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Stereoselective Halogenations of Alkenes and Alkynes in Ionic Liquids

Cinzia Chiappe,*,† Dario Capraro,† Valeria Conte,‡ and Daniela Pieraccini†

Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, via Bonanno 33, 56126 Pisa, Italy, and I.P.P.A. Facoltà di Agraria, Università di Foggia, via Napoli 25, 71100 Foggia, Italy

cinziac@farm.unipi.it

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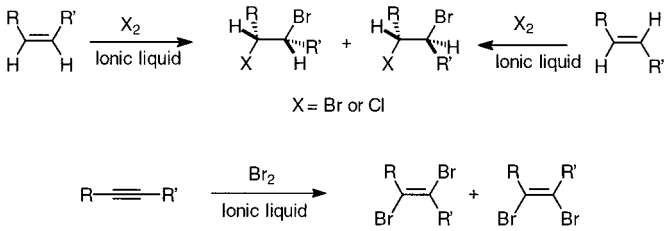
ABSTRACT



Room-temperature ionic liquids, 1-butyl-3-methylimidazolium hexafluorophosphate, 1-butyl-3-methylimidazolium tetrafluoroborate, 1-butyl-3-methylimidazolium bromide, and 1-butyl-3-methylimidazolium chloride, are used as "green" recyclable alternative to chlorinated solvents for the stereoselective halogenation of alkenes and alkynes.

Room-temperature ionic liquids that are air and moisture stable have been subjected to an increasing number of scientific investigations,[1−3] and their application as novel solvent systems for organic synthesis has received in the last years a good deal of attention.[3] The reactions carried out in ionic liquids have a different thermodynamic and kinetic behavior with respect to those in conventional solvents, and in addition, ionic liquids have a number of properties that may be of importance for industrial application. In particular, their lack of measurable vapor pressure characterizes them as media for green synthesis.[1] Room-temperature ionic liquids have been reported as solvents for a number of reactions such as dimerization of alkenes,[4] Friedel−Crafts reactions,[5] Diels−Alder cycloadditions,[6] and hydrogenation reactions[7] and more recently have been introduced in the Heck reaction[8] and in the asymmetric epoxidation using a chiral (salen)Mn as catalyst.[9] At variance with the electrophilic substitutions of aromatic compounds, which have been extensively investigated in chloroaluminate(III) ionic liquids,[3] with the exception of a recent patent[10] no data have been reported for the electrophilic halogen addition reactions to alkenes and alkynes.

Dihalo derivatives are important compounds in the organic synthesis as well as in analytical chemistry. As an example, the selective determination of alkenes in complex hydrocarbon mixtures, such as air, gasolines etc., by GC−flame ionization detection is indeed difficult. Analysis of alkenes in the presence of alkanes may be however achieved after their transformation into the corresponding dibromo-derivatives using saturated aqueous bromine.[11] More recently, a selective and sensitive method for alkenes determination in

† Università di Pisa.
‡ Università di Foggia.

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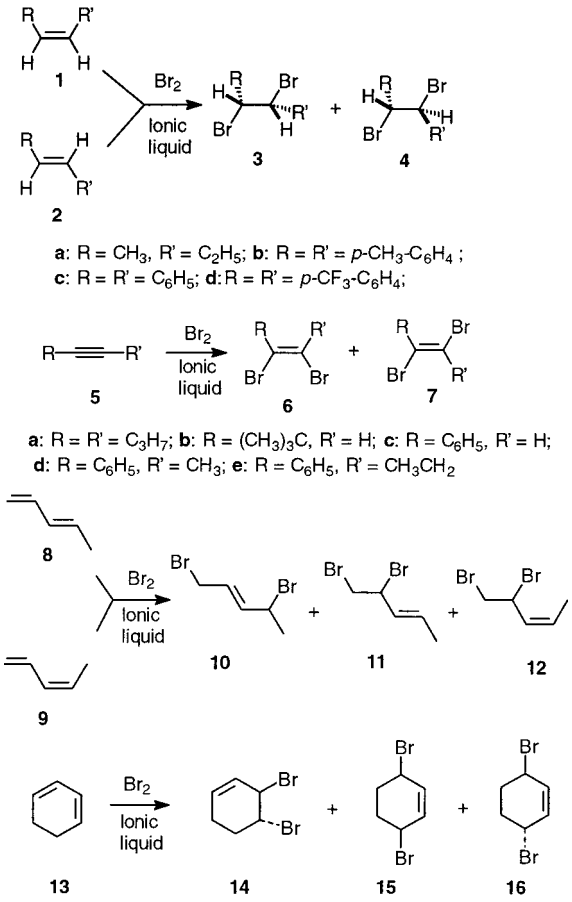
Scheme 1



different complex matrixes has been obtained by using a GC analysis with element-selective plasma spectroscopic detection of the dibromo derivatives.[12] In such a procedure, halogen addition is carried out in CCl_4, one of the chlorinated solvents extensively used for this type of reactions. These solvents, however, are currently on the "environmental blacklist". Furthermore, in CCl_4 the electrophilic additions are slow and radical reactions, bearing to a different product distribution, may occur. On the other hand, the electrophilic additions in water are very fast, yet accompanied by the nucleophilic attack of the solvent which competes with that of the anion and formation of bromohydrins is thus observed. In this respect, the use of ionic liquids may be advantageous if the medium polarity is able to accelerate the electrophilic addition process, the nonnucleophilic nature of the medium avoids the formation of solvent containing byproducts, the addition reaction occurs with a high or complete stereoselectivity. Ionic liquids, finally, may be recycled if the product(s) can be efficiently extracted from the reaction medium.

Here we present results on a practical recycling procedure for the stereoselective halogen addition to alkenes and alkynes in several room-temperature ionic liquids.

The addition of Br_2 to several alkyl and aryl substituted alkenes (**1** and **2**), alkynes (**5**), and dienes (**8**, **9**, and **13**) at room temperature was examined in 1-butyl-3-methylimidazolium hexafluorophosphate, [bmim][PF_6], 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim][BF_4], and 1-butyl-3-methylimidazolium bromide, [bmim][Br]. The products were always conveniently extracted with Et_2O and analyzed by NMR (Scheme 1).

Table 1. Product Distribution for Br_2 Addition to **1**, **2**, **5**, **8**, **9**, and **13** in [bmim][Br] at Room Temperature.

substrate	yield[a] (%)	products	ratio[b]
1a	95	**3** + **4**	>99:1
1b	95	**3** + **4**	>99:1
1c	93	**3** + **4**	>99:1
1d	90	**3** + **4**	>99:1
2a	95	**3** + **4**	<1:99
2b	93	**3** + **4**	<1:99
2c	93	**3** + **4**	<1:99
2d	93	**3** + **4**	<1:99
5a	94	**6** + **7**	<1:99
5b	96	**6** + **7**	<1:99
5c	96	**6** + **7**	<1:99
5d	96	**6** + **7**	<1:99
5e	97	**6** + **7**	<1:99
8	95	**10** + **11**	>99:1
9	95	**10** + **12**	>99:1
13	93	**15** + **16**	20:80

[a] Isolated yields. [b] Determined by ^1H and ^{13}C NMR

Reactions are typically carried out by adding, with stirring, 1 equiv of unsaturated compound to a 0.3 M solution of Br_2 in the ionic liquid.[13] In alkene and diene bromination, complete consumption of the reagents was observed in less than 1 min, longer times were necessary for alkyne bromination in particular when the reactions were carried out in [bmim][Br]. The dibromo adducts were identified on the basis of the ^1H and ^{13}C NMR spectra of the crude extracts.

Selected results are reported in Tables 1 and 2.

As shown in Table 1, the reactions of alkenes **1** and **2** and alkynes **5** with Br_2 in [bmim][Br] were anti stereospecific and those of dienes **8**, **9**, and **13** gave selectively the 1,4 addition products. High anti stereoselectivity was observed also for bromination of **1c** and **2c** in [bmim][BF_4], although in this solvent the reaction of diene **13** gave a more complex reaction mixture (Table 2).

Finally, in [bmim][PF_6] only with dialkyl-substituted alkenes **1a**,**2a**, alkyl substituted alkynes **5a**,**b**, and *trans*-stilbenes **2b**−**d** were detected anti-addition products.

Noteworthy, the substituent on the phenyl ring influenced the stereoselectivity of the reaction of cis isomers **1b**−**d**.

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(13) **General Procedure for Bromination in Ionic Liquids.** To a round-bottom flask equipped with a magnetic stirrer flea the ionic liquid (2 mL) and Br_2 (96 mg, 0.6 mmol) were added. To the Br_2 solution, maintained in the dark at room temperature, an equimolar amount of the unsaturated compound was then added under stirring. A water bath was used in order to avoid the temperature increase during the alkene or alkyne addition. Products were then extracted at the end of the reaction by three subsequent addition of Et_2O (2 mL), followed by decanting off the ethereal solution of the products. The combined extracts were concentrated on a rotary evaporator and the products were analyzed by NMR. When the reactions were carried out in [bmim][PF_6] the uncoloured recovered ionic liquid was reused.

Table 2. Product Distribution for Br_2 Addition to **1**, **2**, **5**, **8**, **9**, and **13** in [bmim][PF_6] and [bmim][BF_4] at Room Temperature

substrate	ionic liquid	yield[a] (%)	products	ratio[b]
1a	[bmim][PF_6]	95	**3** + **4**	>99:1
1b	[bmim][PF_6]	92	**3** + **4**	30:70
1c	[bmim][PF_6]	92	**3** + **4**	70:30
1c	[bmim][BF_4]	92	**3** + **4**	>99:1
1d	[bmim][PF_6]	92	**3** + **4**	>99:1
2a	[bmim][PF_6]	95	**3** + **4**	<1:99
2b	[bmim][PF_6]	92	**3** + **4**	<1:99
2c	[bmim][PF_6]	92	**3** + **4**	<1:99
2c	[bmim][BF_4]	92	**3** + **4**	<1:99
2d	[bmim][PF_6]	92	**3** + **4**	<1:99
5a	[bmim][PF_6]	95	**6** + **7**	<1:99
5b	[bmim][PF_6]	95	**6** + **7**	<1:99
5c	[bmim][PF_6]	95	**6** + **7**	12:88
5d	[bmim][PF_6]	95	**6** + **7**	23:77
5e	[bmim][PF_6]	94	**6** + **7**	25:75
8	[bmim][PF_6]	95	**10** + **11**	48:52
9	[bmim][PF_6]	95	**10** + **12**	66:34
13	[bmim][PF_6]	93	**14** + **15** + **16**	42:42:16
13	[bmim][BF_4]	95	**14** + **15** + **16**	47:39:14

[a] Isolated yields. [b] Determined by ^1H and ^{13}C NMR.

Dienes **8**, **9**, and **13** yielded mixtures of 1,2 and 1,4-addition products. It has been also proved that *d*,*l*-dibromides **3b** and **3c** partially transform into the *meso*-isomers when the reactions were carried on in [bmim][PF_6].

Comparison of these data with the product distribution previously found[14,15] for Br_2 addition to the same compounds in chlorinated solvents suggests the involvement as electrophile of the Br_3^- species, probably arising by the diffusion controlled binding of the Br_2 by the solvent, when the reactions are carried out in [bmim][Br]. At variance with Br_2, no ionic intermediate is involved in the Br_3^- addition to double and triple bonds and, at least in chlorinated solvents, the anti stereospecificity is determined by occurrence of a rate- and product-determining nucleophilic attack by Br^- on a 1:1 unsaturated compound−Br_2 π-complex.

On the other hand, formation of both syn- and anti-addition products in the reaction of **1b**,**c** and **5c**−**e** in [bmim][PF_6] is in agreement with the involvement of an ionic intermediate. The likely electrophile is free Br_2. The stereochemical behavior of these reactions is, however, significantly different with respect to that observed[14,15] in Br_2 addition to the same olefins in chlorinated solvents. In particular, all the reactions are characterized by a higher anti stereoselectivity, suggesting a shorter lifetime of the ionic intermediates in the reactions in ionic liquids.

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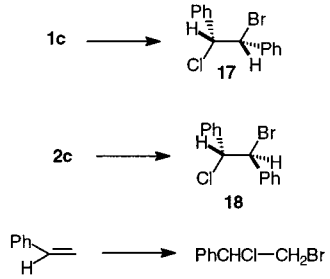
Scheme 2



1,2-Bromochlorides have been instead obtained by anti stereospecific and regioselective addition of Cl_2 to *cis*- and *trans*-stilbene (**1c** and **2c**) and styrene in [bmim][Br] at room temperature (Scheme 2).

In this case, the reactions were carried out by addition of the olefin (0.3 M) under stirring to the ionic liquid containing an equimolar amount of Cl_2, followed byproducts extraction with Et_2O. Gaseous Cl_2 was slowly bubbled in the ionic liquid at low temperature (ca. 0 °C) in order to avoid the partial decomposition of the solvent.

In the presence of Br^- ions Cl_2 should give, in analogy with the behavior observed in other solvents,[16] the $BrCl_2^-$ species. The regiochemistry of the addition product to styrene is in agreement with the presence in solution of the $BrCl_2^-$ anion able to react with the double bonds giving an electrophilic bromine and a nucleophilic chloride.

Finally, it is noteworthy that in the case of Br_2 addition in [bmim][PF_6], after extraction of the products, the ionic liquid could be recovered and reused for further reactions. The NMR spectra of the recovered solvent showed no evidence of liquid degradation thus no appreciable variation in reaction yields and product stereoselectivity has been observed by using recovered ionic liquid.

In conclusion, ionic liquids may be interesting "green" recyclable alternative solvents for synthesis of dibromo- and chlorobromo-derivatives. Depending on the ionic liquid the addition may be stereospecific, *erythro*- (or *meso*-)bromochlorides or dibromides are obtained from *trans*-olefins while *cis*-olefins give the corresponding *threo*- (or *d*,*l*-)adducts. Detailed studies are now under way to investigate the mechanistic aspects of these reactions.

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