Intramolecular Insertion of the Isonitrile Group into an Oxygen–Silicon Bond. Synthesis of a 2-Trimethylsilyloxazole *via* the α-Isocyano Silyl Enol Ether

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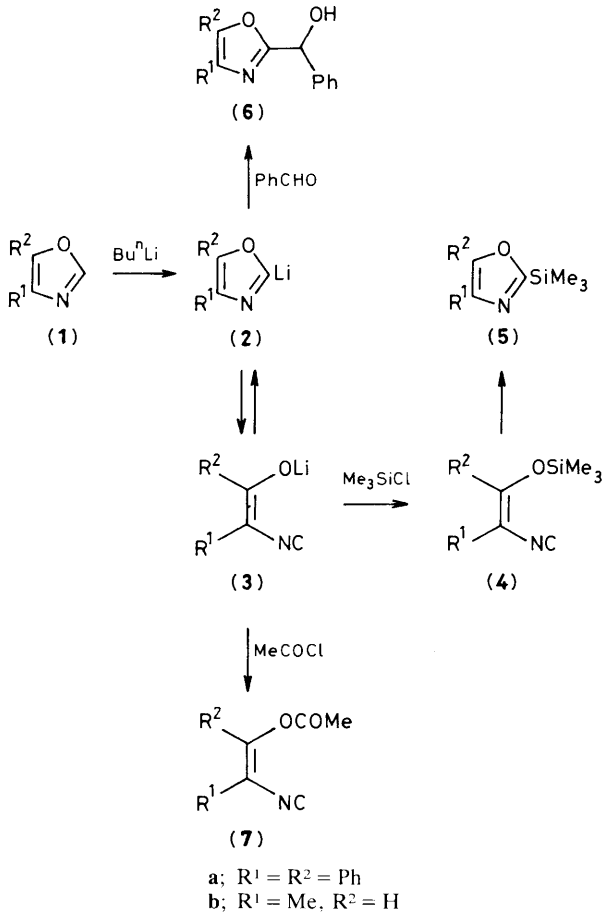
Treatment of lithiated 4-methyloxazole (**1b**) with trimethylsilyl chloride gives the α-isocyano silyl enol ether (**4b**) which when heated in the presence of potassium hydroxide undergoes ring closure to the 2-trimethylsilyloxazole (**5b**) whose reactions with *C*- and *S*-electrophiles afford 2-substituted oxazoles.

Lithiation of oxazoles produces an equilibrium mixture of the C-2 anion and the open-chain isomer, the α-isocyano enolate.[1] The species in equilibrium can be trapped by appropriate electrophiles. For instance, Schöllkopf and co-workers reported[2] that metallation of 4,5-diphenyloxazole (**1a**) and reaction with benzaldehyde gives the alcohol (**6a**), whereas treatment of (**1a**) with trimethylsilyl chloride leads to the silyl enol ether (**4a**) (Scheme 1). Herein we report an extension to the Schöllkopf observations and describe the preparation of the 2-silyloxazole (**5b**) and its reactions with carbon and sulphur electrophiles which show it to be a stable masked form of the corresponding carbanion (**2b**). 2-Silyloxazoles constitute an heretofore unreported class of silylated heterocycles[3] which in analogy with silylthiazoles,[4] are expected to be useful intermediates in the selective functionalization of these heterocycles. The wide application of oxazoles in ring transformation reactions[5] and cycloadditions[6] as well as reactive intermediates for the synthesis of carboxylic acids, amides, and peptides[7] is well documented.

The commercially available 4-methyloxazole (**1b**) was lithiated under standard conditions [Bu^nLi (1 equiv.), diethyl ether, −78 °C] (Scheme 1) and the resulting equilibrium mixture of the lithio salts (**2b**) and (**3b**) when treated with benzaldehyde gave the 2-(α-hydroxybenzyl)oxazole (**6b**)†

† All new compounds gave satisfactory microanalytical and/or mass spectral data and were adequately identified by i.r. and n.m.r. spectroscopy.

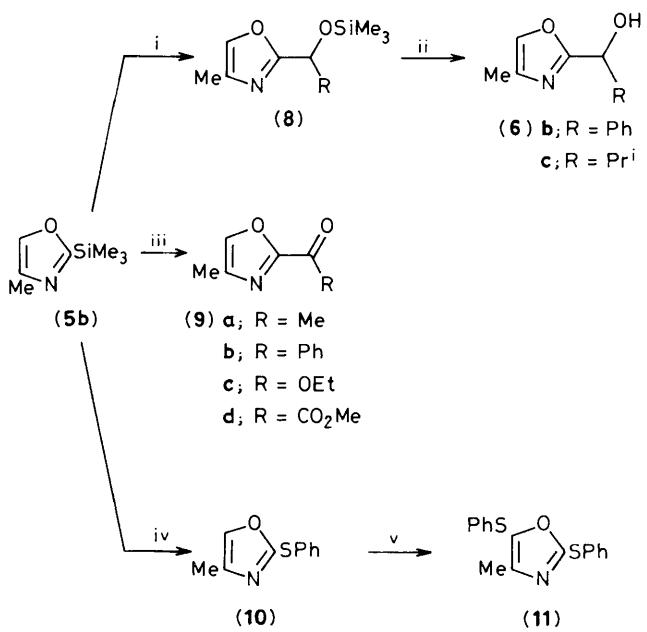


Scheme 1

(30% yield). The α-isocyano silyl enol ether (**4b**) (85% yield) or the acetyl enol ester (**7b**)‡ (80% yield) was formed on treatment of the equilibrium mixture with trimethylsilyl chloride or acetyl chloride, respectively. The reagents PhCHO, MeCOCl, and Me_3SiCl appear to be highly selective towards one of the two lithio salts (**2b**) and (**3b**) since in all three cases no products other than those indicated above could be detected in the ^1H n.m.r. spectra of the crude reaction mixtures.

Compound (**7b**) or (**4b**) could be repeatedly distilled with only partial $Z \rightarrow E$ isomerization, but heating of (**4b**) (oil bath at 100—105 °C) in the presence of a pellet of potassium hydroxide induced cyclisation to 4-methyl-2-trimethylsilyloxazole (**5b**) (*ca.* 60% yield).§ A similar type of cyclization was not observed for (**7b**). The conversion of the kinetically favoured α-isocyano silyl enol ether (**4b**) into the thermodynamically more stable oxazole (**5b**) can be viewed as an intramolecular insertion reaction of the nucleophilic isonitrile group into the oxygen–silicon bond. This reaction among other well known isonitrile insertions[8] is unusual in that it appears to require the presence of an oxygen nucleophile, which probably assists by interaction with silicon in the cleavage of the strong oxygen–silicon bond.

The synthetic utility of (**5b**) was shown by reactions with three different types of electrophiles which all gave 2-oxazole derivatives by substitution of the $SiMe_3$ group (Scheme 2). The reactions with aldehydes gave primarily the silyl ethers (**8**) which were characterized by n.m.r. spectroscopy without isolation. On acid hydrolysis, compounds (**8**) were transformed into the alcohols (**6**) in good overall yields (Table 1). The reactions with the acyl chlorides were significant in that they gave the oxazoles (**9a—d**) which unlike the alcohols (**6**) were not accessible from the equilibrium mixture of the lithio salts (**2b**) and (**3b**). Finally, the reaction of (**5b**) with phenylsulphenyl chloride produced a mixture of the 2-phenylthio- (**10**) and 2,5-di(phenylthio)-oxazole (**11**) the



Scheme 2. *Reagents*: i, (a) PhCHO (2 equiv.), neat, 70 °C, 24 h; (b) Pr^{i}CHO (2 equiv.), neat, 70 °C, 12 h; ii, 5% HCl in tetrahydrofuran; iii, (a) MeCOCl (2 equiv.), CH_2Cl_2, room temperature (r.t.), 19 h; (b) PhCOCl (2 equiv.), benzene, reflux, 12 h; (c) $ClCO_2Et$ (2 equiv.), benzene, reflux, 4 h; (d) $ClCOCO_2Me$ (2 equiv.), benzene, reflux, 2 h; iv, PhSCl (1 equiv.), benzene, r.t., 24 h; v, PhSCl (1 equiv.), benzene, r.t., 24 h.

Table 1. Reactions of 4-methyl-2-trimethylsilyloxazole (**5b**).

Product	Yield[a]/%	B.p. or m.p. (*t*/°C)
(**6b**)	41	79—81
(**6c**)	74	65—66 (0.8 mmHg)
(**9a**)	85	43—44 (1 mmHg)
(**9b**)	40	65—67
(**9c**)	84	102—104 (760 mmHg)
(**9d**)	32	64—66
(**10**)	42[b]	oil
(**11**)	8[b]	oil

[a] Yields are based on chromatographically isolated products [silica gel, diethyl ether–light petroleum (b.p. 40—60 °C)] and are not optimized. [b] A reversed ratio (0.26) between (**10**) and (**11**) was obtained using 2 equiv. of PhSCl.

‡ Both (**4b**) and (**7b**) were predominately in the *Z*-forms (95% by n.m.r.). (**4b**), B.p. 87—90 °C (20 mmHg), i.r. ν_{max} (neat) 2100, 1655 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 6.27 (br., 1 H), 1.85 (br., 3 H), 0.25 (s, 9 H); ^{13}C n.m.r. δ ($CDCl_3$) 166.6 (s), 139.6 (d), 106.0 (s), 15.3 (q), −1.8 p.p.m. (q). (**7b**), B.p. 38—39 °C (1 mmHg), i.r. ν_{max} (neat) 2100, 1765, 1685 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 7.26 (br., 1 H), 2.26 (s, 3 H), 1.95 (br., 3 H); ^{13}C n.m.r. δ ($CDCl_3$) 169.7 (s), 133.9 (d), 108.2 (s), 16.2 (q), 15.9 p.p.m. (q).

§ This yield refers to experiments where the 2-silyloxazole (**5b**) was continuously removed by distillation from the reaction flask; (**5b**), b.p. 78—80 °C (20 mmHg); ^1H n.m.r. δ ($CDCl_3$) 7.56 (q, 1 H, *J* 1.2 Hz), 2.24 (d, 3 H, *J* 1.2 Hz), 0.37 (s, 9 H); ^{13}C n.m.r. δ ($CDCl_3$) 170.4 (s), 136.6 (d), 136.2 (s), 11.2 (q), −2.0 p.p.m. (q).

composition of which depended on the molar ratio of the reactants (Table 1). This constitutes a new method for the thioarylation of the oxazole ring with an apparent low selectivity owing to the comparable reactivity towards the sulphenyl chloride of the C–Si bond in (**5b**) and the C–H bond at C-5 in the resulting product (**10**). This conclusion was supported by the product distribution determined at intervals (t.l.c. and n.m.r. spectroscopy) as well as by the conversion of (**10**) into (**11**) in a control experiment.

The substitution of the $SiMe_3$ group in a 2-silyloxazole may proceed by a variety of mechanisms owing to the possible participation of the aza group as we have suggested for the silylthiazoles,[4] but the reactivity of (**5b**) clearly indicates a new approach to regioselective functionalization of the oxazole ring which should overcome some synthetic difficulties in this important class of synthons.[5—7]

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