A Novel Approach to *C*-Trimethylsilyl-1,3-azoles

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Abstract: Direct silylation of 1,3-azoles with bromotrimethylsilane in the presence of triethylamine was investigated. 5-Phenyloxazole, benzoxazole, 1-methyl-1,2,4-triazole, 2-aryl-1,3,4-oxa- and thiadiazoles were found to give the corresponding 2- or 5-trimethylsilyl derivatives.

Key words: azoles, silylation, heterocycles, electrophilic substitution, silicon

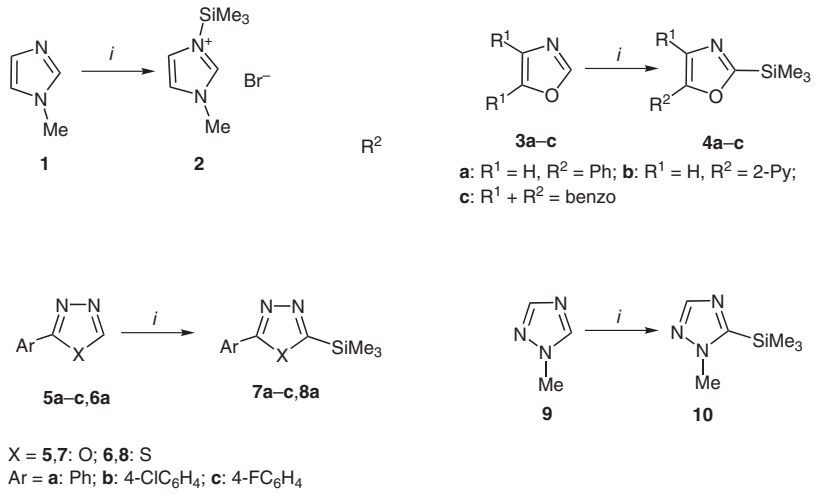
C-Silyl azoles undergo substitution of the *C*-silyl groups with electrophilic reagents[1] making silylazoles synthetic equivalents of organometallic derivatives. 2-Trimethylsilylthiazoles are widely used in asymmetric syntheses with chiral aldehydes affording amino hydroxy aldehydes and *C*-glycosyl amino acids – precursors to modified peptides in high yields.[2] Furthermore, silyl groups can be exploited as protecting groups due to the possibility of straightforward removal by protic acids.[3]

The known general approach to *C*-silylazoles comprises the lithiation of azoles followed by treatment of the lithium derivatives with silyl halides or their equivalents.[4,5]

The method established good results with imidazoles, thiazoles and their benzo derivatives, 1,2,4-triazoles.[4] However, with oxazoles and benzoxazoles certain problems arose connected with the ring-cleavage during lithiation.[5] Finally, for 1,3,4-oxa- and thiadiazoles the lithiation/silylation procedure was not described. Therefore, the elaboration of new methods for the introduction of silyl groups is of interest.

It seemed reasonable to examine the direct electrophilic silylation of 1,3-azoles as an alternative approach to *C*-silylazoles because direct silylation was reported previously for electron-rich heterocycles, namely pyrrole and indole,[6] as well as for *N*-oxides of pyrazole and 1,2,3-triazole.[7] Trimethylsilyl triflate and trimethylsilyl iodide were used as silylating agents. Moreover, recently the transformation of 1-methyl-4-silyl-1,2,4-triazolium triflate into 1-methyl-5-silyl-1,2,4-triazole under treatment with potassium hydride has been reported.[8] Apparently, it occurs through a carbenic mechanism via an intermolecular process.

Treatment of 1-methylimidazole (**1**) with bromotrimethylsilane in the presence of triethylamine yielded only the salt **2** (Scheme 1),[9] which was stable and did not afford carbene.[10,11] However, the oxazoles **3a** and **3b** and benzoxazole **3c** underwent silylation under the same conditions leading to the silyloxazoles **4a–c** in moderate to good yields. Better results were obtained with oxa- and



Scheme 1 *Reagents:* i) 2 equiv Me_3SiBr, Et_3N.

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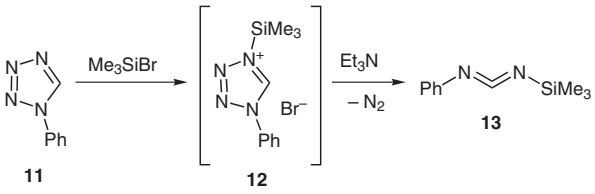
thiadiazoles **5a–c**, **6a**. Thus the yields of silyl derivatives **7a–c**, **8a** increased to 70%, while in certain cases more than 90% yield was achieved. 1-Methyl-1,2,4-triazole (**9**) also afforded silyl derivative **10** in good yield. The position of the trimethylsilyl group in the compound **10** was confirmed by gated ^{13}C experiment. Thus, in the ^{13}C NMR spectrum of derivative **10** recorded with the selective saturation of the $SiMe_3$ protons, the signal of 5-C was observed as a doublet of quartets with $^3J_{Me,5C}$ = 2.0 Hz and $^3J_{3H,5C}$ = 6.5 Hz. The presence of spin-spin coupling between 5-C and *N*-methyl protons proves the structure of **10** since for the isomeric one it is impossible.

In all experiments a two-fold excess of bromotrimethylsilane was used since with equimolar reagents ratio there was a considerable amount of the starting heterocycle in the reaction mixture. Silylazoles **4**, **7**, **8**, **10** are stable during storage but are very sensitive toward moisture. The higher reactivity of compounds **5**, **6**, **9** versus oxazoles **3** is explained by the lower energy of the corresponding carbene formation.[10] Unfortunately, an attempt at thiazole and benzothiazole silylation failed.

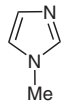
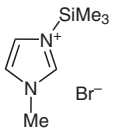
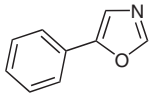
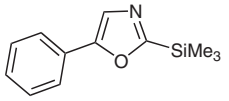
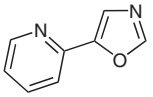
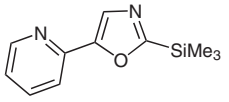
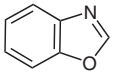
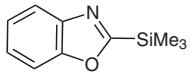
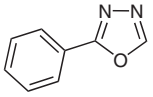
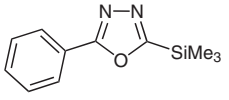
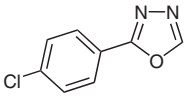
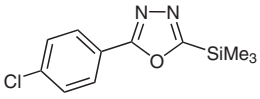
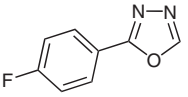
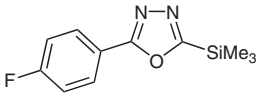
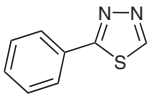
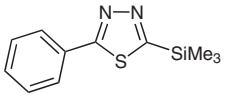
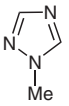
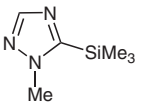
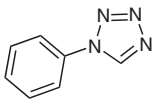
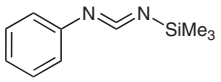
An unexpected result was obtained during silylation of 1-phenyltetrazole **11**. The carbodiimide **13** was isolated instead of the targeted silyltetrazole (Scheme 2). Probably, compound **13** was formed via decomposition of the intermediate salt **12** with nitrogen liberation.



Scheme 2

In conclusion, the direct electrophilic silylation of 1,3-azoles with bromotrimethylsilane under basic conditions has been examined. It has resulted in the novel approach to *C*-trimethylsilylazoles, namely (benz)oxazoles **4**, 1,2,4-triazoles **10**, oxa- and thiadiazoles **7**, **8** (Table 1). The method is complementary to the well known lithiation/silylation procedure. Thus, it provides an easy access to the *C*-silylazoles, which are unavailable through the organometallic approach. The failure of imidazole and thiazole silylation is not serious since these silyl derivatives can be obtained smoothly via lithiation/silylation sequence. Finally, it should be noted that compounds **7** and **8** are the first representatives of trimethylsilyl substituted oxa- and thiadiazoles.

Table 1 Silylation of Azoles

Entry	Azole	Product	Yield (%)
2			95
4a			38
4b			71
4c			53
7a			67
7b			92
7c			50
8a			72
10			56
13			90

All procedures were performed under a dry argon atmosphere using anhydrous solvents. Bromotrimethylsilane, benzoxazole, 1-methylimidazole and 1-methyl-1,2,4-triazole were commercially available. 5-Phenyloxazole,[12] 2-(1,3-oxazol-5-yl)pyridine,[13] 2-aryl-1,3,4-oxa- and thiadiazoles,[14,15] 1-phenyltetrazole[16] were prepared according to the described methods. Melting points were determined in sealed capillary tubes on an electrothermal capillary melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian VXR-300 spectrometer (300 MHz for ^1H NMR, 282 MHz for ^{19}F NMR and 75 MHz for ^{13}C NMR) in anhydrous solvents. Chemical shifts (δ) are given in ppm downfield from the internal standard (TMS). *J* values are given in Hz.

1-Methyl-3-(trimethylsilyl)imidazolium Bromide (2)

Method A: Bromotrimethylsilane (19.29 g, 0.126 mol) was added to a solution of 1-methylimidazole (10.33 g, 0.126 mol) in Et_2O (63 mL) at r.t. in one portion. Precipitated salt **2** was filtered off and washed with Et_2O; yield: 28.20 g (95%).

Method B: Bromotrimethylsilane (9.32 g, 61 mmol) was added to a solution of 1-methylimidazole (5 g, 61 mmol) and Et_3N (6.16 g, 61 mmol) in Et_2O at r.t. Precipitated salt **2** was filtered off and washed with Et_2O; yield: 13.34 g (93%); mp 112–115 °C.

^1H NMR (DMSO-d_6): δ = 0.52 (s, 9 H), 3.84 (s, 3 H), 7.64 (t, *J* = 1.5 Hz, 1 H), 7.70 (t, *J* = 1.5 Hz, 1 H), 8.93 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = –0.98, 35.15, 123.70, 124.23, 139.72.

Anal. Calcd for $C_7H_{15}BrN_2Si$ (235.20): C, 35.75; H, 6.43; N, 11.91. Found: C, 35.44; H, 6.22; N, 11.81.

C-Trimethylsilylazoles; General Procedure

Bromotrimethylsilane (61.2 g, 0.4 mol) was added to a solution of appropriate 1,3-azole **3**, **5**, **6**, **9** (0.2 mol) and Et_3N (55.2 mL, 0.4 mol) in pyridine–toluene mixture (200 mL, 1:1). The reaction mixture was left for 24 h at r.t. The precipitated triethylamine hydrobromide was filtered off and washed with toluene. The combined filtrate and the washings were evaporated in vacuo, hexane was added to the residual oil and the mixture was allowed to stand for 24 h. Then, the hexane solution was filtered, the solvent was removed and the residue was either distilled under reduced pressure (compounds **4a–c**, **7a**, **8a**, **10**) or crystallized (compounds **7b** and **7c**) to give target silylazoles.

5-Phenyl-2-trimethylsilyloxazole (4a)[5]

Bp 123–125 °C/25 Torr.

^{1}H NMR (C_6D_6): δ = 0.31 (s, 9 H), 7.01 (t, *J* = 7.5 Hz, 1 H), 7.10 (t, *J* = 7.5 Hz, 2 H), 7.36 (s, 1 H), 7.52 (t, *J* = 7.5 Hz, 2 H).

^{13}C NMR (C_6D_6): δ = –1.95, 123.14, 124.76, 128.33, 128.93, 129.00, 153.56, 169.98.

Anal. Calcd for $C_{12}H_{15}NOSi$ (217.35): C, 66.32; H, 6.96; N, 6.44. Found: C, 66.48; H, 6.73; N, 6.69.

2-[2-(Trimethylsilyl)-1,3-oxazol-5-yl]pyridine (4b)

Bp 152–153 °C/10 Torr; mp 51–53 °C.

^{1}H NMR (C_6D_6): δ = 0.31 (s, 9 H), 6.56 (ddd, *J* = 0.9, 4.8, 7.7 Hz, 1 H), 7.06 (td, *J* = 1.7, 7.7 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 8.08 (s, 1 H), 8.41 (d, *J* = 4.0 Hz, 1 H).

^{13}C NMR (C_6D_6): δ = –1.96, 119.22, 122.49, 126.71, 136.30, 148.59, 150.20, 153.89, 171.09.

Anal. Calcd for $C_{11}H_{14}N_2OSi$ (218.33): C, 60.51; H, 6.46; N, 12.83. Found: C, 66.69; H, 6.53; N, 12.92.

2-Trimethylsilylbenzoxazole (4c)

Bp 97–98 °C/10 Torr; mp 32–34 °C.

^{1}H NMR (C_6D_6): δ = 0.30 (s, 9 H), 7.04 (m, 2 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.79 (s, *J* = 7.0 Hz, 1 H).

^{13}C NMR (C_6D_6): δ = –2.20, 110.85, 120.85, 124.17, 125.41, 142.42, 152.24, 172.44.

Anal. Calcd for $C_{10}H_{13}NOSi$ (191.31): C, 62.78; H, 6.85; N, 7.32. Found: C, 62.86; H, 6.74; N, 7.38.

2-Phenyl-5-trimethylsilyl-1,3,4-oxadiazole (7a)

Bp 103–104 °C/0.12 Torr; mp 44–46 °C.

^{1}H NMR (C_6D_6): δ = 0.22 (s, 9 H), 7.02–7.03 (m, 3 H), 8.08–8.11 (m, 2 H).

^{13}C NMR (C_6D_6): δ = –2.28, 125.03, 127.36, 129.13, 131.38, 166.03, 170.15.

Anal. Calcd for $C_{11}H_{14}N_2OSi$ (218.33): C, 60.51; H, 6.46; N, 12.83. Found: C, 60.72; H, 6.38; N, 12.59.

2-(4-Chlorophenyl)-5-trimethylsilyl-1,3,4-oxadiazole (7b)

Mp 47–48 °C.

^{1}H NMR (C_6D_6): δ = 0.21 (s, 9 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 7.78 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (C_6D_6): δ = –2.26, 123.46, 128.67, 129.45, 137.50, 165.23, 170.34.

Anal. Calcd for $C_{11}H_{13}ClN_2OSi$ (252.78): C, 52.27; H, 5.18; N, 11.08. Found: C, 52.25; H, 5.30; N, 11.19.

2-(4-Fluorophenyl)-5-trimethylsilyl-1,3,4-oxadiazole (7c)

Mp 92–94 °C.

^{1}H NMR (C_6D_6): δ = 0.27 (s, 9 H), 6.72 (tt, *J* = 1.8, 8.4 Hz, 2 H), 7.86 (m, 2 H).

^{13}C NMR (C_6D_6): δ = –2.26, 116.29 (J_{CF} = 21.9 Hz), 121.28 (J_{CF} = 3.2 Hz), 129.61 (J_{CF} = 8.5 Hz), 164.68 (J_{CF} = 251.1 Hz), 165.07, 170.17.

^{19}F NMR (C_6D_6): δ = –108.016.

Anal. Calcd for $C_{11}H_{13}FN_2OSi$ (236.32): C, 55.91; H, 5.54; N, 11.85. Found: C, 56.10; H, 5.34; N, 12.03.

2-Phenyl-5-trimethylsilyl-1,3,4-thiadiazole (8a)

Bp 131–133 °C/0.4 Torr.

^{1}H NMR (C_6D_6): δ = 0.28 (s, 9 H), 7.01–7.09 (m, 3 H), 7.98–8.04 (m, 2 H).

^{13}C NMR (C_6D_6): δ = –0.85, 128.71, 129.35, 130.88, 130.91, 169.91, 170.74.

Anal. Calcd for $C_{11}H_{14}N_2SSi$ (234.40): C, 56.37; H, 6.02; N, 11.95. Found: C, 56.30; H, 6.14; N, 12.08.

1-Methyl-5-trimethylsilyl-1,2,4-triazole (10)

Bp 82–84 °C/30 Torr.

^{1}H NMR (C_6D_6): δ = 0.17 (s, 9 H), 3.33 (s, 3 H), 8.09 (s, 1 H).

^{13}C NMR (C_6D_6): δ = –1.47, 36.77, 151.87, 157.86.

Anal. Calcd for $C_6H_{13}N_3Si$ (155.28): C, 46.41; H, 8.44; N, 27.06. Found: C, 46.54; H, 8.35; N, 27.25.

N-Phenyl-*N*′-(trimethylsilyl)carbodiimide (13)[17]

Bromotrimethylsilane (6.93 g, 52.5 mmol) was added dropwise to a stirred solution of 1-phenyltetrazole (**11**, 5.116 g, 35 mmol) and Et_3N (7.32 mL, 52.5 mmol) in pyridine (35 mL) at –20 °C. The reaction mixture was maintained at this temperature until the nitrogen evolution stopped and then was left for 24 h at r.t. After addition of toluene (35 mL), the precipitated triethylamine hydrobromide was filtered off. The solvents were removed, and the residue was distilled under reduced pressure to give the title product **13** (5.974 g, 90%) as a colorless liquid; bp 129 °C/35 Torr.

IR (film): 2970, 2170 cm^{-1}.

^{1}H NMR (C_6D_6): δ = 0.02 (s, 9 H), 6.86 (tt, *J* = 1.4, 7.0 Hz, 1 H), 7.07–7.17 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 0.84, 123.01, 123.16, 128.12, 129.27, 141.02.

Anal. Calcd for $C_{10}H_{14}N_2Si$ (190.32): C, 63.11; H, 7.41; N, 14.72. Found: C, 63.28; H, 7.31; N, 14.88.

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