chlorate, and tetraethylammonium tetrafluoroborate (Fluka AG) were all used without further purification.

Cyclic Voltammetry and Controlled Potential Electrolysis. For comprehensive details, see ref 3. All voltammograms were recorded vs Ag wire quasi-reference electrode (+0.39 V vs NHE). Pulses were employed in preparative electrolysis whenever it was necessary to maintain a reasonable level of current. Pulses were given every 10 s for 1 s at 0.5 V (it should be noted that they did not affect the products or their distribution but only shortened the electrolyses duration). By the end of the electrolysis the anolyte was worked up separately from the catholyte solution. The electrolyte was washed several times with water, and the remainder, dichloromethane solution, was dried over $MgSO_4$, filtered, and evaporated. The residue was weighed and sampled for ^1H NMR, IR, GC/MS, and GLC. Separation of products was conducted either by silica gel column (40 cm × 1 cm o.d.) using a 4:1 mixture of petroleum ether (60–80) and ether (or acetone), respectively, or by GLC column (10% SE-30 on Chromosrb W, 7 ft × $^1/_4$ in.) at 150 °C for product mixtures from oxidation of **4** and **5**, at 190 °C for **6** and **7**, and at 200 °C for **8–10**.

Products. Spectral data (^1H NMR, MS, IR, and elemental analysis for **2a–e** and **3a–d** were given elsewhere.[3] Carbodiimides **11a–c** showed a typical stretching frequency at ~2120 cm^{-1} in the IR and each afforded M + 1 mass unit by MS. As to the ^1H NMR, the protons adjacent to nitrogens have chemical shifts in the range of 3.1–3.2 ppm. Spectral data for the dialkylurea derivatives **12a,b** were in agreement with the literature.[15] Oxidation products from **9**: **13a**, ^1H NMR δ 1.58 (s, 2 H), 1.94 (d, 4 H), 2.05 (d, 4 H), 2.32 (br s, 4 H); MS *m/e* (relative intensity) 227 (M^+, 8), 171 (28), 169 (100), 133 (31), 91 (29); **13b**, ^1H NMR δ 1.67 (s, 6 H), 2.14 (br s, 9 H) [in good agreement with 1-bromoadamantane];[16] **13c**, ^1H NMR δ 1.63 (br s, 2 H), 2.06 (d, 8 H), 2.30 (br s, 2 H), 2.46 (s, 2 H) [in good agreement with the corresponding spectrum of 1,3-difluoroadamantane];[16] **14**, ^1H NMR δ 1.74 (s, 6 H), 3.38 (s, 2 H).

Kinetic Measurements by FT-IR. Infrared spectra were taken with a DX-20 Nicolet FT-IR spectrometer operating with a nominal resolution of 2 cm^{-1}. Samples were studied as 0.045 M solutions in $CHBr_3$ by using a cell equipped with KBr windows and having an optical path of 0.1 mm. For kinetic studies the cell was heated to the desired temperature (100 or 117 °C), at which it could be maintained to within better than ±0.5 °C, and the solution introduced into the hot cell. Although the temperature of the solution could not be measured directly it could be judged from the time dependence of the spectral absorption. The heating time of the solution, which takes several minutes, introduces an uncertainty in the origin of the time axis (which in our runs extended over several hours). Clearly, for a first-order reaction, as is the case here, this small uncertainity in time hardly affects the determination of the rate constants.

Acknowledgment. We are grateful to Prof. S. Weiss for his kind assistance and helpful suggestions in carrying out the kinetic experiments by FT-IR and to Elias Shakur for carrying out the chemical reduction of **2**.

Registry No. **2a**, 6320-65-6; **2b**, 108168-82-7; **2c**, 108168-83-8; **2d**, 108168-84-9; **2e**, 113162-00-8; **3a**, 103031-01-2; **3b**, 98484-44-7; **3c**, 98492-89-8; **3d**, 108168-85-0; **4**, 556-61-6; **5**, 542-85-8; **6**, 628-30-8; **7**, 592-82-5; **8**, 1122-82-3; **9**, 4411-26-1; **10**, 590-42-1; **11a**, 821-79-4; **11b**, 693-64-1; **11c**, 538-75-0; **12a**, 623-95-0; **12b**, 1792-17-2; **13a**, 113162-01-9; **13b**, 935-56-8; **13c**, 16104-50-0; **14**, 63206-58-6; EtNHC(S)NHEt, 105-55-5.

(15) Ogura, H.; Takeda, K.; Tokue, R.; Kobayashi, T. *Synthesis* **1978**, *394*.

(16) Pouchert, C. H.; Campbell, J. R. In *The Aldrich Library of NMR Spectra*; Aldrich: Milwaukee, 1974; Vol. 1, p 77.

Synthesis of (Trimethylsilyl)thiazoles and Reactions with Carbonyl Compounds. Selectivity Aspects and Synthetic Utility[1]

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Synthetic routes to all possible regioisomeric mono- and bis(trimethylsilyl)thiazoles as well as to the tris(trimethylsilyl) derivative via lithiation–silylation sequences of the thiazole ring followed by selective protodesilylation in some cases are described. (Trimethylsilyl)thiazoles serve as thiazolyl donor synthons upon reaction with carbonyl compounds (ketenes, acyl chlorides, aldehydes) for the preparation of mono- and bis-substituted thiazoles in very good yields. Carbodesilylation occurs more readily at the 2- than the 5-position, whereas no reaction takes place at the 4-position. A mechanism via a thiazolium 2-ylide as an intermediate is suggested for the carbodesilylation at the 2-position.

The synthetic utility of silicon substitution on carbon–carbon bond-forming processes to heteroarenes[2] is inherent not only in the ready cleavage of the heteroaryl–silicon bond (ipso attack) by a variety of carbon electrophiles (e.g. carbonyl compounds) in the presence of nucleophilic catalysts but also in the high regio- and chemoselectivity of these operations. Thus heteroaryl silanes can be viewed as stable yet reactive heteroaryl carbanion equivalents[3] which allow the synthesis of otherwise poorly accessible functionalized heterocycles. For instance, we have recently described[4] the preparation of 4- and 5-substituted 2-(tri-

(1) Presented in part by A.D. at the Tenth International Congress of Heterocyclic Chemistry, Waterloo (Canada), April 11–16, 1985. See also: Dondoni, A. *Lect. Heterocycl. Chem.* **1985**, *8*, 13.

(2) Reviews: Häbich, D.; Effenberger, F. *Synthesis* **1979**, 841. Birkofer, L.; Stuhl, O. *Top. Curr. Chem.* **1980**, *88*, 33. Weber, W. P. In *Silicon Reagents for Organic Synthesis*; Springer Verlag: Berlin, 1983; Chapter 8. Recent papers on silyl heterocycles. (a) Indoles: Barret, A. G. M.; Dauzonne, D.; O'Neil, I. H.; Renaud, H. *J. Org. Chem.* **1984**, *49*, 4409. Maychrzak, M. W.; Sinken, G. *Synthesis* **1986**, 956. (b) Pyrazoles, isoxazoles, and 1,2,3-triazoles: Birkofer, L.; Richtzenhain, K. *Chem. Ber.* **1979**, *112*, 2829. (c) Benzothiazole and isoxazoles: Ricci, A.; Fiorenza, M.; Grafagni, M. A.; Bartolini, G.; Seconi, G. *Tetrahedron Lett.* **1982**, *23*, 5079. (d) *N*-Methylpyrazoles: Effenberger, F.; Krebs, A. *J. Org. Chem.* **1984**, *49*, 4687. (e) *N*-Methylimidazoles and thiazoles: Jutzi, P.; Gilge, H. *J. Heterocycl. Chem.* **1983**, *20*, 1011.

(3) This definition does not imply any mechanistic formulation on the ipso substitution reaction; it arises from considerations on the ionic character (ca. 12%) of the C–Si bond wherein silicon is the positive end and carbon the negative end of the dipole. For reviews on organosilicon compounds, see: Eaborn, C. *J. Organomet. Chem.* **1975**, *100*, 43. Colvin, E. W. *Chem. Soc. Rev.* **1978**, *7*, 15. Fleming, J. *Chem. Soc. Rev.* **1981**, *10*, 83. Fleming, J. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 3, p 541.

(4) Dondoni, A.; Dall'Occo, T.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Chem. Soc., Chem. Commun.* **1984**, 258. Dondoni, A.; Fantin, G. Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1987**, *52*, 3413.

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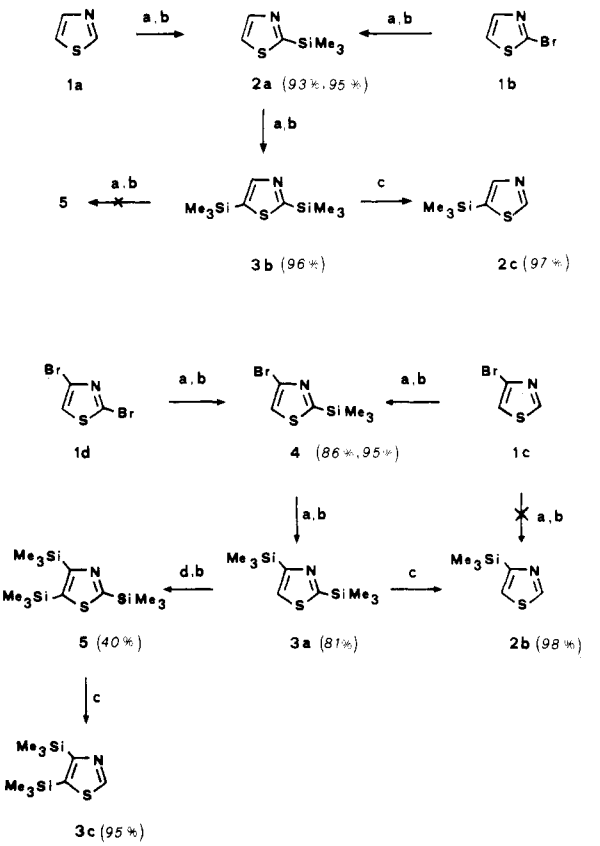
methylsilyl)oxazoles and showed their superior synthetic utility with respect to 2-lithiooxazoles for carbon–carbon bond formation at C-2 of the oxazole ring. We have also reported[5] the synthesis of 2-(trimethylsilyl)thiazole (**2a**) and presented partial reports on reactions with carbon electrophiles[5,6] as well as its use as an effective formyl anion equivalent for the homologation of chiral α-hydroxy aldehydes to higher carbon sugars.[7] Herein we give a full account of the synthesis of all possible regioisomeric mono- and bis(trimethylsilyl)thiazoles as well as the tris(trimethylsilyl) derivative and describe their reactivity toward some carbon electrophiles, namely, ketenes, acyl chlorides, and aldehydes. The interest in substituted thiazoles having manipulatable functionalities stems from their synthetic potential as building blocks for thiazole-containing natural product synthesis[8] and/or as masked aldehydes by virtue of the ready conversion of the thiazole ring into the formyl group.[7,9] Nevertheless, synthetically valuable carbon–carbon bond-forming reactions at the thiazole ring are rare. Only a few electrophilic substitutions and cycloaddition reactions to compounds activated by an electron-releasing group have been described;[10,11] moreover, processes via lithium and Grignard derivatives[12] are limited to the preparation of C-2 substituted thiazoles, as in a method reported earlier by us via *N*-(ethoxycarbonyl)thiazolium chloride and carbon nucleophiles.[13]

Results and Discussion

Synthesis of (Trimethylsilyl)thiazoles 2–5. All synthetic routes to these compounds involved lithiation of the thiazole ring by hydrogen–metal or halogen–metal exchange and quenching with chlorotrimethylsilane. When regioselective monolithiation at C-4 or C-5 could not be achieved, the corresponding silylthiazole was conveniently prepared through a polysilyl derivative and partial protodesilylation (Scheme I). Thus, owing to the higher kinetic and thermodynamic acidity of the 2-H with respect to 5-H and 4-H in the thiazole ring,[14] 2-(trimethylsilyl)-

Scheme I[a]



[a] (a) *n*-BuLi/−78 °C; (b) Me_3SiCl; (c) THF plus 5% HCl; (d) *t*-BuLi/−78 °C.

thiazole (2-TST) (**2a**)[15] was obtained directly by metalation of the parent thiazole (**1a**) in 93% yield. Moreover, **2a** was prepared in equally good yield (95%) from the more readily available starting material 2-bromothiazole (**1b**). The latter method was adopted[16] for routine multigram-scale preparations. Further lithiation and silylation of **2a** gave exclusively 2,5-bis(trimethylsilyl)thiazole (**3b**), in agreement with literature data on the preferential metalation at C-5 with respect to C-4 in 2-substituted thiazoles.[14] Selective protodesilylation at C-2 of **3b** occurred under very mild acid conditions to give 5-(trimethylsilyl)thiazole (5-TST) (**2c**) in almost quantitative yield. Compound **2c** can be equally prepared, although in lower yield (36%), from 5-bromothiazole via the usual lithiation–silylation sequence. 4-Trimethylsilyl derivative **2b** (4-TST) was prepared starting from 2,4-dibromothiazole (**1d**). This was transformed by sequential metalation into 4-bromo-2-(trimethylsilyl)thiazole (**4**) and then into 2,4-bis(trimethylsilyl)thiazole (**3a**), which by protodesilylation at C-2 afforded **2b**. Quite interenstingly, attempts to prepare **2b** from 4-bromothiazole (**1c**) gave instead a very high yield of **4**, indicating the preference for hydrogen–lithium exchange at C-2 over bromide–lithium exchange at C-4. Exhaustive silylation of the thiazole ring was carried out on **3a** by the usual sequence to give 2,4,5-tris(trimethylsilyl)thiazole (**5**) in 40% yield. Also **5** un-

(5) Medici, A.; Pedrini, P.; Dondoni, A. *J. Chem. Soc., Chem. Commun.* **1981**, 655.

(6) (a) Medici, A.; Fantin, G.; Fogagnolo, M.; Dondoni, A. *Tetrahedron Lett.* **1983**, *24*, 2901. (b) Dondoni, A.; Dall'Occo, T.; Galliani, G.; Mastellari, A.; Medici, A. *Ibid.* **1984**, *25*, 3637.

(7) Dondoni, A.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron Lett.* **1985**, *26*, 5477. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 835. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Tetrahedron* **1987**, *43*, 3533.

(8) (a) Thiazole C-nucleosides, thiazofurin, and analogues. Srivastava, P. C.; Revankar, G. R.; Robins, R. K. *J. Med. Chem.* **1984**, *27*, 266. Kini, G. D.; Hennen, W. J.; Robins, R. K. *J. Org. Chem.* **1986**, *51*, 4436. (b) Thiazole cyclopeptides. (i) Ulicyclamide: Schmidt, U.; Gleich, P. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 569. (ii) Patellamides: Hamada, Y.; Shibata, M.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 6501. Schmidt, U.; Griesser, H. *Ibid.* **1986**, *27*, 163. (iii) Ascidiacyclamide: Hamada, Y.; Kato, S.; Shioiri, T. *Ibid.* **1985**, *26*, 3223. (c) Dithiazolyls. (i) Mixothiazol: Trowitzsch, W.; Höfle, G.; Sheldrick, W. S. *Tetrahedron Lett.* **1981**, *22*, 3829. (ii) Bleomycins: Murugesan, N.; Hecht, S. M. *J. Am. Chem. Soc.* **1985**, *107*, 493.

(9) Meyers, A. I. In *Heterocycles in Organic Synthesis*: Wiley: New York, 1974.

(10) (a) Metzger, J. V. In *The Chemistry of Heterocyclic Compounds. Thiazole and its Derivatives*; Wiley: New York, 1979; Vol. 34, Part 1, Chapter 1. (b) Metzger, J. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds., Pergamon Press: Oxford, 1984; Vol. 6, p 235. (c) Reinhaudt, D. N. *Adv. Heterocycl. Chem.* **1977**, *21*, 253.

(11) For our previous work in this area, see: (a) Dondoni, A.; Medici, A.; Venturoli, C.; Forlani, L.; Bertolasi, V. *J. Org. Chem.* **1980**, *45*, 621. (b) Medici, A.; Pedrini, P.; Venturoli, C.; Dondoni, A. *Ibid.* **1981**, *46*, 2790. (c) Medici, A.; Fogagnolo, M.; Pedrini, P.; Dondoni, A. *Ibid.* **1982**, *47*, 3844. (d) Medici, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P.; Dondoni, A.; Andreetti, G. D. *Ibid.* **1984**, *49*, 590.

(12) Metzger, J.; Koester, B. *Bull Soc. Chim. Fr.* **1953**, 702. Beraud, J.; Metzger, J. V. *Bull. Soc. Chim. Fr.* **1962**, 2072.

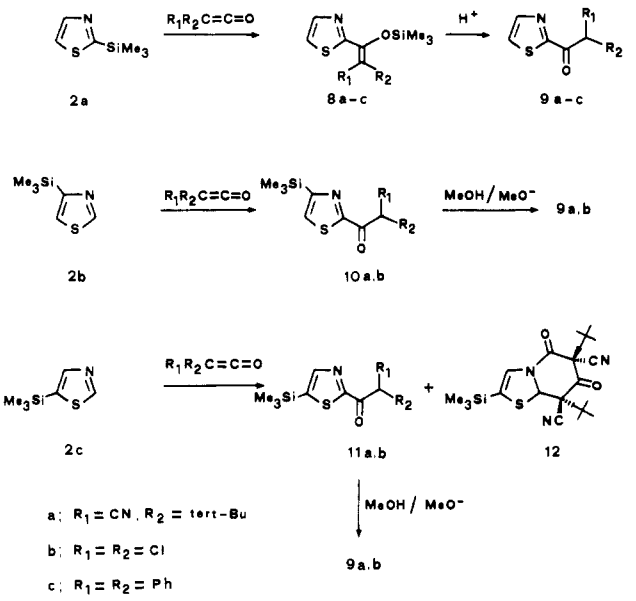
(13) Dondoni, A.; Dall'Occo, T.; Fantin, G.; Fogagnolo, M.; Medici, A. *Tetrahedron Lett.* **1984**, *25*, 3633.

(14) Reference 10a, p 119.

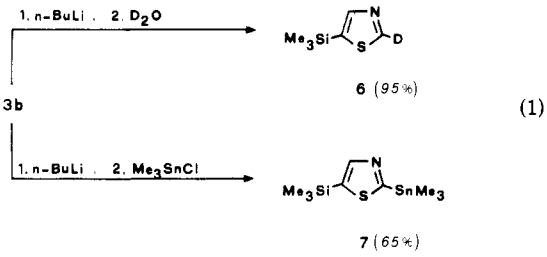
(15) Subsequent to our first report (ref 5), the synthesis of **2a** and reactions with two acyl chlorides (phosgene and pivaloyl chloride) were described (ref 2e).

(16) Thiazole (**1a**) is a relatively expensive commercially available product which however can be prepared (ca. 60%) by a recent three-step procedure (Brandsma, L.; de Jong, R. L. P.; Verkruijsse *Synthesis* **1985**, 948). 2-Bromothiazole (**1b**) can be obtained in multigram scale from 2-aminothiazole (ref 36) which is a very cheap commercially available material.

Scheme II



derwent selective protodesilylation at C-2 under acid conditions to give 4,5-bis(trimethylsilyl)thiazole (**3c**), the final member of the series. Unlike **3a**, the 2,5-bis-silylated compound **3b** could not be converted into the persilylated compound **5** since **3b** was recovered unaltered even when an excess of metalating reagents (*n*-BuLi–Me_3SiCl) was used. It was later proven that **3b** was seemingly inert to metalation because C–Si bond cleavage at C-2 rather than C–H bond cleavage at C-4 took place. In fact, lithiation and quenching with a different electrophile than chlorotrimethylsilane, such as D_2O or trimethyltin chloride (eq 1), produced the corresponding substitution products at



(1)

C-2, viz. **6** and **7**, respectively. This reaction as well as the very facile protodesilylation which was exploited in some sequences of Scheme I, provide examples of the unusually high reactivity of the trimethylsilyl group at C-2 of the thiazole ring.

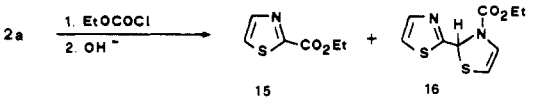
Reactions of Mono(trimethylsilyl)thiazoles 2a–c with Carbon Electrophiles. (A) Selectivity. The reactivity of silylthiazoles **2a–c** as potential regioisomeric thiazolyl donor synthons was studied with ketenes, acyl chlorides, and aldehydes.

(a) Ketenes.[5] Treating solutions of 2-TST (**2a**) in hexane or benzene at room temperature with a slight excess of three substituted ketenes, namely, *tert*-butylcyanoketene (TBCK), dichloroketene (DCK), and diphenylketene (DPK), gave essentially quantitative yields of the corresponding thiazolyl silyl enol ethers **8a–c**. The reaction can be viewed as an addition of the C–Si bond of **2a** to the ketene carbonyl group (Scheme II). The process is formally similar to the addition of trimethylsilyl cyanide to ketenes to give cyano silyl enol ethers.[17,18] From this and other observations showing reactivity similarities between **2** and trimethylsilyl cyanide,[19] the former can be considered a *pseudocyanide*. The addition of **2a** to ketenes, besides giving high yields of silyl enol ethers,[3,20] appeared to occur with high stereoselectivity[21] since in the case of the unsymmetrical ketene TBCK it afforded the single *E* isomer **8a**. A straightforward synthetic application of the *O*-silyl enolate function at C-2 of the thiazole ring stemmed from the ready conversion of **8** by acid catalysis into the corresponding 2-acylthiazole **9**. Compounds **9a** and **9b** were previously obtained in modest yields (ca. 45%) from thiazole (**1a**) and the corresponding ketenes.[11d] Thus, the overall sequence starting from **2a** and ketenes provides a new entry to thiazol-2-yl ketones in good overall yield. Unfortunately, the scope of this synthesis may be seriously limited by the lack of availability of the appropriate ketenes bearing the required substituents.

In contrast to the high reactivity of 2-TST (**2a**), the regioisomers 4-TST (**2b**) and 5-TST (**2c**) were inert toward ipso substitution by ketenes. Actually, DPK did not react at all, while the activated ketenes TBCK and DCK gave products from carbodeprotonation at C-2, namely, the Michael-type adducts **10** and **11** and the 2:1 cycloadduct **12**. The open-chain adducts **10a,b** and **11a,b** were desilylated to give the corresponding thiazol-2-yl ketones **9a** and **9b**; similarly, the cycloadduct **12** was transformed upon desilylation into the product obtained from 1,3-thiazole (**1a**) and TBCK (whose structure was established by X-ray crystallography).[11d] Hence, it appears that 4- and 5-(trimethylsilyl)thiazoles **2b** and **2c** react with ketenes with selectivity identical with that of thiazole (**1a**) or its 4- and 5-methyl derivatives[11d] rather than behaving as 4- and 5-thiazolyl donor synthons.

(b) Acyl Chlorides.[6a] The results of the reactions of TST **2a–c** with acyl chlorides are listed in Table I. As illustrated in the table, the reaction of 2-TST (**2a**) with these electrophiles exhibited an impressive degree of generality to give the corresponding ipso substitution product; in particular, monocarboxylic acid chlorides produced the thiazol-2-yl ketones **13**, whereas with the chloride esters or dichlorides of dicarboxylic acids followed by quenching with an appropriate base gave the thiazol-2-yl keto esters **14**. Since successful reactions were observed with various acyl chlorides, differing in the nature of the substituent R (alkyl, haloalkyl, alkenyl, aryl, heteroaryl), this appears to be an entry to carbonyl-substituted thiazoles at the 2-position which has wide scope and is more convenient than other existing methods.[22] This same methodology should be applicable to benzothiazoles.[23]

The reaction of **2a** with the chloro ester ethyl chloroformate disclosed a new carbodesilylation process (eq 2).



(2)

(17) Hertenstein, U.; Hünig, S.; Reichelt, H.; Schaller, R. *Chem. Ber.* **1982**, *115*, 261.

(18) For addition reactions to ketenes, see: Seikaly, H. R.; Tidwell, T. T. *Tetrahedron* **1986**, *42*, 2587.

(19) Similarly to trimethylsilyl cyanide (Grontas, W. G.; Felker, D. *Synthesis* **1980**, 861. Foley, L. H. *J. Org. Chem.* **1985**, *50*, 5204. Utimoto, K.; Wakabayashi, Y.; Horiie, T.; Inoue, M.; Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967), 2-TST (**2a**) adds to various carbonyl compounds including aldehydes (ref 6a and 7) and β-diketones (unpublished results from this laboratory).

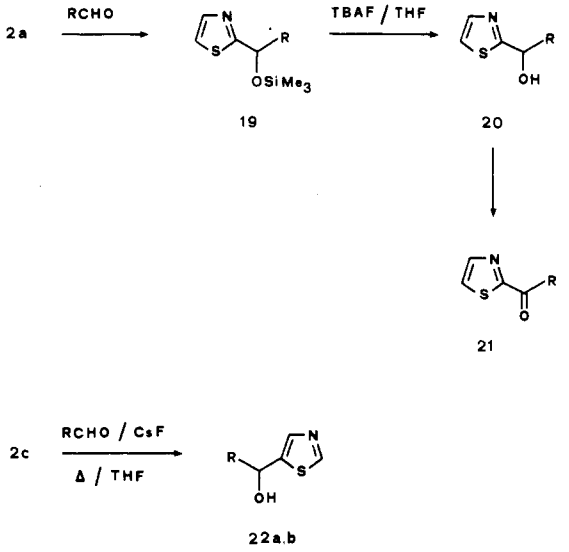
(20) Rasmussen, J. K. *Synthesis* **1977**, 91.

(21) For a recent paper on stereospecific synthesis of silyl enol ethers, see: Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1985**, *107*, 4260.

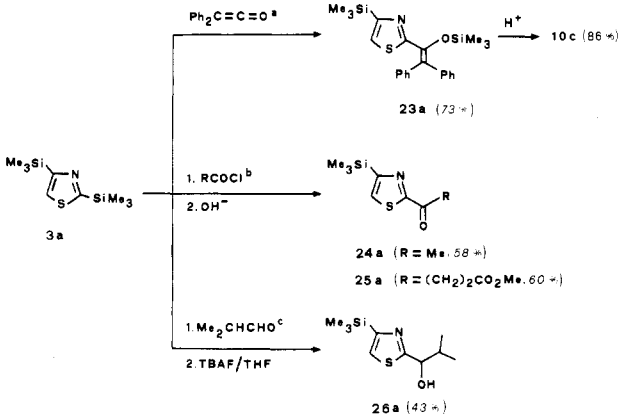
(22) Reference 10a, p 535.

(23) Pinkerton, F. H.; Thames, S. F. *J. Heterocycl. Chem.* **1971**, *8*, 257; **1972**, *9*, 67.

Scheme III



Scheme IV[a]



[a] (a) *n*-Hexane, room temperature, 4 days; (b) benzene, room temperature for **24a**, 80 °C for **24b**; (c) neat, room temperature, 2 days.

In fact, treatment of **2a** with ethyl chloroformate in benzene gave, in addition to the expected thiazole ester **15** (62%), the thiazol-2-ylthiazoline[24] **16** (15%). The latter product formed exclusively, although in low yield (43%), when the reaction was carried out in methylene dichloride. Compounds **15** and **16** arise from ipso substitution on **2a** by two competing electrophiles, viz. ethyl chloroformate and *N*-(ethoxycarbonyl)thiazolium cation. This observation led us to extend the scope of the reaction of **2a** to other aza-aryl cations for the synthesis of bis(heteroaryls).[6b]

Treating solutions of 4-TST (**2b**) with acetyl or benzoyl chloride in refluxing THF and in the presence of fluoride ion as nucleophilic catalyst did not give appreciable amounts of ipso substitution products. On the other hand, 5-TST (**2c**) reacted with acetyl and benzoyl chloride as well as with the chloride ester of succinic acid to give the corresponding ipso product, viz. the ketones **17a,b** and the keto ester **18**. Although quite drastic conditions were required (see Table I) and the yields were lower than for substitutions with 2-TST (**2a**), the reactions of **2c** with acyl chlorides constitute, to the best of our knowledge, the first example of regioselective acylation of the thiazole ring at the 5-position. The scope of this acyldemetalation was not extensively investigated since better yields (80–90%) are obtained from 5-(trimethylstannyl)thiazole.[25]

(c) Aldehydes.[6a] 2-TST (**2a**) reacted smoothly with various aldehydes, resulting in an addition of the C–Si bond to the carbonyl group (Scheme III, Table II). This selectivity in favor of 1,2-addition was also observed with acrolein (entry 3), although 1,4-addition across the conjugated α,β-enone system was also possible. In some cases (entries 1, 2, 3, and 5) the initial *O*-trimethylsilyl ether adduct **19** was characterized by NMR of the crude reaction mixture and then desilylated in situ to the corresponding alcohol **20**; in other cases, specifically for the adducts from heteroaryl aldehydes (entries 7, 8, and 9), it was convenient to isolate the *O*-trimethylsilyl alcohols **19h–j**, which upon desilylation produced the alcohol **20** and/or the ketone **21**. Quite interestingly, from the workup of the reaction mixtures with 2-thiazole and 2-pyridinecarboxaldehyde (entries 6 and 10), ketones **21g** and **21k** were the only products observed. All ketones **21** should form by oxidation[26] of the corresponding alcohols **20**, very likely through an hydroxyalkyl radical[27] or an acyl Δ^4-thiazoline[28] as intermediates. The reaction of **2a** with the α-chiral aldehyde (*R,S*)-2-phenylpropanal (entry 4) showed some degree of diastereoselectivity (1:2.7 molar ratio) in favor of the syn adduct **20e**,[29] as was observed for the addition of 4-(trimethylsilyl)oxazole to the same aldehyde.[4] It is worth mentioning, however, that a significant degree of anti diastereoselection has been achieved in the reaction of **2a** with D-glyceraldehyde and various polyoxygenated higher homologues.[7] In conclusion, the reaction of 2-TST (**2a**) with aldehydes appears to be a general approach to a variety of 2-(α-hydroxyalkyl)thiazoles having some degree of stereochemical control. The method is much superior to those employing other 2-metalated thiazoles such as lithio and Grignard derivatives[12,26] which, in fact, are plagued by low yields and/or no diastereoselectivity.

As with acyl chlorides, 4-TST (**2b**) did not undergo carbodesilylation by aldehydes. For instance, no addition product was obtained on treating **2b** with 2-methylpropanal in refluxing THF for 48 h. By contrast, under similar conditions 5-TST (**2c**) underwent ipso substitution by 2-methylpropanal and benzaldehyde, giving the corresponding thiazol-5-ylcarbinols **22a,b** in good yields (Table II, entries 12 and 13). These reactions are very likely the first examples of regioselective hydroxyalkylation at the 5-position in 2*H*-thiazoles via carbodemetalation.

The simple yet interesting conclusion that may be drawn from reactions of regioisomeric mono(trimethylsilyl)thiazoles **2a–c** with ketenes, acyl chlorides and aldehydes is the enormous difference of reactivity of the C–Si bond at the three positions of the thiazole ring, the order being 2-$SiMe_3$ > 5-$SiMe_3$ ≫ 4-$SiMe_3$. Ipso substitution, however, was observed only at the 2- and 5-position.

Reactions of Bis(trimethylsilyl)thiazoles 3a and 3b with Carbon Electrophiles. The above reactivity order was well-preserved in the bis-silylated compounds **3**, thus allowing highly regioselective and sequential carbo-

(24) In our preliminary work (ref 6a) a chemical shift of δ 5.34 was erroneously assigned to the C-2 H of the thiazoline ring. The correct value is δ 6.90 (see Experimental Section).

(25) Dondoni, A.; Mastellari, A. R.; Medici, A.; Negrini, E.; Pedrini, P. *Synthesis* **1986**, 757.

(26) Erne, M.; Erlenmeyer, H. *Helv. Chim. Acta* **1948**, *31*, 652.

(27) Ledwith, A.; Russel, P. J.; Sutcliffe, L. H. *Proc. R. Soc. London, Ser. A.* **1973**, *33*, 151.

(28) Chikasita, H.; Miyazaki, M.; Itoh, K. *Synthesis* **1984**, 308.

(29) The structure of the major syn diastereoisomer **20e** was established by X-ray crystallography. We thank Professor G. Gilli (Department of Chemistry, University of Ferrara) for X-ray structure determination. Full details of crystallographic analyses of thiazole and oxazole adducts to 2-phenylpropanal will be published in a forthcoming report.

Table I. Reactions of 2-, 4-, and 5-(Trimethylsilyl)thiazoles 2a–c with Carboxylic Acid Chlorides

2a–c 13, 14, 17, 18

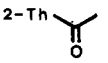
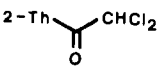
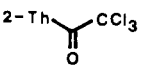
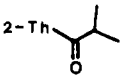
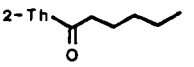
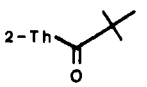
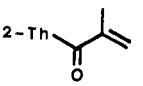
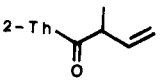
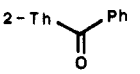
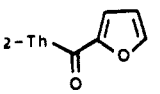
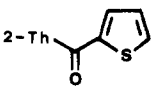
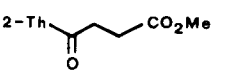
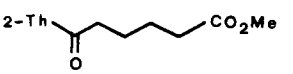
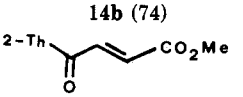
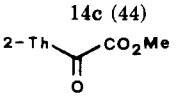
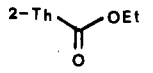
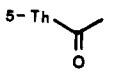
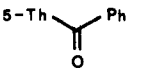
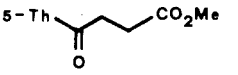
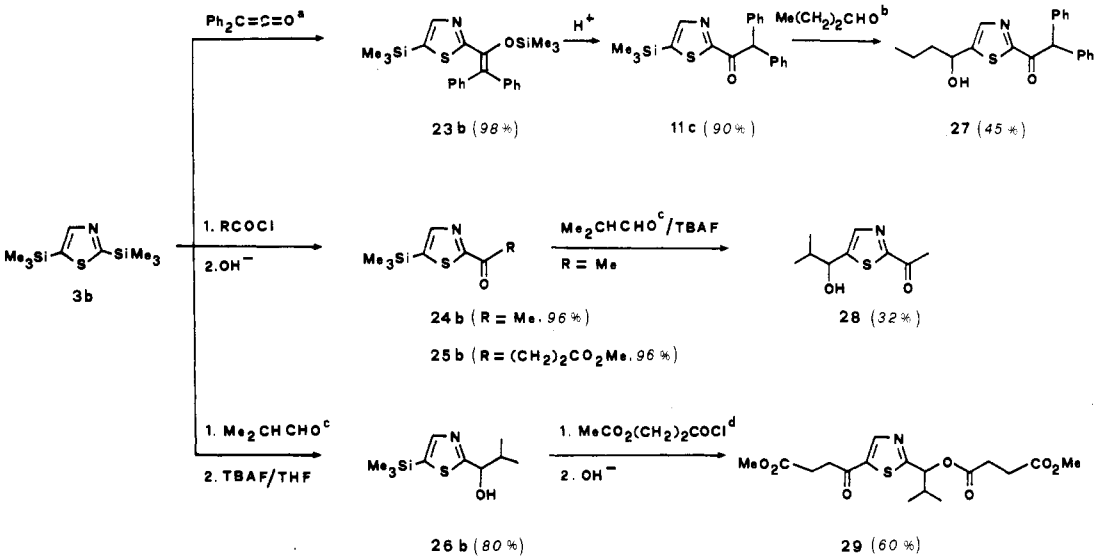
substr	acyl chloride, R =	reaction conditions[a] solvent[b]	temp (°C)	time (h)	product(s)[c] (yield, %)[d]
2a	Me	Md	25	1.5	 **13a** (88)
2a	$CHCl_2$	Md	25	6	 **9b** (70)
2a	CCl_3	Md	25	1.5	 **13b** (84)
2a	$CHMe_2$	Md	25	6	 **13c** (90)
2a	$(CH_2)_4Me$	Md	25	20	 **13d** (60)
2a	CMe_3		25	18	 **13e** (84)
2a	$C(Me)=CH_2$	Md	25	3	 **13f** (62)
2a	$CH(Me)CH=CH_2$	He	25	48[e,f]	 **13g** (11)
2a	Ph	Md	25	3[g]	 **13h** (70)
2a	2-furyl	Md	25	20[e]	 **13i** (82)
2a	2-thienyl	Md	25	20[e]	 **13j** (78)
2a	$(CH_2)_2CO_2Me$		25	18	 **14a** (92)
2a	$(CH_2)_4CO_2Me$	Md	25	2[e,h]	 **14b** (74)
2a	CH=CHCOCl	Md	25	3[h]	 **14c** (44)
2a	COCl	Bz	25	2[i]	 **14d** (76)

Table I (Continued)

substr	acyl chloride, R =	reaction conditions[a] solvent[b]	temp (°C)	time (h)	product(s)[c] (yield, %)[d]
2a	OEt	Bz	25	20[e]	 **15** (62) + **16** (15)
2b	Me, Ph		80	20	
2b	Me, Ph	THF/F^{-}[j]	60	20	
2c	Me		80	24	 **17a** (30)
2c	Ph		80	18[g]	 **17b** (48)
2c	$(CH_2)_2CO_2Me$		80	5	 **18** (73)

[a] All reactions were carried out with 2 equiv of RCOCl and quenched with saturated $NaHCO_3$ unless otherwise stated. [b] Md = methylene dichloride; Bz = benzene; He = *n*-hexane. [c] 2-Th = 2-thiazolyl, 5-Th = 5-thiazolyl. [d] All yields refer to isolated and chromatographically pure products. [e] A solution of the silylthiazole was added to a solution of the proper acyl chloride. [f] Molar ratio **2a**:acyl chloride 1:1. [g] The reaction mixture was treated with 40% NaOH and tetrabutylammonium chloride in a catalytic amount to remove the excess of benzoyl chloride. [h] Quenched with $NaHCO_3$ in MeOH–H_2O. [i] Quenched with MeOH–Et_3N. [j] No product formation was observed when using benzoyl fluoride as electrophile.

Scheme V[a]



[a] (a) *n*-Hexane, room temperature, 3 h; (b) THF, room temperature, 3 h; (c) neat, room temperature, 2 h; (d) neat, 80 °C, 48 h, Et_3N.

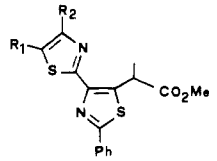
desilylation reactions. Treatment of 2,4-bis-TST (**3a**) (Scheme IV) and 2,5-bis-TST (**3b**) (Scheme V) with three selected carbonyl electrophiles, namely diphenylketene, acetyl chloride, and 2-methylpropanal, gave exclusively the corresponding products from ipso substitution at the 2-position. Compound **3b** reacted under milder conditions (temperature and/or time) than **3a**. While no attempts were made to further react **23a–26a** (Scheme IV) because of the aforementioned inertness of the C–Si bond at the 4-position, successful reactions at the 5-position were carried out by using compounds **23b–26b** (Scheme V). Since in each case the second carbodesilylation was carried out with a carbonyl compound different from that used in the first reaction, the resulting products **27–29** were multifunctionalized 2,5-disubstituted thiazoles. This should make these compounds suitable for a variety of selective synthetic elaborations. We have exploited this sequential electrophilic desilylation strategy for the preparation of 2,4-dithiazolylpropanoic acids[30] (**30**) as potential nonsteroidal antiinflammatory agents.[31]

(B) Mechanism. The most striking aspect of the chemistry described above is the very facile substitution by carbon electrophiles of the trimethylsilyl group[32] at the 2-position of the thiazole ring. Carbodesilylation reactions have been reported to occur smoothly in various 2-trialkylsilyl azaarenes[2,4] (pyridine, *N*-methylimidazoles, pyrazoles, oxazoles, and isoxazoles), whereas sulfur hetero-

(30) Dondoni, A.; Dall'Occo, T.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Gazzetta* **1986**, *116*, 133.

(31) Review: Rien, P.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095.

(32) The effect of changing substituents at silicon has been examined by using 2-(*tert*-butyldimethylsilyl)thiazole. This failed to react with acyl chlorides and aldehydes.



30

$R_1 = R_2 = H$

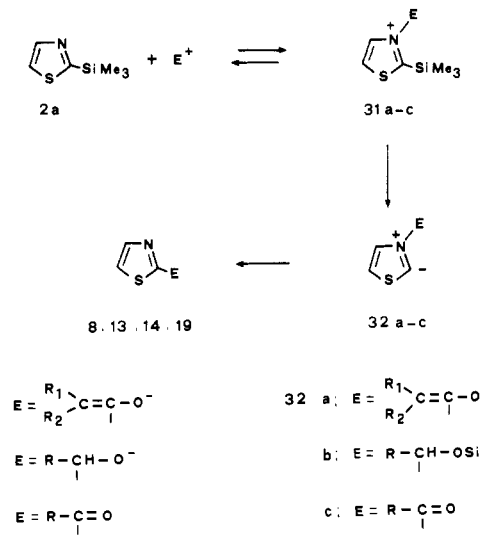
$R_1 = H$, $R_2 = Me$

$R_1 = H$, $R_2 = Cl$

$R_1 = Cl$, $R_2 = H$

cycles (thiophenes[33]) were unreactive. Nevertheless, the presence of both nitrogen and sulfur in thiazole appears to create particularly favorable conditions for carbon–silicon bond cleavage at the 2-position. For instance, 2-(trimethylsilyl)oxazoles[4] are much less reactive than thiazoles. Although mechanistic information is minimal, we propose the general mechanistic Scheme VI which applies equally well to the reactions of the three-carbon electrophiles examined. This involves quaternization of nitrogen by the electrophile to give **31** (**a** and **b**, zwitterions; **c**, thiazolium salt) followed by the rate-determining formation of the ylide **32** which evolves to product by either an intramolecular 1,2-shift of the electrophilic moiety from nitrogen to carbon or by interception of another molecule of electrophile. Two observations support the quaternization of nitrogen of silylthiazoles by carbonyl electrophiles as required by this mechanism. These are (a) the formation of thiazolyl-*N*-carbethoxythiazoline **16** (eq 2) via reaction of an *N*-acylthiazolium cation with **2a**; (b) the decreased reactivity toward ipso substitution at C-2 occurring in 4-substituted derivatives such as **3a** (Scheme IV) and **4** (Scheme I). For instance, compound **4** failed to react with acyl chlorides and aldehydes under the same conditions of **2a**. Thiazolium 2-ylide is assumed as an intermediate in numerous chemical and biochemical processes[34] and its formation is supported by a great deal of experimental observations. In the present case, the formation of **32** should be particularly favored because of the easy cleavage of the carbon–silicon bond by the nucleophilic assistance (oxygen of the carbonyl for ketene or aldehyde reaction; chloride ion for acyl chloride reaction). On the other hand, a mechanism for the ipso substitution at the 5-position by acyl chlorides and aldehydes can be less easily advanced since routes via direct electrophilic attack on the silylthiazole or via the 5-thiazolium ylide, appear equally possible. It is, however, worth mentioning that the lower reactivity of the carbon–silicon bond at the 5-position with respect to the 2-position parallels the order of decarboxylation rate of regioisomeric 2- and 5-thiazolecarboxylic acids,[35] a result that has been interpreted in terms of the relative stabilities of the corresponding 2- and 5-thiazolium ylides.

Scheme VI



Conclusions

2- and 5-substituted (trimethylsilyl)thiazoles are storable thiazolyl anion equivalents prone to reacting with carbonyl compounds. In particular, the high reactivity of the carbon–silicon bond at the 2-position gives ready access to classes of 2-substituted thiazoles such as acyl and hydroxyalkyl derivatives of potential synthetic utility. According to a suggested mechanism, this remarkable reactivity appears to originate from the cascade contribution of the three heteroatoms at C-2 of the thiazole ring, viz. nitrogen for the quaternization (activation), silicon for the stabilization of the positive charge in the thiazolium salt (silicon β-effect), and sulfur for the stabilization of the negative charge in the thiazolium ylide (sulfur α-effect).

Experimental Section

General Comments. All melting and boiling points are uncorrected. ^1H NMR and ^{13}C NMR spectra (in $CDCl_3$) were obtained on a 80-MHz WP80 Bruker spectrometer. Chemical shifts are given in parts per million from tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 297 grating spectrometer. Mass spectra were obtained at 70 eV on a Varian Mat CH7 high-resolution mass spectrometer. Elemental analyses were performed on a 1106 Microanalyzer (Carlo Erba). All experiments were carried out under nitrogen and with freshly distilled and dried solvents. All yields refer to the isolated materials if not otherwise stated.

Starting Materials. 1,3-Thiazole (**1a**) was commercially available (Fluka). 2-Bromothiazole[36] (**1b**) [bp 70–71 °C (20 mmHg)], 4-bromothiazole[37] (**1c**) (bp 189–190 °C), 2,4-dibromothiazole[38] (**1d**) (mp 82 °C), and 5-bromothiazole[36] [bp 81 °C (18 mmHg)] were prepared as described. *tert*-Butylcyanoketene (TBCK) was generated in situ before each experiment by thermolysis of the appropriate azidobenzoquinone;[39] diphenylketene (DPK) [bp 118–120 °C (1 mmHg)] was prepared from diphenylacetyl chloride and triethylamine[40] and redistilled prior to its use; dichloroketene (DCK) was prepared in situ from di-

(33) Meen, R. H.; Gilman, H. *J. Org. Chem.* **1955**, *20*, 73.

(34) Reviews and general papers: Kwart, H.; King, K. G. In *d-Orbitals in the Chemistry of Silicon, Phosphorus and Sulfur*; Springer-Verlag: Berlin, 1977. See also: Aldrich, H. S.; Alworth, W. L.; Clement, N. R. *J. Am. Chem. Soc.* **1978**, *100*, 2362. Scheffers-Sap, M. M. E.; Buck, H. M. *Ibid.* **1979**, *101*, 4807. As intermediate: (a) Thiamine activity: Breslow, R. *Ann. N.Y. Acad. Sci.* **1962**, *98*, 445. Schellenberger, A. *Ibid.* **1982**, *378*, 51. Haake, P.; Nelson, R. M. *Ibid.* **1982**, *378*, 107. (b) Acyloin condensation: Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719. Stetter, H.; Ramsch, R. Y.; Kuhlman, H. *Synthesis* **1976**, 733. Matsumoto, T.; Yamamoto, H.; Inoue, S. *J. Am. Chem. Soc.* **1984**, *106*, 4829. Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem.* **1985**, *50*, 603. Castells, J.; Lopez Calahorra, F.; Domingo, L. *Tetrahedron Lett.* **1985**, *26*, 5457. (c) Nucleophilic acylation: Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639. Stetter, H.; Krassalt, J. *J. Heterocycl. Chem.* **1977**, *14*, 573 and previous papers. H/D exchange in thiazolium salts: Haake, P.; Bausher, L. P.; Miller, W. B. *J. Am. Chem. Soc.* **1969**, *91*, 1113. Haake, L. P. *Tetrahedron Lett.* **1981**, *22*, 2939. Olofson, R. A.; Landesberg, J. M. *J. Am. Chem. Soc.* **1966**, *88*, 4263.

(35) Haake, P.; Bausher, L. P.; McNeal, J. P. *J. Am. Chem. Soc.* **1971**, *93*, 7045.

(36) Roussel, P.; Metzger, J. *Bull. Soc. Chim. Fr.* **1962**, 2075.

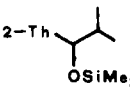
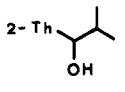
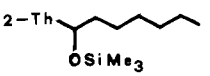
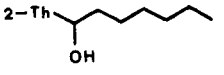
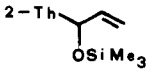
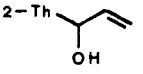
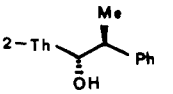
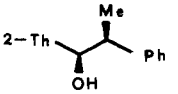
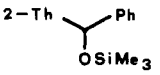
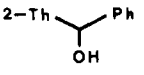
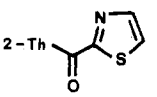
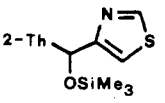
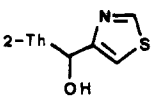
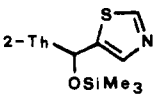
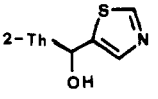
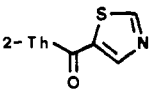
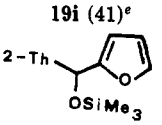
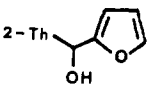
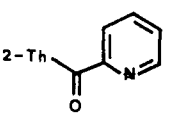
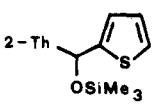
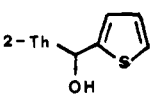
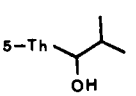
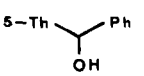
(37) Robba, M.; Moreau, R. C. *Ann. Pharm. Fr.* **1964**, *22*, 201.

(38) Reynaud, P.; Robba, M.; Moreau, R. C. *Bull. Soc. Chim. Fr.* **1962**, 1735.

(39) Weyler, W.; Duncan, W. G.; Siewen, M. B.; Moore, H. W. *Org. Synth.* **1976**, *55*, 32.

(40) Taylor, E. C.; McKillop, A.; Hawks, G. H. *Org. Synth.* **1973**, *52*, 36.

Table II. Reactions of 2- and 5-(Trimethylsilyl)thiazoles 2a and 2c with Aldehydes

entry	substr	aldehyde, R =	reaction conditions[a] solvent[b]	temp (°C)	time (h)	product(s)[c] (yield, %) 19	20 and 22	21
1	2a	$CHMe_2$		25	4	 **19a** (NMR)	 **20a** (96)[d]	
2	2a	$(CH_2)_5Me$		25	24	 **19b** (NMR)	 **20b** (75)[d]	
3	2a	$CH{=}CH_2$		25	3	 **19c** (NMR)	 **20c** (74)[d]	
4	2a			0	6		 *anti*-**20d** (19)[d]  *syn*-**20e** (52)[d]	
5	2a	Ph		25	3	 **19f** (NMR)	 **20f** (95)[d]	
6	2a		Md	25	18			 **21g** (38)[e]
7	2a			25	18	 **19h** (38)[e]	 **20h** (40)[f]	
8	2a			25	18	 **19i** (41)[e]	 **20i** (35)[f]	 **21i** (17)[f]
9	2a		Md	25	18	 **19j** (53)[e]	 **20j** (70)[f]	
10	2a		Md	25	18			 **21k** (27)[e]
11	2a			25	48	 **19l** (78)[e]	 **20l** (97)[f]	
12	2c	$CHMe_2$	THF/CsF	60	48		 **22a** (32)	
13	2c	Ph	THF/CsF	60	48		 **22b** (40)	

[a] All reactions were carried with 1.1–1.5 equiv of the aldehyde. [b] Md = methylene dichloride. [c] 2-Th = 2-thiazolyl, 5-Th = 5-thiazolyl. [d] Obtained on treating the crude *O*-trimethylsilyl derivative **19** with TBAF/THF. [e] Obtained by chromoatography (Florisil) of the reaction mixture. [f] Obtained on treating the isolated (chromatography, Florisil) *O*-trimethylsilyl derivative with TBAF/THF.

chloroacetyl chloride and triethylamine.[41] 2-Methyl-3-butenoyl chloride was prepared as described.[42] Tetrabutylammonium fluoride (TBAF) (1.0 M solution in tetrahydrofuran) was commercially available (Aldrich).

2-(Trimethylsilyl)thiazole (2-TST) (2a). (a) From Thiazole (1a). A solution of **1a** (4.25 g, 50 mmol) in diethyl ether (50 mL) was added over 30 min to a stirred solution of *n*-BuLi (51 mmol) in the same solvent (50 mL) at −78 °C. After stirring the reaction mixture for 30 min, a solution of Me_3SiCl (5.45 g, 50 mmol) in diethyl ether (50 mL) was added dropwise. After 1 h at −78 °C, the reaction mixture was allowed to warm to room temperature and then washed with saturated $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. Distillation gave 7.3 g (93%) of 2-(trimethylsilyl)thiazole (**2a**): bp 58–60 °C (16 mmHg); IR (film) 2950 cm^{-1}; ^1H NMR δ 0.40 (s, 9 H), 7.40 (d, 1 H, J = 3 Hz), 8.01 (d, 1 H, J = 3 Hz); ^{13}C NMR δ −1.2 (q), 121.32 (d), 145.8 (d), 174.3 (s); mass spectrum m/e (relative intensity) 157 (M^+, 25), 142 (71), 115 (76), 85 (55), 73 (100).

Anal. Calcd for $C_6H_{11}NSSi$: C, 45.81; H, 7.05; N, 8.90. Found: C, 45.84; H, 7.01; N, 8.92.

(b) From 2-Bromothiazole (1b). The reaction was carried out as above starting with a solution of **1b** (20 g, 0.122 mol) in diethyl ether (200 mL), *n*-BuLi (0.13 mol) in the same solvent (150 mL), and Me_3SiCl (13.3 g, 0.122 mol) in diethyl ether (200 mL). Distillation gave 18.2 g (95%) of **2a**.

2,5-Bis(trimethylsilyl)thiazole (2,5-bis-TST) (3b). The reaction was carried out as above starting with 2-(trimethylsilyl)thiazole (**2a**) (7.5 g, 50 mmol), *n*-BuLi (51 mmol), and Me_3SiCl (5.45 g, 50 mmol). Usual workup gave after distillation 10.99 g (96%) of 2,5-bis-TST (**3b**): bp 99–100 °C (13 mmHg); mp 54–56 °C; IR (CCl_4) 2950, 2910 cm^{-1}; ^1H NMR δ 0.35 (s, 9 H), 0.42 (s, 9 H), 8.13 (s, 1 H); ^{13}C NMR δ −0.84 (q), 0.19 (q), 135.3 (s), 151.7 (d), 179.1 (s); mass spectrum, m/e (relative intensity) 229 (M^+, 44), 214 (22), 172 (33), 130 (13), 115 (100), 99 (15).

Anal. Calcd for $C_9H_{19}NSSi_2$: C, 47.10; H, 8.34; N, 6.10. Found: C, 47.13; H, 8.32; N, 6.12.

5-(Trimethylsilyl)thiazole (5-TST) (2c). To a solution of 2,5-bis-TST (**3b**) (2.3 g, 10 mmol) in THF (30 mL) was added 5% HCl (1 mL) under stirring. After 1 h, the solvent was removed under vacuum. The residue was diluted with diethyl ether (20 mL) and the solution dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was distilled at reduced pressure to give 1.53 g (97%) of 5-TST (**2c**): bp 73–75 °C (16 mmHg); IR (film) 2955 cm^{-1}; ^1H NMR δ 0.39 (s, 9 H), 7.96 (s, 1 H), 9.01 (s, 1 H); ^{13}C NMR δ −0.05 (q), 132.0 (s), 149.2 (d), 157.2 (d); mass spectrum, m/e (relative intensity) 157 (M^+, 24), 142 (72), 115 (100), 85 (18), 73 (32).

Anal. Calcd for $C_6H_{11}NSSi$: C, 45.81; H, 7.05; N, 8.90. Found: C, 45.84; H, 7.01; N, 8.92.

4-Bromo-2-(trimethylsilyl)thiazole (4). The reaction was carried out according to the general procedure described for the metalation of **2a** starting from 2,4-dibromothiazole (**1d**) (12.5 g, 50 mmol), *n*-BuLi (60 mmol), and Me_3SiCl (55 mmol). Usual workup and distillation of the crude mixture gave 10.15 g (86%) of 4-bromo-2-(trimethylsilyl)thiazole[25] (**4**): bp 75–78 °C (2.5 mmHg).

Compound **4** was also obtained by the same procedure from 4-bromothiazole (**1c**) (50 mmol), *n*-BuLi (60 mmol), and Me_3SiCl (55 mmol): yield 11.16 g (95%).

2,4-Bis(trimethylsilyl)thiazole (2,4-bis-TST) (3a). The reaction was carried out according to the procedure described for the metalation of **2a** starting from 4-bromo-2-(trimethylsilyl)-thiazole (**4**) (11.75 g, 50 mmol), *n*-BuLi (75 mmol), and Me_3SiCl (75 mmol). Usual workup and distillation of the crude mixture gave 9.27 g (81%) of 2,4-bis-TST (**3a**): bp 63–64 °C (0.5 mmHg); IR (CCl_4) 2970, 2910 cm^{-1}; ^1H NMR δ 0.34 (s, 9 H), 0.40 (s, 9 H), 7.62 (s, 1 H); mass spectrum m/e (relative intensity) 229 (M^+, 23), 214 (15), 172 (8), 115 (38), 73 (100).

Anal. Calcd for $C_9H_{19}NSSi_2$: C, 47.10; H, 8.34; N, 6.10. Found: C, 47.08; H, 8.33; N, 6.13.

4-(Trimethylsilyl)thiazole (4-TST) (2b). The reaction was carried out as for the preparation of **2c** starting from a solution of 2,4-bis-TST (**3a**) (2.3 g, 10 mmol) and 5% HCl (1 mL) in THF (20 mL). After usual workup, distillation at reduced pressure gave 1.54 g (98%) of 4-TST (**2b**): bp 61–62 °C (16 mmHg); IR (film) 2960 cm^{-1}; ^1H NMR δ 0.34 (s, 9 H), 7.51 (d, 1 H, J = 2 Hz), 8.96 (d, 1 H, J = 2 Hz); ^{13}C NMR δ −1.2 (q), 125.3 (d), 153.5 (d), 160.9 (s); mass spectrum, m/e (relative intensity) 157 (M^+, 27), 142 (100), 115 (69), 105 (17).

Anal. Calcd for $C_6H_{11}NSSi$: C, 45.81; H, 7.05; N, 8.90. Found: C, 45.79; H, 7.03; N, 8.92.

2,4,5-Tris(trimethylsilyl)thiazole (2,4,5-tris-TST) (5). A solution of 2,4-TST (**3a**) (1 g, 4.37 mmol) in THF (30 mL) was added over 30 min to a stirred solution of *t*-BuLi (13.1 mmol) in the same solvent (50 mL) at −78 °C. After 2 h, a solution of Me_3SiCl (1.42 g, 13.1 mmol) was added and stirring continued for 1 h at −78 °C. The reaction mixture was allowed to warm to room temperature and the solvent was removed under vacuum. Distillation of the crude mixture gave 0.35 g (40%) of unreacted **3a** and 0.37 g (41%) of 2,4,5-tris-TST (**5**): bp 93–94 °C (2 mmHg); IR (film) 2970 cm^{-1}; ^1H NMR δ 0.38 (s, 9 H), 0.39 (s, 9 H), 0.41 (s, 9 H); ^{13}C NMR δ −0.5 (q), 0.99 (q), 1.89 (q), 141.98 (s), 168.03 (s), 175.24 (s); mass spectrum, m/e (relative intensity) 301 (M^+, 7), 286 (10), 228 (4), 202 (15), 187 (67), 172 (30), 155 (10), 97 (52), 83 (18), 73 (100).

Anal. Calcd for $C_{12}H_{27}NSSi_3$: C, 47.77; H, 9.02; N, 4.64. Found: C, 47.79; H, 9.00; N, 4.65.

Attempts to prepare 2,4,5-tris-TST (**5**) from 2,5-bis-TST (**3b**) (1 g, 4.37 mmol) with *n*-BuLi (13.1 mmol) and Me_3SiCl (1.42 g, 13.1 mmol) gave the unreacted **3b** (0.8 g).

4,5-Bis(trimethylsilyl)thiazole (4,5-bis-TST) (3c). The reaction was carried out as for the preparation of **2c** starting from a solution of 2,4,5-tris-TST (**5**) (0.31 g, 1 mmol) and 5% HCl (1 mL) in THF (20 mL). After usual workup, chromatography (silica gel, 7:3 petroleum ether/diethyl ether) gave 0.22 g (95%) of 4,5-bis-TST (**3c**): oil; IR (film) 2970, 1255 cm^{-1}; ^1H NMR δ 0.39 (s, 9 H), 0.4 (s, 9 H), 9.02 (s, 1 H); mass spectrum, m/e (relative intensity) 229 (M^+, 19), 214 (15), 202 (18), 187 (32), 97 (28), 74 (100).

Anal. Calcd for $C_9H_{19}NSSi_2$: C, 47.10; H, 8.34; N, 6.10. Found: C, 47.14; H, 8.30; N, 6.07.

Lithiation of 2,5-bis-TST (3b) and Quenching with D_2O or Trimethyltin Chloride. A solution of 2,5-bis-TST (**3b**) (2 g, 8.73 mmol) in THF (30 mL) was added to a solution of *n*-BuLi (10.5 mmol) in the same solvent (50 mL) at −78 °C. After 1 h of stirring, the reaction mixture was quenched with D_2O or Me_3SnCl.

Quenching with D_2O (5 mL, 250 mmol) in THF (20 mL) and workup gave 1.3 g (95%) of 5-(trimethylsilyl)thiazole-2-*d* (**6**): bp 76–77 °C (16 mmHg); ^1H NMR δ 0.35 (s, 9 H), 7.95 (s, 1 H).

Anal. Calcd for $C_6H_{10}DNSSi$: C, 45.51; H, 6.37; N, 8.84. Found: C, 45.48; H, 6.39; N, 8.87.

Quenching with Me_3SnCl (2.09 g, 10.5 mmol) gave after usual workup and distillation 1.8 g (65%) of 2-(trimethylstannyl)-5-(trimethylsilyl)thiazole (**7**): bp 115–116 °C (4.5 mmHg): ^1H NMR δ 0.33 (s, 9 H), 0.47 (s, 9 H), 8.12 (s, 1 H).

Anal. Calcd for $C_9H_{19}NSSiSn$: C, 33.74; H, 5.98; N, 4.38. Found: C, 33.70; H, 5.99; N, 4.36.

Reaction of 2-TST (2a) with *tert*-Butylcyanoketene (T-BCK). A solution of TBCK prepared as described[39] (2.5 mmol) in benzene (30 mL) was added at room temperature to a stirred solution of 2-TST (**2a**) (0.39 g, 2.5 mmol) in the same solvent (40 mL). After 1 h, the solvent was removed under vacuum and the residue was crystallized from *n*-hexane, giving 0.65 g (93%) of the silyl enol ether **8a**: mp 38–40 °C; IR (KBr) 2950, 2170, 1580, 840 cm^{-1}; ^1H NMR δ 0.19 (s, 9 H), 1.35 (s, 9 H), 7.50 (d, 1 H, J = 3.2 Hz), 7.88 (d, 1 H, J = 3.2 Hz); mass spectrum, m/e (relative intensity) M^+ absent, 208 (4), 193 (6), 152 (45), 124 (8), 112 (100), 84 (12).

Anal. Calcd for $C_{13}H_{20}N_2OSSi$: C, 55.67; H, 7.19; N, 9.99. Found: C, 55.69; H, 7.18; N, 10.00.

Reaction of 2-TST (2a) with Dichloroketene (DCK). A solution of dichloroacetyl chloride (0.24 mL, 2.5 mmol) in *n*-hexane (200 mL) was slowly added (7 h) to a stirred solution of 2-TST (**2a**) (0.39 g, 2.5 mmol) and Et_3N (0.35 mL, 2.5 mmol) in the same solvent (150 mL). After 4 h of stirring, the reaction mixture was

(41) Stevens, H. C.; Reich, D. A.; Brandt, D. R.; Fountain, K. R.; Gaughan, E., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 5257.

(42) Lane, J. F.; Roberts, J. D.; Young, W. G. *J. Am. Chem. Soc.* **1944**, *66*, 543.

concentrated (50 mL) and the white precipitate was filtered off. Washing the filtrate with saturated $NaHCO_3$, drying over anhydrous Na_2SO_4, and evaporation of the solvent under vacuum gave 0.55 g (80%) of the silyl enol ether **8b**: oil; IR (film) 1250, 1100, 840 cm^{-1}; ^1H NMR δ 0.28 (s, 9 H), 7.44 (d, 1 H, J = 3.1 Hz), 7.89 (d, 1 H, J = 3.1 Hz); mass spectrum, m/e (relative intensity) 267 (M^+, 15), 194 (10), 112 (100), 84 (17).

Anal. Calcd for $C_8H_{11}Cl_2NOSSi$: C, 35.82; H, 4.13; N, 5.22. Found: C, 35.84; H, 4.12; N, 5.24.

Reaction of 2-TST (2a) with Diphenylketene (DPK). A solution of DPK (0.5 g, 2.5 mmol) in *n*-hexane (30 mL) was added dropwise to a stirred solution of 2-TST (**2a**) (0.39 g, 2.5 mmol) in the same solvent (40 mL). After 2 h, the solvent was removed under vacuum and the residue was crystallized from *n*-hexane, giving 0.85 g (97%) of the silyl enol ether **8c**: mp 62–64 °C; IR (CCl_4) 2950, 1240, 840 cm^{-1}; ^1H NMR δ 0.06 (s, 9 H), 7.11 (d, 1 H, J = 3.3 Hz), 7.27 (d, 1 H, J = 3.3 Hz); mass spectrum, m/e (relative intensity) 351 (M^+, 3), 295 (4), 279 (44), 183 (18), 167 (100), 165 (63), 152 (28), 112 (7), 105 (18).

Anal. Calcd for $C_{20}H_{21}NOSSi$: C, 68.33; H, 6.02; N, 3.98. Found: C, 68.37; H, 6.01; N, 4.00.

Conversion of the Silyl Enol Ethers 8a–c into Ketones 9a–c. General Procedure. A solution of the silyl enol ether **8** (2 mmol) and 5% HCl (0.5 mL) in THF (30 mL) was stirred for 1 h. The solvent was removed under vacuum and diethyl ether (30 mL) was added. The organic layer was washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, and evaporated under vacuum.

The crude mixture from **8a** gave on chromatography (silica gel, 1:1 petroleum ether/diethyl ether) 0.308 g (74%) of the ketone **9a**: mp 36–37 °C (from *n*-hexane); IR (CCl_4) 2950, 2240, 1700, 1470, 1380 cm^{-1}; ^1H NMR δ 1.18 (s, 9 H), 5.1 (s, 1 H), 7.94 (d, 1 H, J = 2.9 Hz), 8.11 (d, 1 H, J = 2.9 Hz); mass spectrum, m/e (relative intensity) 208 (M^+, 2), 193 (5), 180 (4), 152 (46), 112 (100), 84 (18).

Anal. Calcd for $C_{10}H_{12}N_2OS$: C, 57.66; H, 5.81; N, 13.45. Found: C, 57.63; H, 5.80; N, 13.41.

The crude mixture from **8b** gave on crystallization (from *n*-hexane) 0.34 g (87%) of the ketone **9b**: mp 55–56 °C; IR (KBr) 1700, 1360 cm^{-1}; ^1H NMR δ 7.29 (s, 1 H), 7.87 (d, 1 H, J = 3.1 Hz), 8.12 (d, 1 H, J = 3.1 Hz); mass spectrum, m/e (relative intensity) 195 (M^+, 8), 112 (100), 84 (21).

Anal. Calcd for $C_5H_3Cl_2NOS$: C, 30.63; H, 1.54; N, 7.14. Found: C, 30.61; H, 1.55; N, 7.13.

The crude reaction mixture from **8c** gave on chromatography (silica gel, 7:3 petroleum ether/diethyl ether) 0.43 g (78%) of the ketone **9c**: mp 104–106 °C (from *n*-hexane); IR (KBr) 1680, 1380 cm^{-1}; ^1H NMR δ 6.6 (s, 1 H), 7.34 (m, 10 H), 7.61 (d, 1 H, J = 3 Hz), 7.97 (d, 1 H, J = 3 Hz); mass spectrum, m/e (relative intensity) 279 (M^+, 20), 167 (100), 165 (60), 152 (35), 112 (10).

Anal. Calcd for $C_{17}H_{13}NOS$: C, 73.09; H, 4.69; N, 5.01. Found: C, 73.11; H, 4.67; N, 5.00.

Reaction of 4-TST (2b) with TBCK. A solution of 4-TST (**2b**) (0.2 g, 1.27 mmol) in benzene (20 mL) was added to a refluxing solution of TBCK (2.5 mmol) in the same solvent (30 mL). After 48 h, the solvent was removed under vacuum. Chromatography (silica gel, 7:3 cyclohexane/diethyl ether) of the residue gave 0.097 g (30%) of the ketone **10a** and 0.096 g (48%) of unreacted **2b**.

Ketone **10a**: mp 63–65 °C (from *n*-hexane); IR (KBr) 2960, 2240, 1695 cm^{-1}; ^1H NMR δ 0.35 (s, 9 H), 1.17 (s, 9 H), 5.14 (s, 1 H), 7.85 (s, 1 H); mass spectrum, m/e (relative intensity) M^+ absent, 265 (18), 224 (79), 209 (100), 193 (28), 184 (57), 142 (86), 126 (98).

Anal. Calcd for $C_{13}H_{20}N_2OSSi$: C, 55.67; H, 7.19; N, 9.99. Found: C, 55.65; H, 7.17; N, 9.98.

The reaction was also carried out at room temperature with the same molar ratio of the reactants. After 2 days, the ^1H NMR spectrum of the solution showed only the peaks of unreacted ketene and thiazole **2b**.

Reaction of 4-TST (2b) with DCK. The reaction was carried out as for **2a** starting with 4-TST (**2b**) (0.19 g, 1.21 mmol) and Et_3N (0.34 mL, 2.42 mmol) in *n*-hexane (50 mL) and dichloroacetyl chloride (0.23 mL, 2.42 mmol) in the same solvent (30 mL). After 15 h, usual workup and chromatography of the crude reaction mixture (Florisil, 9:1 cyclohexane/diethyl ether) gave 0.05 g (16%) of the ketone **10b** and 0.07 g (37%) of unreacted **2b**.

Ketone **10b**: oil; IR (film) 2960, 1715 cm^{-1}; ^1H NMR δ 0.36 (s, 9 H), 7.37 (s, 1 H), 7.88 (s, 1 H); mass spectrum, m/e (relative intensity) 267 (M^+, 14), 252 (25), 232 (7), 217 (18), 184 (100), 126 (17), 73 (63).

Anal. Calcd for $C_8H_{11}Cl_2NOSSi$: C, 35.82; H, 4.13; N, 5.22. Found: C, 35.81; H, 4.10; N, 5.23.

Desilylation of Ketones 10a and 10b. A solution of the ketone **10** (1 mmol) and sodium methoxide (0.054 g, 1 mmol) in methanol (30 mL) was refluxed for 3–4 days. The solvent was removed under vacuum, and the crude reaction mixture was treated with chloroform (30 mL) and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. Chromatography of the residue (silica gel, 7:3 petroleum ether/diethyl ether) gave from **10a**, 0.16 g (77%) of product **9a**; from **10b**, 0.155 g (80%) of product **9b**.

Reaction of 5-TST (2c) with TBCK. Refluxing Benzene. A solution of TBCK (2.5 mmol) in benzene (40 mL) was added to a refluxing solution of 5-TST (**2c**) (0.39 g, 2.5 mmol) in benzene (30 mL) and the mixture was heated to reflux for 48 h. The solvent was removed under vacuum and the residue was chromatographed (silica gel, 7:3 petroleum ether/diethyl ether), giving 0.126 g (18%) of ketone **11a** and 0.25 g (65%) of unreacted **2c**.

Ketone **11a**: mp 36–38 °C (from *n*-hexane); IR (film) 2970, 2240, 1690, 1475, 1370 cm^{-1}; ^1H NMR δ 0.4 (s, 9 H), 1.18 (s, 9 H), 5.06 (s, 1 H), 8.02 (s, 1 H); mass spectrum, m/e (relative intensity) M^+ absent, 208 (7), 193 (21), 123 (79), 108 (100).

Anal. Calcd for $C_{13}H_{20}N_2OSSi$: C, 55.67; H, 7.19; N, 9.99. Found: C, 55.69; H, 7.20; N, 10.01.

Room Temperature. The reaction was carried out starting with TBCK (7.6 mmol) and 5-TST (**2c**) (0.3 g, 1.9 mmol) in benzene (80 mL). After 20 h at room temperature, the solvent was removed under vacuum, and the residue was chromatographed (silica gel, 7:3 cyclohexane/diethyl ether), giving 0.482 g (63%) of the 2:1 cycloadduct **12**, 0.106 g (20%) of the ketone **11a**, and 0.039 g (13%) of unreacted **2c**.

2:1 cycloadduct **12**: mp 117–119 °C dec (from diethyl ether–*n*-hexane); IR (KBr) 2970, 1750, 1700, 1350 cm^{-1}; ^1H NMR δ 0.23 (s, 9 H), 1.29 (s, 9 H), 1.38 (s, 9 H), 6.69 (s, 2 H); ^1H NMR (C_6D_6–CH_2Cl_2) δ 0.025 (s, 9 H), 1.02 (s, 9 H), 1.36 (s, 9 H), 6.67 (s, 1 H), 6.7 (s, 1 H); mass spectrum, m/e (relative intensity) 403 (M^+, 3), 346 (8), 332 (6), 280 (3), 157 (100), 142 (31), 115 (30), 108 (22).

Anal. Calcd for $C_{20}H_{29}N_3O_2SSi$: C, 59.51; H, 7.24; N, 10.41. Found: C, 59.53; H, 7.21; N, 10.42.

Reaction of 5-TST (2c) with DCK. The reaction was carried out as for **2a** starting with 5-TST (**2c**) (0.39 g, 2.5 mmol) and Et_3N (0.35 mL, 2.5 mmol) in *n*-hexane (100 mL) and dichloroacetyl chloride (0.24 mL, 2.5 mmol) in the same solvent (200 mL). After 15 h at room temperature, usual workup and chromatography of the residue (silica gel, 7:3 *n*-hexane/diethyl ether) gave 0.133 g (20%) of ketone **11b** and 0.121 g (31%) of unreacted **2c**.

Ketone **11b**: oil; IR (film) 2960, 1715 cm^{-1}; ^1H NMR δ 0.42 (s, 9 H), 7.29 (s, 1 H), 8.09 (s, 1 H); mass spectrum, m/e (relative intensity) 267 (M^+, 1), 252 (1), 184 (100), 115 (29).

Anal. Calcd for $C_8H_{11}Cl_2NOSSi$: C, 35.82; H, 4.13; N, 5.22. Found: C, 35.84; H, 4.11; N, 5.24.

The reaction was also carried out under the same conditions with a 2:1 ratio between DCK and **2c** to give 0.4 g (60%) of **11b** and 0.066 g (17%) of unreacted **2c**.

Desilylation of Ketones 11a and 11b. A solution of the ketone **11** (1 mmol) and sodium methoxide (0.054 g, 1 mmol) in methanol (30 mL) was stirred for 15 h at room temperature. The solvent was removed under vacuum, and the residue was treated with chloroform (20 mL) and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed at reduced pressure. Chromatography of the residue (silica gel, 7:3 petroleum ether/diethyl ether) gave from **11a**, 0.156 g (75%) of the product **9a**; from **11b**, 0.136 g (70%) of the product **9b**.

Reaction of 2-TST (2a) with Carboxylic Acid Chlorides. General Procedure (Table I). A solution of the acyl chloride (2 mmol) in the selected solvent (30 mL) was added to a stirred solution of 2-TST (**2a**) (0.157 g, 1 mmol) in the same solvent (20 mL). After an appropriate time at room temperature, the reaction mixture was treated with saturated $NaHCO_3$ or another basic

solution and stirring was continued for 0.5 h. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was chromatographed (silica gel, 9:1 dichloromethane/ethyl acetate), giving thiazolyl ketone **13** or keto ester **14**.

2-Acetylthiazole (13a) (0.11 g, 88%): bp 103–105 °C (16 mmHg) [lit.[43] bp 102–105 °C (15 mmHg)]; IR (film) 1685 cm^{-1}; ^1H NMR δ 2.75 (s, 3 H), 7.75 (d, 1 H, J = 3 Hz), 8.05 (d, 1 H, J = 3 Hz); mass spectrum, m/e (relative intensity) 127 (M^+, 86), 112 (70), 99 (100), 85 (46), 84 (43).

2-(Dichloroacetyl)thiazole (9b) (0.136 g, 70%) was identical with the product obtained from the reaction of dichloroketene with **2a** followed by desilylation.

2-(Trichloroacetyl)thiazole (13b) (0.19 g, 84%): mp 62–64 °C (from diethyl ether–n-hexane); IR (film) 1710 cm^{-1}; ^1H NMR δ 7.85 (d, 1 H, J = 2.9 Hz), 8.2 (d, 1 H, J = 2.9 Hz); mass spectrum, m/e (relative intensity) 229 (M^+, 2), 158 (6), 112 (100), 85 (24).

Anal. Calcd for $C_5H_2Cl_3NOS$: C, 26.05; H, 0.87; N, 6.08. Found: C, 26.07; H, 0.86; N, 6.89.

2-(2-Methylpropanoyl)thiazole (13c) (0.14 g, 90%): oil; IR (film) 1680 cm^{-1}; ^1H NMR δ 1.27 (d, 6 H, J = 7 Hz), 3.82 (m, 1 H), 7.58 (d, 1 H, J = 3.6 Hz), 7.94 (d, 1 H, J = 3.6 Hz).

Anal. Calcd for C_7H_9NOS: C, 54.17; H, 5.84; N, 9.02. Found: C, 54.14; H, 5.86; N, 9.00.

2-Hexanoylthiazole (13d) (0.11 g, 60%): oil; IR (film) 1680 cm^{-1}; ^1H NMR δ 0.87 (m, 3 H), 1.35 (m, 4 H), 1.67 (m, 2 H), 3.12 (t, 2 H), 7.55 (d, 1 H, J = 3 Hz), 7.9 (d, 1 H, J = 3 Hz).

Anal. Calcd for $C_9H_{13}NOS$: C, 58.98; H, 7.15; N, 7.64. Found: C, 59.01; H, 7.13; N, 7.65.

2-(2,2-Dimethylpropanoyl)thiazole (13e) (0.142 g, 84%): oil; IR (film) 1670 cm^{-1}; ^1H NMR δ 1.48 (s, 9 H), 7.59 (d, 1 H, J = 3.2 Hz), 7.89 (d, 1 H, J = 3.2 Hz); mass spectrum, m/e (relative intensity) 169 (M^+, 3), 154 (5), 141 (21), 126 (12), 113 (45), 85 (100).

Anal. Calcd for $C_8H_{11}NOS$: C, 56.77; H, 6.55; N, 8.28. Found: C, 56.80; H, 6.54; N, 8.25.

2-Thiazolyl 2-propenyl ketone (13f) (0.095 g, 62%): bp 51–53 °C (1 mmHg); IR (film) 1640 cm^{-1}; ^1H NMR δ 2.11 (m, 3 H), 6.2 (m, 1 H), 6.98 (m, 1 H), 7.7 (d, 1 H, J = 3.4 Hz), 8.08 (d, 1 H, J = 3.4 Hz).

Anal. Calcd for C_7H_7NOS: C, 54.88; H, 4.60; N, 9.14. Found: C, 54.86; H, 4.61; N, 9.10.

2-Thiazolyl 2-buten-3-yl ketone (13g) (0.018 g, 11%): oil; IR (film) 1685 cm^{-1}; ^1H NMR δ 1.4 (d, 3 H, J = 7 Hz), 4.55 (m, 1 H, J = 7 Hz), 5.07–5.4 (m, 2 H), 5.82–6.32 (m, 1 H), 7.72 (d, 1 H, J = 3.2 Hz), 8.05 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for C_8H_9NOS: C, 57.46; H, 5.42; N, 8.38. Found: C, 57.43; H, 5.45; N, 8.37.

2-Benzoylthiazole (13h) (0.13 g, 70%): mp 44–46 °C (from diethyl ether–n-hexane; IR (film) 1650 cm^{-1}; ^1H NMR δ 7.61 (m, 3 H), 7.76 (d, 1 H, J = 3.2 Hz), 8.15 (d, 1 H, J = 3.2 Hz), 8.56 (m, 2 H); mass spectrum, m/e (relative intensity) 189 (M^+, 23), 161 (51), 105 (100), 85 (24), 77 (80).

Anal. Calcd for $C_{10}H_7NOS$: C, 63.47; H, 3.73; N, 7.40. Found: C, 63.49; H, 3.71; N, 7.44.

2-Furyl 2-thiazolyl ketone (13i) (0.146 g, 82%): oil; IR (film) 1640 cm^{-1}; ^1H NMR δ 6.56 (m, 1 H), 7.6 (d, 1 H, J = 3.2 Hz), 7.67 (m, 1 H), 7.95 (d, 1 H, J = 3.2 Hz), 8.08 (m, 1 H).

Anal. Calcd for $C_8H_5NO_2S$: C, 53.62; H, 2.81; N, 7.82. Found: C, 53.60; H, 2.82; N, 7.85.

2-Thiazolyl 2-thienyl ketone (13j) (0.15 g, 78%): oil; IR (film) 1650 cm^{-1}; ^1H NMR δ 7.2 (m, 1 H), 7.7 (d, 1 H, J = 3 Hz), 7.75 (m, 1 H), 8.05 (d, 1 H, J = 3 Hz), 8.6 (m, 1 H).

Anal. Calcd for $C_8H_5NOS_2$: C, 49.21; H, 2.58; N, 7.17. Found: C, 49.18; H, 2.59; N, 7.20.

Keto ester **14a**[30] (0.18 g, 92%): oil; IR (film) 1740, 1695 cm^{-1}; ^1H NMR δ 2.8 (t, 2 H, J = 7 Hz), 3.53 (t, 2 H, J = 7 Hz), 3.72 (s, 3 H), 7.71 (d, 1 H, J = 3 Hz), 8.05 (d, 1 H, J = 3 Hz); mass spectrum, m/e (relative intensity) 199 (M^+, 3), 168 (23), 140 (32), 112 (100), 85 (30).

Keto ester **14b** (0.168 g, 74%): bp 85–87 °C (15 mmHg); IR (film) 1735, 1685 cm^{-1}; ^1H NMR δ 1.82 (m, 4 H), 2.42 (m, 2 H), 3.25 (m, 2 H), 3.72 (s, 3 H), 7.82 (d, 1 H, J = 3 Hz), 8.12 (d, 1 H, J = 3 Hz).

Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.84; H, 5.76; N, 6.16. Found: C, 52.80; H, 5.75; N, 6.18.

Keto ester **14c** (0.086 g, 44%): mp 92–95 °C (from diethyl ether–n-hexane); IR (KBr) 1720, 1670 cm^{-1}; ^1H NMR δ 3.9 (s, 3 H), 7.13 (d, 1 H, J = 16.2 Hz), 7.77 (d, 1 H, J = 3.1 Hz), 8.09 (d, 1 H, J = 3.1 Hz), 8.2 (d, 1 H, J = 16.2 Hz); mass spectrum, m/e (relative intensity) 197 (M^+, 23), 166 (24), 137 (100), 113 (38), 112 (30), 85 (15).

Anal. Calcd for $C_8H_7NO_3S$: C, 48.72; H, 3.58; N, 7.10. Found: C, 48.69; H, 3.59; N, 7.13.

Keto ester **14d** (0.13 g, 76%): mp 26–29 °C (from n-hexane); IR (CCl_4) 1755, 1700 cm^{-1}; ^1H NMR δ 4.03 (s, 3 H), 7.87 (d, 1 H, J = 3.2 Hz), 8.18 (d, 1 H, J = 3.2 Hz); mass spectrum, m/e (relative intensity) 171 (M^+, 11), 142 (19), 112 (100), 99 (8), 84 (29).

Anal. Calcd for $C_6H_5NO_3S$: C, 42.10; H, 2.94; N, 8.18. Found: C, 42.97; H, 2.96; N, 8.19.

Reaction of 2-TST (2a) with Ethyl Chloroformate. The reaction was carried out according to the above procedure starting with 2-TST (**2a**) (0.157 g, 1 mmol) and ethyl chloroformate (0.217 g, 2 mmol), giving after workup the 2-thiazolecarboxylic acid ethyl ester (**15**) (0.097 g, 62%) and the thiazol-2-ylthiazoline **16** (0.036 g, 15%).

Compound **15**: mp 47–49 °C (from n-hexane); IR (KBr) 1720 cm^{-1}; ^1H NMR δ 1.45 (t, 3 H), 4.48 (q, 2 H), 7.66 (d, 1 H, J = 3 Hz), 8.04 (d, 1 H, J = 3 Hz).

Anal. Calcd for $C_6H_7NO_2S$: C, 45.84; H, 4.49; N, 8.91. Found: C, 45.83; H, 4.47; N, 8.89.

Compound **16**: mp 35–39 °C (from n-hexane); IR (CCl_4) 1725 cm^{-1}; ^1H NMR δ 1.3 (t, 3 H, J = 7 Hz)), 4.24 (q, 2 H, J = 7 Hz), 5.65 (d, 1 H, J = 4.4 Hz), 6.65 (d, 1 H, J = 4.4 Hz), 6.90 (s, 1 H), 7.35 (d, 1 H, J = 3.2 Hz), 7.80 (d, 1 H, J = 3.2 Hz); mass spectrum, m/e (relative intensity) 242 (M^+, 76), 197 (29), 169 (80), 158 (32), 86 (100), 84 (58).

Anal. Calcd for $C_9H_{10}N_2O_2S_2$: C, 44.61; H, 4.16; N, 11.56. Found: C, 44.63; H, 4.15; N, 11.55.

Reaction of 5-TST (2c) with Carboxylic Acid Chlorides. General Procedure (Table I). 5-TST (**2c**) (0.157 g, 1 mmol) and the selected acyl chloride (2 mmol) were heated at 80 °C for the time indicated in Table I. The crude reaction mixture was diluted with diethyl ether and washed with saturated $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and, after filtration, the solvent was removed under vacuum. Chromatography of the residue (silica gel, 7:3 cyclohexane/diethyl ether) gave the 5-acylthiazoles **17a,b** and the keto ester **18**.

5-Acetylthiazole[44] (17a) (0.038 g, 30%): mp 68–70 °C (from diethyl ether–n-hexane); IR (CCl_4) 1675 cm^{-1}; ^1H NMR δ 2.65 (s, 3 H), 8.51 (s, 1 H), 9.1 (s, 1 H); mass spectrum, m/e (relative intensity) 127 (M^+, 60), 112 (100), 84 (50).

Anal. Calcd for C_5H_5NOS: C, 47.22; H, 3.96; N, 11.01. Found: C, 47.20; H, 3.95; N, 10.98.

5-Benzoylthiazole (17b) (0.09 g, 48%): mp 91–93 °C (from diethyl ether–n-hexane); IR (KBr) 1630 cm^{-1}; ^1H NMR δ 7.64 (m, 3 H), 7.95 (m, 2 H), 8.41 (s, 1 H), 9.1 (s, 1 H).

Anal. Calcd for $C_{10}H_7NOS$: C, 63.47; H, 3.73; N, 7.40. Found: C, 63.45; H, 3.74; N, 7.44.

Keto ester **18** (0.145 g, 73%): mp 42–43 °C (from n-hexane); IR (film) 1735, 1675 cm^{-1}; ^1H NMR δ 2.8 (t, 2 H), 3.31 (t, 2 H), 3.69 (s, 3 H), 8.49 (s, 1 H), 9.0 (s, 1 H).

Anal. Calcd for $C_8H_9O_3S$: C, 48.23; H, 4.05; N, 7.03. Found: C, 48.20; H, 4.06; N, 7.00.

Reaction of 2-TST (2a) with Aldehydes. General Procedure (Table II, Entries 1, 2, 3, and 5). 2-(Trimethylsilyl)thiazole (**2a**) (0.314 g, 2 mmol) and the aldehyde (2 mmol) were allowed to react at room temperature for 4 h. The presence of the O-trimethylsilyl alcohol **19** was proved by NMR of the crude reaction mixture. This was diluted with tetrahydrofuran (30 mL), treated with tetrabutylammonium fluoride (TBAF) in THF (1 mL), and stirred for 1 h. The solvent was removed under vacuum, and the residue diluted with ethyl acetate (20 mL) and washed with saturated $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. Chromatography of the residue (silica gel, 7:3 cyclohexane/diethyl ether)

(43) Erlenmeyer, H.; Weber, O.; Schmidt, P.; Kung, G.; Zinsstag, C.; Prijs, P. *Helv. Chem. Acta* **1948**, *31*, 1142.

(44) Kochetkov, N. K.; Nifant'Ev, E. E.; Molodtsov, N. V. *Zh. Obshch. Khim.* **1959**, *29*, 2330.

gave the corresponding alcohol **20**.

From 2-methylpropanal (entry 1), the *O*-trimethylsilyl alcohol **19a**: ^{1}H NMR δ 0.11 (s, 9 H), 0.87 (d, 3 H, J = 2 Hz), 0.95 (d, 3 H, J = 2 Hz), 1.98 (m, 1 H), 4.8 (d, 1 H, J = 5 Hz), 7.23 (d, 1 H, J = 3.4 Hz), 7.70 (d, 1 H, J = 3.4 Hz).

Alcohol **20a** (0.3 g, 96%): bp 101–102 °C (20 mmHg); IR (film) 2960, 1500 cm^{-1}; ^{1}H NMR δ 0.94 (d, 3 H, J = 3.4 Hz), 1.02 (d, 3 H, J = 3.4 Hz), 2.2 (m, 1 H), 3.37 (br, 1 H), 4.8 (d, 1 H, J = 5.2 Hz), 7.32 (d, 1 H, J = 3 Hz), 7.75 (d, 1 H, J = 3 Hz).

Anal. Calcd for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91. Found: C, 53.49; H, 7.04; N, 8.92.

From 1-heptanal (entry 2), the *O*-trimethylsilyl alcohol **19b**: ^{1}H NMR δ 0.14 (s, 9 H), 0.87 (m, 3 H), 1.30 (br, 10 H), 1.8 (m, 2 H), 5.0 (t, 1 H), 7.22 (d, 1 H, J = 3.2 Hz), 7.70 (d, 1 H, J = 3.2 Hz).

Alcohol **20b** (0.3 g, 75%): oil; IR (film) 3250, 2970, 1510 cm^{-1}; ^{1}H NMR δ 0.87 (m, 3 H), 1.35 (br, 8 H), 1.8 (m, 2 H), 3.25 (br, 1 H), 5.01 (t, 1 H), 7.30 (d, 1 H, J = 3.2 Hz), 7.72 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{10}H_{17}NOS$: C, 60.26; H, 8.60; N, 7.03. Found: C, 60.28; H, 8.57; N, 7.05.

From acrolein (entry 3), the *O*-trimethylsilyl alcohol **19c**: ^{1}H NMR δ 0.18 (s, 9 H), 5.42 (m, 3 H), 6.1 (m, 1 H), 7.32 (d, 1 H, J = 3.4 Hz), 7.8 (d, 1 H, J = 3.4 Hz).

Alcohol **20c** (0.208 g, 74%): oil; IR (film) 3200, 1500 cm^{-1}; ^{1}H NMR δ 4.67 (br, 1 H), 5.45 (m, 3 H), 6.2 (m, 1 H), 7.38 (d, 1 H, J = 3.2 Hz), 7.75 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for C_6H_7NOS: C, 51.04; H, 5.00; N, 9.92. Found: C, 51.06; H, 5.01; N, 9.90.

From benzaldehyde (entry 5), the *O*-trimethylsilyl alcohol **19f**: ^{1}H NMR δ 0.12 (s, 9 H), 6.11 (s, 1 H), 7.25 (d, 1 H, J = 3.2 Hz), 7.37 (m, 5 H), 7.73 (d, 1 H, J = 3.2 Hz).

Alcohol **20f** (0.36 g, 95%): mp 108–110 °C (from diethyl ether–*n*-hexane); IR (KBr) 3120, 1510, 1485, 1450 cm^{-1}; ^{1}H NMR δ 4.2 (d, 1 H, J = 4 Hz), 6.07 (d, 1 H, J = 4 Hz), 7.4 (m, 6 H), 7.7 (d, 1 H, J = 3.2 Hz); mass spectrum, m/e (relative intensity) 191 (M$^+$, 100), 113 (35), 86 (75).

Anal. Calcd for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.83; H, 4.73; N, 7.31.

Reaction of 2-TST (2a) with Heteroaryl Aldehydes. General Procedure (Table II, Entries 6, 7, 8, 9, 10, and 11). A solution of the aldehyde (2 mmol) in dichloromethane (20 mL) was added to a solution of 2-TST (**2a**) (0.31 g, 2 mmol) in the same solvent (30 mL). In some cases the reaction was carried out without solvent. After stirring the reaction mixture for 18 h at room temperature, the solvent was removed under vacuum and the residue was chromatographed (Florisil, 2:1 ethyl acetate/petroleum ether), giving the *O*-trimethylsilyl alcohols **19h**, **19i**, **19j**, and **19l** or the carbonyl compounds **21g** and **21k**.

From 2-thiazolecarboxaldehyde (entry 6), the ketone **21g**[6b] (0.15 g, 38%): mp 140–141 °C dec (from *n*-hexane); IR (KBr) 1640 cm^{-1}; ^{1}H NMR δ 7.87 (d, 2 H, J = 3 Hz), 8.27 (d, 2 H, J = 3 Hz).

Anal. Calcd for $C_7H_4N_2OS_2$: C, 42.84; H, 2.05; N, 14.27. Found: C, 42.80; H, 2.04; N, 14.28.

From 4-thiazolecarboxaldehyde (entry 7), the *O*-trimethylsilyl alcohol **19h** (0.2 g, 38%): oil; IR (film) 2950, 1250 cm^{-1}; ^{1}H NMR δ 0.16 (s, 9 H), 6.27 (s, 1 H), 7.23 (d, 1 H, J = 3 Hz), 7.32 (d, 1 H, J = 2 Hz), 7.68 (d, 1 H, J = 3 Hz), 8.72 (d, 1 H, J = 2 Hz); mass spectrum, m/e (relative intensity) 270 (M$^+$, 13), 255 (100), 181 (12), 73 (62).

Anal. Calcd for $C_{10}H_{14}N_2OS_2Si$: C, 44.41; H, 5.22; N, 10.36. Found: C, 44.43; H, 5.19; N, 10.39.

From 5-thiazolecarboxaldehyde (entry 8), the *O*-trimethylsilyl alcohol **19i** (0.22 g, 41%): oil; IR (film) 2950, 1250 cm^{-1}; ^{1}H NMR δ 0.17 (s, 9 H), 6.35 (s, 1 H), 7.25 (d, 1 H, J = 3 Hz), 7.68 (d, 1 H, J = 3 Hz), 7.81 (s, 1 H), 8.7 (s, 1 H); mass spectrum, m/e (relative intensity) 270 (M$^+$, 48), 255 (100), 181 (36), 73 (84).

Anal. Calcd for $C_{10}H_{14}N_2OS_2Si$: C, 44.41; H, 5.22; N, 10.36. Found: C, 44.46; H, 5.23; N, 10.33.

From 2-furancarboxaldehyde (entry 9), the *O*-trimethylsilyl alcohol **19j** (0.27 g, 53%): oil; IR (film) 2980, 1510 cm^{-1}; ^{1}H NMR δ 0.15 (s, 9 H), 6.11 (s, 1 H), 6.33 (m, 2 H), 7.30 (d, 1 H, J = 3.2 Hz), 7.35 (m, 1 H), 7.75 (d, 1 H, J = 3.2 Hz); mass spectrum, m/e (relative intensity) 253 (M$^+$, 30), 238 (85), 224 (50), 164 (70), 73 (100).

Anal. Calcd for $C_{11}H_{15}NO_2SSi$: C, 52.14; H, 5.97; N, 5.53. Found: C, 52.18; H, 5.95; N, 5.51.

From 2-pyridinecarboxaldehyde (entry 10), the ketone **21k** (0.102 g, 27%): mp 68–70 °C (from diethyl ether–*n*-hexane); IR (KBr) 1655, 1580 cm^{-1}; ^{1}H NMR δ 7.5 (m, 1 H), 7.75 (d, 1 H, J = 3 Hz), 7.9 (m, 1 H), 8.16 (d, 1 H, J = 3 Hz), 8.32 (m, 1 H), 8.8 (m, 1 H).

Anal. Calcd for $C_9H_6N_2OS$: C, 56.83; H, 3.18; N, 14.73. Found: C, 56.80; H, 3.19; N, 14.75.

From 2-thiophenecarboxaldehyde (entry 11), the *O*-trimethylsilyl alcohol **19l** (0.42 g, 78%): oil; IR (film) 2985, 1505 cm^{-1}; ^{1}H NMR δ 0.16 (s, 9 H), 6.32 (d, 1 H), 7.00 (m, 2 H), 7.27 (m, 2 H), 7.35 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_{11}H_{15}NOS_2Si$: C, 49.03; H, 5.61; N, 5.20. Found: C, 49.00; H, 5.64; N, 5.22.

The *O*-trimethylsilyl alcohol **19** (1 mmol) was dissolved in THF (20 mL) and TBAF in THF (1 mL) was added. After stirring the reaction mixture for 1 h, usual workup and chromatography of the residue (silica gel, 1:1 ethyl acetate/*n*-hexane) gave from **19h**, the alcohol **20h** (0.079 g, 40%); from **19i**, the alcohol **20i** (0.059 g, 35%) and the ketone **21i** (0.033 g, 17%); from **19j**, the alcohol **20j** (0.095 g, 70%); from **19l**, the alcohol **20l** (0.19 g, 97%).

Alcohol **20h**: mp 118–120 °C (from diethyl ether–*n*-hexane); IR (KBr) 1600 cm^{-1}; ^{1}H NMR δ 5.2 (br, 1 H), 6.25 (s, 1 H), 7.25 (d, 1 H, J = 3 Hz), 7.35 (d, 1 H, J = 2 Hz), 7.66 (d, 1 H, J = 3 Hz), 8.7 (d, 1 H, J = 3 Hz); mass spectrum, m/e (relative intensity) 198 (M$^+$, 55), 114 (100), 85 (63).

Anal. Calcd for $C_7H_6N_2OS_2$: C, 42.40; H, 5.04; N, 14.13. Found: C, 42.42; H, 5.03; N, 14.11.

Alcohol **20i**: oil; IR (film) 1500 cm^{-1}; ^{1}H NMR δ 6.33 (s, 1 H), 7.3 (d, 1 H, J = 3 Hz), 7.67 (d, 1 H, J = 3 Hz), 7.77 (s, 1 H), 8.68 (s, 1 H); mass spectrum, m/e (relative intensity) 198 (M$^+$, 100), 169 (35), 142 (53), 114 (52), 85 (30).

Anal. Calcd for $C_7H_6N_2OS_2$: C, 42.40; H, 5.04; N, 14.13. Found: C, 42.39; H, 5.06; N, 14.11.

Ketone **21i**: mp 86–88 °C (from diethyl ether–*n*-hexane); IR (CCl_4) 1635 cm^{-1}; ^{1}H NMR δ 7.75 (d, 1 H, J = 3.1 Hz), 8.06 (d, 1 H, J = 3.1 Hz), 9.03 (s, 1 H), 9.2 (s, 1 H); mass spectrum, m/e (relative intensity) 196 (M$^+$, 16), 181 (50), 154 (52), 112 (57), 97 (100).

Anal. Calcd for $C_7H_4N_2OS_2$: C, 42.84; H, 2.05; N, 14.27. Found: C, 42.81; H, 2.07; N, 14.25.

Alcohol **20j**: oil; IR (film) 1510 cm^{-1}; ^{1}H NMR δ 4.55 (br, 1 H), 6.12 (s, 1 H), 6.37 (d, 2 H), 7.35 (d, 1 H, J = 3.1 Hz), 7.40 (m, 1 H), 7.75 (d, 1 H, J = 3.1 Hz).

Anal. Calcd for $C_8H_7NO_2S$: C, 53.02; H, 3.89; N, 7.73. Found: C, 53.00; H, 3.87; N, 7.70.

Alcohol **20l**: oil; IR (film) 3200, 1515 cm^{-1}, ^{1}H NMR δ 3.47 (br, 1 H), 6.33 (d, 1 H, J = 0.6 Hz), 7.05 (m, 2 H), 7.32 (m, 2 H), 7.75 (d, 1 H, J = 3.2 Hz).

Anal. Calcd for $C_8H_7NOS_2$: C, 48.71; H, 3.58; N, 7.10. Found: C, 48.68; H, 3.59; N, 7.12.

Reaction of 2-TST (2a) with (*R*,*S*)-2-Phenylpropanal (Table II, Entry 4). A mixture of 2-TST (**2a**) (0.5 g, 3.2 mmol) and the aldehyde[45] (0.47 g, 3.5 mmol) was stirred at 0 °C for 6 h. The crude reaction mixture was diluted with THF (40 mL) and treated with TBAF in THF (4.5 mL). After additional stirring for 1 h, the solvent was removed under vacuum, the residue was diluted with ethyl acetate (30 mL), and the solution was washed with saturated $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed under vacuum. The residue was chromatographed (silica gel, 1:1 diethyl ether/petroleum ether) to give the anti adduct **20d** (0.133 g, 19%) and the syn adduct **20e** (0.364 g, 52%).

Anti diastereoisomer **20d**: oil; ^{1}H NMR ($CDCl_3$–D_2O) δ 1.3 (d, 3 H, J = 7.2 Hz), 3.25 (m, 1 H), 5.05 (d, 1 H, J = 6.8 Hz), 7.22 (m, 6 H), 7.63 (d, 1 H, J = 3.3 Hz).

Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39. Found: C, 65.70; H, 5.96; N, 6.35.

Syn diastereoisomer **20e**: mp 79–80 °C (from *n*-hexane); ^{1}H NMR ($CDCl_3$–D_2O) δ 1.28 (d, 3 H, J = 7.2 Hz), 3.40 (m, 1 H), 5.06 (d, 1 H, J = 4.8 Hz), 7.2 (m, 6 H), 7.63 (d, 1 H, J = 3.3 Hz).

(45) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214.

Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39. Found: C, 65.76; H, 5.94; N, 6.40.

Reaction of 5-TST (2c) with Aldehydes. General Procedure (Table II, Entries 12 and 13). The solution of 5-TST (**2c**) (0.157 g, 1 mmol), aldehyde (2 mmol), and CsF (0.151 g, 1 mmol) in THF (10 mL) was heated to reflux for 48 h. The solvent was removed under vacuum and chromatography of the residue (silica gel, 20:20:1 cyclohexane/ethyl acetate/methanol) gave the alcohol **22**.

From 2-methylpropanal (entry 12), the alcohol **22a** (0.05 g, 32%): oil; IR (film) 3300, 1520, 1470 cm^{-1}; ^1H NMR δ 0.83 (d, 3 H, J = 5 Hz), 1.03 (d, 3 H, J = 5 Hz), 1.95 (m, 1 H), 3.38 (br, 1 H), 4.75 (d, 1 H, J = 5 Hz), 7.65 (s, 1 H), 8.7 (s, 1 H).

Anal. Calcd for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91. Found: C, 53.45; H, 7.06; N, 8.93.

From benzaldehyde (entry 13), the alcohol **22b** (0.076 g, 40%): mp 75–77 °C (from diethyl ether–*n*-hexane); IR (KBr) 3280, 3070, 1395 cm^{-1}; ^1H NMR δ 4.88 (br, 1 H), 6.01 (s, 1 H), 7.33 (s, 5 H), 7.46 (s, 1 H), 8.54 (s, 1 H).

Anal. Calcd for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.83; H, 4.73; N, 7.30.

Reaction of 2,4-bis-TST (3a) with Diphenylketene (DPK). The reaction was carried out as above for **2a** starting with 2,4-bis-TST (**3a**) (0.81 g, 3.56 mmol) in *n*-hexane (40 mL) and DPK (0.69 g, 3.56 mmol) in the same solvent (30 mL). After 1 day at room temperature, another equivalent of DPK was added and the reaction was stirred for 4 days. Usual workup and chromatography (silica gel, 9:1 cyclohexane/diethyl ether) gave 1.095 g (73%) of the silyl enol ether **23a**: oil; ^1H NMR δ 0.075 (s, 9 H), 0.24 (s, 9 H), 7.25 (m, 11 H).

Desilylation was carried out starting with 1 g (2.3 mmol) of the silyl enol ether **23a** and 5% HCl (3 mL) in THF (40 mL). The reaction mixture was stirred at room temperature for 4 days. Usual workup and chromatography (silica gel, 7:3 benzene/*n*-hexane) gave 0.7 g (86%) of the ketone **10c**: mp 90–92 °C (from *n*-hexane); IR ($CHCl_3$) 1680, 1600 cm^{-1}; ^1H NMR δ 0.32 (s, 9 H), 6.65 (s, 1 H), 7.3 (m, 10 H), 7.67 (s, 1 H); mass spectrum, m/e (relative intensity) 351 (M^+, 79), 336 (7), 323 (10), 184 (18), 167 (100), 152 (23), 126 (10), 73 (14).

Anal. Calcd for $C_{20}H_{21}NOSSi$: C, 68.33; H, 6.02; N, 3.98. Found: C, 68.30; H, 6.00; N, 3.99.

Reaction of 2,4-bis-TST (3a) with Acetyl Chloride. A solution of 2,4-bis-TST (**3a**) (1 g, 4.4 mmol) in benzene (30 mL) was added to a solution of acetyl chloride (3.45 g, 4.4 mmol) in the same solvent (50 mL). Usual workup and chromatography of the residue (silica gel, 7:3 cyclohexane/diethyl ether) gave 0.5 g (58%) of the ketone **24a**: oil; IR (film) 1690 cm^{-1}; ^1H NMR δ 0.35 (s, 9 H), 2.72 (s, 3 H), 7.68 (s, 1 H); mass spectrum, m/e (relative intensity) 199 (M^+, 62), 184 (100), 156 (20), 115 (33), 73 (61).

Anal. Calcd for $C_8H_{13}NOSSi$: C, 48.20; H, 6.57; N, 7.03. Found: C, 48.18; H, 6.59; N, 7.00.

Reaction of 2,4-bis-TST (3a) with 3-Carbomethoxypropionyl Chloride. The reaction was carried out as above starting with 2,4-bis-TST (**3a**) (1 g, 4.4 mmol) and 3-carbomethoxypropionyl chloride (3.31 g, 22 mmol) in refluxing benzene (70 mL) for 24 h. Usual workup and chromatography (silica gel, cyclohexane/diethyl ether) gave 0.715 g (60%) of the keto ester **25a**: mp 53–55 °C (from diethyl ether–*n*-hexane); IR (KBr) 1740, 1695 cm^{-1}; ^1H NMR δ 0.35 (s, 9 H), 2.77 (t, 2 H), 3.55 (t, 2 H), 3.71 (s, 3 H), 7.7 (s, 1 H); mass spectrum, m/e (relative intensity) 271 (M^+, 5), 256 (8), 158 (43), 143 (100), 116 (54), 84 (10), 74 (30).

Anal. Calcd for $C_{11}H_{17}NO_3SSi$: C, 48.68; H, 6.31; N, 5.16. Found: C, 48.71; H, 6.29; N, 5.19.

Reaction of 2,4-bis-TST (3a) with 2-Methylpropanal. The thiazole **3a** (1.15 g, 5 mmol) and the aldehyde (2.27 mL, 25 mmol) were stirred at room temperature for 2 days. The reaction mixture was diluted with THF (20 mL) and a solution of TBAF in THF (1 mL) was added. After stirring for 30 min, the solvent was removed under vacuum. The residue was dissolved in diethyl ether (30 mL) and then washed with saturated $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. Chromatography of the residue (silica gel, 1:1 *n*-hexane/diethyl ether) gave 0.5 g (43%) of the alcohol **26a**: mp 52–54 °C (from diethyl ether–*n*-hexane; ^1H NMR δ 0.3 (s, 9 H), 0.94 (d, 3 H, J = 2 Hz), 1.02 (d, 3 H, J = 2 Hz)), 2.17 (m, 1 H), 3.36 (d, 1 H), 4.83 (dd, 1 H), 7.38 (s, 1 H); mass spectrum, m/e (relative intensity) 229 (M^+, 7), 214 (17), 186 (100), 170 (63), 115 (29), 83 (27), 75 (41), 73 (34).

Anal. Calcd for $C_{10}H_{19}NOSSi$: C, 52.35; H, 8.35; N, 6.10. Found: C, 52.34; H, 8.36; N, 6.13.

Reaction of 2,5-bis-TST (3b) with DPK. The reaction was carried out as above for **2a** starting with DPK (0.388 g, 2 mmol) in *n*-hexane (30 mL) and 2,5-bis-TST (**3b**) (0.458 g, 2 mmol) in the same solvent (40 mL). After 3 h at room temperature, the solvent was removed under vacuum to give 0.83 g (98%) of the silyl enol ether **23b**: mp 93–94 °C (from *n*-hexane); IR (KBr) 2960, 2900, 1590 cm^{-1}; ^1H NMR δ 0.06 (s, 9 H), 0.21 (s, 9 H), 7.25 (m, 10 H), 7.65 (s, 1 H); mass spectrum, m/e (relative intensity) 423 (M^+, 4), 406 (7), 147 (100), 105 (14), 73 (27).

Anal. Calcd for $C_{23}H_{29}NOSSi_2$: C, 65.19, H, 6.90; N, 3.30. Found: C, 65.21; H, 6.91; N, 3.29.

Desilylation of the *O*-Trimethylsilyl Enol Ether 23b. A solution of **23b** (0.423 g, 1 mmol) and 5% HCl (0.5 mL) in THF (40 mL) was stirred for 1 h at room temperature. Usual workup and chromatography of the residue (silica gel, 7:3 petroleum ether/diethyl ether) gave 0.315 g (90%) of the ketone **11c**: mp 119–120 °C (from *n*-hexane); IR (KBr) 2960, 1690 cm^{-1}; ^1H NMR δ 0.34 (s, 9 H), 6.6 (s, 1 H), 7.36 (m, 10 H), 7.97 (s, 1 H); mass spectrum, m/e (relative intensity) 351 (M^+, 37), 184 (43), 167 (100), 152 (31), 115 (12), 73 (37).

Anal. Calcd for $C_{20}H_{21}NOSSi$: C, 68.33; H, 6.02; N, 3.98. Found: C, 68.30; H, 6.01; N, 3.96.

Reaction of the Ketone 11c with Butanal. To a stirred solution of the ketone **11c** (0.5 g, 1.4 mmol) and CsF (0.05 g) in THF (20 mL) was added the aldehyde (0.1 g, 1.4 mmol) in the same solvent (10 mL). After 3 h at room temperature, the solvent was removed under vacuum. The residue was diluted with diethyl ether (30 mL) and washed with saturated $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and filtered and the solvent was removed under vacuum. Chromatography of the residue (silica gel, 7:3 cyclohexane/diethyl ether) gave 0.22 g (45%) of the compound **27**: oil; IR (film) 3420, 2920, 1680, 1395 cm^{-1}; ^1H NMR δ 0.81–1.9 (m, 7 H), 2.42 (br, 1 H), 4.96 (t, 1 H), 6.57 (s, 1 H), 7.22–7.47 (m, 10 H), 7.81 (s, 1 H).

Anal. Calcd for $C_{21}H_{21}NO_2S$: C, 71.76; H, 6.02; N, 3.99. Found: C, 71.73; H, 6.01; N, 3.98.

Reaction of 2,5-bis-TST (3b) with Acetyl Chloride. A solution of 2,5-bis-TST (**3b**) (1 g, 4.4 mmol) in benzene (30 mL) was added with stirring to a solution of acetyl chloride (1.38 g, 17.6 mmol) in the same solvent (50 mL). After 2 days at room temperature, usual workup and chromatography (silica gel, 1:1 cyclohexane/diethyl ether) gave 0.84 g (96%) of the ketone **24b**: oil; IR (film) 1685 cm^{-1}; ^1H NMR δ 0.37 (s, 9 H), 2.7 (s, 3 H), 7.95 (s, 1 H).

Anal. Calcd for $C_8H_{13}NOSSi$: C, 48.20; H, 6.57; N, 7.03. Found: C, 48.16; H, 6.59; N, 7.00.

Reaction of 2,5-bis-TST (3b) with 3-Carbomethoxypropionyl Chloride. A solution of 2,5-bis-TST (**3b**) (2g, 8.7 mmol) in benzene (20 mL) was added to a stirred solution of 3-carbomethoxypropionyl chloride (1.44 g, 9.6 mmol). After 24 h at room temperature, usual workup and chromatography (silica gel, 1:1 cyclohexane/diethyl ether) gave 2.26 g (96%) of the keto ester **25b**: oil; IR (film) 1740, 1685 cm^{-1}; ^1H NMR δ 0.4 (s, 9 H), 2.81 (t, 2 H), 3.55 (t, 2 H), 3.75 (s, 3 H), 8.08 (s, 1 H).

Anal. Calcd for $C_{11}H_{17}NO_3SSi$: C, 48.68; H, 6.31; N, 5.16. Found: C, 48.71; H, 6.28; N, 5.18.

Reaction of 2-Acetyl-5-(trimethylsilyl)thiazole (24b) with 2-Methylpropanal. A mixture of **24b** (0.67 g, 3.37 mmol), the aldehyde (1.2 g, 17 mmol), and TBAF in THF (3.4 mL) was stirred at room temperature for 2 h. The reaction mixture was diluted with diethyl ether and washed with saturated $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. Chromatography of the residue (silica gel, 7:3 diethyl ether/*n*-hexane) gave 0.21 g (32%) of compound **28**: oil; IR (film) 1670 cm^{-1}; ^1H NMR δ 0.9 (d, 3 H, J = 8 Hz), 1.01 (d, 3 H, J = 8 Hz), 1.95 (br, 1 H), 1.97 (m, 1 H), 2.66 (s, 3 H), 4.76 (d, 1 H), 7.74 (s, 1 H); mass spectrum, m/e (relative intensity) 199 (M^+, 12), 156 (100), 128 (31), 113 (22), 87 (29).

Anal. Calcd for $C_9H_{13}NO_2S$: C, 54.25; H, 6.58; N, 7.03. Found: C, 54.28; H, 6.57; N, 7.05.

Reaction of 2,5-bis-TST (3b) with 2-Methylpropanal. A mixture of 2,5-bis-TST (**3b**) (1.15 g, 5 mmol) and the aldehyde (2.27 mL, 25 mmol) was stirred at room temperature for 2 h. The crude reaction mixture was diluted with THF (20 mL) and a solution of TBAF in THF (1 mL) was added. After additional stirring (30 min), the solvent was removed under vacuum and the residue was dissolved in diethyl ether (30 mL). The solution was washed with saturated $NaHCO_3$. Usual workup and chromatography (silica gel, 1:1 diethyl ether–*n*-hexane) gave 0.81 g (80%) of the alcohol **26b**: oil; ^1H NMR δ 0.34 (s, 9 H), 0.94 (d, 3 H, J = 4 Hz), 1.01 (d, 3 H, J = 4 Hz), 2.17 (m, 1 H), 3.24 (d, 1 H), 4.8 (dd, 1 H), 7.66 (s, 1 H).

Anal. Calcd for $C_{10}H_{19}NOSSi$: C, 52.35; H, 8.35; N, 6.10. Found: C, 52.37; H, 8.32; N, 6.11.

Reaction of the Alcohol 26b with 3-Carbomethoxypropionyl Chloride. A mixture of the alcohol **26b** (0.165 g, 0.72 mmol), 3-carbomethoxypropionyl chloride (0.5 mL, 4 mmol), and triethylamine (0.1 mL, 0.72 mmol) was heated at 80 °C for 48 h. The crude mixture was diluted with diethyl ether and washed with saturated $NaHCO_3$. Usual workup and chromatography (silica gel, 1:1 diethyl ether/*n*-hexane) gave 0.166 g (60%) of compound **29**: oil; IR ($CHCl_3$) 1740, 1675 cm^{-1}; ^1H NMR δ 0.98 (d, 6 H, J = 7 Hz), 2.34 (m, 1 H), 2.72 (m, 6 H), 3.24 (m, 2 H), 3.69 (s, 6 H), 5.9 (d, 1 H), 8.3 (s, 1 H); mass spectrum, m/e (relative intensity) M^+ absent, 271 (38), 245 (19), 229 (27), 213 (32), 115 (100).

Anal. Calcd for $C_{17}H_{23}NO_7S$: C, 52.97; H, 6.01; N, 3.63. Found: C, 52.95; H, 6.00; N, 3.64.

Synthesis, Molecular Symmetry, and Chemical Reactivity of *C*-Aryl-Substituted Phosphoraziridines

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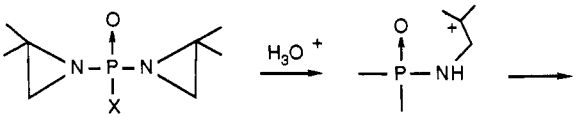
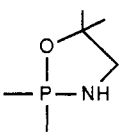
P,P-Bis- and *P,P,P*-tris(1-aziridinyl)phosphoramides containing aryl-substituted aziridine moieties, including para-substituted 2-phenylaziridines, an optically active aziridine, and all the possible *C*-aryl regioisomers of diphenylaziridine were prepared by condensation of the aziridines with the appropriate phosphoryl chlorides. For the preparation of the sterically hindered diphenylaziridine derivatives, an efficient phosphorylation procedure was developed that involved conversion of the aziridines to their lithium salts. The appearance of the aziridine ring regions of the ^1H NMR spectra of these compounds suggested decreased conformational mobility, as well as the presence of an average axis of symmetry in tris(aziridinyl) compounds and a plane of symmetry in certain bis(aziridinyl) systems. The relative reactivities of these new phosphoraziridines with 4-(*p*-nitrobenzyl)pyridine indicate the likelihood of significant S_N1 character in the ring-opening process.

The phosphoraziridines[2] AB-163 (**1a**) and AB-132 (**1b**) have been shown in experimental and clinical studies to be potent antitumor agents as well as radiation sensitizers.[3] Analogues of AB-132 with various alkyl substitution patterns on the aziridine ring have been prepared and considerable variation in both the modes and rates of ring opening by water and 4-(*p*-nitrobenzyl)pyridine (NBP) was observed for these phosphinyl carbamates.[4] The combination of potent antitumor and radiosensitizing activity, as well as the toxic effect of inhibition of acetyl cholinesterase,[5] is exhibited only by compounds such as **1a** and **1b**, which possess geminal dimethyl ring substitution. These properties may be due to a unique mode of hydrolysis involving rapid ring-opening at the substituted position and subsequent ring expansion.[6]



1(a) x = OEt
1(b) x = NHCOOEt



(1)

A pronounced tendency toward ring-opening at the benzylic carbon in *C*-phenyl-substituted aziridines[7] suggests that the corresponding phosphoraziridines might resemble the 2,2-dimethylaziridine series in their chemical reactivity and thereby in their spectrum of biological activity as well. Radiation sensitization by a free radical process would also be expected to be favored. In this report we describe the synthesis of *C*-aryl analogues of the bis(1-aziridinyl) compounds **1** as well as those of tris(2,2-dimethyl-1-aziridinyl)phosphine oxide (TEPA-132),[8] which has geminal dimethyl substitution but lacks the ability of

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(2) Trivial name for class of compounds comprising *N*-phosphinyl derivatives of aziridines.

(3) Bardos, T. J.; Ambrus, J. L.; Ambrus, C. M. *J. Surg. Oncol.* **1971**, *3*, 431. Wampler, G. L.; Kuperminc, M.; Regelson, W. *Cancer Chemother. Pharmacol.* **1980**, *4*, 49. Belgrad, R.; Wampler, G. L. *Int. J. Radiat. Oncol. Biol. Phys.* **1982**, *8*, 1219.

(4) Bardos, T. J.; Barua, A. K.; Chmielewicz, Z. F.; Crevar, G. E.; Dailey, J. P.; Divald, S.; Papanastassiou, Z. B. *J. Pharm. Sci.* **1965**, *54*, 187. Bardos, T. J.; Chmielewicz, Z. F.; Navada, C. K. *J. Pharm. Sci.* **1965**, *54*, 399. Bardos, T. J.; Chmielewicz, Z. F.; Ambrus, J. L.; Back, N. *Int. Congr. Chemother., Proc., 5th* **1967**, 181.

(5) Bardos, T. J.; Ambrus, J. L. *Int. Congr. Chemother., Proc., 3rd* **1964**, 1036. Lalka, D.; Bardos, T. J. *Biochem. Pharmacol.* **1975**, *24*, 455.

(6) Bardos, T. J.; Dunn, J. A.; Perlman, M. E. *Int. J. Radiat. Oncol. Biol. Phys.*, **1979**, *5*, 1653.

(7) Hassner, A.; Burke, S. S. *Tetrahedron* **1974**, *30*, 2613.

(8) Munson, A. E.; Babbitt, H. C.; Segaloff, A.; Chmielewicz, Z. F.; Bardos, T. J.; Ambrus, J. L. *Cancer Chemother. Rep.* **1967**, *51*, 253.

0022-3263/88/1953-1761$01.50/0