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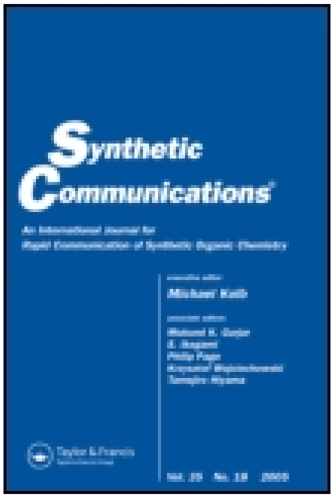

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An Effective Approach for the Silylation of Hydroxyl Compounds in Room Temperature Ionic Liquids

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ABSTRACT

The room temperature ionic liquid (RTIL) 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ($BMImPF_6$) is used as a "green" recyclable alternative to conventional solvents for the silylation of a series of hydroxyl compounds (alcohols and phenols) with *t*-butyldimethylchlorosilane (TBDMCS), which has some advantages such as simplicity of the synthetic procedure, the potential for recycling of the ionic liquid and the environmentally benign.

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Key Words: Room temperature ionic liquid; Silylation; Hydroxyl compound.

Since it was first reported by Corey and Venkatesxarlu in 1972,[1] the *t*-butyldimethylsilyl (TBDMS) group has become one of the most widely used protecting groups for alcohols and phenols, because TBDMS ethers are easily formed with a variety of reagents, readily removed and are quite stable for a number of reactions, such as Wittig reaction, Grignard reaction, Jones reaction, and Saponefication with aqueous of alcoholic bases.[2] The more common method for the formation of TBDMS ethers generally utilizes an excess of *t*-butyldimethylchlorosilane (TBDMCS) with hydroxyl compounds in the solvent, such as DMF, THF, or acetonitrile, containing imidazole. Isolation of the silylated compound is performed by aqueous extraction to remove the solvent and imidazole, followed by crystallization or distillation of the *t*-butyldimethylsilylated product. For many compounds possessing hydroxyl groups, the TBDMCS/imidazole/DMF method produces corresponding TBDMS ethers in high yields, but the time required for each reaction may vary from 1 h to 2 days, or may require elevated temperatures. More importantly, because isolation of the silylated product requires aqueous work-up, the crude product always contains *t*-butyldimethylsilanol among other impurities which leads to difficulty to get pure product and, especially, the organic solvent (DMF) is difficult to recover which causes environmental pollution.

Our recent interest has been in the area of "green chemistry", so the green modification of the traditional chemical process has become a part of our research field. Recently, the versatile applications of room temperature ionic liquids (RTILs) in organic synthesis[3] stimulate us to quest for new synthetic applications of RTILs. The favorable effect of polar solvents on the silylation[2] encourages us to find the feasibility to proceed this kind of silylation in RTILs. In this study, we explored the silylation of TBDMCS with different kinds of alcohols and phenols in RTILs in the presence of imidazole. The RTILs used here were 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$), 1-ethyl-3-methylimidazolium tetrafluoroborate ($EMImBF_4$), *N*-*n*-butylpyridium tetrafluoroborate ($BPyBF_4$) and 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ($BMImPF_6$), which were prepared according to the procedures described in Lit.[4] respectively.

First, we examined the efficiency of different RTILs in the silylation of *n*-butyl alcohol (**1a**), TBDMCS (**2**), and imidazole (Sch. 1). The result is summarized in Table 1. As can be seen from Table 1, all of the RTILs

$$\text{n-C}_4\text{H}_9\text{OH} + t\text{-BuMe}_2\text{SiCl} \xrightarrow[\text{0.5h}]{\text{RTIL, Im}} \text{n-C}_4\text{H}_9\text{OSi-}t\text{-BuMe}_2$$

1a **2** **3a**

Scheme 1.

Table 1. Silylation of *n*-butyl alcohol with TBDMCS in RTIL.[a]

Entry	RTIL	Yield[b] (%)	Purity[c] (%)
1	BMImPF_6	94	98.0
2	BMImBF_4	93	98.5
3	EMImBF_4	95	98.6
4	BPyBF_4	92	98.2

[a] All the reactions were run with *n*-butyl alcohol (5 mmol), TBDMCS (6 mmol) in 2 g RTIL in the presence of imidazole (12 mmol) for 0.5 h at room temperature.
[b] Isolated yield for crude product.
[c] Crude product was analyzed by GC.

tested are effective for the silylation. We considered that BMImPF_6 might be the most favorable choice because of two reasons. On the one hand, a clear two layer formed quickly after reaction and the product can be easily separated from the reaction mixture by simple decanting or suction with a syringe. On the other hand, BMImPF_6 is insoluble in water, so a relative pure RTIL can be recovered by washing with water followed by vacuum drying.

Then, the silylation of a series of alcohols and phenols (**1**) with TBDMCS (**2**) in BMImPF_6 were investigated (Sch. 2). Simple stirring of a mixture of an alcohol or phenol, TBDMCS, imidazole in BMImPF_6 under a N_2 atmosphere at room temperature gave, after isolation, the desired silylated compound. The results are summarized in Table 2. The products were characterized by IR, ^{1}H NMR, and MS, which were consistent with the literature data. For the comparison with literature reported methods, some compared results are also summarized in Table 2.

The method was found to be general and applicable to primary and secondary alcohols (Entries 1–6) even to sterically hindered alcohol, e.g., diphenylmethanol (Entry 4) can be silylated smoothly by this method. But when we select a *tert*-alcohol, the reaction is so sluggish that we cannot get a pure product even after a long period of time. As for phenols, although the reaction speed is a little slower than that of alcohols,

$$\underset{\mathbf{1}}{R(OH)_n} + n\ \underset{\mathbf{2}}{t\text{-}BuMe_2SiCl} \xrightarrow[\text{0.5-2hours}]{BMImPF_6,\ Im} \underset{\mathbf{3}}{R(OSi\text{-}t\text{-}BuMe_2)_n}$$

Scheme 2.

Table 2. Silylation of alcohols and phenols with TBDMCS in $BMImPF_6$.

Entry	Substrate	Product	Time (h)	Purity (%)[a]	Yield (%)[b]	Yield in Lit. (%)
1	n-C_4H_9OH	**3a**	0.5	98	94	
2	$C_6H_5CH{=}CHCH_2OH$	**3b**	0.5	98	96	88[5][c]
3	*cyclo*-$C_6H_{11}OH$	**3c**	2	97	96	90,[5] 95[6][d]
4	$(C_6H_5)_2CHOH$	**3d**	1	99	97	98[7][e]
5	$C(CH_2OH)_4$	**3e**	1	99	96	
6	$C_6H_5CH_2OH$	**3f**	0.5	99	99	80[5]93[7]89[8][f]
7	C_6H_5OH	**3g**	2	94	95	92[7]
8	p-$NO_2C_6H_4OH$	**3h**	2	99	90	
9	o-ClC_6H_4OH	**3i**	2	97	92	
10	p-$AcOC_6H_4OH$	**3j**	2	98	93	
11	p-MeC_6H_4OH	**3k**	2	97	97	
12	m-MeC_6H_4OH	**3l**	2	97	97	
13	o-MeC_6H_4OH	**3m**	2	97	98	
14	p-$C_6H_4(OH)_2$	**3n**	2	99	94	92[7]
15	m-$C_6H_4(OH)_2$	**3o**	2	98	93	
16	4-Me-2,6-$Br_2C_6H_2OH$	**3p**	2	96	92	
17	Naphthyl-2-OH	**3q**	1	98	99	

[a] Purity was analyzed by GC.

[b] Isolated yield.

[c] TBDMCS (10 mmol), alcohol (5 mmol), lithium sulfide (7.5 mmol) in acetonitrile, 5–6 h.

[d] Cyclohexanol with allyl-*t*-butyldimethylsilane at 70–80°C for 2.5 h.

[e] TBDMCS (2.22 mmol), DBU (2.40 mmol), C_6H_6 (4 mL), substrate (2.00 mmol) at room temperature for 3 h.

[f] TBDMCS (1.1 equiv.), triethylamine (1.2 equiv.), DMAP (0.04 equiv.) in CH_2Cl_2, 25°C.

phenols containing various substituents such as nitro, chloro, acetyl, and methyl groups were successfully reacted. The compounds possessing several hydroxyl groups, such as pentaerythritol (Entry 5), hydroquinone (Entry 14), and resorcinol (Entry 15) can be completely silylated when excess of TBDMCS used. Also as can be seen from Table 2 (Entries 2, 3, 4, 6, 7, 14) that in comparison with literature reported methods, present method gives significant rate acceleration and sound yield.

The $BMImPF_6$ can be readily recovered and reused. Usually, after isolation of the silylated product by decantation or extraction with ethyl ether, the left $BMImPF_6$ layer can be recycled without further disposal. And after several times of recycle, the $BMImPF_6$ was washed with water and followed by vacuum drying. The recovered solvent can be recycled with no appreciable decrease in yield.

In summary, we have demonstrated that the room temperature ionic liquid $BMImPF_6$ is surely an alternative to classical molecular solvents for the silylation of hydroxyl group with TBDMCS in the presence of imidazole. It can offer good yields in mild conditions within limited time. The products can be easily separated from reaction mixture by simple decanting or extraction. Due to the simplicity of the synthetic procedure, the potential for recycling of the ionic liquid and the benignity to environment, present method may be more useful in organic synthesis. Further investigation is still under way in our lab.

EXPERIMENTAL SECTION

All starting materials were commercially available and without further purification. The room temperature ionic liquid was dried at 120°C in vacuum for at least 4 h before use. Melting point was detected on a b type melting point detector (uncorrected). Infrared and ^1H NMR spectra were obtained on Bruker Equinox 55 and Bruker Avance 500 ($CDCl_3$, TMS as internal standard) spectrometers. Mass spectrometry spectra were recorded on a Varian CP 3800/Saturn 2000 GC/MS spectrometer. The purity of the products was detected on a ShangFen GC spectrometer (capillary column, column temperature 210°C).

Typical Procedure for Compound 3a

n-Butyl alcohol (0.74 g, 10 mmol) was treated under a N_2 atmosphere with TBDMCS (1.80 g, 12 mmol), imidazole (1.63 g, 24 mmol) and $BMImPF_6$ (4 g) at room temperature. The stirring was continued till all the substrate was converted by GC detection. After completion of reaction, two layers formed and the upper clear layer was separated by either decanting or sucking with a syringe, washed with (2 × 10 mL) distilled water and got the crude product as a colorless liquid (1.79 g, purity 98.0%, yield 94.0%). A more pure sample was obtained by distilling the crude product under reduced pressure. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.6 (t, $J = 6.5$ Hz, 2H, CH_2O), 1.50 (m, 2H, CH_2), 1.34 (m, 2H, CH_2), 0.91 (t, $J = 6.5$ Hz, 3H, CH_3), 0.89 (s, 9H, Me_3C), 0.05 (s, 6H, Me_2Si). IR (film): 2956, 2861, 1256, 1041, 836, 783 cm^{-1}. MS (m/z): 189 ($M + 1$, trace), 173 (trace), 131 (100), 89 (25), 75 (67). The left ionic liquid layer can be recycled without further disposal. And after several times of recycle, the ionic liquid layer was washed with water (3 × 10 mL) and then evaporated to remove the water under reduced pressure, the left ionic liquid can be reused for another several times without apparent effect on yield.

Typical Procedure for Compound 3j

Under the protection of nitrogen atmosphere, *p*-acetylphenol (1.36 g, 10 mmol), TBDMCS (1.80 g, 12 mmol), imidazole (1.63 g, 24 mmol), and $BMImPF_6$ (4 g) were charged successively into a 20 mL round-bottomed flask with mechanical stirrer. The reaction process was monitored by thin layer chromatography (TLC, silica 254, elutent, hexane:ethyl acetate, 2:1) at regular intervals. After completion of the reaction, the mixture was extracted with (3 × 10 mL) ether and then the combined ethereal phase was washed with (3 × 10 mL) pure water, dried over anhydrous $CaCl_2$ for 1 h, evaporated to remove the solvent got the desired product (2.33 g, purity 98.0%, yield 93%). A more pure product can be obtained by crystallization from minimum amount of ethanol. Melting point: 34–36°C. ^{1}H NMR δ: 7.88 (d, $J = 8.7$ Hz, 2H, H_3H_5), 6.87 (d, $J = 8.7$Hz, 2H, H_2H_6), 2.55 (s, 3H, CH_3CO), 0.99 (s, 9H, Me_3C), 0.23 (s, 6H, $(CH_3)_2Si$). IR: 3077, 2936, 2859, 1647, 1597, 1505, 1257, 913, 842 cm^{-1}. MS (m/z): 250 ($M + 1$, 48), 235 (5), 193 (100), 179 (7), 151 (49), 133 (11), 91 (5).

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