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An efficient and chemoselective deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers using tailor-made ionic liquid

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ABSTRACT

Phenolic *tert*-butyldimethylsilyl (TBDMS) ethers can be deprotected to yield phenols in excellent yield using tailor-made ionic liquid [dihexaEGim][OMs] (dihexaEGim = dihexaethylene glycolic imidazolium salt) as an organic catalyst with alkali-metal fluoride in *tert*-amyl alcohol. On the contrary, all TBDMS protecting groups can be cleaved cleanly from the bis-TBDMS ether using the same reaction in CH_3CN solvent instead of *tert*-alcohol at 100 °C. This [dihexaEGim][OMs]/*tert*-amyl alcohol media system allows the highly selective phenolic deprotection reaction of various bis-TBDMS ethers containing both phenolic and aliphatic TBDMS ethers to provide the corresponding phenols in high yield.

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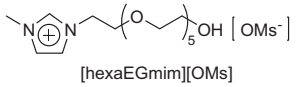
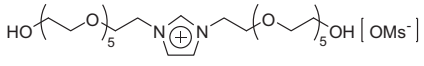
The selective removal of a protecting group is one of the most important and widely used synthetic transformations for the multistep syntheses of complex targeting molecules.[1] The *tert*-butyldimethylsilyl (TBDMS) group has occupied a privileged position in organic synthesis chemistry as a protecting group for alcohols and phenols because of the ease of protecting and deprotecting, its good stability under various reaction conditions.[2] Significant research in silylation chemistry has resulted in the development of various types of desilylation reactions. It is well-known that the deprotection reaction of TBDMS ethers to alcohols using tetrabutylammonium fluoride (TBAF) in THF has been used commonly for the removal of TBDMS. However, TBAF can lead to side reactions due to its strong basicity, and restrict the wide application of this reagent for this purpose.[3] Thus, numerous alternative methods such as (Lewis) acid/based media protocols,[4,5] halide-source protocols (in particular fluoride),[6] and reductive protocols[7] have been developed for the deprotection of silyl ethers. Although there are only a few reports about the selective deprotection reaction of phenolic TBDMS ethers in the presence of aliphatic TBDMS ethers using mild basic media protocols such as K_2CO_3/aqueous EtOH,[8a] Cs_2CO_3/DMF-H_2O,[8b] NaOH/Bu_4NHSO_4,[8c] some of these protocols have synthetic limitations such as a long reaction time, a troublesome aqueous work-up, or a low efficiency. Therefore, the selective cleavage of phenolic TBDMS ethers is still a challenging task.

Due to their unique chemical and physical properties, ionic liquids have played a crucial role in the field of chemistry as an eco-friendly alternative to replace volatile organic solvents.[9] In particular, imidazolium based ionic liquids as a phase-transfer type promoter or catalyst show good performance in the nucleophilic substitution reactions using alkali-metal salts.[10] Recently, we reported tailor-made ionic liquids—hexaethylene glycolic imidazolium salts ([hexaEGmim][OMs] and [dihexaEGim][OMs]) as organic catalysts designed for nucleophilic fluorination with alkali-metal fluorides (Fig. 1). These ionic liquids could generate a low basic fluoride source ('flexible' fluoride[11]) efficiently from alkali-metal fluoride in *tert*-alcohol medium.[12] In this Letter, we introduce the facile chemoselective cleavage of phenolic TBDMS ether in the presence of alkyl TBDMS ether with alkali-metal fluoride, such as KF and CsF, using tailor-made ionic liquid [hexaEGmim][OMs] and [dihexaEGim][OMs] as catalysts.



[hexaEGmim][OMs]



[dihexaEGim][OMs]

Figure 1. Hexaethylene glycolic imidazolium salts; [hexaEGmim][OMs] and [dihexaEGim][OMs] (hexaEGmin = 1-hexaethylene glycolic 3-methylimidazolium cation; dihexaEGim = 1,3-dihexaethylene glycolic imidazolium cation).

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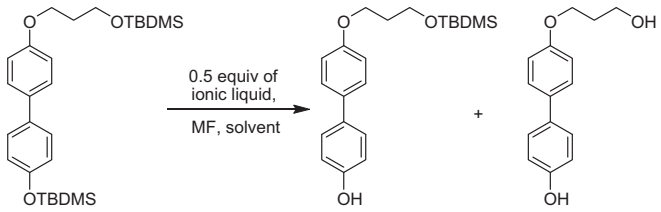
Table 1
Desilylation of bis-TBDMS ether **1**[a]

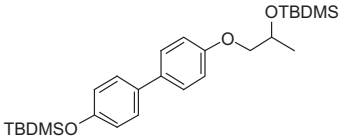
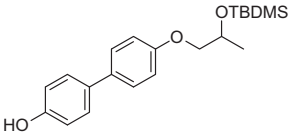
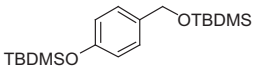
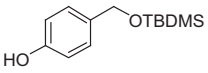
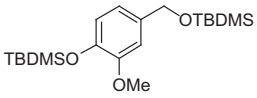
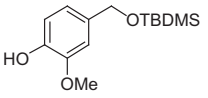
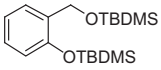
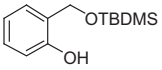
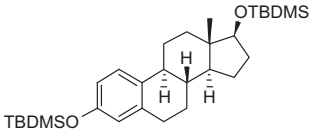
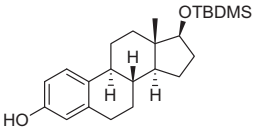
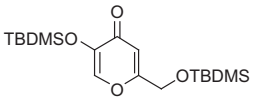
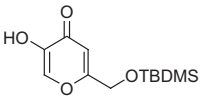
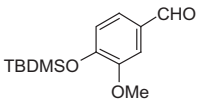
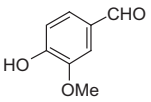


1 **2** **3**

Entry	Ionic liquid (0.5 equiv)	MF	Time (h)	Temp (°C)	Solvent	Yield[b] (%)	
						2	**3**
1	—	CsF	5	70	*t*-Amyl alcohol	76[c]	24[c]
2	—	TBAF	10 (min)	25	THF	—	96
3	$BF_3{\cdot}Et_2O$	—	5	25	CH_2Cl_2	—	95
4	[Hexaegmim][OMs]	CsF	1	70	*t*-Amyl alcohol	93	6[c]
5	[Dihexaegim][OMs]	CsF	40 (min)	70	*t*-amyl alcohol	97	Trace
6	[Dihexaegim][OMs]	CsF	1	70	CH_3CN	71[c]	29[c]
7	[Dihexaegim][OMs]	CsF	1	100	CH_3CN	—	98
8	[Dihexaegim][OMs]	KF	2	70	*t*-Amyl alcohol	93	5[c]

[a] All reactions were carried out on a 1.0 mmol reaction scale of bis-TBDMS ether **1** using 3 mmol of CsF in 4.0 mL of solvent at the mentioned reaction temperature.
[b] Isolated yields.
[c] Yields were determined by ^1H NMR spectroscopy.

Table 2
Selective phenolic deprotection of various substrates with CsF using [dihexaEGim][OMs] in *tert*-amyl alcohol[a]

Entry	Substrate	Product	Time (min)	Yield[b] (%)
1			40	96
2			20	94
3			15	95
4			20	94
5			30	97
6			15	90
7			15	96

[a] All reactions were carried out on a 1.0 mmol scale of substrate with 3.0 equiv of CsF and 0.5 equiv of [dihexaEGim][OMs] in 4.0 mL of *t*-amyl alcohol at 70 °C.
[b] Isolated yields.

Table 1 illustrates the desilylation reactions of bis-TBDMS ether **1** containing both phenolic and aliphatic TBDMS ethers as a model compound under various reaction conditions. Initially, considering the previous results of the highly efficient *tert*-alcohol media system in fluorination using alkali-metal fluoride, we attempted to perform the desilylation of bis-TBDMS ether **1** with CsF in *tert*-amyl alcohol solvent, and this CsF/*tert*-alcohol media system showed a relatively good chemoselective cleavage of phenolic TBDMS ether moiety in the bis-TBDMS ether **1**, providing the phenol compound **2** in a 76% yield with 24% of diol **3** (entry 1), compared with the same deprotection reactions using conventional methods such as TBAF/THF and $BF_3{\cdot}Et_2O$ (entries 2 and 3, respectively). Surprisingly, a comparison of entries 1 and 4 demonstrates that the use of catalytic amount (0.5 equiv) of a tailor-made ionic

liquid [hexaEGmim][OMs] could increase both the reaction rate and the chemoselectivity significantly in this deprotection reaction, affording the phenol product **2** in a 93% yield with only 6% of the diol **3**. Moreover, the deprotection reaction using [dihexaEGim][OMs] containing two hydroxyl components could remove only the TBDMS group of the phenolic position in the bis-TBDMS ether **1** within 40 min, providing phenol **2** in nearly quantitative yield (97%, entry 5).[13] However, the same reaction in CH_3CN solvent instead of *tert*-alcohol showed a relatively low chemoselectivity and afforded phenol **2** in a 71% yield together with diol **3** in a 29% yield (entry 6). In addition, at 100 °C, only the diol compound **3** could be obtained nearly quantitatively (entry 7). These results suggest that the tailor-made ionic liquid [hexaEGmim][OMs] and [dihexaEGim][OMs] can generate the activated fluoride from alkali-metal fluoride such as CsF efficiently by phase-transfer effect, thereby increasing the reaction rate, and also the protic atmosphere from both *tert*-alcohol media and hydroxyl group of these ionic liquids (in particular, two hydroxyl group of [dihexaEGim][OMs]) can reduce the basicity of the activated fluoride, thereby enhancing the chemoselectivity of the phenolic desilylation reaction in the presence of aliphatic silyl ethers. Entry 8 shows that, when using KF as the fluoride source, the selective phenolic desilylation reaction also proceeded smoothly, affording phenol **2** in good yield.

Table 2 shows the selective phenolic desilylation of various bis-TBDMS ethers with CsF using 0.5 equiv of [dihexaEGim][OMs] catalyst in *tert*-amyl alcohol. This protocol allowed the selective deprotection of the phenolic TBDMS ether in the presence of various sec-alkyl or benzylic TBDMS ethers to proceed nearby quantitatively in a series of bis-TBDMS ether substrates (entries 1–4). In entry 5, the monosilylated estradiol[14] was obtained in a 97% yield by this selective phenolic desilylation reaction. Entry 6 shows that the aryl-TBDMS ether component of Kojic acid[15] in the presence of alkyl TBDMS ether could be cleaved by this deprotection method to generate mono-silylated Kojic acid in a 90% yield. Finally, a TBDMS group attached on the vanillin was successfully removed without the loss of aldehyde functionality (96%, entry 7).

In summary, we have developed an efficient method for the selective deprotection of TBDMS-protected phenols in the presence of TBDMS-protected alkyl alcohols with alkali-metal fluoride using tailor-made ionic liquids ([dihexaEGim][OMs]) in *tert*-alcohol. This [dihexaEGim][OMs]/*tert*-alcohol media system can enhance the reaction rate as well as the selectivity of the phenolic deprotection reaction using CsF significantly. Moreover, this protocol was very useful to synthesize various mono-silylated compounds.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterization data of all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.016.

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13. *Typical Procedure of selective deprotection of phenolic TBDMS-ether (Entry 5 in* Table 1*)*: CsF (456 mg, 3 mmol) was added to the mixture of *tert*-butyl(3-(4′-(*tert*-butyldimethylsilyloxy)biphenyl-4-yloxy)propoxy)dimethylsilane (**1**) (473 mg, 1.0 mmol), [dihexaEGmim][OMs] (346 mg, 0.5 mmol) and *t*-amyl alcohol (4 L) in reaction vial. The reaction mixture was stirred over 40 in at 70 °C. We determined the reaction time by checking TLC. The reaction mixture was filtered and washed with diethyl ether. The filtrate was evaporated under reduced pressure. Flash column chromatography (5% EtOAc/hexanes) of the filtrate afforded 347 g (0.97 mol, 97%) of 4′-(3-*tert*-butyldimethylsilyloxy)propoxy)biphenyl-4-ol (**2**).
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