



## Microwave-promoted, one-pot conversion of alkoxyethylated protected alcohols into their corresponding nitriles, bromides, and iodides using [bmim][InCl<sub>4</sub>] as a green catalyst

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### ABSTRACT

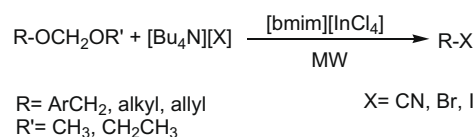
The Lewis acid room temperature ionic liquid, [bmim][InCl<sub>4</sub>], was found to be an efficient and green catalyst for the highly chemoselective and one-pot conversion of MOM- or EOM-ethers into their corresponding nitriles, bromides, and iodides under microwave irradiation. The procedures are simple, rapid, and high yielding. The catalyst exhibited a remarkable reactivity and is reusable.

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One-pot transformations represent a strategy combining economic and environmental aspects. Also, one-pot conversions of functional groups play a critical role in the successful synthesis of multi-functional complex molecules. These processes typically consist of two or more steps, which are performed without isolation of any intermediates, thus leading to savings in energy and raw materials and also reducing time.<sup>1</sup> Due to the importance of these transformations, significant efforts have been, and still are being devoted to find and develop new types of these reactions. Methoxymethyl ethers (MOM-ethers) or ethoxymethyl ethers (EOM-ethers) are important intermediates and are used to protect alcohols due to their easy access and high stability under both basic and moderately acidic conditions.<sup>2</sup> On the other hand, nitriles are important synthetic transformation precursors, especially of esters, amides, carboxylic acids, amines, and nitrogen-containing heterocycles.<sup>3</sup> They have been used as synthetic intermediates for agricultural and pharmaceutical chemicals.<sup>4</sup> Furthermore, organic halides, especially bromides and iodides, are indispensable in organic synthesis, and their transformations into useful compounds are widely documented in the literature.<sup>5</sup> They serve as intermediates in a wide variety of reactions,<sup>6</sup> and also in carbon-carbon bond formation via radical or substitution reactions.<sup>7</sup> Therefore, direct transformation of methoxymethyl- and ethoxymethyl-protected alcohols into nitrile, bromide, and iodide functional groups can be considered important in organic synthesis.

There has been major research effort in the area of ionic liquids over the last two decades. The development and use of room temperature ionic liquids (RTILs) have emerged as a fascinating technology because of their unique physicochemical properties

and specific applications in academic and industrial fields.<sup>8,9</sup> There has been a substantial growth in the use of RTILs as environmentally benign and useful media<sup>8</sup> in diverse applications such as catalysis,<sup>10</sup> biocatalysis,<sup>11</sup> separation technology,<sup>12</sup> biomass dissolution,<sup>13</sup> energetic materials,<sup>14</sup> and active pharmaceutical ingredients (APIs).<sup>15</sup> Due to their ionic nature, ionic liquids are ideal for use in microwave-promoted synthesis on account of their negligible vapor pressure and high thermal stability.<sup>16</sup>



Scheme 1.

Table 1

Direct conversion of benzylmethoxymethyl ether into its corresponding nitrile in the presence of various catalysts<sup>a</sup>

Entry	Catalyst	Yield <sup>b</sup> (%)
1	InCl <sub>3</sub>	56
2	[bmim][AlCl <sub>4</sub> ]	22
3	[bmim][FeCl <sub>4</sub> ]	31
4	[bmim][InCl <sub>4</sub> ]	88
5	No catalyst	0

<sup>a</sup> Reaction conditions: benzylmethoxymethyl ether (1 mmol), (*n*-Bu<sub>4</sub>N)CN (2 mmol), catalyst (0.28 mmol).

<sup>b</sup> Isolated yield.

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Recently, several methods have been reported for the conversion of alcohols and their derivatives into their corresponding halides and nitriles.<sup>17–21</sup> However, to the best of our knowledge, the transformation of MOM- and EOM-ethers into their nitriles, bromides, and iodides has not been described in the literature. Herein, we report the use of 1-butyl-3-methylimidazolium tetrachloroindate [bmim][InCl<sub>4</sub>], as a novel, highly efficient and eco-friendly catalyst for the one-pot conversion of various MOM- or

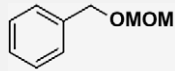
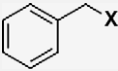
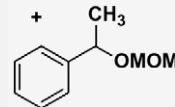
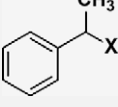
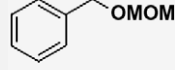
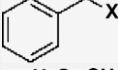
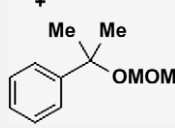
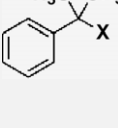
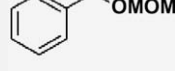
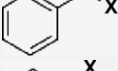
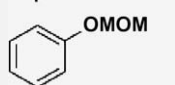
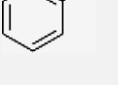
EOM-ethers into their corresponding bromides, iodides, and nitriles in high yields under microwave irradiation conditions (Scheme 1).

In these reactions no corrosive substances were used and no waste formation was observed. The experimental procedure for these reactions was remarkably simple and required no toxic organic solvent or inert atmosphere. We found that the transformations could be accomplished by exposing a mixture of the

**Table 2**Conversion of MOM- and EOM-ethers into their corresponding nitriles, bromide, and iodides catalyzed by [bmim][InCl<sub>4</sub>] under MW irradiation<sup>a</sup>

Entry	R	EOM-ether Yield, % (time, min) <sup>b</sup>			MOM-ether Yield, % (time, min) <sup>b</sup>		
		X = CN	X = Br	X = I	X = CN	X = Br	X = I
1	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	88 (4.5)	83 (4.5)	86 (4.5)	88 (4.5)	82 (4.5)	87 (4.5)
2	4-(CH <sub>3</sub> ) <sub>3</sub> CC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	84 (4.5)	81 (4.5)	83 (4.5)	85 (4.5)	84 (4.5)	85 (4.5)
3 <sup>c</sup>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	86 (4.5)	84 (4.5)	86 (4.5)	87 (4.5)	83 (4.5)	87 (4.5)
4	2-HOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	82 (5.5)	79 (5.5)	82 (5.5)	83 (5.5)	79 (5.5)	83 (5.5)
5	3-CH <sub>3</sub> O, 4-HOC <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>	84 (4.5)	81 (4.5)	83 (4.5)	86 (4.5)	82 (4.5)	86 (4.5)
6	3-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	86 (4)	83 (4)	85 (4)	86 (4)	83 (4)	86 (4)
7	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	82 (5.5)	79 (5.5)	81 (5.5)	82 (5.5)	81 (5.5)	82 (5.5)
8	4-PhCH <sub>2</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	84 (4.5)	82 (4.5)	84 (4.5)	84 (4.5)	82 (4.5)	84 (4.5)
9	2-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	81 (5)	79 (5)	81 (5)	83 (5)	81 (5)	81 (5)
10	4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	83 (5)	81 (5)	82 (5)	84 (5)	81 (5)	83 (5)
11	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>	80 (5.5)	78 (5.5)	79 (5.5)	82 (5.5)	77 (5.5)	80 (5.5)
12	2-BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	80 (5.5)	77 (5.5)	79 (5.5)	80 (5.5)	78 (5.5)	78 (5.5)
13	4-BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	82 (5)	81 (5)	82 (5)	84 (5)	80 (5)	83 (5)
14	3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	88 (3)	84 (3)	86 (3)	89 (3)	86 (3)	88 (3)
15	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	90 (2)	85 (2)	88 (2)	91 (2)	86 (2)	88 (2)
16	C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>	92 (2)	88 (2)	91 (2)	92 (2)	89 (2)	92 (2)
17	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>	86 (4)	82 (4)	84 (4)	86 (4)	83 (4)	86 (4)
18	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> CH <sub>2</sub>	87 (4)	82 (4)	86 (4)	87 (4)	83 (4)	87 (4)
19	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> CH <sub>2</sub>	85 (4)	83 (4)	84 (4)	86 (4)	82 (4)	84 (4)

<sup>a</sup> Reaction conditions: alkoxyethyl ether (1 mmol), [*n*-Bu<sub>4</sub>N][X] (2 mmol), [bmim][InCl<sub>4</sub>] (0.28 mmol).<sup>b</sup> Isolated yield.<sup>c</sup> 0.56 mmol of catalyst and 4 mmol of [Bu<sub>4</sub>N][X] were used.**Table 3**Competitive conversions of various MOM-ethers into nitriles, bromides, and iodides catalyzed by [bmim][InCl<sub>4</sub>] under MW irradiation<sup>a</sup>

Entry	Ethers	Products	X = CN		X = Br		X = I	
			Yield <sup>b</sup> (%)	Time (min)	Yield <sup>b</sup> (%)	Time (min)	Yield <sup>b</sup> (%)	Time (min)
1			88		82		87	
	+ 		19	4.5	13	4.5	17	4.5
2			88		82		87	
	+ 		—	4.5	—	4.5	—	4.5
3			88		82		87	
	+ 		—	4.5	—	4.5	—	4.5

<sup>a</sup> Reaction conditions: alkoxyethyl ether (1 mmol), [*n*-Bu<sub>4</sub>N][X] (2 mmol), [bmim][InCl<sub>4</sub>] (0.28 mmol).<sup>b</sup> Isolated yield.

alkoxymethyl ether (1 mmol), [*n*-Bu<sub>4</sub>N][X] (X = CN, Br or I) (2 mmol), and [bmim][InCl<sub>4</sub>] (0.28 mmol) to MW irradiation (170 W, 135–140 °C) for 2.0–5.5 min. On the other hand, the yields of these reactions did not exceed more than 22% under thermal conditions (135 °C) even after long reactions times. The reaction was not successful in the absence of catalyst or MW irradiation.

The ability of two other common Lewis acidic ionic liquids, [bmim][FeCl<sub>4</sub>] and [bmim][AlCl<sub>4</sub>], as well as InCl<sub>3</sub> to promote the conversion of benzylmethoxymethyl ether into its corresponding nitrile under MW irradiation was investigated. The results showed that the catalytic activities of InCl<sub>3</sub>, [bmim][AlCl<sub>4</sub>], and [bmim][FeCl<sub>4</sub>] were much lower than [bmim][InCl<sub>4</sub>], and these reactions afforded the corresponding nitriles in 56%, 22%, and 31% yields, respectively (Table 1). It would appear that in these ionic liquids, InCl<sub>3</sub>, FeCl<sub>3</sub>, and AlCl<sub>3</sub> act as Lewis acids which activate the MOM- and EOM-ethers toward nucleophilic attack. The advantages of InCl<sub>3</sub> compared to FeCl<sub>3</sub> and AlCl<sub>3</sub> are its hydrolytic stability and lower oxophilicity. By combining InCl<sub>3</sub> with [bmim][Cl], a Lewis acid ionic liquid with good solvating ability is obtained which is water-stable in contrast to other chloroaluminate and chloroferate systems.<sup>22,23</sup> These characteristics make [bmim][InCl<sub>4</sub>] a more reactive catalyst.

Under the optimized reaction conditions, a wide range of substituted and structurally diverse primary aromatic, allylic, and aliphatic MOM- and EOM-ethers containing electron-withdrawing as well as electron-donating groups (chloro, bromo, nitro, methoxy, hydroxy, *t*-butyl, and benzyloxy) easily underwent this one-pot reaction with [Bu<sub>4</sub>N][X] (X = CN, Br, and I) in the presence of a catalytic amount of [bmim][InCl<sub>4</sub>], under MW irradiation, to give the corresponding nitriles, bromides, and iodides in excellent isolated yields and in short reaction times (Table 2).

In order to investigate the chemoselectivity of the present method, a set of competitive reactions was conducted between a primary MOM-ether and secondary, tertiary, and phenolic MOM-ethers (Table 3). The results indicated that this protocol was potentially applicable for the chemoselective conversion of primary alkoxymethyl ethers in the presence of secondary, tertiary, and phenolic ethers. Furthermore, this method was appropriate for the chemoselective transformation of these ethers in the presence of other hydroxy protecting groups such as benzyl or methyl ethers (Table 2, entries 5–8).

The reusability of this ionic liquid was also investigated, and it was observed that it could be reused four times without significant loss of its activity.

In conclusion, a novel, efficient, eco-friendly, and chemoselective protocol has been developed for the microwave-promoted direct transformation of MOM- and EOM-ethers into nitriles, bromides, and iodides, in high yields, in the presence of the recyclable, air- and moisture-stable Lewis acidic ionic liquid, [bmim][InCl<sub>4</sub>].

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.056.

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