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Ionic-Liquid-Supported 1,3-Dimethylimidazolidin-2-one: Application as a Reusable Halogenation Reagent

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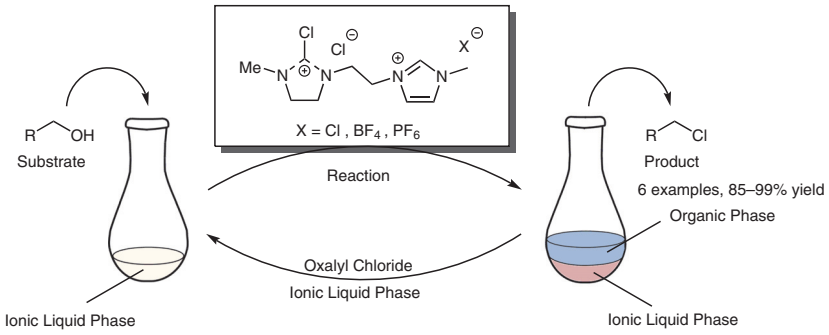

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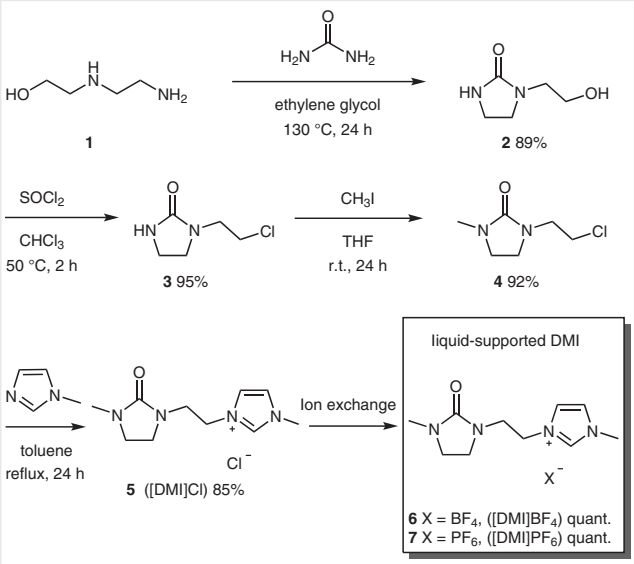
Abstract We describe the synthesis of ionic-liquid-supported 1,3-dimethylimidazolidin-2-one, together with the halogenation of alcohols in a reaction system in which this reagent is combined with oxalyl chloride. A new method was established that does not require additives such as bases, and which permits the ready isolation and purification of the product. Good conversions were obtained, and good reusability of the reagent was observed.

Key words ionic liquid, chlorination, alcohols, dimethylimidazolidinone, supported reagent

1,3-Dimethylimidazolidin-2-one (DMI) is widely used as an aprotic polar solvent.[1] In addition, it has been reported that a compound obtained by polymerization of DMI behaves as a thermoresponsive polymer.[2] Furthermore, 2-chloro-1,3-dimethylimidazolinium chloride (DMC) can be synthesized by treating DMI with oxalyl chloride. DMC is a good halogenation reagent, and it has been reported to be effective in various reactions such as amidation, oxidation, and reduction as well as halogenation. However, when using DMC, it is generally necessary to use a base and to use stoichiometric or superstoichiometric amounts of the reagent, which makes the reuse of DMC difficult.[3] A subsequent synthesis of a polymer-supported DMC and reactions using this material have been reported.[4] However, although this polymer-supported DMC is reported to produce good results, there have been no studies on its recycling; furthermore, because it is difficult to measure the molecular weight of the polymer accurately, an excess of the polymer-supported DMC must be used.[4] To overcome these problems, we investigated the preparation of an ionic-liquid-supported DMI, its subsequent conversion into liquid-supported DMC in situ, and the application of the latter reagent in the halogenation of alcohols.

Ionic liquids have recently attracted the attention of researchers in various fields. The properties of ionic liquids differ from those of other general-purpose solvents. Ionic liquids have several advantages, including thermal conductivity, electrical conductivity, nonvolatility, high polarity, and thermal stability.[5] Various types of ionic liquids have been developed, such as those based on imidazolium salts, pyridinium salts,[6] phosphonium salts,[7] or ammonium salts.[8] We have previously developed an easy-to-use and reusable reaction system by exploiting the advantages of ionic liquids. Specifically, we reported ionic-liquid-carrier catalysts or reagents and a multistep synthesis method using ionic-liquid phases.[9] Here, we report the development of a new reaction system that uses an ionic-liquid-supported DMI and oxalyl chloride as a recyclable reagent for the halogenation of alcohols.

We first synthesized ionic-liquid-supported DMI. 1-(2-Hydroxyethyl)imidazolidin-2-one (**2**) was prepared by cyclocondensation of 2-[(2-aminoethyl)amino]ethanol (**1**) with urea (Scheme 1). Alcohol **1** was then halogenated with thionyl chloride and methylated with iodomethane to give 1-(2-chloroethyl)-3-methylimidazolidin-2-one (**4**). Finally, the methylimidazolium derivative **4** was used to prepare the ionic-liquid-supported DMI with chloride as the counteranion (**5**). Ion exchange was then used to convert **5** into ionic-liquid-supported DMI with BF_4^- and PF_6^- counteranions. (**6** and **7**, respectively). The physical properties of the ionic liquid changed depending on the type of anion. In our previous studies, the reactivity also found to change on changing the anion. Ionic-liquid-supported DMI with the PF_6^- counterion **7** was hydrophobic, whereas the other ionic-liquid-supported DMI derivatives **5** and **6** were hydrophilic.

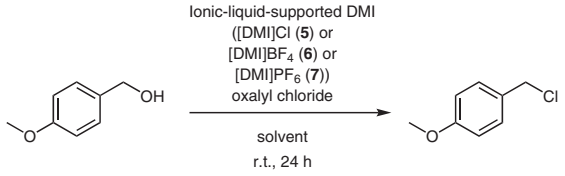


Scheme 1 Synthesis of ionic-liquid-supported DMI

Next, we studied the halogenation of alcohols by using the three ionic-liquid-supported DMI derivatives **5**–**7** and various ionic liquids. The ionic-liquid-supported DMI was converted into the corresponding ionic-liquid-supported DMC in situ by treatment with oxalyl chloride, and halogenation of alcohols by using the resulting reagent was then investigated. (Because ionic-liquid-supported DMC is an unstable compound, it was difficult to isolate it or to characterize its structure.)

The yield varied with the type of ionic-liquid-supported DMI or ionic liquid used in this reaction system. The halogenation of 4-methoxybenzyl alcohol did not proceed in a satisfactory manner, even when the ionic-liquid-supported DMI with a chloride counteranion **5** was used in conjunction with various ionic liquids (Table 1, entries 1–3). On the other hand, the halogenation reaction proceeded well with the ionic-liquid-supported DMI derivatives with BF_4^- and PF_6^- as counterions (**6** and **7**, respectively) in various ionic liquids (Table 1, entries 4 and 5). Furthermore, we found that the optimal amount of oxalyl chloride in this reaction was 2.0 equivalents, and the yield of the target product decreased when 1.0 or 1.5 equivalents of oxalyl chloride with respect to the substrate were used. The reason for this is that it was difficult to completely dehydrate the ionic liquid, and the small amount of residual water present decomposed the oxalyl chloride. Although, in general, bases are necessary for halogenation reactions using DMC, our results surprisingly indicated that a base is not necessary in the present reactions with ionic liquids. The conditions shown in entry 5 confirmed that the reaction proceeds better in a hydrophobic environment: 1-butyl-3-methylimidizazolium hexafluorophosphate ([bmim]PF_6) is a hydrophobic solvent, and the ionic-liquid-supported [DMI]PF_6 reagent **7** is also hydrophobic. After completion of the reaction, the product was successfully extracted in good purity by using diethyl ether. Furthermore, this reaction system can be washed with water. Therefore, the conditions shown in entry 5 were determined to be optimal for this reaction.

Table 1 Investigation of the Halogenation of Alcohol with Three Ionic-Liquid-Supported DMIs in Various Ionic Liquids[a]

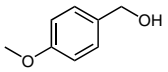
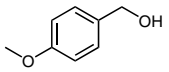
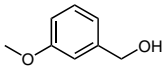
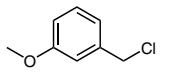
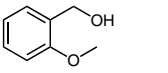
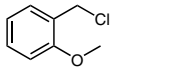
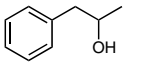
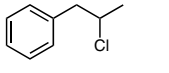
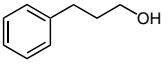
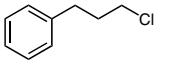
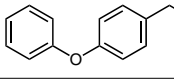
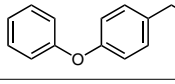


Entry	Solvent[b]	Ionic-liquid-supported DMI	Yield[c] (%)
1	[emim] BF_4	[DMI]Cl (**5**)	8
2	[bmim] BF_4	[DMI]Cl (**5**)	64
3	[bmim] PF_6	[DMI]Cl (**5**)	21
4	[bmim] PF_6	[DMI]BF_4 (**6**)	99
5	[bmim] PF_6	[DMI]PF_6 (**7**)	99

[a] Reagents and conditions: 4-methoxybenzyl alcohol (1.5 mmol), ionic-liquid-supported DMI (2.2 mmol), oxalyl chloride (2.0 mmol), ionic liquid (2 mL), r.t., 24 h.
[b] emim = 1-ethyl-3-methylimidazolium; bmim = 1-butyl-3-methylimidazolium.
[c] Yield of the isolated product.

Next, we investigated the halogenation reactions of various alcohols by using our newly developed halogenation system consisting of hydrophobic ionic-liquid-supported [DMI]PF_6 (**7**) and the hydrophobic ionic liquid [bmim] PF_6.

Table 2 Halogenation of Alcohols by Ionic-Liquid-Supported DMI[a]

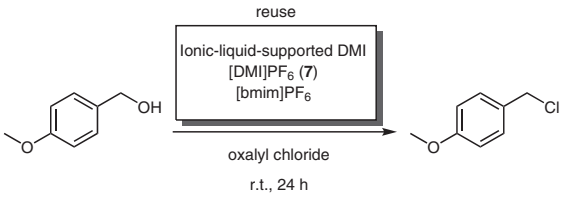
Entry	Alcohol	Product	Yield[b] (%)
1			99
2			82
3			94
4			95
5			95
6			85

[a] Reagents and conditions: alcohol (1.5 mmol), **7** (2.2 mmol), oxalyl chloride (2.0 mmol), [bmim]PF_6 (2 mL), r.t., 24 h.
[b] Yield of the isolated product.

With this system, the halogenation of alcohols proceeded well (Table 2, entries 1–5). However, when the slightly larger alcohol (4-phenoxyphenyl)methanol was used, the yield decreased slightly (entry 6).

Finally, we examined the reuse of this reaction system. Ether was added to the ionic-liquid phase after completion of the reaction to extract the target compound. Then, oxalyl chloride was added to the ionic-liquid phase to convert the ionic-liquid-supported DMI ([DMI] PF_6; **7**) back into ionic-liquid-supported DMC ([DMC]PF_6) in situ. Fresh reagents were then added to the ionic-liquid phase, and the reaction was run again. As mentioned before, the synthesis of this novel ionic-liquid catalyst, the ionic-liquid separation, and the recycling of the product are operationally simple. Excellent conversions were obtained for up to five consecutive cycles of recycling and reuse (Table 3).

Table 3 Recovery and Reuse of the Ionic-Liquid Phase Containing the Ionic-Liquid-Supported DMI[a]



Run	1	2	3	4	5
Yield[b] (%)	93	92	95	97	93

[a] Reagents and conditions: 4-methoxybenzyl alcohol (1.5 mmol), **7** (2.2 mmol), oxalyl chloride (2.0 mmol), [bmim]PF_6 (2 mL), r.t., 24 h.
[b] Yield of the isolated product.

In summary, we synthesized hydrophobic ionic-liquid-supported DMI and demonstrated that it can be used in the halogenation of alcohols.[10] A base is not required in this reaction. After completion of the reaction, purification steps, such as column chromatography, are not required because the product can be extracted. After the reaction, the ionic-liquid reagent can be regenerated by using oxalyl chloride. This system is advantageous because of its environmental friendliness and good yields. Moreover, this reaction system can be reused up to five times.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612413.

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(10) **Chlorination of Alcohols (Table 2); General Procedure**
The solution of ionic-liquid-supported DMI **7** (2.2 mmol) in [bmim]PF_6 (2 mL) was added to oxalyl chloride (2.0 mmol), and the mixture was stirred at 60 °C for 2 h. The mixture was then added to the appropriate alcohol (1.5 mmol), and the resulting mixture was stirred at r.t. overnight. Finally, the mixture was extracted with hexane 10 mL x 3, and the organic layer was concentrated.
1-(2-hydroxyethyl)imidazolidin-2-one (2)
The solution of 2-((2-aminoethyl) amino) ethanol (6.24g, 60mmol) in ethylene glycol (4 ml) was added to ureal (3.60g, 60 ml). The mixture was stirred at 130 °C for 24 h. The mixture extracted with ethyl acetate, and organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated. The product was isolated by silica gel column chromatography to give the title compound **2** (6.94 g, 89%) as white solid; mp 45 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ =3.30–3.77 (9H, m), 5.80 (1H, s). ^{13}C NMR ($CDCl_3$) δ = 38.4, 46.0, 46.3, 60.2, 164.0. HRMS (APCI): m/z [M + H]$^+$ calcd for $C_5H_{11}N_2O_2$, 131.08205; found: 131.08390.
1-(2-chloroethyl)imidazolidin-2-one (3)
The solution of 1-(2-hydroxyethyl) imidazolidin-2-one (5.07g, 39.1mmol) in chloroform (10 ml) was added to thionyl chloride (5.70ml, 78.2mmol). The mixture was stirred at 50 °C for 3 h. The mixture was evaporated, and the product was isolated by silica gel column chromatography to give the title compound **3** (5.50 g, 95%) as white solid; mp 85–88 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.45–3.64 (8H, m), 5.60 (1H, s). ^{13}C NMR ($CDCl_3$) δ = 38.3, 42.5, 45.6, 46.0, 163.0. HRMS (APCI): m/z [M + Na]$^+$ calcd for $C_5H_9ClN_2NaO$, 171.03011; found: 170.03091.

1-(2-chloroethyl)-3-methylimidazolidin-2-one (4)

The solution of 1-(2-chloroethyl) imidazolidin-2-one (4.00g, 26mmol) in THF (56 ml) was added to sodium hydride (1.86g, 45mmol) at 0 °C. And then the mixture was added to iodomethane (3.4ml, 53.8mmol) and stirred at room temperature for 24 h. The mixture extracted with chloroform, and organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated. The product was isolated by silica gel column chromatography to give the title compound **3** (4.03 g, 92%) as yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.80 (3H, s), 3.32–3.63 (8H, m). ^{13}C NMR ($CDCl_3$) δ = 31.2, 42.5, 43.5, 45.0, 46.3, 161.2. HRMS (APCI): m/z $[M + H]^+$ calcd for $C_6H_{12}ClN_2O$, 163.06382; found: 163.06851.

1-methyl-3-(2-(3-methyl-2-oxoimidazolidin-1-yl)ethyl)-1H-imidazol-3-ium chloride (5)

The solution of 1-(2-chloroethyl)-3-methylimidazolidin-2-one (4.00 g, 24.6mmol) in toluene (30 ml) was added to 1-methylimidazole (2.02g, 24.4 ml). The mixture was stirred at 110 °C for 24 h. The mixture was washed with hexane and evaporated to give the title compound **5** (5.11 g, 85%) as yellow liquid. ^{1}H NMR (500 MHz, DMSO): δ = 2.59 (3H, s), 7.13 (1H, s), 3.15–3.88 (6H, m), 3.88 (3H, s), 4.37 (2H, m), 7.77 (1H, s), 7.86 (1H, s), 9.47 (1H, s). ^{13}C NMR ($CDCl_3$) δ = 31.4, 36.2, 42.7, 44.7, 44.9, 47.3, 123.1, 123.9, 137.3, 161.2. HRMS (APCI): m/z $[M]^+$ calcd for $C_{10}H_{17}N_4O$, 209.1402; found: 209.14283.

1-methyl-3-(2-(3-methyl-2-oxoimidazolidin-1-yl)ethyl)-1H-imidazol-3-ium tetrafluoroborate (6)

The solution of 1-methyl-3-(2-(3-methyl-2-oxoimidazolidin-1-yl) ethyl)-1H-imidazol-3-ium chloride (0.54 g, 2.2 mmol) in methanol (2 ml) was added to sodium tetrafluoroborate (0.24 g, 2.2 mmol). The mixture was stirred at room temperature for 24 h. The mixture was filtered and evaporated to give the title compound **6** (0.65 g, quant.) as yellow liquid.^{1}H NMR (500 MHz, DMSO): δ = 2.60(3H, s), 3.24–3.28(4H, m), 3.47(2H, t, *J*=6), 3.85(3H, s), 4.30(2H, t, *J*=6), 7.68(1H, s), 7.75(1H, s), 9.10(1H, s). ^{13}C-NMR(125 MHz, DMSO): δ =31.4, 36.2, 42.7, 44.7, 44.9, 47.4, 123.1, 123.9, 137.2, 161.3. HRMS (APCI): m/z $[M]^+$ calcd for $C_{10}H_{17}N_4O$, 209.1402; found: 209.13960.

1-methyl-3-(2-(3-methyl-2-oxoimidazolidin-1-yl)ethyl)-1H-imidazol-3-ium hexafluorophosphate (7) The solution of 1-methyl-3-(2-(3-methyl-2-oxoimidazolidin-1-yl) ethyl)-1H-imidazol-3-ium chloride (0.75 g, 3.0 mmol) in methanol (2 ml) was added to potassium hexafluorophosphate (0.55 g, 3.0 mmol). The mixture was stirred at room temperature for 24 h. The mixture was filtered and evaporated to give the title compound **7** (1.06 g, quant.) as white solid. mp 85–102 °C.^{1}H NMR (500 MHz, DMSO): δ = 2.60 (3H, s), 3.22–3.30 (4H, m), 3.47 (2H, t, *J*=6), 3.85 (3H, s), 4.29 (2H, t, *J*=6), 7.68 (1H, s), 7.75 (1H, s), 9.10 (1H, s). ^{13}C-NMR (125 MHz, DMSO): δ =31.4, 36.2, 42.7, 44.7, 44.9, 47.4, 123.1, 123.9, 137.3, 161.3. HRMS (APCI): m/z $[M]^+$ calcd for $C_{10}H_{17}N_4O$, 209.1402; found: 209.13975.