Using the ‘Chemical Tunability’ of Ionic Liquids to Increase Sustainability in the Electrophilic Bromination of Unsaturated Compounds

Cinzia Chiappe,* Angelo Sanzone

Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via Risorgimento 35, 56126 Pisa, Italy
Fax +30(50)2219669; E-mail: cinziac@farm.unipi.it.

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Abstract: Tribromide-based ionic liquids have been synthesized and investigated as efficient bromination agents. The different physicochemical properties of the reaction media, which depend on the cation structure, have been used to improve the efficiency of the bromination process.

Key words: electrophilic addition, ionic liquids, stereoselectivity, bromination, green chemistry

Electrophilic bromination of double and triple bonds or aromatic compounds is a fundamental reaction in organic chemistry (Figure 1) providing products that are key intermediates in fine chemicals, pharmaceutical production, and analytical sciences. The mechanisms and synthetic aspects of bromination in molecular solvents have been extensively investigated over the years and fundamental features have been discovered through kinetic and product distribution studies.[1] The large number of papers published on this topic can be related to three main classes of synthetic procedures: (1) direct reaction of unsaturated compounds with molecular bromine;[1,2] (2) use of carrying agents that support bromine;[3] and (3) in situ generation of bromine using bromide compounds and oxidants.[4] A comparison of many bromination techniques taking into account their resource demands, waste production, and environmental and health and safety aspects has been recently published.[5]

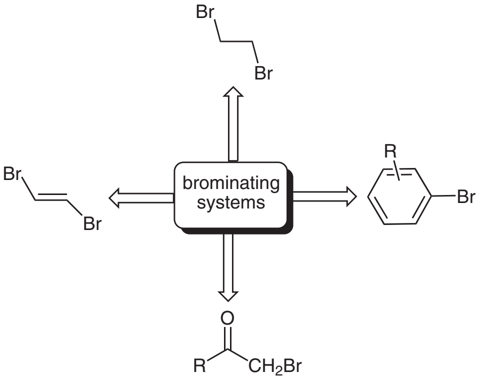

Figure 1 Products arising from the bromination of unsaturated compounds

Bromine addition to alkenes and alkynes in chlorinated solvents represents a fundamental reaction in organic chemistry, reported in all basic textbooks,[6] that gives the corresponding addition products in a short time and quantitative yields.[7] Although the process is still employed for the production of dibromides in small amounts on a laboratory scale for research purposes, the drawbacks related to the use of bromine and chlorinated solvents make the reaction unsuitable for preparations on an industrial scale. The hazardous nature of bromine means that special care is required for its storage, transport, and handling, whereas concerns for worker safety and the environment related to the use of chlorinated solvents require the use of alternative solvents. Actually, the efficiency of the bromine addition reaction is strictly related to the solvent: in solvents of low polarity (such as hexane, ethers, etc.) radical processes can ensue, leading to different product distributions with respect to chlorinated solvents.[8] On the other hand, in more polar nucleophilic solvents (such as alcohols, water, MeCN) solvent incorporation products are predominantly formed.[9,10] Therefore, molecular bromine addition in molecular solvents is an efficient procedure for the preparation of dibromides but it is not easy to improve the sustainability of the process using these media.

However, many other protocols developed to circumvent the use of molecular bromine, including many oxidative processes, are often based on problematic substances or they do not give same product distribution that arises from molecular bromine addition in chlorinated solvents (dibromoalkanes, dibromoalkenes, bromoarenes).[5]

Alternative reagents able to give exclusively dibromo adducts from alkenes and alkynes with a stereoselectivity comparable or higher than molecular bromine are tribromide organic salts. These carrying agents of bromine, however, due to the low stability of the anion in protic media are traditionally used in chlorinated solvents or in acetonitrile. The advantages arising from the easier handling and storage of these reagents with respect bromine have new limits for large-scale applications in the low-atom efficiency of the processes, the use of toxic solvents, and the need to remove the residue from the reagent through tedious washing procedures.

Recently, it has been shown that it is possible to use ionic liquids, salts with melting points below 100 °C, as alternative solvents in electrophilic halogenations using both molecular halogens (Br_2, BrCl, ICl, or IBr) or trihalide salts (Br_3^-, $BrCl_2^-$, $ICl_2^-IBr_2^-$).[11–15] In ionic liquids, as well

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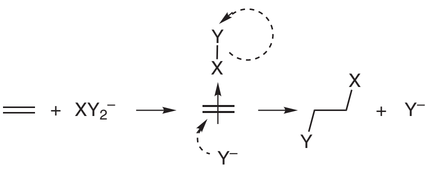
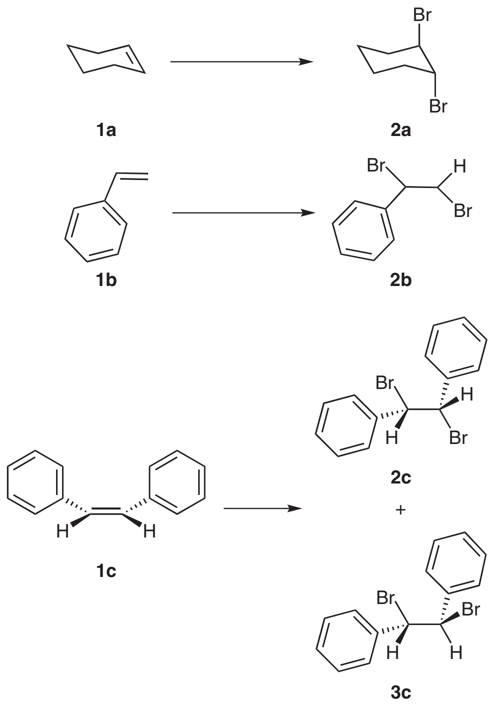
as in aprotic molecular solvents, trihalide anions are stable and halogenation of double and triple bonds occurs through attack of the proper anion on the initially formed halogen–unsaturated compound charge-transfer complex (Scheme 1), practically without the involvement of an ionic intermediate; only the *anti*-addition products are, therefore, formed both with alkyl- or aryl-substituted alkenes and alkynes.[11–14]



Scheme 1 Electrophilic addition of trihalides to alkenes

However, the replacement of a molecular solvent with an ionic liquid, despite the improved physicochemical and solvent properties of these media (low vapor pressure, not flammable, high solvent power, high chemical stability),[16] is not necessarily able to increase the sustainability of the process or to give significant improvements to the procedure.

Here, we report the possibility of increasing the sustainability of the electrophilic bromination of unsaturated compounds using selected tribromide-based ionic liquids as carrying agents and media. Furthermore, we show that the choice of the ionic liquid cation may favor the recovery of the products as determined by the physicochemical properties of the system. The optimal conditions for three representative compounds cyclohexene (**1a**), styrene (**1b**), and *cis*-stilbene (**1c**) giving, respectively, a liquid product, a solid compound soluble in common molecular solvents, and a solid compound insoluble in most of the widely used organic solvents, have been examined taking into account waste production and as well as environmental and health and safety aspects (Scheme 2).



Scheme 2 Bromination of various alkenes

cis-Stilbene (**1c**) was selected since it allows evaluation of the stereoselectivity of the process; mixtures of *anti* and *syn* adducts (dibromides **2c** and **3c**) are generally obtained starting from this olefin in the absence of strong nucleophiles (halide anions or nucleophilic solvents).

In previous works carried out in this laboratory, 1-methyl-3-butylimidazolium tribromide ([bmim][Br_3])[17] was used as a brominating agent both in hydrophilic or hydrophobic ionic liquids. In all the investigated reactions the products were recovered[11–14] by extraction with diethyl ether. Although it was possible to recycle the reaction system, relevant amounts of waste products were generated for each kilogram of dibromo adduct.[5]

Considering that immobilization of bromine in a halide based ionic liquid can give a halogen carrier with different physicochemical properties depending on the cation, we have prepared a series of tribromide-based ionic liquids by bromine addition to selected bromide salts, 1-methylimidazolium bromide ([mim]Br), 1-ethyl-3-methylimidazolium bromide ([emim]Br), 1-butyl-3-methylimidazolium bromide ([bmim]Br), 1-octyl-3-methylimidazolium bromide ([omim]Br), and *N*-butyl-*N*-methylpyrrolidinium bromide ([bmpyr]Br) (Figure 2); with the exception of [omim]Br all the other bromides were solid at room temperature. As expected,[17,18] the transformation of the Br^- anion into the more charge-diffused $[Br_3]^-$ anion resulted in a decrease in water affinity (all five tribromide salts can be included in the class of water immiscible ionic liquids) and a significant reduction of the melting point, the sole exception being [omim][Br_3]. More in particular, [bmim][Br_3] and [bmpyr][Br_3] appeared as low viscous liquids at room temperature and below, [omim][Br_3] as a liquid–low melting solid (mp ~28–30 °C) and [emim][Br_3] and [mim][Br_3] as crystalline compounds (mp 49 and 70 °C, respectively).

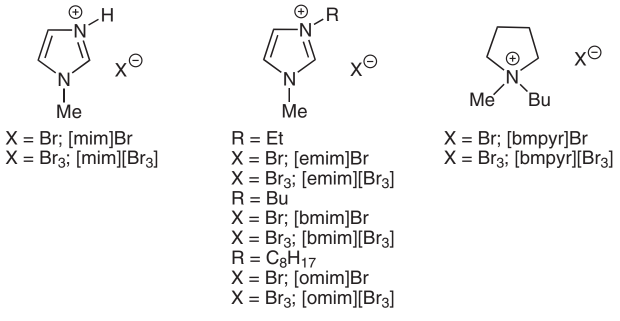


Figure 2 Investigated ionic liquids in bromination reactions

However, it should be noted that the cation structure affects not the only physicochemical properties of these salts but also their environmental impact. In the case of bromide salts, it has been shown[19] that toxicity towards the aquatic environment increases on going from pyrrolidinium to imidazolium salts and, in the case of these latter compounds, toxicity increases on increasing the alkyl chain length; the environmental impact of [bmpyr]Br and [mim]Br is therefore lower than that of all the other salts here investigated.

To test the efficiency of the selected tribromide-based ionic liquids, the reactions were carried out at room temperature or at the lowest temperature at which the systems were liquid (ranging from 40 to 70 °C) by addition of the three target alkenes to an equimolar amount of the ionic liquid with stirring (Table 1). The alkene addition always resulted in the rapid disappearance of the color and the formation of a solid phase due to the transformation of the tribromide salt into the corresponding bromide or to the formation of a solid dibromo adduct or to both phenomena. When the reaction product was a liquid, as in the case of cyclohexene, the formation of a biphasic system at room temperature allowed an easy and efficient separation of the reaction product from the formed bromide salts. The latter could be eventually washed with the minimal amount of a nonpolar solvent (toluene or hexane) and recycled after transformation into the corresponding tribromides. The workup procedure for alkenes giving a solid product was more complicated and more medium-dependent. In this case the most effective ionic liquid [bmpyr][Br$_3$] gave a semi-solid mixture that allowed efficient stirring until the end of the process, even at room temperature. Then, the solid dibromides could be isolated from the reaction mixture by extraction with diethyl ether or by filtration after dissolution of the thus formed [bmpyr]Br in a minimal amount of water or alcohol (MeOH or EtOH). This latter procedure is particularly suitable for dibromides, such as those arising from stilbenes, which have very low solubility in organic solvents or water. The solid dibromides, recovered in quantitative yield, were pure by NMR analysis. On the other hand, after solvent removal the bromide salts could be converted into the corresponding tribromides and reused repeatedly.

NMR and GC-MS analysis of the reaction products confirmed that the reaction occurs in all investigated ionic liquids in a stereospecific way, giving exclusively the *anti*-addition products. Nevertheless, should be noted that the expected dibromo adducts were practically the sole reaction products also when the protic [mim][Br$_3$] was used as brominating agent: only traces (<2%) of the HBr addition product were detected in the GC-MS chromatogram of the reaction product arising from bromination of styrene in this medium.

In conclusion, considering that tribromide salts are one of the most efficient systems to obtain dibromo derivatives with high stereo- and chemoselectivity, these data show that it is possible to use the 'chemical tunability' of ionic liquids to modulate the properties of the system and to increase the sustainability of the process. Using tribromide-based ionic liquids, it is possible to carry out these reactions practically under solvent-free conditions; products can be recovered by simple phase separation or by filtration after addition of a very small amount of ethanol or water. The exhausted ionic liquids can be easily recycled reducing the problems of the low-atom economy related to the application of bromine carriers. Among the investigated ionic liquids, which cannot be considered exhaustive, the best systems appeared to be [mim][Br$_3$] and [bmpyr][Br$_3$]; the first is associated with relatively low toxicity towards the aquatic environment and extremely easy procedure of synthesis (it is obtained by neutralization of *N*-methylimidazole by HBr in aqueous medium), the second is associated with relatively low environmental impact and it has the properties of a reagent liquid at room temperature (i.e. a more efficient stirring of the reaction mixture even at r.t., a higher solvent power). Finally, it is to note that these ionic liquids can be used for several other organic transformations previously investigated:[14] aromatic bromination and carbonyl functionalization.

Table 1 Bromination of Alkenes **1a**–**c** with Tribromide-Based Ionic Liquids

Alkene	Ionic liquid	Product	Yield (%)	Selectivity (%)
1a	[mim][Br$_3$]	**2a**	98[a]	98
	[emim][Br$_3$]		93[a]	99
	[bmim][Br$_3$]		92[a]	99
	[omim][Br$_3$]		93[a]	99
	[bmpyr][Br$_3$]		97[a]	99
1b	[mim][Br$_3$]	**2b**	92,[b] 95[c]	98
	[emim][Br$_3$]		93[b]	99
	[bmim][Br$_3$]		95[b]	99
	[omim][Br$_3$]		94	99
	[bmpyr][Br$_3$]		98[c]	99
1c	[mim][Br$_3$]	**2c**	90[c]	98
	[emim][Br$_3$]		92[c]	99
	[bmim][Br$_3$]		90[c]	99
	[omim][Br$_3$]		90[c]	99
	[bmpyr][Br$_3$]		98[c]	99

[a] Workup procedure A.
[b] Workup procedure B.
[c] Workup procedure C.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 250 MHz spectrometer. GC-MS were performed with a gas-chromatograph equipped with a DB-5 capillary column (30 m × 0.25 mm; coating thickness 0.25mm) and an ion trap mass detector. Analytical conditions: injector and transfer line temperatures 220 °C and 240 °C, respectively; oven temperature programmed from 60 °C to 240 °C at 3 °C min; carrier gas He at 1 mL/min; injection of 0.2 mL (10% hexane soln); split ratio 1:30. Identification of the constituents was based on comparison of the retention times with those of authentic samples, and matching against commercial (NIST 98 and ADAMS) and home-made mass spectra library built up from pure substances and MS literature data. 1-Methylimidazolium bromide ([mim]Br), 1-ethyl-3-methylimidazolium bromide ([emim]Br), 1-butyl-3-methylimidazolium bromide ([bmim]Br), 1-octyl-3-methylimidazolium bromide ([omim]Br), and *N*-butyl-*N*-methylpyrrolidinium bromide ([bmpyr]Br) were prepared following literature procedures.[12–14]

Synthesis of Tribromide-Based Ionic Liquids

To an appropriate amount of the starting ionic liquid (bromide or chloride) an equimolar amount of Br_2 was added slowly under stirring. Attention was paid to avoid an excess of halogen which, at least in the case of Br_2, could be eventually removed under vacuum.

1-Methylimidazolium Tribromide [mim][Br_3]

^{1}H NMR (DMSO-d_6): δ = 3.87 (s, 3 H, CH_3), 7.66 (s, 1 H, CH), 7.68 (s, 1 H, CH), 9.04 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 35.6 (CH_3), 119.8 (CH), 123.2 (CH), 135.9 (CH).

1-Ethyl-3-methylimidazolium Tribromide [emim][Br_3]

^{1}H NMR (DMSO-d_6): δ = 1.41 (t, *J* = 7.5 Hz, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 4.17 (q, *J* = 7.5 Hz, 2 H, CH_2), 7.66 (s, 1 H, CH), 7.75 (s, 1 H, CH), 9.07 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 15.2 (CH_3), 35.8 (CH_3), 44.3 (CH_2), 112.0 (CH), 123.6 (CH), 136.3 (CH).

1-Butyl-3-methylimidazolium Tribromide [bmim][Br_3]

^{1}H NMR (DMSO-d_6): δ = 0.89 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.25 (sext, *J* = 7.5 Hz, 2 H, CH_2), 1.76 (quint, *J* = 7.5 Hz, 2 H, CH_2), 3.84 (s, 3 H, CH_3), 4.15 (t, *J* = 7.5 Hz, 2 H, CH_2), 7.67 (s, 1 H, CH), 7.74 (s, 1 H, CH), 9.08 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 13.4 (CH_3), 15.9 (CH_2), 31.4 (CH_2), 35.9 (CH_3), 48.6 (CH_2), 112.4 (CH), 123.7 (CH), 136.5 (CH).

1-Octyl-3-methylimidazolium Tribromide [omim][Br_3]

^{1}H NMR (DMSO-d_6): δ = 0.84 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.24 (m, 8 H, CH_2), 1.76 (m, 2 H, CH_2), 3.84 (s, 3 H, CH_3), 4.13 (t, *J* = 7.3 Hz, 2 H, CH_2), 7.67 (s, 1 H, CH), 7.74 (s, 1 H, CH), 9.07 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 14.1 (CH_3), 22.2 (CH_2), 25.7 (CH_2), 28.5 (CH_2), 28.6 (CH_2), 29.6 (CH_2), 31.3 (CH_2), 35.9 (CH_3), 48.9 (CH_2), 112.4 (CH), 123.7 (CH), 136.5 (CH).

N-Butyl-*N*-methylpyrrolidinium Tribromide [bmpyr][Br_3]

^{1}H NMR (DMSO-d_6): δ = 0.92 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.31 (m, 2 H, CH_2), 1.67 (m, 2 H, CH_2), 2.08 (m, 4 H, 2 CH_2), 2.97 (s, 3 H, CH_3), 3.30 (m, 2 H, CH_2), 3.45 (m, 4 H, 2 CH_2).

^{13}C NMR (DMSO-d_6): δ = 13.7 (CH_3), 19.4 (CH_2), 21.2 (CH_2), 25.9 (CH_2), 47.6 (CH_3), 63.1 (CH_3), 63.6 (CH_2).

Bromination Procedures and Product Analysis

To a round-bottom flask equipped with a magnetic stirrer and containing the halogenating ionic liquid (3–4 g, ca. 10 mmol) (eventually warmed to the minimal temperature to obtain a liquid system) was added the unsaturated compound (1 equiv). The mixture was stirred at the same temperature until disappearance of the color and subjected to the most suitable workup procedure.

Workup A: formation of a liquid product: After cooling to r.t. the liquid product was separated by decantation and the residue was washed with a small amount of toluene (1 mL). The collected product was analyzed by GC-MS.

Workup B: formation of a solid product: After cooling to r.t., the reaction product was extracted with Et_2O (3 × 3 mL). The combined extracts were analyzed by GC-MS and by NMR.

Workup C: formation of a solid product: After cooling to r.t., a protic solvent (0.5 mL) was added (EtOH or H_2O) and the insoluble reaction product was separated by filtration through a sintered funnel. The product was analyzed by NMR.

GC-MS and NMR spectra of compounds **2a–c** were identical to those reported in the literature.

Recycling Procedure

After product recovery, traces of organic solvents or water were eliminated from the collected ionic liquids at reduce pressure and the salt was reused after transformation into the corresponding tribromide-based ionic liquids.[20]

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