ORGANIC
LETTERS

2013
Vol. 15, No. 9
2108–2111

Metal and H_2O_2 Free Aerobic Oxidative Aromatic Halogenation with $[RNH_3^+][NO_3^-]$/HX and $[BMIM(SO_3H)][NO_3)_x(X)_y]$ (X = Br, Cl) as Multifunctional Ionic Liquids

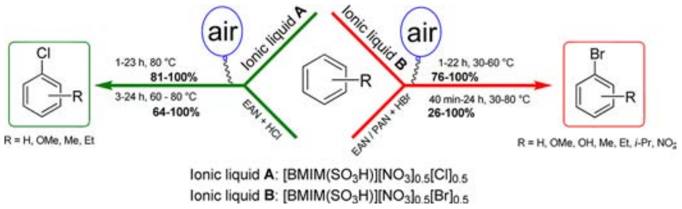
Rok Prebil,[†,‡,§] Kenneth K. Laali,[*,‡] and Stojan Stavber[*,†]

Department of Physical and Organic Chemistry, "Jožef Stefan" Institut, Jamova 39,1000 Ljubljana, Slovenia, and Department of Chemistry, University of North Florida, 1 UNF Drive, Jacksonville, Florida 32224, United States

Kenneth.Laali@UNF.edu; Stojan.Stavber@ijs.si

Received February 28, 2013

ABSTRACT



Novel multifunctional ionic liquids (ILs) are generated by addition of HBr or HCl to alkylammonium nitrates ($[RNH_3^+][NO_3^-]$) and to 3-methyl-1-(butyl-4-sulfonyl)imidazolium nitrate ($[BMIM(SO_3H)][NO_3]$). The resulting $[RNH_3^+][NO_3^-]$/HX and mono (3-methyl-1-(butyl-4-sulfonyl)-imidazolium) monohalogenide mononitrate ($[BMIM(SO_3H)][NO_3)_x(X)_y]$ (X = Br, Cl)) systems act as solvent and promoter for aerobic oxidative halogenation of arenes under mild conditions in high yields that can be repeated over several cycles.

Haloarenes are highly versatile synthetic intermediates and building blocks that are extensively employed in cross-coupling reactions and in nucleophilic substitutions and utilized as precursors to organometallic reagents. Bromo- and chloroarenes are widely used as building blocks of fine chemicals, pharmaceuticals and agrochemicals and are routinely elaborated in the synthesis of natural products and materials. Given the worldwide demand for these compounds, there is ever increasing need to synthesize them under environmentally more acceptable green conditions while at the same time achieving atom economy, selectivity, and high yields. It is therefore logical to devise alternative strategies to the conventional methods of halogenations that employ molecular halogen X_2 and N-halosuccinimides NXS and to also avoid the use of halogenated solvents. In this context, there is active ongoing interest in oxidative halogenation of arenes in which bromide and chloride ions are converted *in situ* to electrophilic reagents. The large majority of the systems studied earlier employ metal catalysts as well as Brønsted or Lewis acids and typically use hydrogen peroxide as oxidant or work under aerobic conditions.[1−6] The system KBr/HNO_3 (65%) in Ac_2O as solvent was used by a Norwegian group for mild ring bromination of representative activated arenes.[7] The use of green media such as supercritical CO_2, water, and ionic liquids (ILs) have also met with some success but left much room for improvement particularly with regard to selectivity.[3,6] A notable report by Chiappe and co-workers[8] utilized the Brønsted acidic 3-methylimidazolium nitrate

---

[†] "Jožef Stefan" Institut
[‡] University of North Florida
[§] Visiting PhD student at UNF
(1) Kikushima, K.; Moriuchi, T.; Hirao, T. *Tetrahedron* **2010**, *66*, 6906.
(2) Kikushima, K.; Moriuchi, T.; Hirao, T. *Tetrahedron Lett.* **2010**, *51*, 340.
(3) Review: Podgorsek, A.; Zupan, M.; Iskra, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 8424.
(4) Podgorsek, A.; Stavber, S.; Zupan, M.; Iskra, J. *Tetrahedron* **2009**, *65*, 4429.
(5) Wang, J. A.; Wang, W.; Li, J. H. *Green Chem.* **2010**, *12*, 2124.
(6) Pavlinac, J.; Zupan, M.; Laali, K. K.; Stavber, S. *Tetrahedron* **2009**, *65*, 5625.
(7) Tsoukala, A.; Liguori, L.; Occhipinti, G.; Bjorsvika, H. R. *Tetrahedron Lett.* **2009**, *50*, 831.
(8) Chiappe, C.; Leandri, E.; Tebano, M. *Green Chem.* **2006**, *8*, 742.

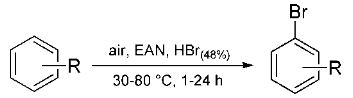
10.1021/ol4001476

([HMIM][NO_3]) as cosolvent and promoter in oxidative chlorination of alkylbenzenes and representative aromatic aldehydes and ketones using aqueous HCl. Depending on the substrate structure, ring halogenation, side chain halogenation or oxidation were observed. By comparison, the [HMIM][NO_3]-HBr system proved less effective for bromination.

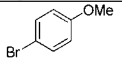
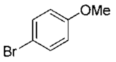
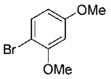
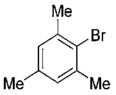
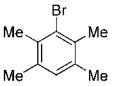
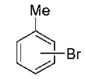
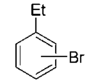
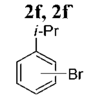
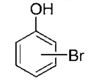
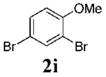
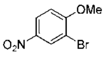
In the context of projects focusing on electrophilic chemistry in ILs,[9] and our continuing joint studies on halofunctionalization of aromatic compounds in ILs,[10−12] we report here on the generation of novel multifunctional ionic liquids (ILs) alkylammonium nitrates [RNH_3^+] [NO_3^-]/HX and mono(3-methyl-1-(butyl-4-sulfonyl)imidazolium) monohalogenide mononitrate ([BMIM(SO_3H)][$(NO_3)_x(X)_y$] (X = Br, Cl)) and their utility as solvent and promoter for aerobic oxidative ring bromination and chlorination of arenes under mild conditions in high yields with repeated recycling and reuse. The multifunctional ILs are readily formed by addition of HBr or HCl to ethyl- or propylammonium nitrates (EAN or PAN) and to 3-methyl-1-(butyl-4-sulfonyl)-imidazolium nitrate ([BMIM(SO_3H)][NO_3]).

Table 1 summarizes the bromination outcomes for activated and deactivated arenes with the [$EtNH_3^+$] [NO_3^-]/HBr system formed by addition of HBr to the readily available EAN ionic liquid. The reactions were carried out at 30−50 °C, except for *p*-nitroanisole which was performed at 80 °C. It is noteworthy that anisole (entry 1) gives only the para isomer **2a** whereas both ortho and para isomers were formed with toluene (entry 6) and ethylbenzene (entry 7), with para isomers predominating. Ring substitution products were regioselectively formed with cumene (entry 8). No meta halogenated isomers (entries 6−8) were detected. Bromination of phenol (entry 9) was strongly para selective with the ortho isomer also present. Whereas *p*-bromoanisole (entry 10) could be brominated to 2,4-dibromo-1-methoxybenzene (**2i**) in good yield, further deactivation of aromatic ring as in *p*-nitroanisole (entry 11) resulted in low conversion to 2-bromo-4-nitroanisole (**2j**). Electron-rich arenes such as 1,3-dimethoxybenzene (entry 3), 1,3,5-trimethylbenzene (entry 4) or 1,2,4,5-tetramethylbenzene (entry 5) gave regioselectively monobrominated products **2b**, **2c**, or **2d**, respectively. Only in the case of 1,2,4,5-tetramethylbenzene (entry 4) small amounts of dibrominated product was formed. Using only 1.1 mmol of HBr (48%) in EAN, anisole (entry 2) was quantitatively converted and 89% of pure *p*-bromoanisole **2a** was isolated.

Table 1. Bromination of Activated and Deactivated Aromatics in EAN/HBr[a]



1(a-j)

entry	bromine products	temp (°C)	time (h)	ortho: para	conv (%)[b]	yield (%)[c]
1	 **2a**	30	1	0:1	100	90
2[d]	 **2a**	30	1.5	0:1	95	89
3	 **2b**	30	0,6	-	92	80
4	 **2c**	30	4	-	100	70
5[e]	 **2d**	30	3	-	90	61
6	 **2e, 2e`**	50	6	1:1.8	91	-
7	 **2f, 2f`**	50	7	1:2.3	62	-
8	 **2g, 2g`**	50	7	1:2.7	100	-
9	 **2h, 2h`**	40	2	1:4.3	82	-
10	 **2i**	40	7	-	74	64
11	 **2j**	80	24	-	26	-

[a] Reaction conditions: Arene (1 mmol), EAN (3 mmol), HBr (aqueous 48% solution, 1.8 mmol), 30−80 °C, 35 min−24 h, air balloon. [b] Conversions and isomer distribution were determined by ^{1}H NMR and GC-MS spectroscopy of crude reaction mixture. [c] Isolated yield. [d] Arene (1 mmol), EAN (3 mmol), HBr (aqueous 48% solution, 1.1 mmol), air balloon. [e] 5% of 1,4-dibromo-2,3,5,6-tetramethylbenzene (**2d′**).

As a representative case, 2-acetylthiophene was regioselectively ring brominated to 2-acetyl-5-bromothiophene after two hours at r.t. in 64% yield. The need for the presence of the nitrate ion was shown in a control experiment by replacing EAN/HBr with 3-methyl-1-(butyl-4-sulfonyl)-imidazolium hexafluorophosphate(V)/HBr in a reaction with anisole, where no reaction was observed.

The recycling and reuse aspect of EAN/HBr in aerobic oxidative bromination of anisole was explored for five consecutive runs with quantitative yields for 4-bromoanisole formation (see Supporting Information, SI). Under similar reaction conditions there is a slightly higher tendency

---

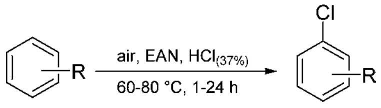
(9) (a) Kumar, G. G. K. S. N.; Laali, K. K. *Org. Biomol. Chem.* **2012**, *10*, 7347. (b) Kumar, G. G. K. S. N.; Aridoss, G.; Laali, K. K. *Tetrahedron Lett.* **2012**, *53*, 3066. (c) Aridoss, G.; Laali, K. K. *J. Org. Chem.* **2011**, *76*, 8088. (d) Aridoss, G.; Laali, K. K. *Tetrahedron Lett.* **2011**, *52*, 6859.

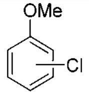
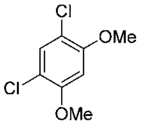
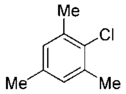
(10) Hubbard, A.; Okazaki, T.; Laali, K. K. *Aust. J. Chem.* **2007**, *60*, 923.

(11) Pavlinac, J.; Laali, K. K.; Zupan, M.; Stavber, S. *Aust. J. Chem.* **2008**, *61*, 946.

(12) Vrazic, D.; Jereb, M.; Laali, K. K.; Stavber, S. *Molecules* **2012**, *17*, 74.

Table 2. Chlorination of Activated Aromatic Substrates in EAN/HCl[a]



entry	chlorine products	temp (°C)	time (h)	ortho: para	conv (%)[b]	yield (%)[c]
1	 **3a, 3a`**	60	24	1:2.4	64	-
2[d]	 **3b`**	50	1	-	100	65
3	 **3c**	80	24	-	82	76

[a] Reaction conditions: Arene (1 mmol), EAN (3 mmol), HCl (aqueous 37% solution, 1.8 mmol), 60−80 °C, 1−24 h, air baloon. [b] Conversions and isomer distribution were determined by ^{1}H NMR and GC-MS spectroscopy of crude reaction mixture. [c] Isolated yield. [d] 24% of 1-chloro-2,4-dimethoxybenzene (**3b**) was formed.

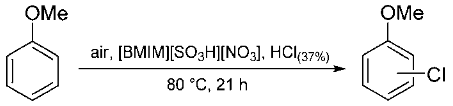
for dibromination of 1,3-dimethoxybenzene and durene in PAN as compared to EAN (see SI).

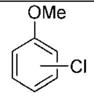
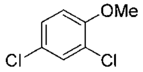
Focusing on the $[\mathrm{EtNH_3^+}]$ $[\mathrm{NO_3^-}]$/HCl system, anisole (entry 1), 1,3-dimethoxybenzene (entry 2) and mesitylene (entry 3) were chlorinated under mild conditions in high yields (Table 2). In the case of 1,3-dimethoxybenzene competing dichlorination was observed as the main process, while anisole (entry 1) was transformed to the para **3a** and ortho **3a′** products in 2.4:1 relative ratio.

We had previously used the Brønsted acidic IL 3-methyl-1-(butyl-4-sulfonyl)imidazolium triflate as catalyst and solvent for aromatic chlorination with trichloroisocyanuric acid (TfOH).[10] In the present study $[\mathrm{BMIM(SO_3H)}][\mathrm{NO_3}]$ was prepared by adding $\mathrm{HNO_3}$ instead of trifluoromethanesulfonic acid (TfOH) to 3-methyl-1-(butyl-4-sulfonate)-imidazolium $[\mathrm{BMIM(SO_3^-)}]$ zwitterion. The system $[\mathrm{BMIM(SO_3H)}][\mathrm{NO_3}]$/HCl proved very effective for aerobic chlorination of anisole in test experiments as indicated in Table 3. In the presence of slight molar excess of HCl (entry 1) 4-chloro- (**3a**) and 2-chloroanisole (**3a′**) were formed in 2.7:1 relative ratio, while higher concentration of HCl (entry 2) caused the formation of considerable amounts of 2,4-dichloroanisole **3a″**.

Subsequent studies showed that isolation of $[\mathrm{BMIM(SO_3H)}][\mathrm{NO_3}]$ is unnecessary and multifunctional $[\mathrm{BMIM(SO_3H)}][(\mathrm{NO_3})_x(\mathrm{X})_y]$ ILs can be prepared directly at room temperature by addition of $\mathrm{HNO_3}$ and HX to the zwitterion without the need to dry $[\mathrm{BMIM(SO_3H)}][\mathrm{NO_3}]$.

Table 3. Chlorination of Activated Aromatic Substrates in $[\mathrm{BMIM}][\mathrm{SO_3H}][\mathrm{NO_3}]$/HCl[a]



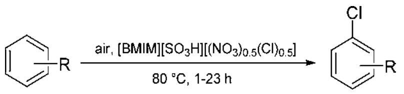
entry	chlorine products	temp (°C)	time (h)	ortho: para	conv (%)[b]	yield (%)[c]
1[d]	 **3a, 3a`**	80	21	1:2.7	93	-
2[e,f]	 **3a``**	80	21	1:2.7	100	60

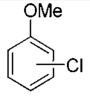
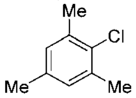
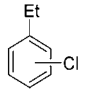
[a] Reaction conditions: Arene (1 mmol), $[\mathrm{BMIM(SO_3H)}][\mathrm{NO_3}]$ (2 mmol), 30−60 °C, 21 h, air balloon. [b] Conversions and product ratios between were determined by NMR and GC-MS. [c] Isolated yield. [d] 1.1 mmol of added HCl (aqueous 37% solution). [e] 2.5 mmol of added HCl (aqueous 37% solution). [f] 9% of 1-chloro-2-methoxybenzene (**3a′**) and 24% of 4-chloro-2-methoxybenzene were formed.

Optimization reactions were performed for chlorination of anisole with the $[\mathrm{BMIM(SO_3H)}][(\mathrm{NO_3})_x(\mathrm{Cl})_y]$ by varying x and y (see SI), and the best chemoselectivity for monohalogenation and quantitative conversion was reached with $x{:}y = 1$ (see SI).

The multifunctional IL mono(3-methyl-1-(butyl-4-sulfonyl)imidazolium) monochloride mononitrate ($[\mathrm{BMIM(SO_3H)}][(\mathrm{NO_3})_{0.5}(\mathrm{Cl})_{0.5}]$) prepared by addition of 37% aqueous HCl and 65% aqueous $\mathrm{HNO_3}$ to the zwitterion

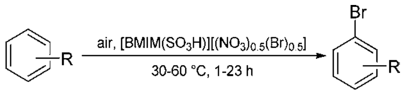
Table 4. Chlorination of Activated Aromatic Substrates in $[\mathrm{BMIM}][\mathrm{SO_3H}][(\mathrm{NO}_{3)0.5}(\mathrm{Cl})_{0.5}]$[a,c]

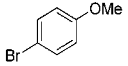
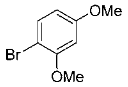
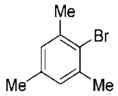
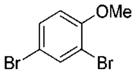


entry	chlorine products	temp (°C)	time (h)	ortho: para	conv (%)[b]	yield (%)[c]
1	 **3a, 3a`**	80	4	1:2.5	100	-
2[d]	 **3c**	80	9	-	100	90
3	 **3f, 3f`**	80	23	1:1.9	100	-

[a] Reaction conditions: Arene (1 mmol), EAN (3 mmol), HCl (aqueous 37% solution, 1.8 mmol), 60−80 °C, 1−24 h, air balloon. [b] Determined by ^{1}H NMR and GC-MS spectroscopy of crude reaction mixture. [c] Isolated yield. [d] 12% of 2,4-dichloro-1,3,5-trimethylbenzene (**3c′**) was formed. [e] $[\mathrm{BMIM}][\mathrm{SO_3H}][(\mathrm{NO}_{3)0.5}(\mathrm{Cl})_{0.5}]$ contained water.

Table 5. Bromination of Aromatic Substrates in $[BMIM][SO_3H][(NO_3)_{0.5}(Br)_{0.5}]$[a,b]



entry	bromine products	temp (°C)	time (h)	ortho: para	conv (%)[b]	yield (%)[c]
1	 **1a**	30	1	1:2	100	90
2[d]	 **2b**	30	1	-	100	54
3	 **2c**	60	4	-	100	80
4	 **2i**	40	23	-	76	65

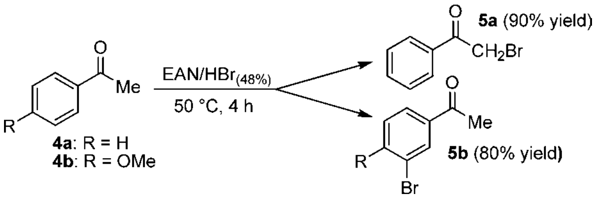
[a] Reaction conditions: Arene (1 mmol), EAN (3 mmol), HBr (aqueous 48% solution, 1.8 mmol), 60−80 °C, 1−23 h, air baloon. [b] Determined by ^1H NMR and GC-MS of crude reaction mixture. [c] Isolated yield. [d] 38% of 1,5-dibromo-2,4-dimethoxybenzene (**2b′**) was formed and 20% was isolated. $[BMIM][SO_3H][(NO_{3)0.5}(Br)_{0.5}]$ contained water.

was used directly (without drying) for aerobic chlorination of arenes (Table 4). This highly practical method proved superior to those when the $[EtNH_3^+]$ $[NO_3^-]$/HCl was used.

In a subsequent step the mono(3-methyl-1-(butyl-4-sulfonyl)imidazolium) monobromide mononitrate ($[BMIM(SO_3H)][NO_3)_{0.5}(Br)_{0.5}]$) was prepared in a similar manner and employed in aerobic bromination of representative aromatics in high yields under very mild conditions (Table 5).

Finally, the selectivity of halofunctionalization was examined by using acetophenone (**4a**) and 1-(4-methoxyphenyl)ethanone (**4b**) as model compounds bearing two potentially reactive sites. Bromination of acetophenone in EAN/HBr mixture gave only 2-bromo-1-phenylethanone in 90% yield (**5a**, Scheme 1), while 1-(4-methoxyphenyl)-ethanone was ring brominated to give 3-bromo-4-methoxy acetophenone (**5b**, Scheme 1) in 80% yield (see SI). Chlorination of these compounds with EAN/HCl mixture were unsuccessful under the reaction conditions employed.

Scheme 1. Bromination of Acetophenone (**4a**) and 1-(4-Methoxyphenyl)ethanone (**4b**)



In summary, we have devleoped novel metal-free and peroxide-free multifucntional IL systems for mild and green aerobic oxidative bromination and chlorination of activated arenes from the readily available alkylammonium nitrate and HX with the possibility of recycling and reusing over several cycles. The imidazolium-based systems prepared by direct addition of HX and HNO_3 to $[BMIM(SO_3^-)]$, without drying or any additional steps, offer greater promise as multifunctional ILs for aerobic oxidative halogenation of arenes. Protocols for the regeneration and reuse of these multifunctional ionic liquids, insight into the role of nitrate anion in the reported oxidative halogenations, and the larger scope of this chemistry are under current investigation.

Acknowledgment. The authors are grateful to the Slovenian Research Agency (contracts: Programme P1-0134, Young Researchers Fellowship PR-03767-1, USA/SI bilateral project BI-US/12-13-004), Human Resources Development and Scholarship fund (contract: 4-Month research fellowship #11012-1712012-7), European Regional Development Found (OP 13.1.1.02.0005), and UNF for financial support.

Note Added after ASAP Publication. We regret having missed the reference Earl, M. J.; Katdare, S. P.; Seddon, K. R. Paradigm Confirmed: The First Use of Ionic Liquids to Dramatically Influence the Outcome of Chemical Reactions. *Org. Lett.* **2004**, *6*, 707−710. This paper reposted on April 12, 2013.

Supporting Information Available. Full experimental details and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.