

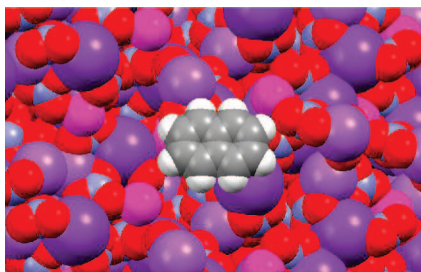
## Aromatic Nitration in Liquid $\text{Ag}_{0.51}\text{K}_{0.42}\text{Na}_{0.07}\text{NO}_3$

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Aromatic molecules have a strong affinity for silver(I) and dissolve to a limited extent in  $\text{Ag}_{0.51}\text{K}_{0.42}\text{Na}_{0.07}\text{NO}_3$ , a low-melting eutectic mixture of silver, potassium, and sodium nitrates. Aromatic nitration in this inorganic ionic liquid leads to products which arise from nonelectrophilic substitution pathways.

### Introduction

Organic reactions have been carried out in diverse phases. Thus, chemistry may occur at the solid–solid interface by grinding reactants together, the solid–liquid and solid–gas interfaces by allowing mobile phases to permeate solids, at the liquid–liquid and liquid–gas (e.g., aerosol) interfaces, in the vapor phase, neat liquids, crystals (topochemically), structured micromedia (e.g., gels, liquid crystals, micelles, emulsions, monolayers), and in solution with water, supercritical solvents, fluoruous phases, and, of course, organic solvents. In recent years, ionic liquids have emerged as yet another medium for performing organic reactions.<sup>1</sup> Based mainly on imidazolium and pyridinium cations with noncoordinating counterions, these low-melting salts have become a popular choice for a number of applications due to their solvent characteristics across a range of polarities, low volatility/flammability, enhancement of various kinds of reactivity, and phase behavior which allows for efficient partitioning. They are, however, essentially organic solvents, and their often-cited green nature has been called into question due to their common derivation from petroleum and toxicity concerns.<sup>2</sup>

Recognizing the affinity of  $\text{Ag}^{\text{I}}$  for organic  $\pi$  electron donors, we wondered how molecules with a substantial  $\pi$  bond content might interact with an *inorganic* ionic liquid containing silver. The advantages of such a medium might be similar to those of organic ionic liquids, i.e., promotion of reactivity, involatility, nonflammability, phase separation, and recyclability. Common silver salts are less expensive than typical ethylmethylimidazolium-based ionic liquids, relatively nontoxic to humans,<sup>3</sup> and known to participate in low-melting (80–120 °C) eutectics.<sup>4</sup> They may also be considered “green” in the sense that they are not petroleum-derived.

A literature search for applications of inorganic ionic liquids in organic reactions turns up a trail of scattered reports from the 1960s onward. In a 1965 review, molten salts are described being used as catalysts in the chlorination, nitration, and cracking of hydrocarbons at high temperatures.<sup>5</sup> Later reviews discuss inorganic eutectics and early uses of organic ionic liquids side by side.<sup>6</sup> The types of reactions promoted by fused salts are

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(3) (a) Lansdown, A. B. G. *Crit. Rev. Toxicol.* **2007**, 37, 237. (b) Lansdown, A. B. *Curr. Probl. Dermatol.* **2006**, 33, 17.

(4) (a) Janz, G. J. *Molten Salts Handbook*; Academic Press: New York, 1967. (b) Grimes, W. R.; Cuneo, D. R. In *Reactor Handbook*; Tipton, C. R., Jr., Ed.; Wiley Interscience: New York, 1960; Vol. 1. (c) Janz, G. J.; Allen, C. B.; Downey, J. R., Jr.; Tomkins, R. P. T. *Eutectic Data: Safety Hazards, Corrosion, Melting Points, Compositions and Biography*; Molten Salts Data Center, Renssler Polytechnic University: Troy, NY, 1976.

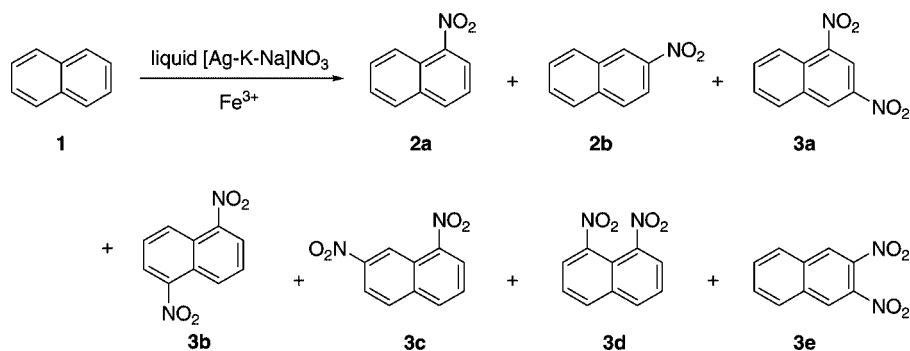
(5) Sundermeyer, W. *Angew. Chem., Int. Ed. Engl.* **1965**, 4, 222.

<sup>†</sup> University of California Davis.

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(1) Reviews: (a) Heintz, A.; Wertz, C. *Pure Appl. Chem.* **2006**, 78, 1587. (b) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, 61, 1015. (c) Forsyth, S. A.; Pringle, J. M.; Mac Farlane, D. R. *Aust. J. Chem.* **2004**, 57, 113. (d) Seddon, K. R. *Nat. Mater.* **2003**, 2, 363. (e) Earle, M. J.; Seddon, K. R. *Pure Appl. Chem.* **2000**, 72, 1391. (f) Welton, T. *Chem. Rev.* **1999**, 99, 2071.

## SCHEME 1



remarkably varied and include hydrocarbon C–H bond activation, various aromatic substitution reactions, aryl couplings, alkali fusion, fragmentations, and rearrangements, among others. In the bulk of this work, the inorganic liquid appears to be acting as a heterogeneous catalyst, since the reaction temperature is often above the boiling point of the organic compound and/or solubility in the medium would be expected to be very limited. Subsequent research in this area seems to have declined in the tide of interest in the aforementioned organic ionic liquids.

Of the types of reactivity mentioned above, we were particularly interested in nitration. The nitration of aromatic molecules is an industrial process which is central to the preparation of numerous synthetic intermediates and end products. Of all reactions done in the practice of organic chemistry, nitration remains one of the most intensively studied.<sup>7</sup> With the above background material in mind, the question became this: Could we exploit the affinity of silver(I) for aromatic molecules to develop an efficient, green, acid-free method for aromatic nitration in an inorganic medium?

## Results and Discussion

The eutectic we chose for this study was a mixture of  $AgNO_3$ ,  $KNO_3$ , and  $NaNO_3$  in a 51:42:7 mol % ratio, respectively, which is a free-flowing liquid above 116 °C. The aromatic substrate was naphthalene, the boiling point of which (218 °C) would be well above the fusion point of the eutectic. Mixtures of the eutectic components and naphthalene formed two phases when heated above the melting point. Interestingly, however, naphthalene was found to possess a solubility of 1.9 mg mL<sup>-1</sup> in this medium.<sup>8</sup> The naphthalene could be quantitatively recovered by dissolving the cooled mixture in water and extracting with dichloromethane.

Turning to nitration, it was supposed that the disproportionation of nitrate into nitronium and oxide ions would be promoted by the addition of a Lewis acid. We were aware that iron(III) catalyzed the nitration of arenes with either  $NO_2-O_2$  or

**TABLE 1.** Molar Equivalents of  $K_3Fe(CN)_6$ , Reaction Time, and Isolated Percent Yields of Recovered **1**, **2** (**2a:2b** Ratio), and **3** (**3a:3b:3c:3d:3e** Ratio) in the Nitration of 2 mmol of Naphthalene with 10 g of the  $Ag_{0.51}K_{0.42}Na_{0.07}NO_3$  Eutectic<sup>a</sup>

entry	$K_3Fe(CN)_6$ (equiv)	time (h)	<b>1</b>	<b>2</b>	<b>3</b>
1	<b>0.25</b>	1	27	37 (6:1)	14 (30:4:15:15:35)
2	<b>0.5</b>	1	17	57 (6:1)	13 (33:8:11:11:36)
3	<b>1.0</b>	1	16	54 (5:1)	15 (24:12:10:39:15)
4	<b>2.0</b>	1	15	50 (5:1)	16 (23:13:10:42:13)
5	0.5	<b>0.5</b>	26	47 (6:1)	17 (33:9:18:16:24)
6	0.5	<b>2</b>	11	43 (5:1)	15 (35:5:15:20:25)

<sup>a</sup> The reaction temperature was 160 °C in each case. Entries in bold denote key variables.

$N_2O_5$ ,<sup>9–11</sup> and potassium ferricyanide was found to dissolve in the liquid eutectic to give an orange solution. When naphthalene was added, nitration was observed (Scheme 1). As can be seen in Table 1, the yield of nitration products reaches a maximum in the presence of 0.5 equiv of  $Fe^{III}$  and a reaction time of 1 h (entry 2). Longer reaction times lead to mechanical losses due to the tendency of naphthalene and its simple derivatives to sublime.

The reaction gives the two mononitro isomers in an  $\alpha/\beta$  ratio lower than would be expected under conditions where  $NO_2^+$  is the nitrating agent (i.e., >10:1).<sup>12,13</sup> The most striking feature, however, of this reaction is the formation of the 1,3- and 2,3-dinitronaphthalenes **3a** and **3e**, which is unprecedented in nitrations carried out under ionic conditions. There are two literature accounts of the observation of the 1,3- and 2,3-isomers, both of which employed nitrogen dioxide as the nitrating agent, either with<sup>14</sup> or without<sup>15</sup> irradiation. Iron(III) is capable of decomposing nitrate into  $NO_2$  and  $Fe_2O_3$ ,<sup>16</sup> and the above reaction is accompanied by traces of a red-brown gas and the gradual accumulation of a brown solid, so the participation of  $NO_2$  in some form is evident.<sup>17</sup> The nature of the ligands on the iron was not crucial, since the reaction also worked with  $FeCl_3$ , although the yields were somewhat lower. While the de facto nature of the nitrating agent in this reaction is not certain, the participation of  $Ag^I$  is essential, since use of the K–Na–Li

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(7) A *Chemical Abstracts* search of the of the term “nitration” produces over 40000 hits.

(8) Solubilities were determined by vigorously stirring 500 mg of aromatic compound and 10 g of the eutectic together in a test tube at 160 °C for 30 min and then allowing the mixture to stand undisturbed for 10 min before cooling to rt. The resulting hard pellet was divided approximately in two, and the top half of which (including the solidified organic layer) was discarded. The remainder was weighed and then dissolved in water and extracted with dichloromethane. The solvent was dried ( $MgSO_4$ ) and evaporated and the mass of the aromatic compound determined.

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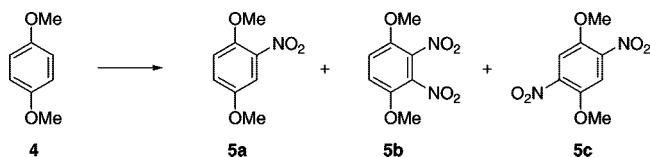
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(16)  $4 Fe^{3+} + 12 NO_3^- \rightarrow 2 Fe_2O_3 + 12 NO_2 + 3 O_2$ . See: Hill, W. D., Jr. *Inorg. Chim. Acta* **1986**, *121*, L33.

## SCHEME 2



**TABLE 2.** Nitrate Eutectic, Additive, Temperature, Reaction Time, and Isolated % Yields of Products in the Nitration of 2 mmol of Hydroquinone Dimethyl Ether (4) with 10 g of Eutectic in the Presence of 0.5 molar equiv of Additive<sup>a</sup>

entry	nitrate eutectic	additive	<i>T</i> (°C)	time (h)	5a	5b
1	<b>K–Na–Li</b>	K <sub>3</sub> Fe(CN) <sub>6</sub>	160	1	0	0
2	<b>Ag–Na–NH<sub>4</sub></b>	K <sub>3</sub> Fe(CN) <sub>6</sub>	160	1	77	2
3	<b>Ag–K–Na</b>	K <sub>3</sub> Fe(CN) <sub>6</sub>	160	1	88	3
4	Ag–K–Na	<b>FeCl<sub>3</sub></b>	160	1	64	0
5	Ag–K–Na	<b>AlCl<sub>3</sub></b>	160	1	58	0
6	Ag–K–Na	<b>K<sub>2</sub>S<sub>2</sub>O<sub>7</sub></b>	160	1	25	0
7	Ag–K–Na	<b>ZnCl<sub>2</sub></b>	160	1	12	0
8	Ag–K–Na	K <sub>3</sub> Fe(CN) <sub>6</sub>	<b>120</b>	1	75	3
9	Ag–K–Na	K <sub>3</sub> Fe(CN) <sub>6</sub>	<b>140</b>	1	86	3
10	Ag–K–Na	K <sub>3</sub> Fe(CN) <sub>6</sub>	<b>180</b>	1	87	2
11	Ag–K–Na	K <sub>3</sub> Fe(CN) <sub>6</sub>	160	<b>0.25</b>	82	2
12	Ag–K–Na	K <sub>3</sub> Fe(CN) <sub>6</sub>	160	<b>0.5</b>	86	2
13	Ag–K–Na	K <sub>3</sub> Fe(CN) <sub>6</sub>	160	<b>2</b>	87	3

<sup>a</sup> Entries in bold denote key variables.

nitrate eutectic (mp 120 °C) resulted in no product under otherwise identical conditions. Interestingly, silver nitrate has been previously used for the nitration of aromatic compounds,<sup>18</sup> including naphthalene,<sup>12</sup> but in acetonitrile solution and in the presence of boron trifluoride. The products of such reactions are similar to those observed in normal acid-catalyzed nitration. Attempting the nitration of naphthalene with potassium ferricyanide and silver nitrate in acetonitrile returned only unchanged starting material, even after 6 h reflux. Grinding the components of the reaction together or wet milling them as an aqueous paste also gave no product.

While the study of naphthalene provided useful insights into the reactivity of the silver(I)-based medium, its high vapor pressure did not enable us to follow the reaction to 100% conversion.<sup>19</sup> Further study of this chemistry took the form of the nitration of hydroquinone dimethyl ether **4** (Scheme 2). Compound **4**, in contact with the liquid nitrate eutectic described above, showed no tendency to sublime from the reaction vessel. Its solubility in the medium was determined to be 1.2 mg mL<sup>-1</sup>,<sup>8</sup> which was somewhat lower than that of **1**.

The results of the systematic evaluation of four variables (eutectic composition, promoter, reaction temperature, and reaction time) in the nitration of **4** are shown in Table 2. As with naphthalene, eutectics containing no silver gave no evidence of nitration. The promoter used in the nitration of naphthalene, K<sub>3</sub>Fe(CN)<sub>6</sub>, proved also to work best here, with FeCl<sub>3</sub> and AlCl<sub>3</sub> giving less satisfactory results. Pyrosulfate, the

(17) A reviewer brought up the question of whether the eutectic could be regenerated after the reaction and reused. Since the reaction consumes NO<sub>3</sub><sup>-</sup> and produces Fe<sub>2</sub>O<sub>3</sub>, titration of the aqueous phase (see workup procedure in the Experimental Section) with nitric acid followed by drying could, in principle, regenerate a reactive eutectic, although we have not yet attempted this.

(18) Olah, G. A.; Fung, A. P.; Narang, S. C.; Olah, J. A. *J. Org. Chem.* **1981**, *46*, 3533.

(19) It might be supposed this problem could simply be surmounted by performing the reaction in a sealed vessel. However, doing so led on one occasion to a detonation, possibly due to the buildup of higher concentrations of polynitro species.

**TABLE 3.** Molar Equivalents of K<sub>3</sub>Fe(CN)<sub>6</sub> and Isolated % Yields of Products for the Nitration of 2 mmol of Hydroquinone Dimethyl Ether (4) with 10 g of the Ag<sub>0.51</sub>K<sub>0.42</sub>Na<sub>0.07</sub>NO<sub>3</sub> Eutectic at 160 °C<sup>a</sup>

entry	K <sub>3</sub> Fe(CN) <sub>6</sub> (equiv)	5a	5b	5c
1	0	0	0	0
2	0.25	53	2	0
3	0.5	88	3	0
4	1.0	75	9	6
5	2.0	36	24	19
6 <sup>b</sup>	2.0	16	29	28
7	4.0	18	32	44
8 <sup>b</sup>	4.0	13	35	42

<sup>a</sup> The reaction time was 1 h unless otherwise noted. <sup>b</sup> Reaction time 6 h.

additive of choice in early work in this area,<sup>20</sup> gave low yields of nitro products, and zinc chloride was even less effective. Raising the temperature beyond 140 °C had no effect on yield. Interestingly, the reaction was shown to be essentially complete within 15 min.

While negligible amounts of dinitration products were observed when the molar ratio of additive to substrate was 1:2, raising the amount of ferricyanide increased the degree of nitration of **4**. As shown in Table 3, the reaction could be controlled to give >75% dinitration, as a mixture of 2,3- (**5b**) and 2,5- (**5c**) dinitro products. As with naphthalene, the product distribution in this reaction is also unusual. Dinitration of **4** with aqueous HNO<sub>3</sub> typically gives **5b** to **5c** ratios of about 8:1, respectively,<sup>21</sup> whereas we observe a less than 1:1 ratio.

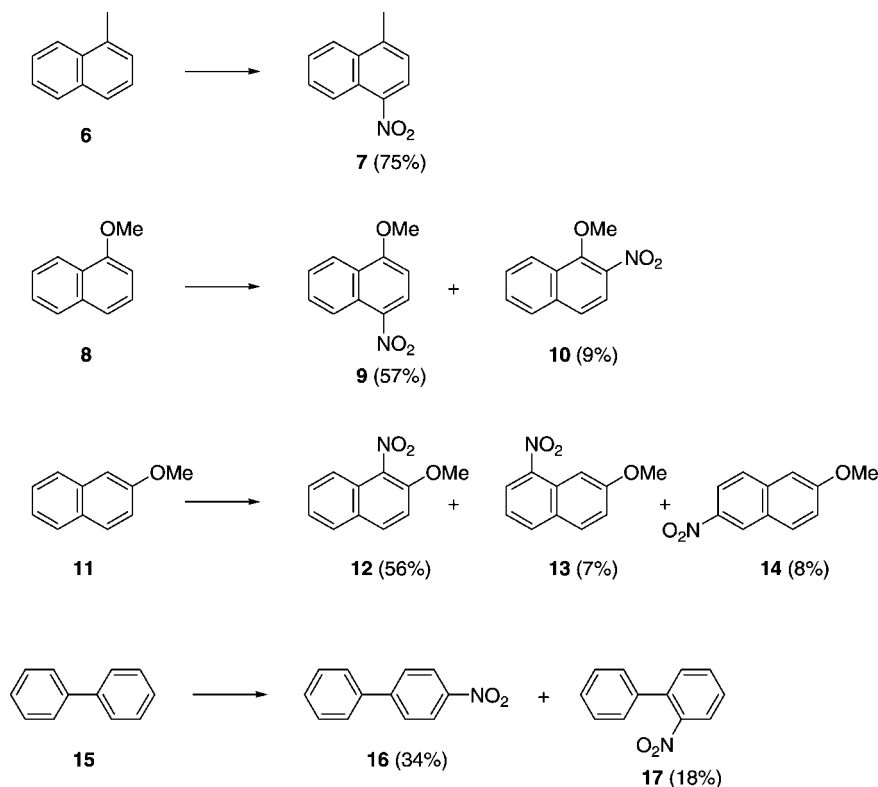
Finally, we submitted related molecules to the silver eutectic nitration conditions to probe the generality of the reaction. Thus, 1-methylnaphthalene (**6**), 1-methoxynaphthalene (**8**), 2-methoxynaphthalene (**11**), and biphenyl (**15**) gave the respective nitro products indicated in Scheme 3. The optimal parameters for the mononitration of **4** were used in each case, and no attempt was made to tune the reactivity to the individual substrates. Phenol and imidazole conflagrated to ash under the same conditions, and the method appears to be generally unsuitable for highly oxidizable aromatics.

In conclusion, we have demonstrated that the silver–potassium–sodium nitrate eutectic is an effective medium for nitrating aromatic molecules. Naphthalene (**1**) and hydroquinone dimethyl ether (**4**) are nitrated with unusual regioselectivities indicative of free radical processes. In the case of **4**, the reaction can be controlled to give either mono- or predominantly disubstitution products in high yields. We suggest here that any number of aromatic systems may be amenable to this method of nitration, giving access in some cases to substitution patterns which are not normally available by acid-catalyzed nitration. Beyond this, we have established in a more general sense that the silver–potassium–sodium nitrate eutectic can act as a solvent for molecules like **1** and **4**, which possess solubilities between ca. 1–2 g L<sup>-1</sup> in this medium. This raises the question as to whether other aspects of the chemistry of π-rich systems might be probed in low-melting, silver(I)-containing inorganic liquids, such as radical reactions, substitution, or aryl coupling, and whether these will likewise demonstrate unusual reactivity.

(20) Temple, R. B.; Fay, C.; Williamson, J. *J. Chem. Soc., Chem. Commun.* **1967**, 966.

(21) (a) Fisher, G. H.; Moreno, H. R.; Oatis, J. E., Jr.; Schultz, H. P. *J. Med. Chem.* **1975**, *18*, 746. (b) Flader, C.; Liu, J.; Borch, R. F. *J. Med. Chem.* **2000**, *43*, 3157.

## SCHEME 3



## Experimental Section

**General Procedure for Nitration of Aromatics.** A flask was charged with an intimate mixture of silver nitrate, potassium nitrate, and sodium nitrate in a molar ratio of 51:42:7, respectively, and placed under vacuum. The mixture was immersed in a heating bath at 160 °C, resulting in the fusion of the components to a free-flowing liquid. The vacuum was broken by backfilling with argon. Potassium hexacyanoferrate (or other additive from Table 2) was then added, and the mixture was vigorously stirred for 30 s, at which point the aromatic was introduced. Stirring was continued for the required time (see Tables 1–3), after which the reaction mixture was removed from the heating bath. The resulting solid residue was dissolved in water and extracted at least three times with dichloromethane. The combined organic fractions were dried and evaporated to give the crude product, which was chromatographed on silica gel using a hexane/ethyl acetate gradient. In the case of naphthalene, the yields were determined by quantification of the following isolated fractions: (a) recovered naphthalene (by mass);

(b) 1- and 2-nitronaphthalenes (by mass of the mixture and  $^1H$  NMR integration); and (c) dinitronaphthalenes (by mass of the mixture and  $^1H$  NMR integration). In all other cases, the individual products themselves were isolated. The nitro compounds described in this work were all identified by comparison with published NMR data.

**Cautionary Note.** Polynitroaromatics are high energy materials and present an explosion hazard. Due care must be taken when preparing and handling such compounds.

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**Supporting Information Available:**  $^1H$  NMR spectra of compounds **5a–c**, **7**, **9**, **10**, **12–14**, **16**, and **17**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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