Conversion of Dimethyl Acetals of α-Hydroxyacetophenones and α-Hydroxypropiophenone to Monoazides and Tetrazoles Using Trimethylsilyl Azide

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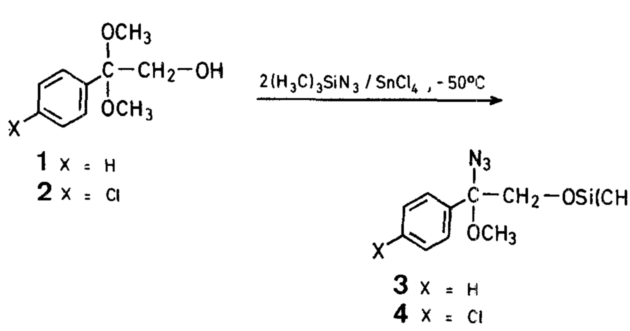
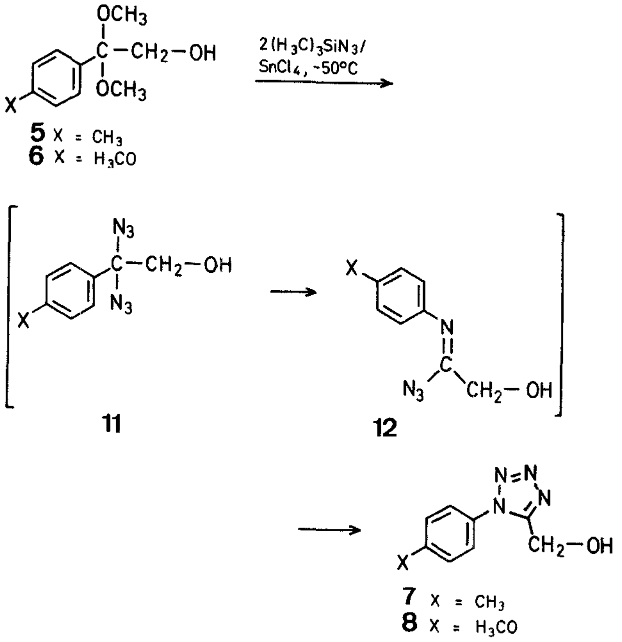
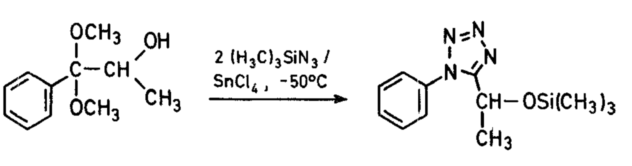
Recently we published a widely applicable method for the conversion of enolizable carbonyl compounds to α-hydroxy dimethyl acetals using (diacetoxyiodo)-benzene in methanolic base[1a-d]. Others have found that ketone acetals react with trimethylsilyl azide under Lewis acid catalysis to yield monoazides, geminal diazides, or tetrazole derivatives depending upon reaction conditions and substrate[2].

We report the application of this latter reaction to α-hydroxy dimethyl acetals of *p*-substituted phenyl derivatives. In the case of **1** and **2** (phenyl, *p*-chlorophenyl), one methoxy group of the dimethyl acetal is replaced by an azido group with formation of the trimethylsilyl derivative of the primary alcohol originally present (**3** and **4**, respectively) in the starting material. This result is similar to the reaction of dialkyl acetals with trimethylsilyl cyanide[3,4] in which one alkoxyl group is replaced by cyano. In the case of **5** and **6**, which possess the electron donating groups methoxyl and methyl in the *para*-positions, tetrazoles **7** and **8** are formed probably via geminal diazide **11** as in the case of **5**, and subsequent





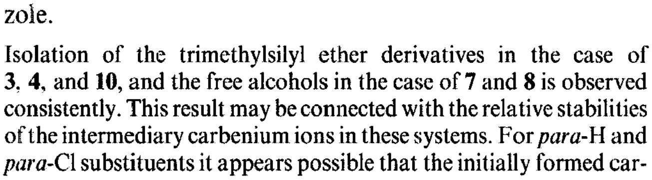


9 10

Lewis acid-induced loss of a molecule of dinitrogen, 1,2-phenyl migration, **11** → **12**, and cyclization of the thus formed azomethine-azide, to yield the tetrazole. Lewis acid-catalysed decomposition of alkyl azides is well known[5a-g]. The formation of tetrazoles in the thermal decomposition of other geminal diazides[6a-c] is well documented.

The final example **9** → **10**, is unusual in that **9** possesses a hydrogen atom in the *para*-position like **1** but yields a geminal diazide which yields tetrazole **10**. Olah et al.[2] found in the case of benzophenone dimethyl acetal, reaction under the conditions used in this study yielded 1,5-diphenyltetrazole.

Isolation of the trimethylsilyl ether derivatives in the case of **3**, **4**, and **10**, and the free alcohols in the case of **7** and **8** is observed consistently. This result may be connected with the relative stabilities of the intermediary carbenium ions in these systems. For *para*-H and *para*-Cl substituents it appears possible that the initially formed carbenium ion is neutralized intramolecularly to yield an epoxide which then reacts with trimethylsilyl azide as shown below.



1 or 2

3 or 4

Cyclic acetals undergo analogous ring-opening with trimethylsilyl azide or trimethylsilyl cyanide to yield the silylated azidoalcohols or cyanoalcohols[2,4]. Epoxides react with trimethylsilyl halides to yield β-silyloxyalkyl halides[8].

In the case of *para*-CH_3 and *para*-OCH_3 substituents a relatively more stable open-carbenium ion may occur which adds azide ion followed by repetition of loss of methoxytrimethylsilane and addition of a second azide ion to yield the geminal diazide precursor of the tetrazoles. Since no epoxide intervenes, the hydroxymethyl group is unsilylated. Formation of the silylated tetrazole in the case of **9** → **10** may likewise involve the intermediacy of an epoxide analogous to that proposed in the cases of **1** and **2**. Opening of this epoxide by azide anion yields 1-azido-1-methoxy-1-phenyl-2-trimethylsiloxypropane. The secondary methyl group would sterically stabilize epoxide formation from this intermediary compound upon loss of methoxytrimethylsilane. Finally opening of this epoxide by azide ion yields the silylated geminal diazide which converts thermally to **10**.

Reaction of Dimethyl Acetals of α-Hydroxyaceto- and -propiophenones with Trimethylsilyl Azide; General Procedure:

The α-hydroxy dimethyl acetal (5 mmol) and trimethylsilyl azide (10 mmol) are placed in a 3-necked 50 ml round-bottomed flask equipped with a magnetic stirrer and the flask is cooled to about $-50°$ in a Dry Ice/ethanol bath under nitrogen. Then anhydrous tin(IV) chloride (20 μl) is added to the mixture through a syringe. The mixture is allowed to come to room temperature and is kept at this temperature overnight. Completion of the reaction is monitored by ^{1}H-N.M.R. spectroscopy. The mixture is diluted with ether (20 ml) and the ether layer is separated and washed with aqueous sodium hydrogen carbonate (2 × 20 ml). The aqueous layer is further extracted with ether (3 × 20 ml) and the combined ether extracts are dried with anhydrous magnesium sulfate and the solvent is removed in vacuo. The product is chromatographed on silica gel.

2-Azido-2-methoxy-phenethyl Trimethylsilyl Ether (**3**): prepared from 2,2-dimethoxy-2-phenylethanol (**1**; 0.91 g, 5 mmol) as described; yield: 0.77 g (58 %); colourless oil; b.p. 125–128 °C/0.6 torr.

$C_{12}H_{19}N_3O_2Si$	calc.	C 54.33	H 7.17	N 15.84
(265.4)	found	54.47	7.00	15.15

M.S. (20 eV): m/e = 250 ($M^+ - CH_3$, < 1 %); 236 ($M^+ - 29$, 13 %); 223 ($M^+ - N_3$, 18 %); 192 [$M^+ - (H_3C)_3Si$, 7 %]; 176 [$M^+ - (H_3C)_3SiO$, 5 %]; 162 [$M^+ - (H_3C)_3SiOCH_2$, 10 %]; 134 ($162 - N_3$, 38 %); 119 ($134 - CH_3$, 100 %); 105 (119 – N, 29 %); 103 (119 – O, 28 %); 91 (27 %); 89 [$(H_3C)_3SiO^+$, 29 %]; 73 [$(H_3C)_3Si^+$, 28 %].

I.R. (neat): ν = 2115 cm^{-1} (N_3).

^{1}H-N.M.R. ($CDCl_3$): δ = 0.19 (s, 9H); 3.50 (s, 3H); 4.10 (d, J = 4 Hz, 2H); 7.67–7.87 ppm (m, 5H).

^{13}C-N.M.R. ($CDCl_3$): δ = 1.5; 53.5; 72.7; 98.5; 129.3; 130.6; 131.0; 139.2 ppm.

2-Azido-2-methoxy-p-chlorophenethyl Trimethylsilyl Ether (**4**): prepared from 2,2-dimethoxy-2-(p-chlorophenyl)-ethanol (**2**; 1.10 g, 5 mmol) as described; yield: 0.64 g (43 %); colourless liquid; b.p. 120–122 °C/0.075 torr.

$C_{12}H_{18}ClN_3O_2Si$	calc.	C 48.08	H 6.01	Cl 11.85	N 14.02
(299.8)	found	48.20	5.64	12.61	14.35

M.S. (20 eV): m/e = 272 ($M^+ + 2 - 29$, 1 %); 270 ($M^+ - 29$, 3 %); 226 [$M^+ - (H_3C)_3Si$, 2 %]; 210 [$M^+ - (H_3C)_3SiO$, 6 %]; 196 [$M^+ - (H_3C)_3SiOCH_2$, 10 %]; 168 ($196 - N_2$, 15 %); 153 ($168 - CH_3$, 99 %); 139 (153 – N, 14 %); 125 (153 – CO, 27 %); 103 [$(H_3C)_3SiOCH_2^+$, 100 %]; 89 [$(H_3C)_3SiO^+$, 35 %]; 73 [$(H_3C)_3Si^+$, 85 %].

I.R. (neat): ν = 2120 cm^{-1} (N_3).

^{1}H-N.M.R. ($CDCl_3$): δ = 0.10 (s, 9H); 3.32 (s, 3H); 3.83 (d, J = 3 Hz, 2H); 7.47–7.53 ppm (m, 4H).

^{13}C-N.M.R. ($CDCl_3$): δ = 1.4 (q); 53.8 (q); 70.8 (t); 98.1 (s); 130.2, 130.8, 137.1, 137.8 ppm (phenyl C).

1-(p-Tolyl)-5-hydroxymethyltetrazole (7):
2,2-Dimethoxy-2-(p-tolyl)-ethanol (**5**; 0.98 g, 5 mmol) is treated as described in the general procedure. After recrystallisation from 1/4 dichloromethane/hexane, white crystalline **7** is obtained; yield: 0.39 g (41 %); m.p. 134–136 °C.

$C_9H_{10}N_4O$	calc.	C 56.84	H 5.26	N 29.40
(190.2)	found	56.86	5.58	29.39

M.S. (70 eV): m/e = 191 ($M^+ + 1$, 10 %); 190 (M^+, 5 %); 162 ($M^+ - N_2$, 8 %); 161 ($M^+ - 29$, 10 %); 148 ($M^+ - N_3$, 60 %); 133 (90 %); 132 (100 %); 105 (90 %). 91 (85 %); 77 (90 %).

I.R. (KBr): ν = 3300 cm^{-1} (OH).

^{1}H-N.M.R. ($CDCl_3$: δ = 2.47 (s, 3H); 4.87 (d, J = 6 Hz, 2H); 5.97 (t, J = 6 Hz, 1H, exchangeable with D_2O); 7.47–7.83 ppm (AA'BB'-q, 4H).

^{13}C-N.M.R. ($CDCl_3$/DMSO-d_6): δ = 20.8; 52.1; 124.3; 130.2; 131.5; 140.2; 154.3 ppm.

1-(p-Methoxyphenyl)-5-hydroxymethyltetrazole (8):
The general procedure is used starting with 2,2-dimethoxy-2-(p-methoxyphenyl)-ethanol (**6**; 1.06 g, 5 mmol). After recrystallisation from 1/4 dichloromethane/hexane, white crystalline **8** is obtained; yield: 0.39 g (38 %); m.p. 117–119 °C.

$C_9H_{10}N_4O_2$	calc.	C 52.43	H 4.85	N 27.18
(206.2)	found	52.58	4.99	27.08

M.S. (70 eV): m/e = 207 ($M^+ + 1$, 3 %); 206 (M^+, 2 %); 178 (5 %); 149 (75 %); 148 (90 %); 134 (82 %); 133 (100 %); 121 (81 %); 106 (79 %); 105 (83 %); 92 (65 %); 78 (57 %); 77 (69 %).

I.R. (KBr): ν = 3360 cm^{-1} (OH).

^{1}H-N.M.R. (CDCl$_3$/DMSO-d_6): δ = 3.97 (s, 3H); 4.87 (d, J = 5 Hz, 2H), 5.87 (t, J = 5 Hz, 1H, exchangeable with D$_2$O); 7.13–7.83 ppm (AA'BB'-q, 4H).

^{13}C-N.M.R. (CDCl$_3$/DMSO-d_6): δ = 53.1; 55.8; 115.2; 126.1; 154.3; 162.1 ppm.

1-Phenyl-5-(1-trimethylsilyloxyethyl)-tetrazole (10):

The general procedure is used with 1,1-dimethoxy-1-phenyl-2-propanol (**9**; 0.98 g, 5 mmol). After distillation, **10** is obtained as a white solid; yield: 0.62 g (47%); b.p. 178 °C/0.6 torr; m.p. 58–60 °C.

$C_{12}H_{18}N_4OSi$	calc.	C 54.96	H 6.87	N 21.37
(262.4)	found	55.52	6.82	21.43

M.S. (20 eV): m/e = 247 (M$^+$ −15, 3.7%); 175 (20%); 144 (14%); 118 (26%); 117 (63%); 73 (100%).

^{1}H-N.M.R. (CDCl$_3$): δ = 0.27 (s, 9H); 1.90 (d, J = 7 Hz, 3H); 5.74 (q, J = 7 Hz, 1H); 8.04 ppm (m, 5H).

^{13}C-N.M.R. (CDCl$_3$): δ = 1.5; 23.9; 63.6; 127.5; 131.2; 132.1; 136.2; 158.4 ppm.

The authors thank the Office of Naval Research for support of this work under N00014-83K-0306.

Received: December 31, 1983

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