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Paradigm Confirmed: The First Use of Ionic Liquids to Dramatically Influence the Outcome of Chemical Reactions

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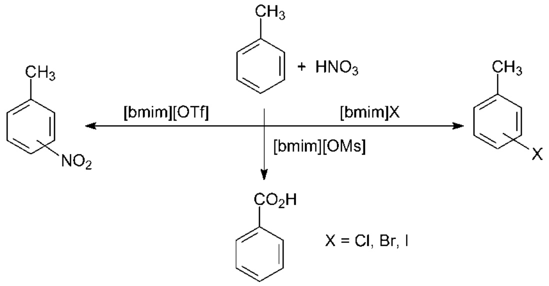
ABSTRACT



It has been an unproven paradigm that the choice of which ionic liquid to use in a chemical reaction can have a dramatic effect on the outcome of that chemical reaction. We demonstrate, for the first time, that the reaction of toluene and nitric acid in three different ionic liquids gives rise to three completely different products in high yield. Furthermore, ionic liquids can catalyze these reactions with the only byproduct being water.

It has been claimed on a number of occasions that ionic liquids represent a new paradigm in organic synthesis: to control the products of a given reaction by fine-tuning the solvent (ionic liquids have been described by Freemantle as "designer solvents").[1] It is of course well-known that by making changes to the structure of either the anion, or the cation, or both, physical properties such as solubility, density, refractive index, and viscosity can be adjusted to suit requirements.[2,3] However, we are unaware of any literature example where the reaction outcome (i.e., where the chemical identity of the product is different, and not merely an isomer of the same material, or where the reaction is turned on or off) can be changed by altering the identity of the ionic liquid.[4]

Here we present a dramatic demonstration, for the first time, that by changing the solvent in which an arene and nitric acid react, it is possible to produce three totally different reaction types and products with very little cross contamination. The effect of ionic liquids on the overall outcome of a chemical reaction has received little attention to date; however, chemical reactions in ionic liquids have been reviewed exhaustively by a number of authors,[5−8] and an excellent book on synthesis in ionic liquids has recently been published.[4] Although there are, unsurprisingly, examples where changing the ionic liquid alters the isomer ratio of products (such as in the Diels−Alder reaction)[9] and also where reactions proceed or do not proceed (for example the

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Friedel−Crafts reaction in acidic or basic chloroaluminate(III) ionic liquids),[10] we have found no case where the type of reaction that occurs is completely changed by the choice of the ionic liquid.[4−8]

We have investigated here a number of ionic liquids as media for chemical reactions, in particular, classical chemical reactions such as aromatic nitration, halogenation, and oxidation. Conventionally, the nitration of an aromatic compound involves the use of a nitrating agent made from mixtures of nitric and sulfuric acid.[11] At the end of the reaction, a large amount of sulfuric acid waste is formed, which is then neutralized prior to disposal. These reactions have also been investigated using lanthanide(III) triflate catalysts,[12] in perfluorocarbon solvents,[13] and by ourselves.[14] Nitrations in ionic liquids such as $[Et_3NH][NO_3]$ using ultrasound[15] and reactions involving nitrating agents such as $[NO_2][BF_4]$, $[NH_4][NO_3]$/trifluoroethanoic acid or alkyl nitrates[16] are known, but in these cases, the ionic liquids were either consumed or the reaction required toxic and/or explosive nitrating agents.

Halogenation of aromatic compounds usually involves the reaction of the arene with a halogen, using a metal halide catalyst.[11] This process produces hydrogen chloride as a stoichiometric waste product.[11] Halogenations have also been attempted in chloroaluminate ionic liquids on both alkenes[17] and arenes,[18] but again the arene halogenation procedure produces hydrogen chloride waste. Oxidative halogenation, using nitric acid and a metal halide, has also been described in the patent literature.[19,20]

The oxidation of compounds such as toluene or xylene is an important reaction and is carried out on a large scale.[21] The products of the oxidation reactions, e.g., benzoic or terephthalic acid, are widely used in the polymer industry. The aerial oxidations of alkyl arenes such as toluene are well-known. These can be achieved by the action of homogeneous cobalt(II) catalysts,[22] by the vapor-phase reaction with dioxygen over a V_2O_5 catalyst,[23] or by the action of concentrated nitric acid (under carefully controlled conditions).[24] To date, an effective reaction has not been reported outside of the patent literature[25] in ionic liquids, but one is described here.

These three classes of reactions were attempted in a number of ionic liquids. The ionic liquids chosen were those that were stable to the reagents, were not water sensitive, and could be recycled and reused. Also, reactions were chosen to produce the minimum amount of waste products, with water as the only byproduct. In the course of this investigation, it was found that the outcomes of these classical reactions were highly dependent on the ionic liquid employed.

The nitration of various aromatic compounds was attempted using 67% nitric acid as the nitrating agent, leaving water as the only byproduct of reaction. The nitration of benzene proceeds smoothly to give nitrobenzene in quantitative yield in the hydrophobic ionic liquid 1-decyl-3-methylimidazolium trifluoromethane sulfonate, $[C_{10}mim][OTf]$,[26] and in the hydrophilic ionic liquid 1-butyl-3-methylimidazolium trifluoromethane sulfonate, [bmim][OTf]. The nitration of chlorobenzene was much slower than with benzene and gave the three isomers of nitrochlorobenzene in excellent yield, in a 69:2:29 ratio of 2-:3-:4-isomers. To determine if the ionic liquids enhanced the reaction rate or selectivity in the nitration of toluene, a control experiment was performed. This involved heating toluene and 67% nitric acid at 110 °C for a day, which gave a 73% conversion to the three isomeric nitrotoluenes. The nitration of toluene with 67% HNO_3 in [bmim][OTf] gave the three isomers of nitrotoluene in quantitative yield. Quantitative dinitration could be achieved by prolonged heating with 100% HNO_3. A reaction was performed with 10 mol % [bmim][OTf]. This gave similar results to the use of stoichiometric quantities of [bmim][OTf], which means that [bmim][OTf] acts as a nitration catalyst. It is interesting to note that neither 2,4,6-trinitrotoluene (TNT) nor the nitrated imidazolium cation were detected by NMR spectroscopy using this method of nitration. Reactions in $[C_{10}mim][OTf]$ and 1-ethyl-3-methylimidazolium hydrogensulfate $[emim][HSO_4]$[27] gave similar reaction rates but lower ortho:para isomer ratios than [bmim][OTf]. The nitration of biphenyl gave a maximum yield of 94% after 18 h; for longer reaction times, dinitrobiphenyls are formed. The reaction of anisole with 67% nitric acid in [bmim][OTf] is rapid and exothermic at room temperature, so cooling of the reaction vessel is essential. A 2:1 ratio of *para*-:*ortho*-nitroanisole was obtained in 99% yield. The

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(26) **Typical Experimental Procedure.** Benzene (0.78 g, 10 mmol) and 67% nitric acid (2.8 g, 30 mmol) were heated under reflux in $[C_{10}mim]$-[OTf] (2.5 g) for 18 h to give a monophasic solution (99% conversion by GC analysis). The residual nitric acid and nitrobenzene were separated from the ionic liquid by Kugelrohr distillation from the reaction vessel at 100 °C, 1 mmHg. The nitrobenzene was separated from the dilute nitric acid by phase separation. NMR analysis was in accordance with authentic nitrobenzene (Aldrich). NMR analysis of the ionic liquid showed that it did not undergo nitration in the imidazole ring and was unchanged.

(27) Ethyl-3-methylimidazolium hydrogensulfate was synthesized from the reaction of 1-methylimidazole with diethyl sulfate to give 1-ethyl-3-methylimidazolium ethyl sulfate, followed by hydrolysis for 5 days at 100 °C with water. The excess water was distilled off and the ionic liquid dried at 120 °C (1 mmHg) for 48 h.

Table 1. Reactions of Aromatic Compounds with Nitric Acid in Various Ionic Liquids

aromatic compound	ionic liquid	temp (°C)	time (h)	product(s)	% *o*-:*m*-:*p*-isomer ratio	% total yield
benzene	$[C_{10}mim][OTf]$	110	18	$C_6H_5-NO_2$		99
chlorobenzene	[bmim][OTf]	130	108	$NO_2-C_6H_4-Cl$	25:1:74	99
toluene	[bmim][OTf]	110	18	$NO_2-C_6H_4-CH_3$	69:2:29	100
toluene	10 mol % [bmim][OTf]	110	23	$NO_2-C_6H_4-CH_3$	64:1:35	100
toluene	[bmim][OTf][a]	110	120	$2,4-(NO_2)_2-C_6H_3-CH_3$	74	100
				$2,6-(NO_2)_2-C_6H_3-CH_3$	26	
toluene	none	110	25	$NO_2-C_6H_4-CH_3$	40:4:29	73
toluene	$[C_{10}mim][OTf]$	110	18	$NO_2-C_6H_4-CH_3$	50:3:44	97
toluene	$[emim][HSO_4]$	110	18	$NO_2-C_6H_4-CH_3$	50:4:45	99
biphenyl	[bmim][OTf]	50	18	2-nitrobiphenyl	60	94
				4-nitrobiphenyl	34	
anisole	[bmim][OTf]	50	3	$NO_2-C_6H_4-OCH_3$	35:0:65	100
benzene	$[C_{10}mim]Cl$	80	120	C_6H_5-Cl	99	99
toluene	$[C_{10}mim]Cl$	110	120	$Cl-C_6H_4-CH_3$	62:1:36	99
toluene	$[C_{12}mim]Br$	110	72	$Br-C_6H_4-CH_3$	39:0:60	99
anisole	$[C_{10}mim]Cl$	20	72	$Cl-C_6H_4-OCH_3$	20:0:79	99
anisole	$[C_{12}mim]Br$	50	1	$4-Br-C_6H_4-OCH_3$	1:0:98	99
anisole	$[NBu_4]I$[a]	100	24	$4-I-C_6H_4-OCH_3$	1:0:96	97
naphthalene	$[C_{12}mim]Br$	50	2	$1-Br-C_{10}H_7$		98

[a] 100% nitric acid used.

products of the reaction can be separated from the ionic liquid, and the ionic liquids can be recycled and reused. This was achieved by either vacuum distillation or steam distillation. This represents a major improvement over the previous nitration reactions reported in ionic liquids.[15,16] The "attempted nitration" reactions of arenes (benzene, toluene, naphthalene, and anisole) using 67% nitric acid in combination with a halide ionic liquid were found to give halogenated products (Table 1). In addition, the reaction of hydrohalic acid with an aromatic compound in a nitrate ionic liquid such as $[bmim][NO_3]$ also gave halogenated arenes. The halogenations of benzene, toluene,[28] and anisole by the reaction of hydrohalic acid with a nitrate ionic liquid catalyst are shown in Figure 2 and Table 2. The mechanism of this oxidative halogenation reaction is thought to involve the nitric acid oxidizing halide to hypohalous acid,[19] which is a well-known halogenating agent.[11]

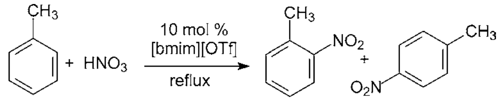

Figure 1. Nitration of toluene in [bmim][OTf] as the catalyst, where $[bmim]^+ = $ 1-butyl-3-methylimidazolium (see Table 1).

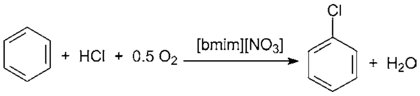

Figure 2. $[bmim][NO_3]$-Catalyzed oxidative halogenation of benzene with hydrochloric acid.

Table 2. Halogenation of Aromatic Compounds with HX in $[bmim][NO_3]$

aromatic compound	acid	temp (°C)	time (h)	product(s)	% yield
benzene	37% HCl	80	96	$Cl-C_6H_5$	99
toluene	37% HCl	100	96	$2-Cl-C_6H_4-CH_3$	60
				$4-Cl-C_6H_4-CH_3$	38
toluene	49% HBr	100	96	$2-Br-C_6H_4-CH_3$	49
				$4-Br-C_6H_4-CH_3$	50
anisole	38% HCl	100	72	$2-Cl- C_6H_4-OCH_3$	20
				$4-Cl- C_6H_4-OCH_3$	79
anisole	49% HBr	80	18	$4-Br- C_6H_4-OCH_3$	99

The products of these reactions were isolated in three different ways. Vacuum distillation allows the products to be separated from the ionic liquid, which leaves the ionic liquid dry and ready for reuse. However, this method cannot be used for the separation of high molecular weight products from the ionic liquid because of the high temperatures

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(28) **Typical Experimental Procedure.** Toluene (0.91 g, 10 mmol) and 37% hydrochloric acid (2.0 g, 20 mmol) were heated under reflux with $[C_4mim][NO_3]$ (2.5 g, 12.5 mmol) in a 25 cm^3 round-bottom flask equipped with a reflux condenser, open to the air. This was heated for 96 h to give a biphasic solution (99% yield {60% ortho and 38% para isomers} conversion by GC analysis) on cooling. The products were separated by phase separation, and the flask was washed with hexane. The combined organic extracts were dried ($MgSO_4$), and the isomers of chlorotoluene were purified by Kugelrohr distillation (50−60 °C at 10 mmHg). NMR analysis of the ionic liquid showed that it did not undergo chlorination in the imidazole ring and was unchanged.

involved. Solvent extraction with cyclohexane or diethyl ether can be used to isolate most organic products from the reaction, and the ionic liquid was then regenerated by distilling off water or unreacted hydrohalic or nitric acids. The third approach was the use of steam distillation. Complete separation of the organic products from the ionic liquid was achieved by the addition of water, followed by distillation at 120−140 °C at atmospheric pressure. The products can then be separated from the residual aqueous dilute acid by phase separation.

In ionic liquids such as methanesulfonate salts, nitric acid acts as an oxidizing agent rather than a nitrating agent. The reaction involves the oxidation of the alkyl side chain of the aromatic compound in the presence of a nitrogen oxoacid species such as nitrate or nitric acid. This transformation can be carried out by the addition of nitric acid to [bmim][OMs][29] or using methane sulfonic acid dissolved in [bmim][NO_3]. As the reaction proceeds, nitrate or nitric acid (the oxidizing agent) is reduced to nitrous acid, which is unstable under the acidic conditions employed. This was in turn reoxidized to nitrate/nitric acid by an oxidizing agent (air).[19] The reaction can be carried out using a stoichiometric amount of nitric acid (or nitrate) or can be performed catalytically.[25] In a remarkable demonstration, a methanesulfonic acid (MsOH)−[bmim][NO_3] mixture (50 mol %) catalyzed the air oxidation of toluene to benzoic acid in 85−90% yield. At the end of the reaction, the [bmim][NO_3]/MsOH was recovered and could be used for further reactions.[30]

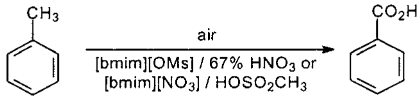

Figure 3. Oxidation of toluene to benzoic acid in nitrate or methanesulfonate ionic liquids.[30]

We have thus demonstrated that the reaction of toluene with nitric acid can give a nitrated product in triflate and hydrogensulfate ionic liquids, that halogenation using nitric acid and a halide salt proceeds efficiently to give the monohalogenated product in excellent yield, and that nitric acid acts as an oxidizing agent in methanesulfonate ionic liquids. The ionic liquids in the nitration and oxidation reactions could all be reused in further reactions and were not destroyed, despite being in contact with acids under reflux. Separation of the products was achieved by vacuum distillation, solvent extraction, or most notably, steam distillation. The only byproduct from these reactions was water. In all of the nitration, halogenation (with HX/O_2), and oxidation reactions, it was found that the ionic liquid acts as a catalyst for the reaction. As a demonstration of the efficiency of this methodology, benzene was chlorinated with concentrated hydrochloric acid using 50 mol % [bmim][NO_3] as a catalyst and air as the oxidant, and the only byproduct of the reaction was water.

Acknowledgment. We thank QUILL for funding this work and the industrial members for their insightful comments.

Note Added after ASAP Posting. Figure 3 was incorrect in the version posted ASAP February 4,2004; The corrected version was posted February 5, 2004.

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[29] Carmichael, A. J.; Earle, M. J.; Seddon, K. R. World Patent WO 0140146, 2001.

[30] **Typical Experimental Procedure.** Toluene (0.91 g, 10.0 mmol) and methanesulfonic acid (0.72 g, 7.5 mmol) were heated under reflux with [C_4mim][NO_3] (1.01 g, 5.0 mmol) in a 25 cm^3 round-bottom flask equipped with a reflux condenser, open to the air. This was heated for 96 h to give a monophasic solution. A white precipitate formed on cooling. The products were isolated by washing the flask with boiling cyclohexene (3 × 5 cm^5). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated to give 1.15 g of crude product. NMR analysis showed that benzoic acid was the major product (89%), with nitrotoluene isomers as a minor byproduct (2%).