

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-SiMe₃ group with various ketens affording the thiazolyl-trimethylsiloxy-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 electrophiles¹ 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 ring² and report the preparation of thiazolylsilanes and their reactions with C-electrophilic ketens. Surprisingly, there are no reports of reactions of aryltrimethylsilanes with heterocumulenes.

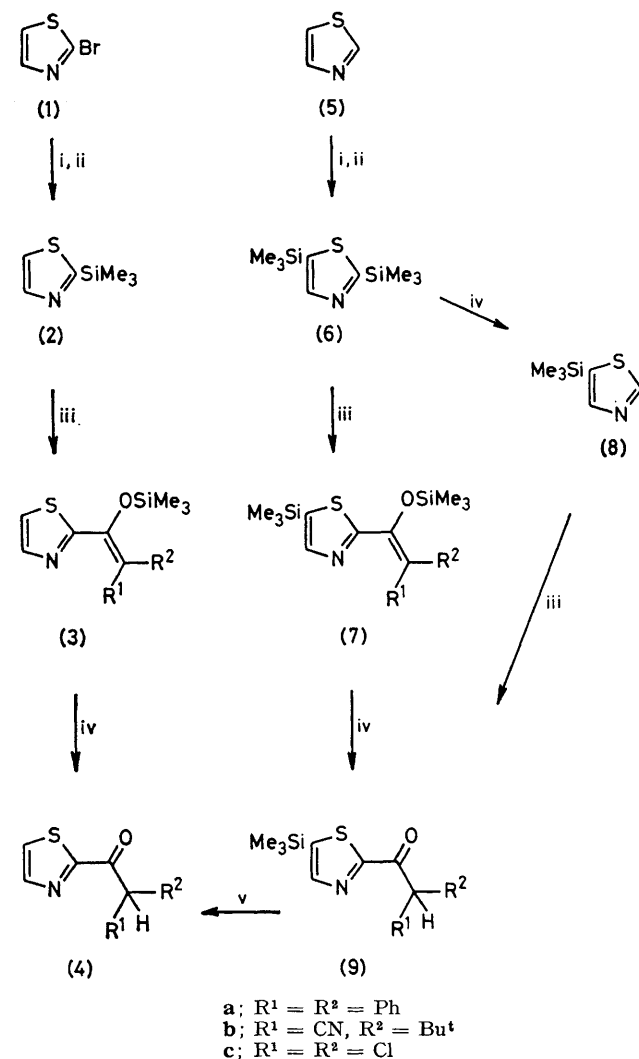
2-Trimethylsilylthiazole (**2**)[†] was prepared in good yield from 2-bromothiazole (**1**)³ *via* halogen-metal exchange with 1 mol. equiv. of BuⁿLi at -78 °C in diethyl ether and subsequent reaction with trimethylsilyl chloride. Treating solutions of (**2**) (0.1–0.05 M) in hexane or benzene at room 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 OSiMe₃ group.

Silylation of thiazole (**5**) *via* hydrogen-metal exchange with 1–2 mol. equiv. of BuⁿLi–Me₃SiCl produced mixtures of the monosilylthiazole (**2**) and 2,5-bis(trimethylsilyl)thiazole (**6**) in comparable amounts. The reactivities of the 2- and 5-SiMe₃ 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 Cl₂CHCOCl to a mixture of (**2**) and Et₃N 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



SCHEME. Reagents: i, BuⁿLi; ii, Me₃SiCl; iii: (a) Ph₂C=C=O (DPK); (b) Bu^t(CN)C=C=O (TBCK); (c) Cl₂C=C=O (DCK); iv, silica or 5% HCl in tetrahydrofuran; v, 10% MeO⁻ in MeOH.

formation of the silyl enol ether (7a) by regioselective *ipso*-substitution of the SiMe₃ group at C-2. Similarly, acid-catalysed desilylation of (6) occurred exclusively at the 2-SiMe₃ group to give 5-trimethylsilylthiazole (8).§ The side-chain SiMe₃ 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).

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 BuⁿLi—Me₃SiCl.

The formation of compounds (3) and (7a) represents a novel silyl enol ether synthesis⁵ 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-bromothiazole³ and BuⁿLi—Me₃SiCl 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.