Indium Tribromide: An Efficient Catalyst for the Silylation of Hydroxy Groups by the Activation of Hexamethyldisilazane[1]

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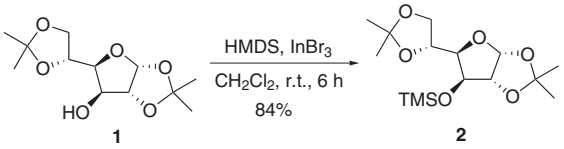
Abstract: A variety of substrates containing hydroxy groups have been protected as their corresponding trimethylsilyl ethers using 1,1,1,3,3,3-hexamethyldisilazane in the presence of indium tribromide. The catalyst indium tribromide activates the 1,1,1,3,3,3-hexamethyldisilazane and accelerates the reaction under mild reaction conditions at room temperature.

Keywords: indium tribromide, 1,1,1,3,3,3-hexamethyldisilazane, protection, hydroxy group, silylation

In the postgenomic age, a premium has been placed on versatile, complexity-generating reactions in which a multitude of natural products, drugs, and lead-like compounds can be rapidly assembled and funneled into biological screening programmes.[2] Furthermore, the ability of chemists to optimize newly discovered lead compounds, as well as to produce analogues or mimics of biologically active natural products, relies upon the advancement of current synthetic technologies. Total synthesis of these compounds necessarily involves the protection and deprotection of a variety of functional groups. Of these, the hydroxy group is familiar and its protection as its silyl ether[3] is most frequently used. Generally, the formation of silyl ethers is carried out by the treatment of alcohols with silyl chlorides or silyl triflates under basic conditions.[4] However, some of these methods frequently suffer from drawbacks, such as lack of reactivity or difficulty in removing the amine salts derived from the reaction of byproduct acids and co-bases during the silylation reaction. Over the course of several decades, a wide variety of methods using 1,1,1,3,3,3-hexamethyldisilazane (HMDS) as a silylating agent have been developed.[5] 1,1,1,3,3,3-Hexamethyldisilazane is a stable, commercially available, and inexpensive reagent that is used for the trimethylsilylation of hydrogen-labile substrates, giving ammonia as the sole byproduct. Silylation using this type of disilazane reagent is nearly neutral and does not require special precautions. Even though the handling of this reagent is easy, its main drawback is its poor silylating power; it needs forceful conditions and long reaction times.[6] Therefore, to circumvent these problems, considerable attention has been focused on the activation of 1,1,1,3,3,3-hexamethyldisilazane by using a variety of catalysts.[7] Lewis acids have been found to catalyze this reaction under mild reaction conditions[8] and recently indium halides have emerged as mild and water-tolerant Lewis acids, particularly showing regio-, stereo-, and chemoselectivity in various organic transformations.[9]

Compared to conventional Lewis acids, indium tribromide has the advantages of low catalyst loading and moisture stability. We are especially interested in exploring the potential use of indium tribromide for various organic transformations[10] due to its mild and neutral nature. As part of our ongoing program for the development of new synthetic methodologies,[11] we wish to report herein an efficient procedure for the rapid trimethylsilylation of a wide variety of alcohols using 1,1,1,3,3,3-hexamethyldisilazane and a catalytic amount of indium tribromide as shown in Scheme 1.



Scheme 1

For example, treatment of glucose diacetonide **1** with 1,1,1,3,3,3-hexamethyldisilazane in the presence of indium tribromide (5 mol%) at room temperature affords the corresponding trimethylsilyl ether **2** (Scheme 1) in 84% yield without affecting the acetonide groups. The product **2** was very clean by ^{1}H NMR and did not require further purification. In a similar fashion, a wide range of structurally diverse and functionalized alcohols, such as primary, secondary, benzylic, phenolic, allylic, and tertiary alcohols underwent smooth reaction with 1,1,1,3,3,3-hexamethyldisilazane/indium tribromide to give the corresponding silyl ether derivatives in excellent yields (Table 1). Phenolic and benzylic alcohols reacted little faster than aliphatic alcohols (entries 1, 5, 6, 8, 14, and 15). The acid-sensitive Baylis–Hillman alcohol (entry 17) was converted into the corresponding trimethylsilyl ether derivative **19** without forming any side products. This protocol has been used successfully where the acid-sensitive protecting groups like tetrahydropyranyl ethers and *tert*-butoxycarbonyl esters were present (entries 10, 11, and 18). In such cases the reactions were very clean and did not yield any products from the deprotection of existing groups.

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Table 1 Indium Tribromide Catalyzed Silylation of Alcohols by Activation of 1,1,1,3,3,3-Hexamethyldisilazane

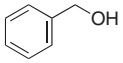
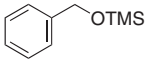
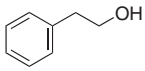
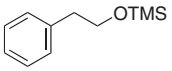
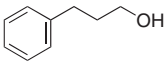
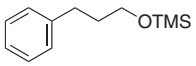
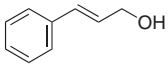
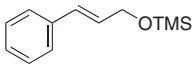
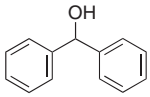
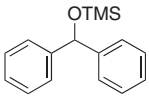
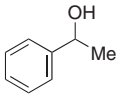
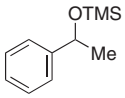
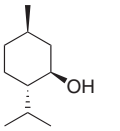
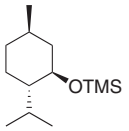
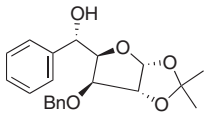
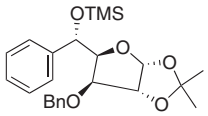
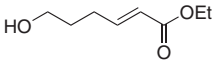
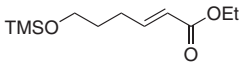
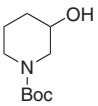
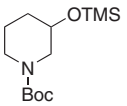
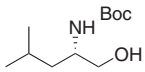
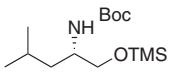
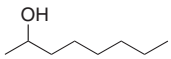
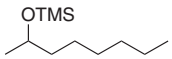
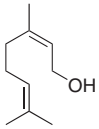
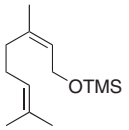
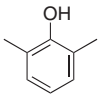
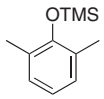
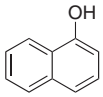
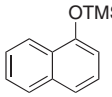
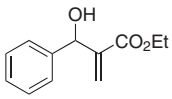
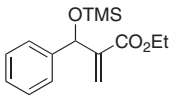
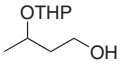
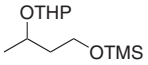
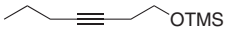
Entry	Substrate	Products[a]		Time (h)	Yield[b] (%)
1			**3**	4.0	89
2			**4**	4.5	86
3			**5**	5.0	84
4			**6**	4.0	81
5			**7**	4.5	92
6			**8**	4.0	93
7			**9**	6.0	86
8			**10**	5.0	89
9			**11**	6.0	89
10			**12**	4.5	90
11			**13**	4.5	86
12			**14**	6.0	89
13			**15**	5.0	82
14			**16**	4.5	92
15			**17**	4.0	94
16			**18**	6.0	80
17			**19**	4.5	88

Table 1 Indium Tribromide Catalyzed Silylation of Alcohols by Activation of 1,1,1,3,3,3-Hexamethyldisilazane (continued)

Entry	Substrate	Products[a]		Time (h)	Yield[b] (%)
18			**20**	5.0	82
19			**21**	5.5	86

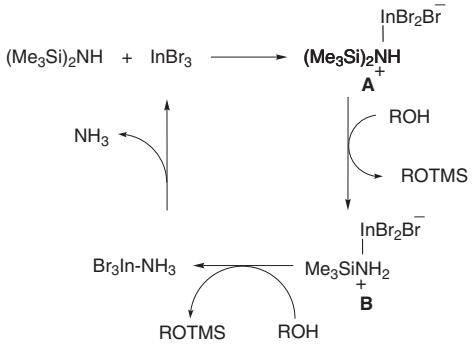
[a] All products were characterized by ^{1}H NMR, IR, and MS and compared with literature reports.
[b] Isolated and unoptimized yield.

The sterically hindered alcohols (Table 1, entries 7, 8, and 16 and Scheme 1, **1**) also reacted very smoothly while giving the products **9**, **10**, **18**, and **2** in very good yields. In the case of *N*-*tert*-butoxycarbonyl amino alcohols (entry 11) the reaction is comparatively faster (4.5 h) and gave the corresponding product **13** in very good yield. The substrates like cinnamyl alcohol (entry 4) and hept-3-yn-1-ol (entry 19) also underwent smooth conversion. In general, the reactions were carried out at room temperature and the solvent used was dichloromethane. All the reactions were completed within 4–6 hours and the obtained yields were in the range 80–94%.

The probable mechanism (Scheme 2) shows that the indium tribromide initially forms a complex **A** with 1,1,1,3,3,3-hexamethyldisilazane. This complex **A** will polarize the Si–N bond to produce the reactive silylating agent, which on reaction with one mole of alcohol gives the corresponding silyl ether derivative. In a similar manner, complex **B** is formed with the catalyst and a second trimethylsilyl group reacts with a mole of alcohol to give the corresponding silyl ether derivative. The mechanism clearly shows that one mole of 1,1,1,3,3,3-hexamethyldisilazane reacts with two moles of alcohol. Finally, the indium tribromide–ammonia complex evolves of gaseous ammonia and gives the indium tribromide catalyst, which recycles (Scheme 2).

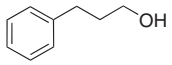
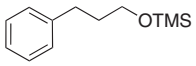
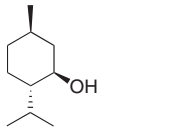
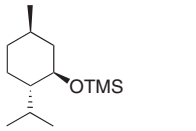
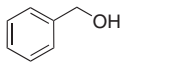
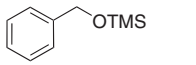
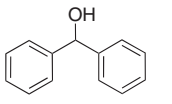
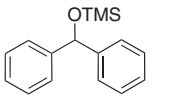
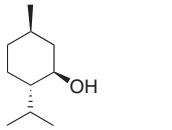
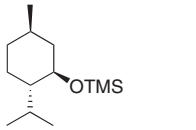
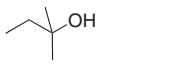
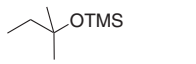
The selectivity and versatility of the reaction was further confirmed by application of the general procedure to various examples (Table 2), in the first of which a mixture of 3-phenylpropan-1-ol (1 mmol) and menthol (1 mmol) was treated with 1,1,1,3,3,3-hexamethyldisilazane (0.7 mmol) in presence of the catalyst (entry 1). The reaction mixture was stirred for a period of two hours and after this time it was found that 85% of 3-phenylpropan-1-ol and 15% of menthol had been converted into their respective silyl ether derivatives. In the second example, a mixture of benzyl alcohol (1 mmol) and diphenylmethanol (1 mmol) was treated with 1,1,1,3,3,3-hexamethyldisilazane (0.7 mmol), in the presence of the catalyst, for a period of three hours; in this case 90% of benzyl alcohol and 10% of diphenylmethanol were converted into their respective silyl ether derivatives (entry 2). In the third example, an equimolar mixture of menthol and *tert*-pentyl alcohol was treated with 1,1,1,3,3,3-hexamethyldisilazane (0.7 mmol) and the catalyst for a period of four hours, but only menthol was protected as its silyl ether and *tert*-pentyl alcohol was unaffected. The above selectivity study shows that the reactivity order is primary > secondary > benzylic > tertiary alcohol.

In summary, we have found that indium tribromide is a mild and efficient catalyst for the activation of 1,1,1,3,3,3-hexamethyldisilazane in the silylation of hydroxy groups.



Scheme 2

Table 2 Comparative Study of the Silylation of Alcohols Using 1,1,1,3,3,3-Hexamethyldisilazane/Indium Tribromide

Entry	Alcohols	Products	Time (h)	Conversion (%)
1			2	85
				15
2			3	90
				10
3			4	100
				0

This method is applicable to a wide range of alcohols containing multiple functionalities. The experimental conditions are very simple and the isolation of products also very easy. The highly catalytic nature of indium tribromide and its wide applicability should make this protocol an attractive alternative over existing methods.

^{1}H NMR spectra were recorded on a Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. All commercially available reagent-grade chemicals were purchased from Aldrich and were used as received without further purification. All solvents were distilled.

All products were characterized by ^{1}H NMR, IR, and MS and compared with literature reports.

Menthol Trimethylsilyl Ether (9); Typical Procedure

To a mixture of menthol (312 mg, 2 mmol) and HMDS (225 mg, 1.4 mmol) in CH_2Cl_2 (10 mL) was added the catalyst $InBr_3$ (36 mg, 0.1 mmol). The resulting mixture was stirred at r.t. for 6 h (Table 1); the progress of the reaction was monitored by TLC. After complete consumption of the starting material as confirmed by TLC, the mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was washed with H_2O and brine and then it was dried (Na_2SO_4), and concentration under reduced pressure afforded the crude product. The structure of the product was confirmed by its ^{1}H NMR, IR, and MS data.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.50 (s, 9 H), 0.65 (s, 3 H), 0.93 (s, 6 H), 0.98–1.20 (m, 4 H), 1.30–1.40 (m, 1 H), 1.60 (t, *J* = 6.5 Hz, 2 H), 1.85 (d, *J* = 6.5 Hz, 1 H), 2.10–2.25 (m, 1 H), 3.30–3.50 (m, 1 H).

(5*S*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*C*-phenyl-5-*O*-(trimethylsilyl)-α-d-xylofuranose (10)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.50 (s, 9 H), 1.30 (s, 6 H), 3.38 (d, *J* = 3.5 Hz, 1 H), 4.05–4.18 (m, 1 H), 4.22–4.35 (m, 1 H), 4.40–4.55 (m, 2 H), 4.95 (d, *J* = 7.5 Hz, 1 H), 5.98 (d, *J* = 3.5 Hz, 1 H), 7.20–7.40 (m, 10 H).

Ethyl (*E*)-6-(Trimethylsiloxy)hex-2-enoate (11)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.50 (s, 9 H), 1.20 (t, *J* = 6.5 Hz, 3 H), 1.50–1.70 (m, 2 H), 2.10–2.22 (m, 2 H), 3.50 (t, *J* = 6.5 Hz, 2 H), 4.10 (q, *J* = 6.5 Hz, 2 H), 5.70 (d, *J* = 11.0 Hz, 1 H), 6.78–6.98 (m, 1 H).

MS (EI): *m*/*z* (%) = 231 (M^+, 12), 216 (20), 201 (10), 198 (12), 183 (15), 171 (10), 135 (22), 93 (45), 91 (100), 83 (65), 65 (40), 51 (32), 43 (50).

1-(*tert*-Butoxycarbonyl)-3-(trimethylsiloxy)piperidine (12)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.50 (s, 9 H), 1.20–1.35 (m, 2 H), 1.40 (s, 9 H), 1.60–1.90 (m, 2 H), 2.58–2.80 (m, 2 H), 3.40–3.55 (m, 1 H), 3.78–3.90 (m, 2 H).

(2S)-*N*-(*tert*-Butoxycarbonyl)-4-methyl-1-(trimethylsiloxy)pentan-2-amine (13)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.50 (s, 9 H), 0.90 (2 s, 6 H), 1.25–2.35 (m, 2 H), 1.45 (s, 9 H), 1.50–1.70 (m, 1 H), 3.45–3.70 (m, 3 H), 4.50 (br s, 1 H).

Ethyl 2-[Phenyl(trimethylsiloxy)methyl]acrylate (19)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.50 (s, 9 H), 1.20 (t, *J* = 7.0 Hz, 3 H), 4.10 (q, *J* = 7.0 Hz, 2 H), 5.50 (s, 1 H), 5.90 (s, 1 H), 6.20 (s, 1 H), 7.20–7.30 (m, 5 H).

1,2:5,6-Di-*O*-isopropylidene-3-*O*-(trimethylsilyl)-α-D-glucofuranose (2)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.50 (s, 9 H), 1.25 (2 s, 6 H), 1.50 (s, 3 H), 1.40 (s, 3 H), 3.80–3.90 (m, 2 H), 3.95–4.10 (m, 2 H), 4.22 (d, *J* = 3.5 Hz, 1 H), 5.75 (d, *J* = 3.5 Hz, 1 H).

MS (EI): *m*/*z* (%) = 332 (M^+, 10), 317 (20), 305 (12), 271 (18), 259 (10), 231 (14), 217 (28), 204 (20), 189 (15), 157 (10), 147 (35), 135 (10), 129 (20), 103 (12), 85 (15), 73 (100), 59 (25), 45 (20).

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