THE [2-(TRIMETHYLSILYL)ETHOXY]METHYL FUNCTION AS A SUITABLE *N*-1 PROTECTING GROUP IN LITHIATION REACTIONS WITH PYRAZOLES AND 1,2,4-TRIAZOLES[1]

Natalie Fugina,[2] Wolfgang Holzer,* and Michael Wasicky[3]

Institute of Pharmaceutical Chemistry, University of Vienna
Währinger Straße 10, A-1090 Vienna, Austria

Abstract - Metallation of 1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-pyrazole or 1-[2-(trimethylsilyl)-ethoxy]methyl-1*H*-1,2,4-triazole, respectively, with one equivalent of n-BuLi followed by reaction with appropriate electrophiles leads to 5-substituted 1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-pyrazoles and 5-substituted 1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-1,2,4-triazoles. Deprotection can be achieved either by heating with aqueous ethanolic HCl or by treatment with anhydrous tetrabutylammonium fluoride.

INTRODUCTION

Within the last two decades some efforts have been undertaken in the search for efficacious *N*-protecting groups to be used in metallation reactions (proton loss adjacent to NH) with azoles. Particularly with imidazoles, a considerable number of groups have been evaluated in this regard.[4,5] With pyrazoles and 1,2,4-triazoles, methyl,[6-10] benzyl,[6,8,11,12] tetrahydropyranyl,[13,14] benzenesulfonyl,[15] aminal,[5,16,17] hemiaminal,[18] *N,N*-dimethylsulfamoyl,[19] and trityl[12] protection, for instance, has been described. However, some of these functions suffer from certain limitations and disadvantages.[4,5] Thus, methyl and benzyl groups require drastic deprotection conditions (methyl: heating with anhydrous pyridinium chloride to ~ 200°C for several hours;[20] benzyl: treatment with sodium/liquid ammonia[11,21]), additionally competetive lithiation of the protecting group was observed.[7-9] With trityl-protected azoles problems of solubility[4] and reactivity[12] can arise. Other groups are very sensitive to hydrolysis.[4,5] Most of these problems have been overcome with Katritzkys'

pyrrolidinomethyl group[5,16,17]. However, 1-pyrrolidinomethyl-1*H*-pyrazoles are cleaved even by diluted acids at room temperature.[5] Thus, if the protecting group should block the azole N-H also in subsequent reaction steps, this group seems to be too labile. A protecting group which has proven to fulfill nearly all the requirements (i.e. easy protection, easy deprotection under mild and selective conditions, sufficient stability under the reaction conditions, no lithiation of the protecting group) in the course of lithiation reactions with pyrroles,[22,23] imidazoles[24] and indoles,[23,25] is the [2-(trimethylsilyl)ethoxy]methyl (SEM) function. Moreover, this group is presumed to stabilize the intermediate azolyl lithium species by intramolecular coordination.[22a,23,25] These findings prompted us to investigate the suitability of the SEM group also for the protection of pyrazoles and 1,2,4-triazoles.

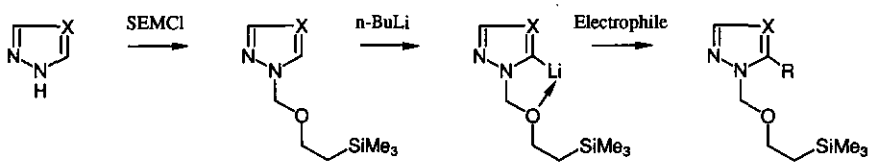
RESULTS AND DISCUSSION

Protection: The protecting group could be readily introduced by reacting 1*H*-pyrazole (**1**), 4-bromo-1*H*-pyrazole (**2**), and 1*H*-1,2,4-triazole (**3**), respectively, with sodium hydride in tetrahydrofuran (THF) followed by reaction with SEM chloride. The resulting *N*-SEM-azoles (**4**, **5**, and **6**) were purified by Kugelrohr distillation before used in the lithiation step. In the case of **3**, where two possible isomers may result upon alkylation, nmr analysis revealed only the *N*-1 substituted product (**6**) (two different heteroaromatic protons) to be present in the reaction mixture.

Lithiation and Electrophilic Substitution: The metallation step was accomplished by treatment of **4**, **5**, or **6**, respectively, with a slight excess of n-BuLi at -70°C in THF. After quenching the lithio intermediates (**4a**) and (**6a**) with D_2O, deuterium incorporations of ~ 60% for **4** and ~ 80% for **6** were detected by ^{1}H-nmr. With **5**, the metallation reaction turned out to be not regioselective, as halogen-metal exchange as well as α-lithiation occurred simultaneously. Switching to ether as the solvent, the ratio of halogen-metal exchange was found to increase.[26]

In the following, several 5-substituted 1-SEM-1*H*-pyrazoles and 1-SEM-1*H*-1,2,4-triazoles were prepared by treatment of **4a** and **6a** with appropriate electrophiles (products, electrophiles and yields[27] are given in Table 1). Reaction of **4a** and **6a** with benzaldehyde led to the expected secondary alcohols (**9**) and (**13**), the corresponding ketones (**8**) and (**12**) were obtained by employing ethyl benzoate or benzoyl chloride (which gave nearly the same results) as the electrophile. Inverse addition (dropwise addition of **4a** or **6a** solution to

PhCOOEt or PhCOCl in THF) did not change the results. For the introduction of chlorine into the 1,2,4-triazole nucleus (compound **15**), hexachloroethane turned out to be a suitable trapping agent. Whereas **6a** could be readily methylated to **16** with iodomethane, problems were encountered when reacting **4a** with benzyl bromide, *as glc/ms analysis revealed only ~ 10% of the desired 5-benzyl-1-SEM-1H-pyrazole to be* present in the multi-component mixture. No reaction of **4a** or **6a** with DMF was found to occur.



1,2,3 **4,5,6** **4a,5a,6a** **7 - 16**

HCl or $n\text{-}Bu_4NF$

No.	X
1,4	CH
2,5	CBr
3,6	N

No.	X	R
17	CH	COPh
18	CH	SPh
19	N	SPh

17,18,19

Table 1. Reaction of **4a** and **6a** with Electrophiles

No.	*X*	*R*	*Electrophile*	*Yield (%)*
7	CH	COOH	CO_2	33
8	CH	COPh	PhCOOEt (PhCOCl)	32 (31)
9	CH	CH(OH)Ph	PhCHO	46
10	CH	SPh	PhSSPh	46
11	CH	$SiMe_3$	Me_3SiCl	29
12	N	COPh	PhCOCl	30
13	N	CH(OH)Ph	PhCHO	39
14	N	SPh	PhSSPh	57
15	N	Cl	Cl_3CCCl_3	41
16	N	Me	MeI	35

Deprotection: Finally, as tested with some model substrates (**4, 6, 8, 10, 14**), removal of the SEM protecting group could be easily achieved either by refluxing the *N*-protected azole with dilute hydrochloric acid in ethanol or by treatment with an excess of tetra-n-butylammonium fluoride in dry THF at reflux temperature.[22-25]

In summary, the SEM function has proven to be a possible *N*-protecting group in lithiation reactions with

pyrazoles and 1,2,4-triazoles. Introduction of the SEM group onto the pyrazole and 1,2,4-triazole nucleus proceeds in high yields, the resulting 1-SEM-azoles are stable, distillable oils which are easy to purify. Their 5-lithio derivatives (**4a**) and (**6a**) react with a variety of different electrophiles affording the corresponding 5-substitution products. Finally, the fluoride lability of the SEM group permits deprotection under mild conditions. In our opinion, employment of the SEM protecting group can be recommended especially if continuing protection for following reaction steps is desired (the SEM group tolerates a variety of basic and acidic conditions)[22a,23,24a] or when highly selective deprotection conditions are required.

Analytical: The structures of all novel compounds were confirmed by elemental analyses as well as by ir, ms, and nmr spectra. The ir spectra of all SEM-azoles exhibit strong absorption bands at $\nu \sim 2900$ cm^{-1} due to the aliphatic C-H stretching vibrations. The mass spectra of all SEM-protected azoles are characterized by the fragmentation of the C-$SiMe_3$ bond incorporated in the SEM group. Thus, in nearly all cases base peaks with m/z = M^+-73 (i.e. M^+-$SiMe_3$) or 73 ($SiMe_3$) are observed. The 1,5-disubstitution pattern[28] of compounds (**5** - **16**) emerged from ^{1}H and ^{13}C nmr data as well as from NOE difference experiments according to refs.[30,31] (e.g. **13**: NOE on CHOH upon irradiation of NCH_2O; **14**: NOE on Ph-H upon irradiation of NCH_2O; **16**: NOE on NCH_2O upon irradiation of 5-Me). The latter technique was also employed to assign the signals of the heteroaromatic protons in compounds (**4** - **6**): irradiation of the NCH_2O resonance gave the corresponding azole H-5 signal a significant NOE, whereas the azole H-3 resonance remained nearly unaffected, thus permitting the unambiguous distinction between these two lines.[30,31]

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. Ir spectra (neat oils between NaCl disks, ν in cm^{-1}) were recorded on a Jasco IRA-1 spectrophotometer. Glc/ms analyses were performed on a Hewlett-Packard 5890A/5970B-GC/MSD instrument (70 eV), high resolution mass spectra were obtained on a Finnigan MAT 8230 instrument. Nmr spectra were recorded on a Bruker AC-80 spectrometer (spectrometer frequency for ^{1}H: 80.13 MHz, for ^{13}C: 20.15 MHz; δ values in ppm) equipped with an Aspect 3000 computer and standard software. For the acquisition parameters of the NOE difference spectra see refs.[30,31] CHN-analyses were carried out by Mikroanalytisches Laboratorium, Institute of Physical Chemistry, University of Vienna. Medium pressure liquid chromatography (mplc) was performed using

Lobar® glass columns filled with LiChroprep® Si-60 (230-400 mesh, Merck); column chromatography was carried out using Merck Kieselgel 60 (70-230 mesh) as stationary phase. Tetrahydrofuran was dried by passage through a column of aluminia (activity I, basic).

General Procedure for SEM Protection of 1*H*-Pyrazole (**1**), 4-Bromo-1*H*-pyrazole (**2**), and 1*H*-1,2,4-Triazole (**3**)

Under argon, 900 mg of sodium hydride (80% suspension in mineral oil, 30 mmol) were suspended in 20 ml of dry THF. Then 30 mmol of 1*H*-pyrazole (2.042 g), 4-bromo-1*H*-pyrazole (4.409 g), or 1*H*-1,2,4-triazole (2.072 g), respectively, in 10 ml of dry THF were added and the mixture was stirred for 1 h. After cooling to 0°C, a solution of 5.002 g (30 mmol) of [2-(trimethylsilyl)ethoxy]methyl chloride in 5 ml of dry THF was added slowly *via* syringe. Then the cooling bath was removed and the mixture was stirred at room temperature for 1.5 h. After addition of water (40 ml), the organic layer was separated, the water phase was exhaustively extracted with ethyl acetete and the combined organic layers were dried over anhydrous sodium sulfate. The solvents were evaporated *in vacuo* and the remaining residue was subjected to Kugelrohr distillation. The 1-SEM-azoles came over at ~ 80°C/0.03 mbar.

1-[2-(Trimethylsilyl)ethoxy]methyl-1*H*-pyrazole (**4**)

Yield: 94%, colorless oil; ^{1}H-nmr ($CDCl_3$):[30] δ 7.56 (m, 2 H, pyrazole H-3,H-5), 6.33 (m, 1 H, pyrazole H-4), 5.44 (s, 2 H, NCH_2O), 3.55 (m, 2 H, OCH_2C), 0.89 (m, 2 H, $SiCH_2$), -0.03 (s, 9 H, $SiCH_3$); ^{13}C-nmr ($CDCl_3$): δ 139.5 (pyrazole C-3, ^1J = 185.0 Hz, ^2J = 5.9 Hz, ^3J = 8.4 Hz), 129.1 [pyrazole C-5, ^1J = 186.1 Hz, ^2J = 9.1 Hz, ^3J(C5,H3) = 4.7 Hz, ^3J(C5,NCH_2) = 2.9 Hz], 106.4 [pyrazole C-4, ^1J = 176.5 Hz, ^2J(C4,H3) = 10.7 Hz, ^2J(C4,H5) = 8.6 Hz], 79.7 (NCH_2O, ^1J = 157.8 Hz), 66.3 ($O\underline{C}H_2C$, ^1J = 142.3 Hz), 17.5 ($C\underline{C}H_2Si$, ^1J = 118.4 Hz), -1.7 ($SiCH_3$, ^1J = 118.6 Hz); ms (m/z, %): 198 (M^+, 1), 155 (20), 125 (100), 98 (15), 97 (16), 82 (59), 81 (63), 73 (50), 53 (11). Anal. Calcd for $C_9H_{18}N_2OSi$: C, 54.50; H, 9.15; N, 14.12. Found: C, 54.51; H, 9.28; N, 14.02.

4-Bromo-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-pyrazole (**5**)

Yield: 92%, colorless oil; ^{1}H-nmr ($CDCl_3$):[30] δ 7.58 (s, 1 H, pyrazole H-5), 7.49 (s, 1 H, pyrazole H-3), 5.38 (s, 2 H, NCH_2O), 3.54 (m, 2 H, OCH_2C), 0.90 (m, 2 H, $SiCH_2$), -0.02 (s, 9 H, $SiCH_3$); ^{13}C-nmr ($CDCl_3$): δ 140.2 (pyrazole C-3, ^1J = 192.3 Hz, ^3J = 7.0 Hz), 129.4 [pyrazole C-5, ^1J = 192.5 Hz, ^3J(C5,H3) = 3.3 Hz,

^3J(C5,NCH_2) = 3.3 Hz], 94.4 [pyrazole C-4, ^2J(C4,H3) = 8.1 Hz, ^2J(C4,H5) = 5.8 Hz], 80.5 (NCH_2O, ^1J = 158.2 Hz), 66.8 ($O\underline{C}H_2C$, ^1J = 142.4 Hz), 17.6 ($C\underline{C}H_2Si$, ^1J = 118.7 Hz), -1.6 ($SiCH_3$, ^1J = 118.7 Hz); ms (m/z, %): 276/278 (M^+, 1/1), 233/235 (27/23), 203/205 (68/67), 160/162 (49/46), 159/161 (31/31), 137/139 (12/13), 115 (13), 73 (100), 59 (11), 52 (17). Anal. Calcd for $C_9H_{17}N_2OBrSi$: C, 38.99; H, 6.18; N, 10.10. Found: C, 38.99; H, 6.18; N, 10.16.

1-[2-(Trimethylsilyl)ethoxy]methyl-1*H*-1,2,4-triazole (**6**)

Yield: 80%, colorless oil; ^{1}H-nmr ($CDCl_3$):[31] δ 8.24 (s, 1 H, triazole H-5), 7.96 (s, 1 H, triazole H-3), 5.49 (s, 2 H, NCH_2O), 3.62 (m, 2 H, OCH_2C), 0.90 (m, 2 H, $SiCH_2$), -0.03 (s, 9 H, $SiCH_3$); ^{13}C-nmr ($CDCl_3$): δ 151.5 (triazole C-3, ^1J = 207.6 Hz, ^3J = 12.1 Hz), 143.4 [triazole C-5, ^1J = 210.1 Hz, ^3J(C5,H3) = 7.5 Hz, ^3J(C5,NCH_2) = 3.0 Hz], 77.3 (NCH_2O, ^1J = 159.5 Hz), 67.1 ($O\underline{C}H_2C$, ^1J = 142.4 Hz), 17.4 ($C\underline{C}H_2Si$, ^1J = 118.5 Hz), -1.9 ($SiCH_3$, ^1J = 118.7 Hz); ms (m/z, %): 184 (M^+-CH_3, 1), 156 (34), 126 (100), 115 (13), 83 (14), 73 (58), 55 (12). Anal. Calcd for $C_8H_{17}N_3OSi$: C, 48.21; H, 8.60; N, 21.08. Found: C, 48.00; H, 8.47; N, 21.37.

General Procedure for Lithiation/Electrophilic Addition of 1-[2-(Trimethylsilyl)ethoxy]methyl-1*H*-pyrazole (**4**) and 1-[2-(Trimethylsilyl)ethoxy]methyl-1*H*-1,2,4-triazole (**6**)

At -70°C, 2.1 ml of n-BuLi (1.6 M solution in n-hexane, 3.3 mmol) were added dropwise to a stirred solution of the *N*-1-SEM-azole (3 mmol, in 10 ml of dry THF) under argon. After stirring for 1 h at this temperature, 3 mmol of the electrophile (see Table 1) in 5 ml of dry THF were added *via* syringe and the mixture was allowed to reach ambient temperature within 1.5 h (in the preparation of **7** an excess of dry ice was added). Then saturated ammonium chloride solution (30 ml) was added and the mixture was sucessively extracted with ether and ethyl acetate. The combined organic layers were dried and evaporated *in vacuo*. The residue was purified by column chromatography or mplc using mixtures of dichloromethane - ethyl acetate as eluents.

1-[2-(Trimethylsilyl)ethoxy]methyl-1*H*-pyrazole-5-carboxylic Acid (**7**)

The reaction mixture was acidified to pH 3 with 0.1 N HCl and then extracted with ether and ethyl acetate. The combined organic layers were treated with saturated $NaHCO_3$ solution and the bicarbonate layer was acidified with diluted HCl. The precipitated material was collected by filtration, washed with water and dried to afford colorless crystals, mp 48-49°C. Ir (KBr): 3480 (OH), 2900 (CH aliph.), 1710 (C=O) cm^{-1};

^{1}H-nmr (DMSO-d_6): δ 14.00 - 10.00 (very broad s, 1 H, exchangeable with D_2O, OH), 7.60 (d, J = 1.9 Hz, 1 H, pyrazole H-3), 6.87 (d, J = 1.9 Hz, 1 H, pyrazole H-4), 5.74 (s, 2 H, NCH_2O), 3.52 (m, 2 H, OCH_2C), 0.77 (m, 2 H, $SiCH_2$), -0.09 (s, 9 H, $SiCH_3$). Anal. Calcd for $C_{10}H_{18}N_2O_3Si$: C, 49.56; H, 7.49; N, 11.56. Found: C, 49.41; H, 7.39; N, 11.68.

Phenyl 1-[2-(Trimethylsilyl)ethoxy]methyl-1*H*-pyrazol-5-yl Ketone (**8**)

Colorless oil; ir: 2900 (CH aliph.), 1710, 1640 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 7.96 - 7.83 (m, 2 H, Ph H-2,6), 7.65 - 7.45 (m, 4 H, Ph H-3,4,5 and pyrazole H-3), 6.69 (d, J = 1.9 Hz, 1 H, pyrazole H-4), 5.88 (s, 2 H, NCH_2O), 3.60 (m, 2 H, OCH_2C), 0.88 (m, 2 H, $SiCH_2$), -0.07 (s, 9 H, $SiCH_3$); ms (m/z, %) 302 (M^+, 1), 259 (31), 245 (19), 230 (19), 229 (100), 186 (72), 185 (52), 105 (36), 91 (32), 77 (40), 73 (76). Anal. Calcd for $C_{16}H_{22}N_2O_2Si$: C, 63.54; H, 7.33; N, 9.26. Found: C, 63.94; H, 7.50; N, 9.14.

α-Phenyl-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-pyrazole-5-methanol (**9**)

Colorless oil; ir: 3300 (OH), 2940, 2880 (CH aliph.) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.37 - 7.30 (m, 6 H, Ph-H, pyrazole H-3), 6.06 (part of an AB system, J = 5.1 Hz, 1 H, exchangeable with D_2O, OH), 5.95 (d, J = 1.7 Hz, 1 H, pyrazole H-4), 5.87 (part of an AB system, J = 5.1 Hz, s after addition of D_2O, 1 H, C<u>H</u>OH), 5.56 and 5.30 (AB system, J = 10.9 Hz, 2 H, NCH_2O), 3.45 (m, 2 H, OCH_2C), 0.75 (m, 2 H, $SiCH_2$), -0.06 (s, 9 H, $SiCH_3$); ^{13}C-nmr ($CDCl_3$): δ 145.5 (pyrazole C-5), 141.0 (Ph C-1), 138.2 (pyrazole C-3, ^1J = 185.3 Hz, ^2J = 5.6 Hz), 128.2 (Ph C-3,5), 127.7 (Ph C-4), 126.3 (Ph C-2,6), 107.1 (pyrazole C-4, ^1J = 177.0 Hz, ^2J = 10.3 Hz, ^3J = 2.9 Hz), 78.1 (NCH_2O), 67.4 (CHOH), 66.3 (OCH_2C), 17.5 (CCH_2Si), -1.7 ($SiCH_3$); ms (m/z, %): 261 (M^+-$SiCH_3$, 18), 231 (10), 188 (40), 186 (13), 185 (12), 173 (15), 157 (43), 130 (12), 115 (16), 105 (11), 97 (100), 92 (32), 91 (60), 79 (13), 77 (23), 75 (34), 73 (87). Anal. Calcd for $C_{16}H_{24}N_2O_2Si$: C, 63.12; H, 7.95; N, 9.20. Found: C, 63.42; H, 7.97; N, 9.05.

5-Phenylthio-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-pyrazole (**10**)

Colorless oil; ^{1}H-nmr ($CDCl_3$):[30] δ 7.63 (d, J = 1.8 Hz, 1 H, pyrazole H-3), 7.25 - 7.10 (m, 5 H, Ph-H), 6.55 (d, J = 1.8 Hz, 1 H, pyrazole H-4), 5.52 (s, 2 H, NCH_2O), 3.52 (m, 2 H, OCH_2C), 0.80 (m, 2 H, $SiCH_2$), -0.05 (s, 9 H, $SiCH_3$); ms (m/z, %): 306 (M^+, 6), 263 (34), 261 (21), 233 (32), 206 (23), 190 (100), 189 (65), 176 (23), 171 (18), 167 (15), 157 (46), 151 (14), 116 (13), 113 (15), 109 (17), 91 (23), 87 (20), 77 (11), 75 (11), 73 (83). Anal. Calcd for $C_{15}H_{22}N_2OSSi$: C, 58.78; H, 7.23; N, 9.14. Found: C, 58.78; H, 7.29; N, 9.00.

5-Trimethylsilyl-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-pyrazole (**11**)

Colorless oil; ^{1}H-nmr ($CDCl_3$): δ 7.50 (d, J = 1.7 Hz, 1 H, pyrazole H-3), 6.45 (d, J = 1.7 Hz, 1 H, pyrazole H-4), 5.50 (s, 2 H, NCH_2O), 3.51 (m, 2 H, OCH_2C), 0.89 (m, 2 H, $SiCH_2$), 0.34 (s, 9 H, pyrazole-$SiCH_3$), -0.03 (s, 9 H, $SiCH_3$ of SEM); ms (m/z, %): 270 (M^+, 1), 227 (22), 170 (36), 155 (12), 154 (70), 153 (30), 141 (16), 140 (13), 139 (95), 77 (14), 73 (100). Anal. Calcd for $C_{12}H_{26}N_2OSi_2$: C, 53.28; H, 9.69; N, 10.36. Found: C, 53.67; H, 9.59; N, 10.13.

Phenyl 1-[2-(Trimethylsilyl)ethoxy]methyl-1*H*-1,2,4-triazol-5-yl Ketone (**12**)

Colorless oil; ir: 1650 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$): δ 8.39 - 8.27 (m, 2 H, Ph H-2,6), 8.07 (s, 1 H, triazole H-3), 7.62 - 7.40 (m, 3 H, Ph H-3,4,5), 5.91 (s, 2 H, NCH_2O), 3.67 (m, 2 H, OCH_2C), 0.89 (m, 2 H, $SiCH_2$), -0.06 (s, 9 H, $SiCH_3$); ms (m/z, %): 273 (M^+-$2CH_3$, 9), 260 (42), 231 (20), 230 (100), 187 (32), 186 (34), 170 (14), 105 (43), 77 (35), 73 (61). Anal. Calcd for $C_{15}H_{21}N_3O_2Si$: C, 59.37; H, 6.98; N, 13.85. Found: C, 59.64; H, 6.70; N, 14.10.

α-Phenyl-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-1,2,4-triazole-5-methanol (**13**)

Colorless oil which solidified on standing, mp 40-43°C; ^{1}H-nmr ($CDCl_3$): δ 7.85 (s, 1 H, triazole H-3), 7.37 (s, 5 H, Ph-H), 6.08 (broad s, sharp s after addition of D_2O, 1 H, CHOH), 5.33 (s, 2 H, NCH_2O), 4.00 (broad s, 1 H, exchangeable with D_2O, OH), 3.49 (m, 2 H, OCH_2Si), 0.81 (m, 2 H, $SiCH_2$), -0.04 (s, 9 H, $SiCH_3$); ms (m/z, %): 305 (M^+, 3), 262 (23), 232 (27), 189 (26), 186 (18), 158 (93), 115 (24), 98 (30), 91 (20), 75 (31), 73 (100), 55 (15). High resolution ms: Calcd for $C_{15}H_{23}N_3O_2Si$: 305.1560. Found: 305.1585 ± 0.0031. Anal. Calcd for $C_{15}H_{23}N_3O_2Si \cdot 0.2\ H_2O$: C, 58.30; H, 7.63; N, 13.60. Found: C, 58.40; H, 7.76; N, 13.26.

5-Phenylthio-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-1,2,4-triazole (**14**)

Colorless oil; ^{1}H-nmr ($CDCl_3$):[31] δ 7.92 (s, 1 H, triazole H-3), 7.46 - 7.30 (m, 5 H, Ph-H), 5.53 (s, 2 H, NCH_2O), 3.61 (m, 2 H, OCH_2C), 0.89 (m, 2 H, $SiCH_2$), -0.02 (s, 9 H, $SiCH_3$); ms (m/z, %): 307 (M^+, 19), 264 (40), 262 (28), 250 (19), 249 (20), 248 (57), 235 (11), 234 (62), 207 (35), 191 (48), 172 (16), 168 (13), 158 (15), 109 (16), 88 (17), 77 (13), 73 (100), 55 (19). Anal. Calcd for $C_{14}H_{21}N_3OSSi$: C, 54.69; H, 6.88; N, 13.67. Found: C, 54.43; H, 6.95; N, 13.69.

5-Chloro-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-1,2,4-triazole (**15**)

Colorless oil; ^{1}H-nmr ($CDCl_3$):[31] δ 7.86 (s, 1 H, triazole H-3), 5.47 (s, 2 H, NCH_2O), 3.66 (m, 2 H, OCH_2C), 0.91 (m, 2 H, $SiCH_2$), -0.02 (s, 9 H, $SiCH_3$); ^{13}C-nmr ($CDCl_3$): δ 151.2 (triazole C-3, ^1J = 211.1 Hz), 142.3 [triazole C-5, ^3J(C5,H3) = 9.0 Hz, ^3J(C5,NCH2) = 3.1 Hz], 76.6 (NCH_2O, ^1J = 160.5 Hz), 67.5 (OCH_2C, ^1J = 142.7 Hz), 17.6 (CCH_2Si, ^1J = 118.8 Hz), -1.6 ($SiCH_3$, ^1J = 118.7 Hz); ms (m/z, %): 203/205 (M^+-2CH_3, 3/1), 190/192 (49/17), 160/162 (100/35), 115 (12), 103 (20), 73 (92), 55 (16). Anal. Calcd for $C_8H_{16}N_3OClSi$: C, 41.10; H, 6.90; N, 17.97. Found: C, 41.02; H, 6.73; N, 18.18.

5-Methyl-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-1,2,4-triazole (**16**)

Colorless oil; ^{1}H-nmr ($CDCl_3$): δ 7.78 (s, 1 H, triazole H-3), 5.42 (s, 2 H, NCH_2O), 3.59 (m, 2 H, OCH_2C), 2.52 (s, 3 H, pyrazole-CH_3), 0.88 (m, 2 H, $SiCH_2$), -0.03 (s, 9 H, $SiCH_3$); ms (m/z, %): 212 (M^+-1, 1), 170 (33), 140 (100), 115 (16), 113 (15), 97 (53), 73 (69), 55 (23). High resolution ms: Calcd for $C_9H_{19}N_3OSi$: 213.1297. Found: 213.1293 ± 0.0021. Anal. Calcd for $C_9H_{19}N_3OSi$: C, 50.67; H, 8.98; N, 19.69. Found: C, 50.79, H, 9.13; N, 19.90.

Deprotection of 1-SEM-1*H*-pyrazoles and 1-SEM-1*H*-1,2,4-triazoles

Method a): The SEM-protected substrate (1 mmol) in ethanol (7 ml) was treated with 3 N aqueous HCl (15 ml) and the mixture was refluxed for 2 h. After evaporation of ethanol, the cooled reaction mixture was neutralized with saturated K_2CO_3 solution and extracted with dichloromethane. After drying, the solvent was evaporated and the residue was purified by column chromatography.

Method b): The SEM-protected azole (1 mmol) was treated with 5 ml of an 1 M solution of tetrabutylammonium fluoride in THF and the mixture was refluxed for 4 h. The residue obtained after evaporation of the solvent was subjected to column chromatography to give the corresponding NH-azoles. Thus were obtained:

1 (Starting from **3**), yield: 75% (method a).

2 (Starting from **6**), yield: 90% (method a).

Phenyl 1*H*-Pyrazol-3-yl Ketone (**17**)

(Starting from **8**), yield: 63% (method b), colorless crystals, mp 97-98°C (lit.,[32] mp 98°C); ^{1}H-nmr ($CDCl_3$): δ 9.69 (s, 1 H, exchangeable with D_2O, NH), 8.13 - 8.01 (m, 2 H, Ph H-2,6), 7.64 (d, J = 2.1 Hz, 1 H, pyrazole

H-5), 7.60 - 7.35 (m, 3 H, Ph H-3,4,5), 6.89 (d, J = 2.1 Hz, 1 H, pyrazole H-4).

3-Phenylthio-1*H*-pyrazole (**18**)

(Starting from **10**), yield: 60% (method b), colorless oil which solidified with time, mp 38-41°C; ^{1}H-nmr in accordance with data given in ref.[18]

3-Phenylthio-1*H*-1,2,4-triazole (**19**)

(Starting from **14**), yield: 90% (method a), colorless crystals, mp 79-82°C (lit.,[17] mp 79-81°C); ^{1}H-nmr in accordance with data given in ref.[17]

ACKNOWLEDGEMENT

The authors wish to express their gratitude to Ing. J. Dolezal (Institute of General Chemistry, Technical University of Vienna) for recording the high resolution mass spectra. The glc/ms spectrometer was made available by the Austrian "Fonds zur Förderung der wissenschaftlichen Forschung" (grant P 6260 C).

REFERENCES AND NOTES

1. Partly presented at the "23. Hauptversammlung der Gesellschaft Deutscher Chemiker", Munich, September 1991; abstract No. OC 21.
2. Part of the Diploma Thesis of N. Fugina, University of Vienna.
3. Part of the Diploma Thesis of M. Wasicky, University of Vienna.
4. For a discussion see: a) D. J. Chadwick and R. I. Ngochindo, J. Chem. Soc., Perkin Trans. 1, 1984, 481; b) B. Iddon, Heterocycles, 1985, **23**, 417; c) T. S. Manoharon and R. S. Brown, J. Org. Chem., 1988, **53**, 1107.
5. A. R. Katritzky, G. W. Rewcastle, and W.-Q. Fan, J. Org. Chem., 1988, **53**, 5685.
6. R. Hüttel and M. E. Schön, Liebigs Ann. Chem., 1959, **625**, 55.
7. D. E. Butler and S. M. Alexander, J. Org. Chem., 1972, **37**, 215.
8. A. R. Katritzky, C. Jayaram, and S. N. Vassilatos, Tetrahedron, 1983, **39**, 2023.

9. F. Effenberger and A. Krebs, J. Org. Chem., 1984, **49**, 4687.

10. P. Jutzi and U. Gilge, J. Organomet. Chem., 1983, **246**, 163.

11. H. Behringer and R. Ramert, Liebigs Ann. Chem., 1975, 1264.

12. D. K. Anderson, J. A. Sikorski, D. B. Reitz, and L. T. Pilla, J. Heterocycl. Chem., 1986, **23**, 1257.

13. H. W. Gschwend and H. R. Rodriguez, Org. React., 1979, **26**, 23.

14. B.-R. Tolf, R. Dahlbom, H. Theorell, and A. Akeson, Acta Chem. Scand. B, 1982, **36**, 101.

15. G. Heinisch, W. Holzer, and S. Pock, J. Chem. Soc., Perkin Trans. 1, 1990, 1829.

16. A. R. Katritzky, J. N. Lam, S. Saumitra, and G. W. Rewcastle, Progr. Heterocycl. Chem., 1989, **1**, 1.

17. A. R. Katritzky, P. Lue, and K. Yannakopoulou, Tetrahedron, 1990, **46**, 641.

18. A. R. Katritzky, P. Lue, and K. Akutagawa, Tetrahedron, 1989, **45**, 4253.

19. P. J. Dudfield, C. T. Ekwuru, K. Hamilton, C. E. Osbourn, and D. J. Simpson, Synlett, 1990, 277.

20. D. E. Butler and H. A. De Wald, J. Org. Chem., 1975, **40**, 1353.

21. R. G. Jones, J. Am. Chem. Soc., 1949, **71**, 3994.

22. a) J. M. Muchowski and D. R. Solas, J. Org. Chem., 1984, **49**, 203; b) M. P. Edwards, S. V. Ley, S. G. Lister, and B. D. Palmer, J. Chem. Soc., Chem. Commun., 1983, 630; c) M. P. Edwards, S. V. Ley, S. G. Lister, B. D. Palmer, and D. J. Williams, J. Org. Chem., 1984, **49**, 3503.

23. M. P. Edwards, A. M. Doherty, S. V. Ley, and H. M. Organ, Tetrahedron, 1986, **42**, 3723.

24. a) J. P. Whitten, D. P. Matthews, and J. R. McCarthy, J. Org. Chem., 1986, **51**, 1891; b) B. H. Lipshutz, W. Vaccaro, and B. Huff, Tetrahedron Lett., 1986, **27**, 4095; c) B. H. Lipshutz, B. Huff, and W. Hagen, Tetrahedron Lett., 1988, **29**, 3411.

25. T. Kline, J. Heterocycl. Chem., 1985, **22**, 505.

26. Investigations to direct the course of the reaction either towards halogen-metal exchange or towards deprotonation in 5-position by application of lithiating agents other than n-BuLi as well as by variation of temperature and solvent are in progress.

27. The yields given in Table 1 are not optimized and refer to analytically pure products.

28. With the 1-SEM-5-substituted triazoles (**12** - **16**) in no case isomerisation to 1,3-disubstitution products (as described by Katritzky[17,29] for 5-substituted 1-pyrrolidinomethyl-1,2,4-triazoles) could be observed.

29. A. R. Katritzky, A. Jozwiak, P. Lue, K. Yannakopoulou, G. J. Palenik, and Z.-Y. Zhang, Tetrahedron, 1990, **46**, 633.

30. W. Holzer, Tetrahedron, 1991, **47**, 1393.

31. W. Holzer, Tetrahedron, 1991, **47**, 5471.

32. K. Bowden and E. R. H. Jones, J. Chem. Soc., 1946, 953.

Received, 24th October, 1991