Reactions of Trimethylsilylthiazoles with Ketens: A New Route to Regioselective Functionalisation of the Thiazole Ring

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Summary 2-Trimethylsilylthiazole (**2**) and 2,5-bis(trimethylsilyl)thiazole (**6**) undergo *ipso*-substitution of the 2-$SiMe_3$ group with various ketens affording the thiazolyltrimethylsiloxy-ethylenes (**3**) and (**7**), respectively, which are hydrolysed to the 2-acylthiazoles (**4**), whereas 5-trimethylsilylthiazole (**8**) undergoes attack at C-2 by dichloroketen giving the Michael-type adduct 2-dichloroacetyl-5-trimethylsilylthiazole (**9c**).

SILYLATION of aromatic compounds followed by *ipso*-substitution of the silyl group by electrophiles[1] is currently employed in organic synthesis since the higher reactivity and selectivity of C–Si over C–H bonds allows the preparation of compounds access to which is difficult by direct electrophilic substitution. We are now applying this synthetic strategy to the functionalisation of the heteroaromatic thiazole ring[2] and report the preparation of thiazolylsilanes and their reactions with C-electrophilic ketens. Surprisingly, there are no reports of reactions of aryltrimethylsilanes with heterocumulenes.

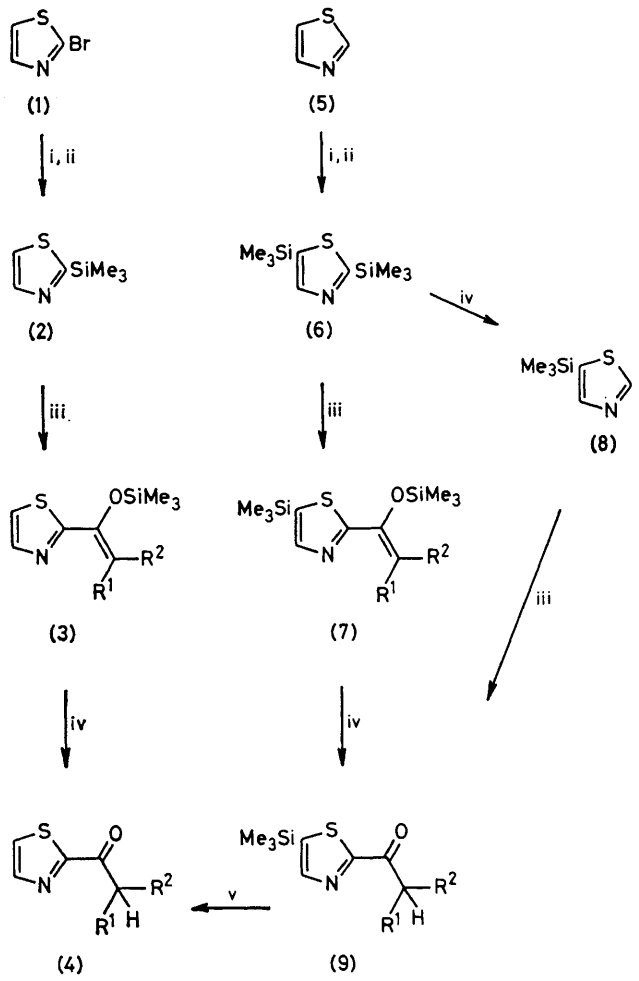
2-Trimethylsilylthiazole (**2**)† was prepared in good yield from 2-bromothiazole (**1**)[3] *via* halogen–metal exchange with 1 mol. equiv. of Bu^nLi at −78 °C in diethyl ether and subsequent reaction with trimethylsilyl chloride. Treating solutions of (**2**) (0·1—0·05 M) in hexane or benzene at room temperature with 1·2 mol. equiv. of three substituted ketens‡ of markedly different reactivity, *viz.* diphenylketen (DPK), t-butylcyanoketen (TBCK), and dichloroketen (DCK), gave essentially quantitative yields of the corresponding thiazol-2-yl-trimethylsiloxy-ethylenes (**3**) (Scheme). This reaction appeared to be highly stereospecific since the asymmetric keten TBCK gave solely the stereoisomer (**3b**) which we tentatively assigned the less hindered *E*-configuration. The silyl enol ethers (**3**) were readily converted into the 2-acylthiazoles (**4**) by acid-catalysed hydrolysis of the $OSiMe_3$ group.

Silylation of thiazole (**5**) *via* hydrogen–metal exchange with 1—2 mol. equiv. of Bu^nLi–Me_3SiCl produced mixtures of the monosilylthiazole (**2**) and 2,5-bis(trimethylsilyl)-thiazole (**6**) in comparable amounts. The reactivities of the 2- and 5-$SiMe_3$ groups of (**6**) towards electrophiles were

† All new compounds were characterized by elemental analyses (C, H, and N) and spectral data (^1H n.m.r., i.r., and mass). Yields and m.p.s or b.p.s are given in the Table.

‡ Reactions were carried out by the very slow addition of (**2**) to the keten in the case of DPK[4a] and TBCK[4b] or addition of the keten precursor $Cl_2CHCOCl$ to a mixture of (**2**) and Et_3N in the case of DCK.[4c]

dramatically different, thus permitting highly selective reactions. For example, treatment of (**6**) with either 1 or 2 mol. equiv. of DPK in hexane resulted exclusively in the formation of the silyl enol ether (**7a**) by regioselective *ipso*-substitution of the $SiMe_3$ group at C-2. Similarly, acid-catalysed desilylation of (**6**) occurred exclusively at the 2-$SiMe_3$ group to give 5-trimethylsilylthiazole (**8**).§ The side-chain $SiMe_3$ group of (**7a**) was readily removed on acid catalysis to give the 2-acyl-5-silylthiazole (**9a**) which in turn was totally desilylated on basic hydrolysis to give the acylthiazole (**4a**). Compounds of type (**9**) could also be prepared by direct acylation of 5-trimethylsilylthiazole (**8**) with highly reactive ketens, as illustrated by the exclusive formation of the Michael-type adduct (**9c**) from the reaction with DCK (15 h, room temperature).



a; $R^1 = R^2 = Ph$
b; $R^1 = CN$, $R^2 = Bu^t$
c; $R^1 = R^2 = Cl$

SCHEME. *Reagents:* i, Bu^nLi; ii, Me_3SiCl; iii: (a) $Ph_2C{=}C{=}O$ (DPK); (b) $Bu^t(CN)C{=}C{=}O$ (TBCK); (c) $Cl_2C{=}C{=}O$ (DCK); iv, silica or 5% HCl in tetrahydrofuran; v, 10% MeO^- in MeOH.

TABLE. Thiazolyl-silanes and thiazolyl-siloxy-ethylenes.

Compound	Yield/%[a]	M.p. or b.p. (*T*/°C)
(**2**)	55	56—57 at 10 mmHg
(**3a**)	97	62—64[b]
(**3b**)	90	38—40[b]
(**3c**)	99	Oil
(**6**)	40[c]	54—56[b]
(**7a**)	98	93—94[b]
(**8**)	97	64—65 at 13 mmHg
(**9a**)	89	119—120[b]
(**9c**)	60	Oil

[a] Yields are based on isolated products from the reactions shown in the Scheme. [b] From n-hexane. [c] Using 2 mol. equiv. of Bu^nLi–Me_3SiCl.

The formation of compounds (**3**) and (**7a**) represents a novel silyl enol ether synthesis[5] which can be accounted for on the basis of an electrophilic attack of keten on C-2 of the thiazole ring and transfer of the silyl group to oxygen of the cumulene, probably *via* a four-membered transition state or intermediate.[1,6] The presence of the O-silylated enolate function at C-2 of the thiazole ring should facilitate further synthetic elaboration and provide an efficient route to the selective functionalisation of this heterocycle. The formation of the 2-acylthiazoles (**4**), a class of substituted thiazole which has been so far inaccessible by direct Friedel–Crafts reaction,[7] is but one example of the promising synthetic utility of the silyl enol ethers (**3**) and (**7**) in thiazole chemistry.

(*Received, 24th March* 1981; *Com.* 333.)

§ Identical with a specimen prepared from 5-bromothiazole[3] and Bu^nLi–Me_3SiCl as described for (**2**).

[1] C. Eaborn, *J. Organomet. Chem.*, 1975, **100**, 43; D. Häbich and F. Effenberger, *Synthesis*, 1979, 841; T. H. Chan and I. Fleming, *ibid.*, p. 761.
[2] (a) A. Dondoni, A. Medici, C. Venturoli, L. Forlani, and V. Bertolasi, *J. Org. Chem.*, 1980, **45**, 621; A. Medici, P. Pedrini, M. Fogagnolo, and A. Dondoni, *J. Chem. Soc., Chem. Commun.*, 1980, 1077; (b) for recent reviews see 'The Chemistry of Heterocyclic Compounds—Thiazole and its Derivatives,' ed. J. V. Metzger, Wiley, New York, 1979, Vol. 34, p. 1.
[3] P. Roussel and J. V. Metzger, *Bull. Soc. Chim. Fr.*, 1962, 2075.
[4] (a) E. C. Taylor, A. McKillop, and G. H. Hawks, *Org. Synth.*, 1973, **52**, 36; (b) W. Weiler, Jr., W. G. Duncan, M. B. Liewen, and H. W. Moore, *ibid.*, 1976, **55**, 32; (c) L. Ghosez, R. Montaigne, A. Roussel, H. Van Lierde, and P. Mollet, *Tetrahedron*, 1971, **27**, 615.
[5] J. K. Rasmussen, *Synthesis*, 1977, 91; E. W. Colvin, *Chem. Soc. Rev.*, 1978, **7**, 15.
[6] F. H. Pinkerton and S. F. Thames, *J. Organomet. Chem.*, 1970, **24**, 623; *J. Heterocycl. Chem.*, 1971, **8**, 257.
[7] Ref. 2b, p. 535.

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