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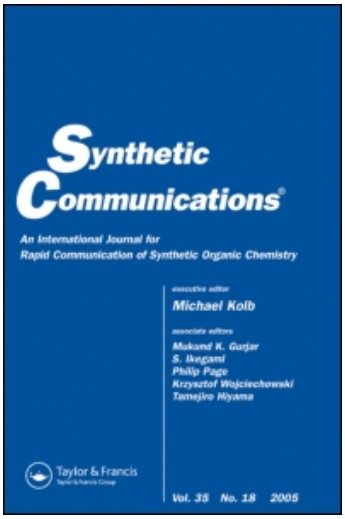

Synthetic Communications
Publication details, including instructions for authors and subscription information:
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Facile Method for Trimethylsilylation of Alcohols using Hexamethyldisilazane and Ammonium Thiocyanate under Neutral Conditions

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To cite this Article Jadhav, Vrushali H. , Kumar, K. S. Ajish , Chaudhari, Vinod D. and Dhavale, Dilip D.(2007) 'Facile Method for Trimethylsilylation of Alcohols using Hexamethyldisilazane and Ammonium Thiocyanate under Neutral Conditions', Synthetic Communications, 37: 8, 1363 — 1370
To link to this Article: DOI: 10.1080/00397910701227440
URL: http://dx.doi.org/10.1080/00397910701227440

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ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701227440

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Facile Method for Trimethylsilylation of Alcohols using Hexamethyldisilazane and Ammonium Thiocyanate under Neutral Conditions

Vrushali H. Jadhav, K. S. Ajish Kumar, Vinod D. Chaudhari, and Dilip D. Dhavale
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Abstract: A highly efficient method for trimethylsilylation of primary, secondary, tertiary, allylic, and a variety of sugar-derived alcohols using hexamethyldisilazane in the presence of a catalytic amount of ammonium thiocyanate under neutral conditions is reported.

Keywords: alcohols, ammonium thiocyanate, 1,1,1,3,3,3-hexamethyldisilazane, trimethylsilylation

The protection–deprotection steps of active protic functional groups are frequently required in multistep synthesis to prevent their interference while modifying other functional groups in the same molecule. Because hydroxyl functionality is a largely encountered functional group in many natural products, its protection under different conditions is in demand.

Among the various types of protecting groups, trimethylsilyl protection of hydroxyl functionality is most popular and widely used in organic synthesis because of its easy removal under mild reaction conditions.[1] A number of methods are available for trimethylsilyl protection of hydroxyl groups that include the use of trimethylsilyl halides or trimethylsilyltriflate in the

Received September 22, 2006
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presence of lithium sulphide (Li_2S)[2] and/or different bases.[3] Allylsilanes in conjunction with *p*-toluenesulphonic acid,[4] iodine,[5] trifloromethane–sulphonic acid,[6] and scandium triflate ($Sc(OTf)_3$)[7] are also reported to give trimethylsilyl derivatives. In these methods, the use of acid or base as a catalyst is always associated with the formation of by-products and requires careful use of the catalyst to get an optimum yield without affecting other sensitive functionalities. This problem has partially been overcome by substituting a cheap, stable, and commercially available 1,1,1,3,3,3-hexamethyl-disilazane (HMDS) for trimethylchlorosilane (TMSCl). The very low reactivity of HMDS, as a silylating agent, requires activation in the form of additives.[8] Recently, activators such as iodine (I_2),[9] coppersulphate pentahydrate ($CuSO_4 \cdot 5H_2O$),[10] and lithiumperchlorate ($LiClO_4$)[11] have been used in such type of reactions.

While working in the field of carbohydrate chemistry and its utility for the synthesis of azasugars,[12] we came across a difficulty in the protection of a secondary hydroxyl functionality, at C-3 of pyrrolidine derivative (Table 1, entry q), which failed with variety of protecting groups (benzyl(Bn), p-methoxybenzyl (PMB), tertiary-butyl-dimethyl-silyl (TBDMS), trimethylsilyl (TMS)) under different reaction conditions.[13] Our surveillance with different reagents resulted in a new method for the protection of hydroxyl functionality using HMDS in association with a catalytic amount of ammonium thiocyanate as a catalyst. (The use of ammonium thiocyanate as a reagent is well known in the metal complex and pesticide industry; however, to the best of our knowledge, no report is available on its application in organic synthesis.) Thus, the reaction of different alcohols (1 mmol) with HMDS (0.6 mmol) in the presence of catalytic amount of ammonium thiocyanate (0.05 mmol) in dry dichloromethane afforded excellent yields of corresponding trimethylsilyl ethers (Eq. (1)).

$$\mathrm{ROH} \xrightarrow[CH_2Cl_2]{\mathrm{HMDS(0.6\,eq),NH_4SCN(0.05\,eq)}} \mathrm{ROTMS}$$

$$\mathrm{R} = \text{aliphatic/benzylic/sugar/steroid/terpenoid} \qquad (1)$$

As shown in Table 1, the trimethylsilylation reaction was found to be successful with primary, secondary, tertiary, benzylic, and propargylic hydroxyl groups (Table 1, entries a–f, h, i, r). Trimethylsilylation with conformationally locked and relatively hindered hydroxyl groups was found to be sluggish albeit high yielding (Table 1, entries j, k, l). The functional groups such as nitrile, chloride, and acetonide were found to be persistent under the reaction conditions. In the case of sugar substrates, primary, secondary, and allylic alcohols afforded high yields of the products (Table 2, entries m–p). Our attempts to protect different phenols (with electron-withdrawing and donating substituents) and quinols (Table 1,

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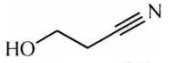
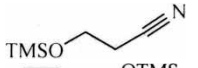
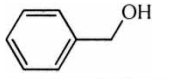
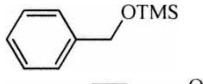
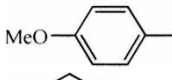
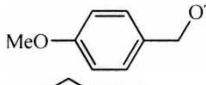
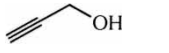
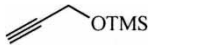
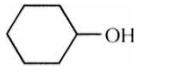
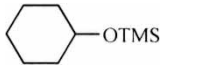
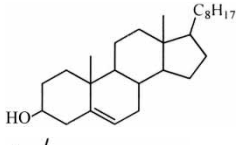
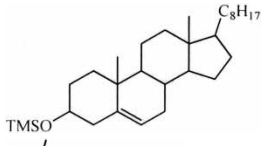
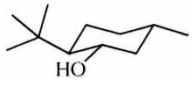
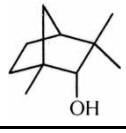
Table 1. Trimethylsilylation of various alcohols using HMDS and catalytic amount of ammonium thiocyanate

Entry	Substrate (1)	Product (2)	Time	Temp. (°C)	Yield (%)
a	$C_7H_{15}CH_2OH$	$C_7H_{15}CH_2OTMS$	10 min	0	99
b	$C_{11}H_{23}CH_2OH$	$C_{11}H_{23}CH_2OTMS$	10 min	0	97
c			10 min	0	93
d			10 min	0	98
e			10 min	0	97
f			10 min	0	98
g			10 min	0	97
h			10 min	0	98
i			10 min	0	95
j			10 h	0 to rt	95
k			6 h	0 to rt	95
l			8 h	0 to rt	98

entries s–u) did not afford the product, and starting material was recovered under a variety of reaction conditions: temperature, time, solvents, and stoichiometry of reagents.

The trimethylsilylation of hydroxyl group using HMDS in combination with I_2 was reported recently via an ionic pathway. In the present investigation, we presume that the ammonium thiocyanate is acting as an activator (initiator) to HMDS giving hexamethyldisilazonium species (A) in which Si-N bond is polarized (Fig. 1). In the next step, nucleophilic attack of hydroxyl group on silicon, facilitated by oxophilicity of the silicon, affords

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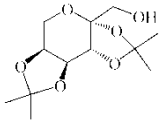
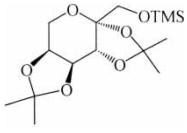
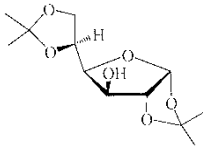
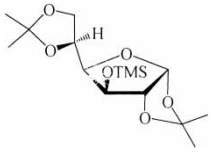
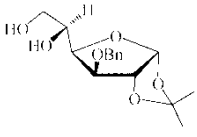
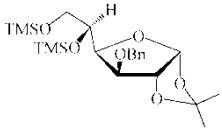
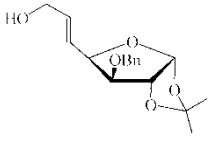
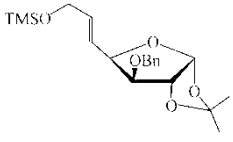
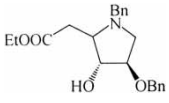
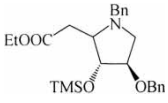
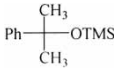
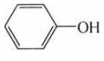
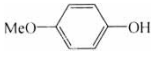
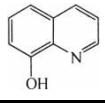
Table 2. Trimethylsilylation of sugar substrates and tertiary alcohol using HMDS and ammonium thiocyanate

Entry	Substrate (1)	Product (2)	Time	Temp. (°C)	Yield (%)
m			5 min	0	91
n			8 min	0	90
o			10 min	0	85
p			10 min	0	90
q			20 min	0 to rt	88
r			25 min	0 to rt	92
s		No reaction			
t		No reaction			
u		No reaction			

trimethylsilylated product and trimethylsilylammonium ion (B), which further reacts with the second molecule of alcohol to give the oxonium intermediate (C) and ammonia (g). Subsequently, HMDS abstracts the proton from the oxonium intermediate (C) to regenerate the activated species (A) that continues the cycle. The driving force for the reaction is believed to be the evolution of ammonia gas as confirmed by testing with turmeric paper and conc. HCl.

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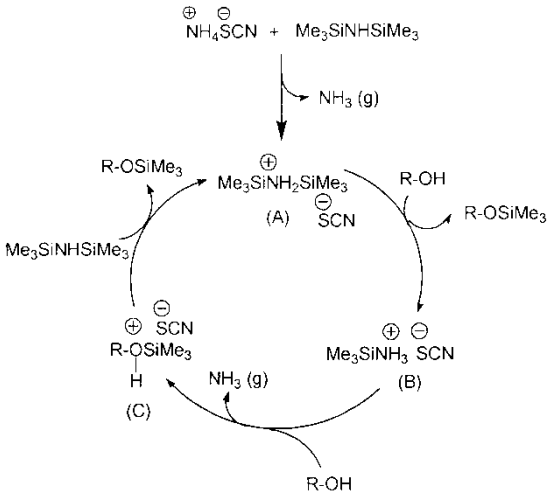

Figure 1. Catalytic cycle.

CONCLUSION

In conclusion, our protocol demonstrates the use of ammonium thiocyanate as an effective catalyst for the trimethylsilylation of alcohols using HMDS under neutral reaction conditions affords high yields in short reaction time. The reaction is environmentally benign with atom economy of HMDS.

GENERAL PROCEDURE

To a solution of alcohol (1 mmol) in dry dichloromethane, HMDS (0.6 mmol) was added followed by a catalytic amount of ammonium thiocyanate (0.05 mmol) at 0°C. The reaction mixture was stirred and monitored by thin-layer chromatography (TLC). After completion of the reaction, water (3 mL) was added, and the reaction mixture was extracted with dichloromethane (3 × 5 mL). Evaporation of the solvent gave product (~95% trimethylsilyl derivatives as evident from the ^{1}H NMR spectra of the crude product) that was purified by column chromatography on neutral alumina using n-hexane as an eluent. In some cases, loss in the yield of the product was observed because of the highly volatile nature of the trimethylsilyl derivatives.

Data

Spectroscopic data of 2d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.1 (s, 9H), 1.97 (m, 2H), 3.64 (t, $J = 5.7$ Hz, 2H), 3.72 (t, $J = 6.3$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta -0.5$ (s), 35.2, 41.7, 58.8.

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Spectroscopic data of 2e: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 9H), 2.53 (t, $J = 6.3$ Hz, 2H), 3.78 (t, $J = 6.3$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.6 (s), 21.6, 57.8, 117.9.

Spectroscopic data of 2l: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 9H), 0.79 (s, 3H), 0.96 (s, 3H), 1.01 (s, 3H), 0.90–1.80 (m, 7H) 3.22 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.6 (s), 19.9, 21.1, 25.5, 26.3, 30.5, 39.3, 40.9, 48.4, 49.4, 85.3.

Spectroscopic data of 2m: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 9H), 1.20 (s, 3H), 1.27 (s, 3H), 1.33 (s, 3H), 1.40 (s, 3H), 3.47 (d, $J = 10.5$ Hz, 1H), 3.57 (dd, $J = 6.6$, 12.9 Hz, 2H), 3.77 (dd, $J = 2.1$, 12.9 Hz, 1H), 4.08 (bd, $J = 7.8$ Hz, 1H), 4.24 (d, $J = 2.4$ Hz, 1H), 4.45 (dd, $J = 2.7$, 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.1 (s), 23.8, 24.4, 24.8, 26.1, 61.2, 64.5, 69.8, 71.1, 71.3, 103, 108.5, 109.0.

Spectroscopic data of 2n: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 9H), 1.32 (s, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.46 (s, 3H), 3.96 (dd, $J = 6.0$, 8.4 Hz, 1H), 4.06 (dd, $J = 8.1$ Hz, 1H), 4.07 (dd, $J = 2.7$, 8.1 Hz, 1H), 4.22 (dd, $J = 1.5$, 6.0 Hz, 1H), 4.23 (d, $J = 2.7$ Hz, 1H), 4.35 (d, $J = 3.6$ Hz, 1H), 5.89 (d, $J = 3.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ − 0.0 (s), 25.4, 26.3, 26.8, 26.9, 67.4, 72.3, 75.2, 81.8, 85.5, 105.2, 108.7, 111.7.

Spectroscopic data of 2o: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 9H), 0.11 (s, 9H), 1.29 (s, 3H), 1.48 (s, 3H), 3.53 (dd, $J = 6.9$, 10.5 Hz, 1H), 3.83 (dd, $J = 1.8$, 10.5 Hz, 1H), 4.03 (d, $J = 2.7$ Hz, 1H), 4.08 (m, 2H), 4.54 (d, $J = 3.9$ Hz, 1H), 4.57 (d, $J = 11.7$ Hz, 1H), 4.65 (d, $J = 11.7$ Hz, 1H), 5.86 (d, $J = 3.9$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ − 0.4 (s), 0.9 (s), 26.3, 26.8, 65.5, 70.8, 72.0, 80.4, 81.4, 82.0, 105.2, 111.6, 127.1, 127.2, 127.6, 128.3, 137.6.

Spectroscopic data of 2p: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.1 (s, 9H), 1.32 (s, 3H), 1.49 (s, 3H), 3.85 (d, $J = 3$ Hz, 1H), 4.15 (t, $J = 6$ Hz, 1H), 4.56 (d, $J = 12.4$ Hz, 1H), 4.63 (m, $J = 3$, 5.4, 12 Hz, 4H), 5.94 (m, $J = 3.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.02 (s), 26.2, 26.7, 62.7, 72.1, 80.5, 82.7, 83.2, 104.6, 111.4, 124.6, 127.5 (s), 127.7, 128.3 (s), 134.1, 137.2.

Spectroscopic data of 2q: ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.10 (s, 9H), 0.22 (s, 9H), 1.25 (t, $J = 7.1$ Hz, 3H), 2.38 (dd, $J = 10.9$, 6.3 Hz, 1H), 2.47 (d, $J = 5.7$ Hz, 2H), 2.73 (dd, $J = 11.8$, 5.7 Hz, 1H), 2.80 (dd, $J = 10.9$, 1.9 Hz, 1H), 3.14 (d, $J = 13.1$ Hz, 1H), 3.61–3.65 (m, 1H), 3.89 (d, $J = 13.1$ Hz, 1H), 3.98 (dd, $J = 7.1$, 4.6 Hz, 1H), 3.99 (q, $J = 7.1$ Hz, 2H), 4.27 (ABq, $J = 11.8$ Hz, 2H), 7.05–7.23 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.13 (s), 14.1, 36.6, 56.3, 58.3, 60.3, 66.9, 71.4, 80.9, 83.5, 126.8, 127.5, 127.6 (s), 128.1 (s), 128.2 (s), 128.6 (s), 138.0, 138.8, 171.9.

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Spectroscopic data of 2r: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 9H), 1.63 (s, 6H), 7.25 (d, $J = 6.6$ Hz, 1H), 7.34 (t, $J = 7.2$ Hz, 2H), 7.48 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.5 (s), 32.5(s), 124.5 (s), 126.1, 127.7 (s).

ACKNOWLEDGMENT

We are thankful to the Department of Science and Technology (SP/S1/G-32/2000), New Delhi, for financial support. V. H. J. and A. K. S. are thankful to Council of Scientific and Industrial Research-University Grants Commission (CSIR-UGC), New Delhi, for fellowships.

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