled on icebath and 29.4 mmol1-bromobutaneis added dropwise. Icebath is removed and reaction mixture is stirredfor 15 min at room temperature. Evaporation of solvent in vacuo resulted in colorless liquid in 98% yield.

Synthesis of 1-hextyl-3-methylimidazolium bromide ($[hmim]^+[Br]^-$)2:

IL **2** was synthesized using same method as in **1**.

Synthesis of 1-benzyl-3-methylimidazolium bromide ($[bnmim]^+[Cl]^-$)3:

IL **3** was synthesized using same method as in **1**.

Synthesis of Dibutyl-methylimidazolium bromide ($[bmim]^+[Br]^-$)4:

Synthesis of **4** was carried out using reported method (Dzyuba,et al., 2001).A flask containing a magnetically stirred mixture of NaH powder 29.4 mmol in THF 20 mL is cooled in an ice bath and a solution of imidazole 29.4 mmol in THF 20mL is added dropwise. The icebath is removed and the mixture is stirred for 2hrs. at room temperature. 1-bromobutane 58.8 mmolis added drop-wise at room temperature and the mixture is refluxed for 7.5 hrs. Evaporated in vacuum and extracted with DCM. It was dried in vacuum to obtain the product. Light brown liquid is obtained, Yield 75-78%.

Synthesis of Dihexylmethylimidazolium bromide ($[hmim]^+[Br]^-$)5:

IL **5** was synthesized using same method as in **3**.

Synthesis of IL-6-13:

The Ils 6-13 were prepared through metathesis of ions (Dinarès,et al., 2009). In a general procedure, a flask containing 20 mmoles of aromatic acid (Salicylic acid, p-amino-benzoic acid, Thiosalisylic acid or p-hydroxy-benzoic acid) was treated with 22 mmoles of sodium bicarbonate solution in water. After complete neutralization, 20 mmol of methylalkylimidazolium halide (**1**-**3**) or dialkylimidazolium (**4**-**5**) was added and reaction mixture was stirred for 30 minutes at room temperature. Water is evaporated; cold anhydrous ethanol is added to extract the product.

Antibacterial activity:

Antimicrobial screening of ILs were performed by agar well method. 100 µL of 24 hours old test bacteria was inoculated in 1% soft nutrient agar and pour onto nutrient agar plate. Wells were cut off from agar by sterile borers and 100 µL of ILs were added in different wells (Ahmed and Beg, 2001).

RESULTS

Two different types of imidazolium ions were prepared. For the synthesis of methyl alkyl imidazolium ions methyl imidazole was treated with alkyl halide in dichloromethane at room temperature **Scheme-1**. Reaction completion was monitored through TLC.

Scheme-1: Synthesis of Methyl butyl imidazloium

On the other hand synthesis of dialkylimidazolium, imidazole was first treated with NaH powder in THF at 0 °C followed by addition of alkyl halide **Scheme-2**. Evaporation of THF and extraction with dichloromethane resulted in dialkylimidazolium halide.

Scheme-2: Synthesis of dibutylimidazloium

Metathesis of ions is a crucial step to obtain ionic liquid with desired anion. First carboxylic acid was taken to make its salt by treating with sodium bicarbonate solution. Four different ortho or para substituted aromatic acids were selected including, salicylic acid, p-mino-benzoic acid, thiosalisylic acid and p-hydroxy-benzoic acid)Thenimidazolium halide is introduced to the reaction as shown in **Scheme 3**. Metathesis occurred in the specific time. Water evaporation followed by treatment with cold ethanol to separate sodium halide.

Scheme 2: Metathesis of ions

Compound #					
6	$[bmim]^+ [PHB]^-$	R^1 = methyl,	R^2 = n-butyl,	R^3 = OH,	R^4 = H
7	$[bmim]^+ [PAB]^-$	R^1 = methyl,	R^2 = n-butyl,	R^3 = H,	R^4 = NH_2
8	$[bmim]^+ [TS]^-$	R^1 = methyl,	R^2 = n-butyl,	R^3 = SH,	R^4 = H
9	$[bbim]^+ [TS]^-$	R^1 = n-butyl,	R^2 = n-butyl,	R^3 = SH,	R^4 = H
10	$[hhim]^+ [TS]^-$	R^1 = n-hexyl,	R^2 = n-butyl,	R^3 = SH,	R^4 = H
11	$[bnmim]^+ [OHB]^-$	R^1 = methyl,	R^2 = benzyl,	R^3 = OH,	R^4 = H
12	$[bnmim]^+ [OHB]^-$	R^1 = methyl,	R^2 = benzyl,	R^3 = H,	R^4 = OH
13	$[bnmim]^+ [PAB]^-$	R^1 = methyl,	R^2 = benzyl,	R^3 = H,	R^4 = NH_2

Characterization of all these compounds was carried out through comparison of spectral data including ^{1}H-NMR,^{13}C-NMR,FTIR, ESI-MS Positive Mode, ESI-MS Negative Mode, with reported literature (Dzyuba, et al., 2001; Muhammad, et al., 2015; Dinarès, et al., 2009, Jork, et al., 2005, Liu, et al., 2006; Wilfred, et al., 2013; Chan, et al., 1977). IL**1-5** are water soluble while IL **6-13** are water Insoluble.

DISCUSSIONS

It is quite clear that ionic liquids needed to be melted much lower than conventional salts like sodium chloride. They caught interest more and more soon as they meant to be made as Room-Temperature Ionic Liquids (RTIL). So, our first objective is to control temperature by variation in cation and/or anion. In cation, we took imidazole to make 1,3-dialkyl imidazolium and 1-alkyl-3-methylimidazolium. According to London Dispersion Forces, the 1,3-dialkylimidazoliums should have more melting points than non-symmetrical 1-alkyl-3-methylimidazoliums if anion is unchanged. We observe reverse of it. It seems to be non-symmetrical sp^3 carbons of the 1,3-alkyl chains which makes them less packed to have a clear crystal lattice.

Delocalization in cations or in anions causes weak electrostatic interactions (Figure 1). Due to weaker electrostatic interactions, packing of ions is not permitted and hence these ionic species might exist as liquids at room temperature. In actual, we could not see the change in melting points of the ionic liquids by varying the either of the anion. As we discussed that 1,3-dialkylimidazolium have lower melting point makes them more influential over varying the anions.

For the characterization of imidazolium – benzoate based ionic liquids we have four distinct protons in H^1-NMR specra. Position 2 of imidazolium gives singlet at δ 9.0-10.5. Position 4 and 5 gives double of doublet or two singlets near δ 7.5. Proton of heteroatom of anion gives singlet near δ 7.0. In FT-IR we got little difficulty as our ionic liquids were not quite clear of water. Even hydrophobic ionic liquids have some water to give significant broad peak of hydroxyl group. These water molecules are required to be removed at high vacuum and at high temperature followed by analysis on Karl Fischer Titration. We determine mass of the ionic liquids by Electron Spray Ionization (ESI). We got masses of cations and anions by ESI positive and negative mode respectively.

All the thirteen ILs were tested against four clinical isolates including B.subtilis, S. aureus, S. epidermidis, M. luteus. It was observed that ionic liquids containing dihexylimidazolium (IL **5** and **10**) as cation showed positive activity against all the four microbes irrespective of solubility. This behavior was attributed to long chain alkyl groups. As well as dibutylimidazolium (**4**) showed positive activity against all four isolates, while **9** showed activity against three isolates (Table-1) the change in activity may be due to difference in solubility of the two. IL **1**, **6**, **7**, **8**, **11** and **13** did not show any activity against any one of the four isolates. ILs **1**, **6**, **7** and **8** contain 1-butyl-3-methyl imidazolium while 11 and 13 have 1-benzyl-3-methyl imidazolium ascation suggesting inactivity due to small alkyl chains. These results are also in accordance with previous results (Pernak,et al., 2003; Pernak,et al., 2004; Pernak,et al., 2004; Pernak,et al., 2007).

Table 1: Primary screening of Ionic Liquids against clinical isolates

IL / Organisms	1	2	3	4	5	6	7	8	9	10	11	12	13
B.subtilis	-	+	+	+	+	-	-	-	+	+	-	+	-
S.aureus	-	+	+	+	+	-	-	-	+	+	-	-	-
S.epidermidis	-	-	-	+	+	-	-	-	-	+	-	-	-
M.luteus	-	+	-	+	+	-	-	-	+	+	-	+	-

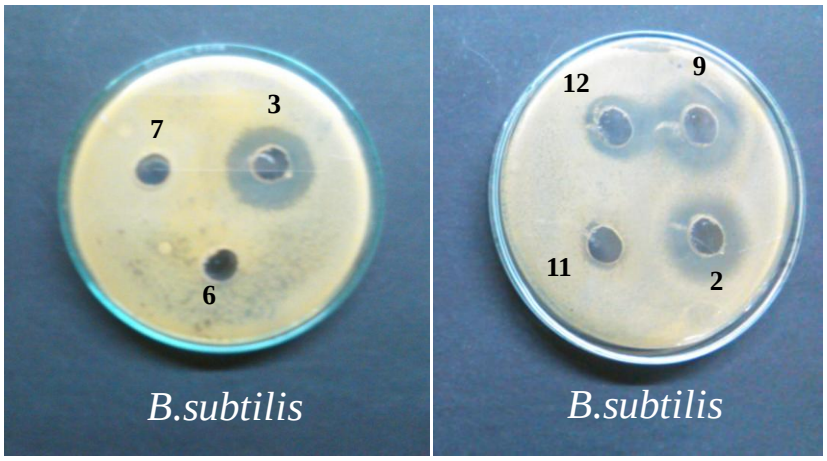

Figure 1: Antibacterial activity of ILs on B.subtilis

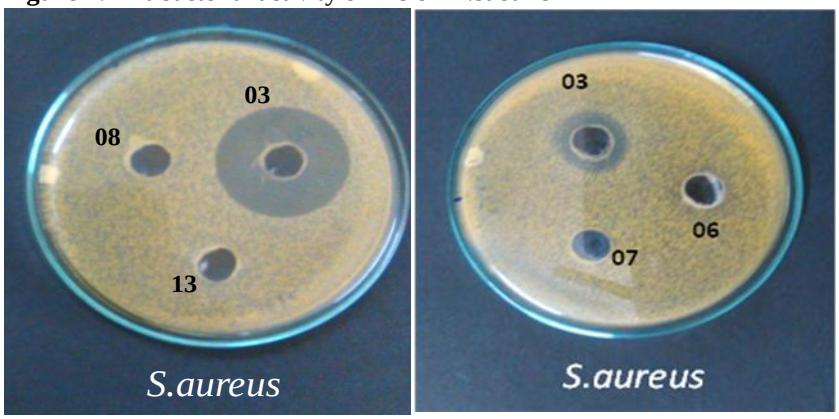

Figure 2: Antibacterial activity of ILs on S.aureus

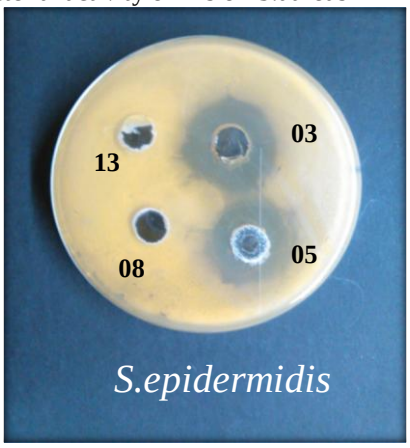

Figure 3: Antibacterial activity of ILs on S.epidermidis

Conclusion:

In present research study we found antibacterial potential of some imidazolium based Room temperature ionic liquids against tested bacterial cultures, however, further research work is needed to explore the spectrum of these RTILs on pathogenic bacteria.

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