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Highly efficient bromination of aromatic compounds using 3-methylimidazolium tribromide as reagent/solvent

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3-Methylimidazolium tribromide proves to be an alternative highly efficient reagent/solvent for the halogenation of non-activated aromatic compounds.

Halogenated aromatic compounds are key intermediates in organic synthesis as they are precursors to a number of organometallic species useful for the preparation of natural products and pharmaceutically active molecules. Conventional methods used for the direct halogenation of aromatic systems involve the use of potentially hazardous elemental halogen,[1] expensive transition-metal based catalysts,[2] alkali metal halides associated with $NaIO_4$[3] or the combination of aqueous TBHP or H_2O_2 together with a hydrohalic acid.[4] Though this latter procedure is considered the most effective from an environmental point of view, as the byproduct is water, it often requires an excess of hydrohalic acid to successfully perform the halogenation, together with the use of chlorinated solvents, in order to achieve a complete solubilization of the substrates. Moreover, the proper choice of the solvent (water or methanol) under acidic conditions determines the nature of the products, often leading to the formation of halohydrins and haloethers. In this respect, it has been already demonstrated that the use of ionic liquids may be advantageous for the stereoselective halogenation of unsaturated compounds, as it avoids the formation of solvent-containing byproducts, it enhances the regio- and stereoselectivity, and accelerates the electrophilic addition processes.[5] Brønsted acidic ionic liquids have been successfully applied to a variety of reactions including esterification of carboxylic acids,[6] protection of aldehydes and ketones,[7] as well as cleavage of ethers.[8] Then, following this mainstream, and stimulated by the promising results obtained using trihalide-based ILs as reagent-solvents for iodochlorination and iodobromination of unsaturated compounds,[9] we decided to extend the use of acidic ionic liquids to electrophilic aromatic substitutions.

Here we present our recent results on an alternative, practical procedure for the bromination of different substituted aromatic compounds using 3-methylimidazolium tribromide as reagent/solvent. The data will be compared to those obtained by the use of non-acidic trihalide-based ILs.

The combination of 1-methylimidazole with anhydrous hydrogen bromide in a 1:1 molar ratio produced the 3-methylimidazolium bromide ionic liquid at room temperature. Therefore, 3-methylimidazolium tribromide ($[Hmim][Br_3]$) has been prepared from the corresponding bromide by reaction with an equimolar amount of molecular bromine. The red solid thus obtained (mp 70 °C) is stable, easy to handle and can be stored in the dark for several months without degradation. The non-acidic 1-butyl-3-methylimidazolium tribromide ($[bmim][Br_3]$) was prepared following the reported procedure.[5] Both the ILs are miscible with liquids of medium dielectric constants such as alcohols, acetonitrile and dimethyl sulfoxide. They are only slightly soluble in chlorinated solvents, whereas they are completely immiscible with water, alkanes, toluene and diethyl ether.

Reactions were typically carried out at 70 °C in air adding an equimolar amount of substrate to 0.01 mol of the ionic liquid used. They were followed by TLC and stopped after the disappearance of the aryl substrate or at prefixed times, to evaluate the different efficiency of $[Hmim][Br_3]$ with respect to $[bmim][Br_3]$ (these latter data are reported in Table 1). When the products were immiscible

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Table 1 Product distribution for electrophilic bromination of aromatic substrates at 70 °C in $[Hmim][Br_3]$ and $[bmim][Br_3]$

Substrate	Solvent	Time	Conv. (%)	Products[a]		
				2	**3**	
1a	$[bmim][Br_3]$	21 h	32	74	26	
	$[Hmim][Br_3]$	21 h	52	67	33	
1b	$[bmim][Br_3]$	21 h	0	0		
	$[Hmim][Br_3]$	21 h	24	100		
				5		
4	$[bmim][Br_3]$	15 min	38	100		
	$[bmim][Br_3]$	Overnight	97	100		
	$[Hmim][Br_3]$	15 min	60	100		
	$[Hmim][Br_3]$	Overnight	97	100		
				7		
6	$[bmim][Br_3]$	Overnight	68	100		
	$[Hmim][Br_3]$	Overnight	90	100		
				9	**10**	**11**
8a	$[bmim][Br_3]$	15 min	58	100	0	0
	$[Hmim][Br_3]$	15 min	69	100	0	0
8b	$[bmim][Br_3]$	15 min	67	80	20	0
	$[Hmim][Br_3]$	15 min	100	29	0	71
				13	**14**	
12a	$[bmim][Br_3]$	15 min	89	100	0	
	$[Hmim][Br_3]$	15 min	91	100	0	
12b	$[bmim][Br_3]$	24 h	74	100	0	
	$[Hmim][Br_3]$	24 h	87	58	42	
				16	**17**	
15	$[bmim][Br_3]$	23 h	10	100	0	
	$[Hmim][Br_3]$	23 h	100	100	0	

[a] Yields of the isolated product >90%.

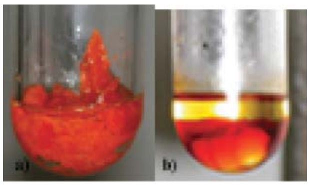
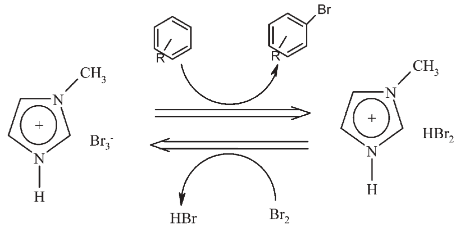
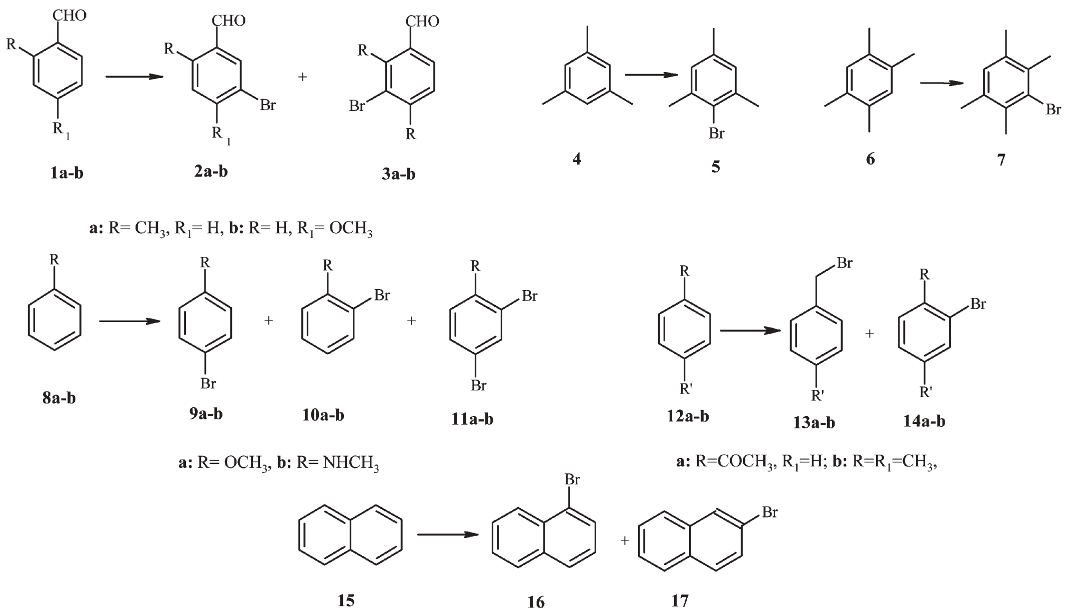


Fig. 1 (a) Mesitylene and $[Hmim][Br_3]$ at room temperature (1:1 molar ratio); (b) reaction mixture at 70 °C, after 24 h (the upper phase constitutes the product).



Scheme 1 Reaction scheme.



Scheme 2

with the solvent, the recovery of the bromo-adduct was achieved by simple decantation (see Fig. 1), alternatively products were extracted with *n*-hexane.

By comparing the NMR spectrum of the ionic liquid recovered at the end of the reaction carried out in [Hmim][Br_3] with literature data, it was possible to verify the conversion in 3-methylimidazolium bromohydrogenate. This new IL has been recently used as reagent/solvent for ether cleavage.[8] Moreover, by addition of the proper amount of molecular bromine to [Hmim][HBr_2], [Hmim][Br_3] can be re-obtained (Scheme 1).

As shown in Table 1, the reactions carried out in [Hmim][Br_3] exhibit significantly higher conversions, although they are characterized by a product distribution very similar to that found in [bmim][Br_3]. Aromatic compounds are brominated generally with complete selectivity and in excellent yields: only with substrate **8b** (Scheme 2) in [Hmim][Br_3], the polybrominated species is recovered as major product. Moreover, while using [bmim][Br_3] as reagent for the halogenation of **12b** only α-bromination occurs, in the presence of the acidic IL 30% of *o*-bromination is achieved. The halogenations were effective not only with activated compounds, but also with aldehydes (**1**) as well as with sterically hindered aromatic compounds (**4**, **6**). With activated substrates (**8a,b**), complete consumption of the reagent was observed in less than 30 min: anisole **8a** was cleanly monobrominated affording exclusively the *p*-bromo-adduct with yields comparable to those obtained with conventional methods.[4] Longer reaction times were necessary for non-activated derivatives (up to 24 h). It is of note that no phenol was detected in the halogenation of anisole in [Hmim][Br_3]. Apparently, in the conditions used for the aromatic bromination, [Hmim][HBr_2] formed at the end of the reaction was not able to cleave the C–O bond (1:2 molar ratio is generally required for this substrate in order to cleave the ether functionality).[8]

It must be remarked that the bromination of **12a** did not occur on the ring but exclusively on the methyl group. Moreover, the successful halogenation of naphthalene (**15**) in the absence of any catalyst and in excellent yields, is an indication of the reasonably reactive nature of the electrophilic species involved. On the other hand, bromobenzene, iodobenzene and benzonitrile were completely non-reactive. No product was detected, even after longer reaction times (data not reported in Table 1), either in [bmim][Br_3] or in [Hmim][Br_3].

The ionic liquid under investigation was also effective for the synthesis of vicinal dibromides: indeed a complete consumption of the reagent was observed in less than 20 min in the case of *trans*-β-methylstyrene. At the end of the reaction 90% of *anti* adduct was recovered, together with 10% of *syn* adduct, the latter formed by a nucleophile substitution at benzylic carbon of the initially formed *anti* adduct. This side reaction is faster using [bmim][Br_3] as reagent/solvent, so that a higher quantity of *syn* adduct is achieved.

In summary, an acidic ionic liquid having tribromide as anion was synthesized: this crystalline derivative is safer, easier to handle, maintains the desired stoichiometry and above all, displays improved reactivity as compared to non-acidic trihalide-based ionic liquids. With this work, an alternative method for the electrophilic bromination of aromatic compounds, aldehydes, ketones and olefins has been proposed, which minimizes the use of organic solvents and is effective with non-activated or sterically hindered compounds. At the end of the reaction, the halogenating agent is readily recycled. Alternatively, 3-methylimidazolium bromohydrogenate (the only by-product of the reaction), can be isolated and used as reagent/solvent for other reactions.[8]

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