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Catalytic Rosenmund–von Braun reaction in halide-based ionic liquids

Jeff Xin Wu, Brandon Beck and Rex X. Ren*

Max Tishler Laboratory of Organic Chemistry, Department of Chemistry, Wesleyan University, Middletown, CT 06459, USA

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Abstract—Ionic liquids based on 1-*n*-butyl-3-methylimidazolium halide salts (bmiX) have been used as an effective reusable reaction media in the Rosenmund–von Braun reaction of aryl halides and NaCN using copper(I) salts as catalysts. Product isolation is achieved by simple extraction using organic solvents. The copper catalysts immobilized in ionic liquid media can be reused continuously. © 2002 Elsevier Science Ltd. All rights reserved.

Room-temperature ionic liquids, particularly those based on 1,3-dialkylimidazolium cations such as 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($bmiBF_4$) and 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ($bmiPF_6$), have been shown as the promising new reaction media for organic synthesis. Their utility in alkylation, acylation, hydrogenation, Diels–Alder and Heck reactions as well as other organic transformations has been demonstrated.[1] On the other hand, 1,3-dialkylimidazolium halide-based ionic liquids have received little attention as reaction media, even though they have been known for at least 80 years.[2]

The Rosenmund–von Braun reaction has been known for almost the same length of time, which gives rise to aryl nitriles from the coupling of copper cyanide (CuCN) with aryl halides.[3] This reaction is usually carried out in polar solvents such as nitrobenzene, DMF and pyridine using excess of CuCN at 150–250°C. The product isolation is a tedious process, involving washings with water followed by extensive silica gel column chromatography. Most recently, the Rosenmund–von Braun reaction has experienced a rekindled interest in the synthetic community for the preparation of nitrile-containing aromatics as photogenic materials[4] and as intermediates for pharmaceutical industry. However, the use of excess of CuCN and high boiling point organic solvents may not be the preferred choices. Hence, a more realistic catalyzed Rosenmund–von Braun reaction is needed for contemporary chemical synthesis with less waste and more facile isolation of products, perhaps with reuse of the catalysts and reaction media as well.

We initially set out to investigate the feasibility of using ionic liquids, especially 1-*n*-butyl-3-methylimidazolium halides (bmiX, X = I, Br, Cl)[5] as reaction media to replace DMF and pyridine in the Rosenmund–von Braun reaction. We reasoned that because of the non-volatility of ionic liquids, the products could be distilled directly from the reaction mixture. On the other hand, owing to the limited solubility of these ionic liquids in certain organic solvents such as hexanes, ethyl acetate and toluene, isolation of products could be achieved directly via simple extraction using common organic solvents.

A mixture of 2 mmol of CuCN, 1 mmol of iodobenzene in 0.5 mL of 1-*n*-butyl-3-methylimidazolium iodide (bmiI) sealed in a vial was heated at 90°C with stirring for 24 h. A complete conversion of iodobenzene to benzonitrile was observed (Table 1, entry 1). The product was extracted using either hexanes or a mixture of 2:1 hexanes:EtOAc (3×) and characterized based on GC/MS and NMR after removal of organic solvents.[6] Table 1 shows the Rosenmund–von Braun reaction of iodobenzene with CuCN in various ionic liquids such as bmiI, bmiBr and bmiCl. It was found that 2 equiv. of CuCN was necessary to complete the reaction (entries 1b and c, 2b and c and 3b and c). When 1 equiv. of CuCN was used, the conversion only reached 50%, and addition of a catalytic amount of palladium chloride ($PdCl_2$) to the reaction mixture resulted in essentially the same conversion rate. Other aryl iodides also gave

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Keywords: Rosenmund–von Braun reaction; copper catalysts; aryl nitrile; ionic liquids.

* Corresponding author. Fax: 1-860-685-2211; e-mail: rren@wesleyan.edu

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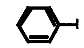
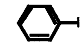
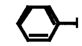
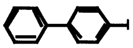
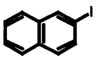
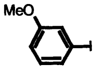
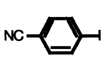
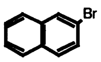
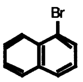
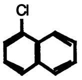
satisfactory results when 2 equiv. of CuCN were used (entry 4–7), regardless of the halide-based ionic liquids used. It should be pointed out that the isolated yields were lower than the conversion. This is presumably attributable to insufficient extraction using 1:2 of EtOAc:hexanes. By employing a higher ratio of EtOAc:hexanes such as 1:1 or 2:1 it was possible to remove essentially all the desired products from ionic liquid media.[6] On the other hand, it seemed that the electronic character of the substituents (such as methoxy and cyano group) did not have significant effects on the reaction. Aryl bromides such as 2-bromonaphthalene and 1-bromonaphthalene gave satisfactory results only when the reaction temperature was raised to 130°C for 24 h (entries 8 and 9). 1-Chloronaphthalene presented much lowered reactivity (entry 10).

Table 1. Rosenmund–von Braun reaction of iodobenzene with CuCN in ionic liquids

$$\text{ArY} \xrightarrow[\text{heating}]{\text{CuCN, in bmiX}} \text{ArCN}$$

Entry	ArY (1 mmol)	bmiX	CuCN	Yield (%)[b]
1a		bmiI	1 eq[a]	~50
1b			2 eq	100
1c			3 eq	100
2a		bmiBr	1 eq[a]	~50
2b			2 eq	100
2c			3 eq	100
3a		bmiCl	1 eq[a]	~50
3b			2 eq	100
3c			3 eq	100
4		bmiBr	2 eq	100 (44)
		bmiCl		100 (40)
5		bmiBr	2 eq	100 (55)
		bmiCl		100 (84)
6		bmiBr	2 eq	100 (67)
		bmiCl		100 (50)
7		bmiBr	2 eq	100 (60)
		bmiCl		100 (63)
8		bmiBr[c]	2 eq	91
9		bmiBr[c]	2 eq	77
10		bmiBr[c]	2 eq	~20

Notes: All reactions were carried out in 0.5 mL of ionic liquids at 90°C for 24 hours, unless indicated otherwise.

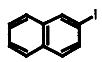
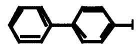
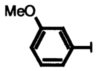
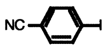
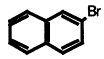
[a] 5 mol% of $PdCl_2$ added.

[b] Conversion is based on GC/MS analysis and NMR; numbers in parenthesis denote the isolated yields from extractions using 1 ml of 2:1 hexanes:EtOAc (3x).

[c] Reaction temperature was 130 °C.

Table 2. Catalytic Rosenmund–von Braun reaction of Aryl Iodides and bromides with NaCN in ionic liquids

$$\text{ArY} + \text{NaCN} \xrightarrow[\text{heating}]{\text{Cu catalysts, in bmiX}} \text{ArCN}$$

Entry	ArY	bmiX	Catalyst	Yield (%)[b]
1a		bmiI	CuCN	100
1b		bmiI	CuI	100
1c		bmiI	CuI[a]	95
1d		bmiCl	CuCl	50
2a		bmiI	CuI	100
2b		bmiI	CuI[a]	95
3		bmiI	CuI	50
4a		bmiI	CuI	65
4b		bmiI	CuI[a]	95
5		bmiBr	CuCN	55

Notes: All reaction were carried out at 2 M concentration in 0.5 mL of ionic liquids at 120°C for 24 hours with 5 mol % catalysts, 1 mmol of ArY and 2 eq of NaCN.

[a] CuI was pre-mixed with bmiI at 100°C. Yields are based on NMR.

[b] Conversion is based on GC/MS analysis.

The mechanism of the Rosenmund–von Braun reaction most likely involves a copper-assisted nucleophilic aromatic substitution. That is, activation of the aromatic ring by a cationic copper(I) species is achieved via the formation of either a σ-complex between copper metal and the lone pairs of the halogen atom or a π-complex between the metal species and the aromatic ring. This is followed by nucleophilic attack of cyanide (CN^-), which leads to elimination of iodide. Radical mechanisms may also operate. Nevertheless, copper(I) plays a catalytic role.[7] It is also known that a copper catalyst together with a sufficient amount of NaCN or KCN can bring about the same transformation.[3c] Hence we examined the utility of halide-based ionic liquids in catalytic Rosenmund–von Braun reaction employing NaCN as the cyanide source. Table 2 shows the results.

Thus, using a catalytic amount (5 mol%) of CuCN and 2 equiv. of NaCN in halide-based ionic liquids (bmiX, X = Cl, Br or I) at 120°C, 2-iodonaphthalene was converted to 2-cyano-naphthalene in high yield. Switching from bmiI/CuI (entries 1b and c) to bmiCl/CuCl lowered the conversion rate (entry 1d). Other aryl iodides also underwent the catalytic Rosenmund–von Braun reaction to give the nitrile compounds (entries 2–4). The premixing of copper catalysts with ionic liquids seemed to have no effect on the conversion rates (entries 1c, 2b and 4b). It is reasoned that by premixing there is formation of clathrate[8] (CuI_2^-) between CuI and the iodide anion (I^-) of bmiI ionic liquid. Therefore, the catalysts should be expected to remain active even when they were to be reused, although it is arguably true that the immobilized catalysts should have formed clathrates with the halide anions of ionic liquids upon first use.

2-Bromonaphthalene underwent transformation (~55% based on GC/MS) to nitrile product in bmiBr using CuCN as catalyst and 2 equiv. of NaCN (entry 5). When only 1 equiv. of NaCN was used in conjunction with CuCN as catalyst, all of the above reactions proceeded much more slowly. It is known that the addition of cyanide to the activated aryl halides is a reversible process, therefore it is not surprising that higher concentration of cyanide is the key to render this type of reaction toward completion.[3c]

It is noteworthy that the copper catalysts immobilized in ionic liquids can indeed be reused for several times without loss of activity. Thus, upon removal of products via similar extraction procedure using organic solvents, another 1 equiv. of substrates and 1 equiv. of NaCN were added to the ionic liquid reaction media containing copper catalyst. We observed that these reactions led to similar results. Studies on the possible catalyst leaching from ionic liquids are in progress.

In summary, in this preliminary communication the Rosenmund–von Braun-type reaction of aryl halides and NaCN using copper(I) salts as catalysts in ionic liquids based on 1-*n*-butyl-3-methylimidazolium halide salts (bmiX) has been demonstrated. Isolation of the desired products can be achieved via a simple extraction using organic solvent mixes. The ionic liquids containing immobilized copper catalyst can be reused continuously.[9]

Acknowledgements

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4. Drechsler, U.; Hanack, M. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vogtle, F., Eds.; Pergamon, 1996; Vol. 9, p. 283.
5. bimCl (mp 41°C), bmiBr (mp below room temperature) and bmiI (mp −72°C) were prepared by heating a mixture of *n*-butyl halides (1.5 equiv.) with 1-methylimidazole followed by removal of unreacted *n*-butyl halides, respectively. Although bmiCl is solid at room temperature, warming up or addition of co-solvents such as water can render them liquid-like due to their hydrophilicity. For the latest reference regarding the melting points of bmiCl and bmiI, see: Huddleston, J. G.; Visser, A. E.; Reichert, W. M.; Willauer, H. D.; Broker, G. A.; Rogers, R. D. *Green Chem.* **2001**, *3*, 156.
6. When more polar solvent mix was used in extraction, trace amount of ionic liquids were observed in NMR. Filtration of the extractant through a thin pad of silica gel could get rid of this impurity.
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9. (a) A general procedure for cyanation reaction in ionic liquids using a catalytic amount of copper catalysts: In capped 2-dram vials, mixtures of 1 mmol of aromatic halides, 0.05 mmol of copper catalysts, 2 mmol of NaCN and 0.5 mL of halide-based ionic liquids were heated at 120°C with stirring for 24 h. The reactions were monitored using GC/MS or NMR, and products were extracted using solvent mixes (2:1 or 1:1 hexanes:EtOAC) or straight EtOAc (3×3 mL).

   (b) A general procedure for cyanation reaction catalyzed by pre-mixed catalysts: In capped 2-dram vials, 0.05 mmol of copper iodide and 0.5 mL of bmiI ionic liquid were mixed at 100°C for 5 min until the mixtures became homogeneous. 1 mmol of aryl halides and 2 mmol of NaCN were then added. The mixtures were stirred at 120°C for 24 h. The reactions were monitored using GC/MS or NMR, and products were extracted using solvent mixes (2:1 or 1:1 hexanes:EtOAC) or straight EtOAc (3×3 mL).

   (c) 2-Cyanonaphthalene: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.92 (m, 3H), 7.64 (m, 3H).

   (d) 1,4-Dicyanobenzene: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 4H).

   (e) *p*-Phenylbenzonitrile: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, 8 Hz, 2H), 7.70 (d, 8 Hz, 2H), 7.60 (d, 8 Hz, 2H), 7.52–7.46 (m, 3H).