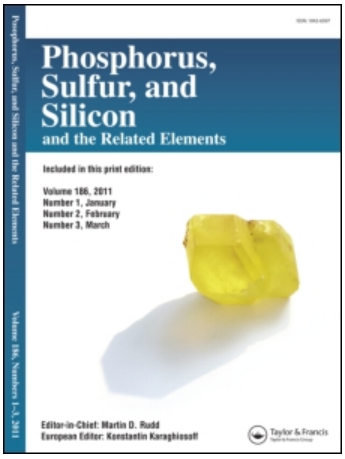

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Ionic Liquids—Promoted S-Methylation of Thiols Utilizing Dimethyl Carbonate

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IONIC LIQUIDS—PROMOTED S-METHYLATION OF THIOLS UTILIZING DIMETHYL CARBONATE

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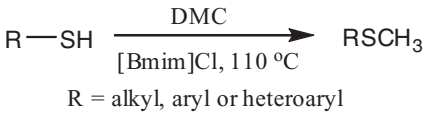
GRAPHICAL ABSTRACT



Abstract *Convenient and efficient S-methylation of mercaptans or thiophenols occurs with dimethyl carbonate (DMC) in room temperature ionic liquids (RTILs) [Bmim]Cl. [Bmim]Cl can be recycled in four subsequent runs with only a gradual decrease in activity. A possible mechanism of this transformation is also discussed.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords Dimethyl carbonate; ionic liquids; methyl thioether; thiol

INTRODUCTION

As organic sulfur compounds have become increasingly important in organic synthesis, the development of convenient and practical methods for preparing methyl thioethers, especially those that carry heterocyclic functional groups, is desirable. At present, the usual route involves the methylation of thiol groups using methylic halides[1] or dimethyl sulfate.[2] However, substrate factors and operational issues have restricted the synthesis of methyl thioethers due to the toxicity of reagents and generation of a stoichiometric amount of salt. For these reasons, dimethyl carbonate (DMC) is currently considered to be a genuine

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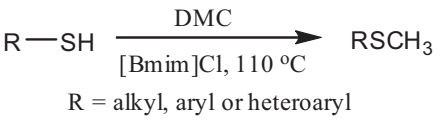
example of a green and versatile methylating reagent. It has also been widely used as an alternative methylating reagent to replace hazardous compounds in organic synthesis.[3] The most common examples involve using some catalysts, such as K_2CO_3-crown ether,[4] K_2CO_3-Bu_4NBr,[5] DBU,[6] or 2,4-diaminotoluene.[7] In such cases, separation of the catalysts and reutilization can be problematic. Hence, the development of recycling catalytic systems is of importance for the methylation reaction. In this respect, room temperature ionic liquids (RTILs) are attracting a growing interest as alternative reaction media for various chemical and biotransformations. RTILs have emerged as a set of green solvents with unique properties such as tunable polarity, high thermal stability, immiscibility with a number of organic solvents, negligible vapor pressure, and recyclability.[8] Since 2004, there have been extensive studies on the S-alkylation reactions in [Bmim][PF_6] or [Bmim][BF_4].[9] Shen et al. performed the reactions of phenols with DMC using RTILs as a catalyst.[10] However, there are no examples on the use of RTILs for the conversion of thiols to methyl thioethers in the open literature. In conjunction with our interest in readily accessing diversified sulfoxide and sulfone, we are keen to develop a convenient and efficient method for the construction of methyl thioethers.

In this article, we report on the methylation reaction of thiols with DMC promoted by RTILs in the absence base and organic solvents (Scheme 1). Simple stirring of a mixture of various thiols and DMC in [Bmim]Cl gave the desired methyl thioethers in high yields. Because [Bmim]Cl and DMC are green reagents and [Bmim]Cl can be recycled and reused, the reaction has notable advantages and remarkable environmentally benign features. The possible mechanism relating to this transformation is also discussed.



Scheme 1 The route of S-methylation of thiols with DMC promoted [Bmim]C1.

RESULTS AND DISCUSSION

Initially, we carried out the experiment with 2-mercaptobenzothiazole (**1a**) and DMC in different reaction media. The product was obtained after a simple extraction stage with ethyl acetate. The results are shown in Table 1. When the mixture of **1a** and DMC was heated to 90°C in the absence of catalyst, no products were detected (Table 1, entry 1). Similarly, the reaction was sluggish when using [Bmim]PF_6 or [Bmim]BF_4 as catalyst (Table 1, entries 2 and 3). In the presence of RTILs, such as [Bmim]Br, [Emim]Br, [BmPy]Br, [EmPy]Br, [Emim]Ac, or [Bmim]Cl, products were obtained in 45–77% yields (Table 1, entries 4–9), indicating that these ionic liquids are moderately effective for the methylation reaction. [Bmim]Cl was the most efficient catalyst and gave the highest yield of 2-methylthiobenzothiazole (**2a**) at 90°C (77%). It was noteworthy that ionic liquids with different anions showed varying catalytic activities (Table 1, entries 2–4 and 9). The results suggested that the anion had a strong impact on the catalytic activity of the ionic liquid in the reaction. Similar yields of **2a** were obtained when [Bmim]Br, [Emim]Br, [BmPy]Br, or [EmPy]Br were employed in the reaction of **1a** with DMC. This suggested that the chain length of the substituted group of imidazole or pyridine was not a crucial factor in the

Table 1 Reaction of **1a** with DMC in the presence of different catalysts[a]

Entry	Catalyst	Reaction time (h)	Temperature (°C)	Isolated yield[b] (%)
1	None	20	90	—
2	[Bmim]PF_6	20	90	<5
3	[Bmim]BF_4	20	90	<5
4	[Bmim]Br	3	90	46
5	[Emim]Br	3	90	45
6	[BmPy]Br	3	90	65
7	[EmPy]Br	3	90	62
8	[Emim]Ac	3	90	77
9	[Bmim]Cl[c]	3	90	77
10	[Bmim]Cl	12	70	—
11	[Bmim]Cl	3	110	82
12	Bu_4NCl[d]	20	90	<5

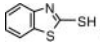
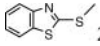
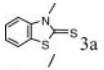
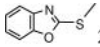
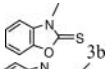
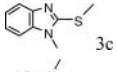
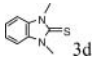
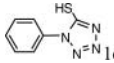
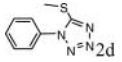
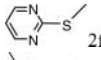
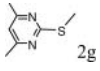
[a]Reaction conditions: **1a** = 10 mmol, DMC = 20 mmol, ionic liquid = 20 mmol.
[b]Isolated yield of S-methylated product based on **1a** after column chromatography.
[c]N-methylated byproduct (**3a**) was 6%.
[d]Reaction conditions: **1a** = 10 mmol, DMC = 200 mmol, Bu_4NCl = 2 mmol.

catalytic activity of the ionic liquid (Table 1, entries 4–7). Compared with the ionic liquids, Bu_4NCl showed poor catalytic activity (Table 1, entry 12). This was also applied to the selectivity of **2a** as well. The main byproduct was N-methylated byproduct (Table 1, entry 9). This suggested that the imidazolium moiety of the ionic liquids has a significant function in catalytic S-methylation of **1a** with DMC. This is similar for O-methylation of phenol with DMC.[10] The reactivity of DMC at moderate temperatures can be significantly lower than that of methyl iodide or dimethyl sulfate.[7] We found that no products were obtained when using [Bmim]Cl as catalyst in DMC at 70°C after 12 h (Table 1, entry 10). However when the reaction was carried out at 110°C for 3 h, the yield was further enhanced to 82% yield (Table 1, entry 11).

The results given in Table 2 outline the reactions of thiols with DMC in [Bmim]Cl. The Supplemental Materials (available online) include the characterization data for the compounds. Clearly alkyl, aryl, and heterocyclic thiols reacted well with DMC to producing corresponding thioethers. Interestingly, the alkyl thiols were found to lower the reactivity (Table 2, entries 1 and 2). Higher yields of aryl methyl thioethers were obtained compared to alkyl methyl thioethers (Table 2, entries 3–5). Heterocyclic thiols such as **1e**, **1f**, and **1g** were converted into the corresponding heteroaryl methyl thioethers giving high yields and good regioselectivity (Table 2, entries 10–12). This is probably due to the higher stability of nucleophilic anions (RS^-) in the reaction. Heterocyclic thiols such as **1a**, **1b**, and **1c** were converted into the corresponding heteroaryl methyl thioethers giving a bit of N-methylated byproduct at the same time. This is probably the result of proton migration between thiol form and thione form (Table 2, entries 6–8).[11] Moreover, for reactions of thiophenol, an electron-donating substituent such as methyl group was found to increase the reactivity, while electron-withdrawing substituent on the thiophenol such as chloro was found to lower the reactivity at 90°C (Table 2, entries 3–5). Heterocyclic thiols such as **1f** and **1g** gave similar results (Table 2, entries 11–12).

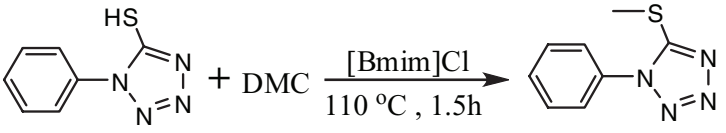
We performed reactions at 90°C and 110°C to compare the influence of temperature on the catalytic process (Table 2). Although, the reactions did occur at 90°C, longer

Table 2 Reaction of thiols with DMC in [Bmim]Cl[a]

Entry	Substrates	Product		Time (h)/90°C	Isolated yield (%)/90°C		Time (h)/110°C	Isolated yield (%)/110°C	
		S-Methyl	N-Methyl		S-methyl	N-methyl		S-methyl	N-methyl
1	$CH_3(CH_2)_3SH$	$CH_3(CH_2)_3SCH_3$	—	12	35[b]	—	—	—	—
2	$C_6H_5CH_2SH$	$C_6H_5CH_2SCH_3$	—	20	45	—	5	56	—
3	C_6H_5SH	$C_6H_5SCH_3$	—	4	62	—	1.5	72	—
4	$4\text{-}CH_3C_6H_4SH$	$4\text{-}CH_3C_6H_4SCH_3$	—	2	65	—	1	77	—
5	$4\text{-}ClC_6H_4SH$	$4\text{-}ClC_6H_4SCH_3$	—	8	56[c]	—	2	76	—
6	 1a	 2a	 3a	4	77	6	3	82	3
7	 1b	 2b	 3b	4	60	5	3	73	4
8	 1c	 2c	 3c  3d	12	39	20/3[d]	6	45	23/2[e]
9	 1d	 2d	—	2	61	—	1.5	76	—
10	 1e	 2e	—	6	78	—	3	91	—
11	 1f	 2f	—	10	73	—	3.5	90	—
12	 1g	 2g	—	5	79	—	3	92	—

[a]Reaction conditions: thiols = 10 mmol, DMC = 20 mmol, ionic liquid = 20 mmol.
[b]Total yields of two products (n-butyl methyl sulfide and butyl disulfide); the ratio (52:45) of two products based on GC.
[c]Total yields of two products (4-chlorothioanisole and 4,4′-dichlorodiphenyl disulfide); the ratio(64:23) of two products based on GC.
[d]Isolated yield of **3c** is 20%; isolated yield of **3d** is 3%.
[e]Isolated yield of **3c** is 23%; isolated yield of **3d** is 2%.

Table 3 Reuse of [Bmim]Cl for the reaction of 1d with DMC[a]



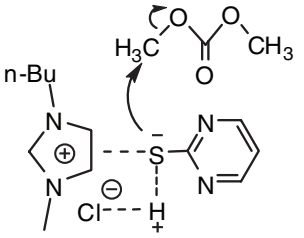
Cycle	1	2	3	4
Isolated yield (%)	76	75	73	71

[a]Reaction conditions: 1d = 10 mmol, DMC = 20 mmol, [Bmim]Cl = 20 mmol, 110°C, 1.5 h.

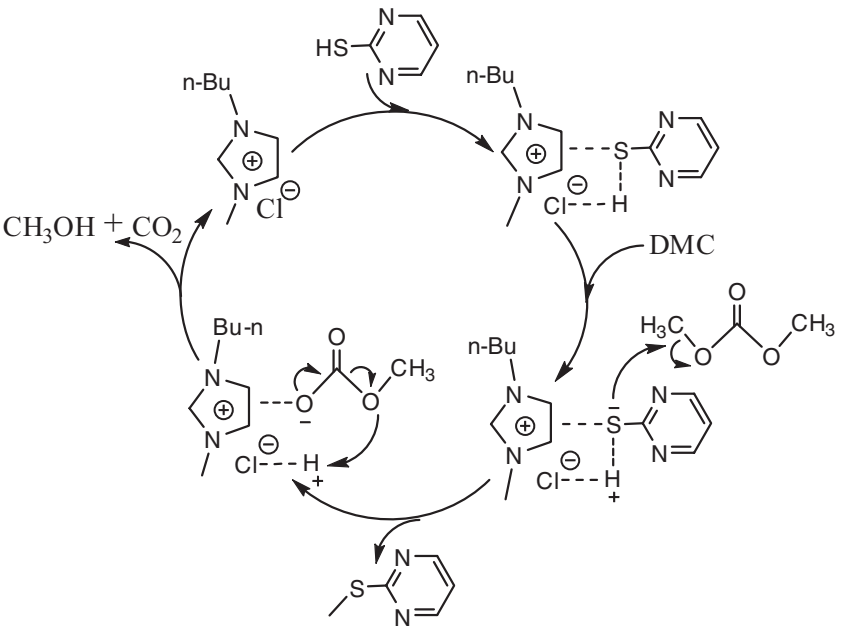
incubation times were required to produce methyl thioethers, and the yields were low. When the reactions did occur at 110°C, methyl thioethers were produced in a short time, and the yields were higher. Clearly temperature is an influencing factor on the yields and reaction times.

We further investigated the recyclability of ionic liquid. The recovery potential of [Bmim]Cl in the reaction of **1d** and DMC was investigated. As shown in Table 3, the ionic liquid was further recycled in four subsequent runs with little decrease in activity. For example, in the fourth run, the yield was still 71%. Even though yields gradually decreased in runs carried out using recovered ionic liquid, the products obtained were of the same purity (∼97.2% base on GC) as in the first run.

To study the possible mechanism relating to this transformation, [Bmim]Br was used as a promoter to the reaction of **1a** with DMC, and **2a** was obtained in 46% yield at 90°C after 3 h. When [Bmim]Cl was used as the promoter, a 77% yield was recorded (Table 1, entries 4 and 9). This implied that the chloride ion may play a key role in this process. Moreover, when Bu_4NCl was used as the promoter, the reaction was slow and gave a low yield (Table 1, entry 12). This implied that the imidazolium cation may also influence this transformation. The change of proton chemical shift of the mercapto group of the pyrimidine was investigated using ^{1}H NMR. It was found that the mercapto group proton of the pyrimidine was shifted downfield from 13.84 ppm to 14.30 ppm in the presence of [Bmim]Cl. The proposed key intermediate relating to this reaction is proposed (Scheme 2). Due to the chloride ion and the imidazolium cation, the hydrogen bond interaction of [Bmim]Cl with the mercapto group may enhance the formation of a complex containing nucleophilic anion (ArS^-).[7] If this occurs, then the nucleophile anion (ArS^-) may attack DMC through the $B_{Al}2$ mechanism to generate the product (Scheme 3).[12]



Scheme 2 Proposed key intermediate for the methylation reaction promoted by [Bmim]Cl.



Scheme 3 Plausible catalytic cycle.

In this study, [Bmim]Cl was shown to be a useful and alternative reaction medium for the synthesis of methyl thioethers from thiols by playing a dual role as both solvent and catalyst. Additional factors make the reaction have notable advantages: (i) [Bmim]Cl and DMC are non toxic; (ii) [Bmim]Cl can be easy recovered and reused; (iii) for heterocyclic thiols, the high yields and good regioselectivity are very attractive. This method indeed provides a less toxic system for the preparation of thioethers from thiols.

EXRERIMENTAL

The General Procedure of S-Methylation of Thiols in Ionic Liquid

Thiols (10 mmol), DMC (20 mmol), and ionic liquid [Bmim]Cl (20 mmol) were added in a 25 mL reaction flask equipped with a magnetic stirrer. The mixture was stirred at 90°C or at 110°C for the time indicated in Table 1 or Table 2. The reaction was monitored by thin-layer chromatography (TLC). After the reaction was completed, the resulting mixture was extracted with diethyl ether (entries 1–5) or ethyl aceate (entries 6–12) (3 × 15 mL). The organic layers were washed with water (10 mL) and were dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the crude product, which was purified by preparative column chromatography (silica gel).

Recovery of the Ionic Liquid

After extraction of the products, the ionic liquid was washed with diethyl ether (10 mL) and was evaporated under reduced pressure at 60°C. Then the residue was dried

under vacuum at 90°C for 4 h, and 96% of the ionic liquid was recovered and reused for subsequent reactions (Table 3).

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