Synthesis of Stannylthiazoles and Mixed Stannyl-silylthiazoles and their Use for a Convenient Preparation of Mono- and Bis-halothiazoles

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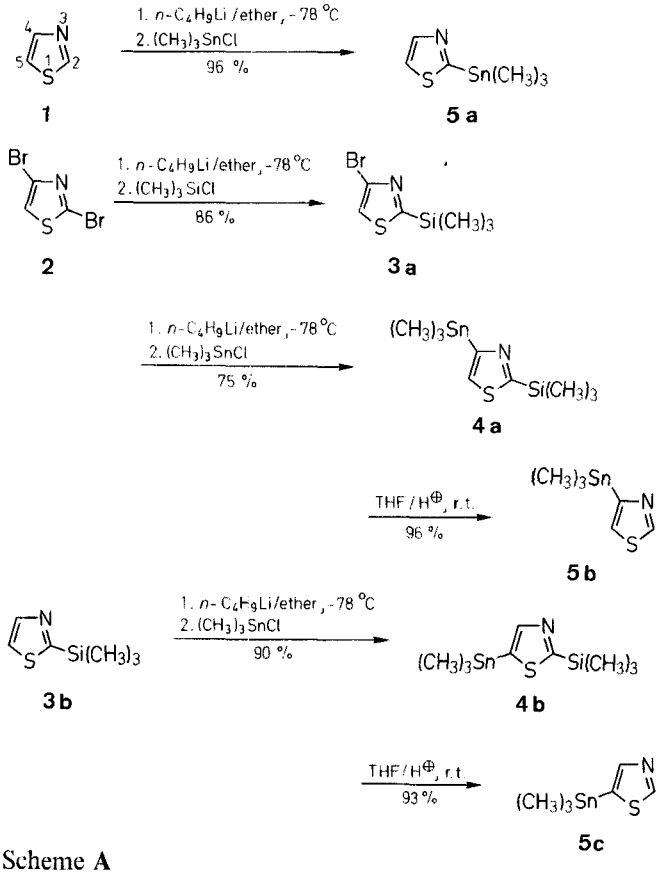
Stannylthiazoles and stannyl-silylthiazoles have been prepared and employed as thiazolyl carbanion equivalents in reactions with halogens to give mono- and mixed bis-halothiazoles in good yields.

Halothiazoles constitute an important class of thiazole derivatives due to their wide use as intermediates in heterocyclic chemistry[1] and their possible biological activity as insecticides[2]. Classical methods for the preparation of mono-derivatives include the Sandmeyer reaction on aminothiazoles[3] and the cyclization of sodium *N*-acetylaminomethane sulfonate by thionyl halides[4]. These methods, however, are limited in scope and versatility as, for instance, they cannot be applied to the preparation of mixed bis-derivatives. Following our work on silyloxazoles and silylthiazoles[5], we report here a convenient method for the preparation of stannylthiazoles and mixed stannyl-silylthiazoles and their use for the regioselective halodemetallation into iodo- and iodo-bromothiazoles, a series of hitherto unreported thiazole derivatives. A similar approach has been recently employed for the preparation of halopyridines and haloquinolines[6].

2-Trimethylstannylthiazole **(5a)** was prepared in good yield by quenching 2-lithiothiazole with trimethyltin chloride (Scheme **A**). On the other hand, the selective stannylation at C-4 or C-5 of the thiazole ring was carried out by protecting C-2 by the easily removable trimethylsilyl group[5]. Thus, treatment with trimethyltin chloride of 4- and 5-lithio-2-trimethylsilylthiazole generated from the appropriate precursors **3a** and **3b** by metal-halogen or metal-hydrogen exchange respectively, gave the mixed metalated (silicon and tin) thiazoles **4a** and **4b** in high yields. Protodesilylation of these compounds produced 4- and 5-trimethylstannylthiazoles **(5b)** and **(5c)** (Table 1).



Scheme **A**

Treatment of stannylthiazoles **5a–c** with iodine in tetrahydrofuran at room temperature resulted in the almost instantaneous iododestannylation reaction leading to the corresponding iodothiazoles **6a–c** (Scheme **B**, Route A), two of which, **6b** and **6c**, (Table 2) were not previously reported. It is noteworthy that the iododemetalation on trimethylsilylthiazoles failed under the same conditions[7]. Thus, the chemoselective iododestannylation on **4a** and **4b**

Table 1. Stannyl- and Silylthiazoles **3–5** Prepared.

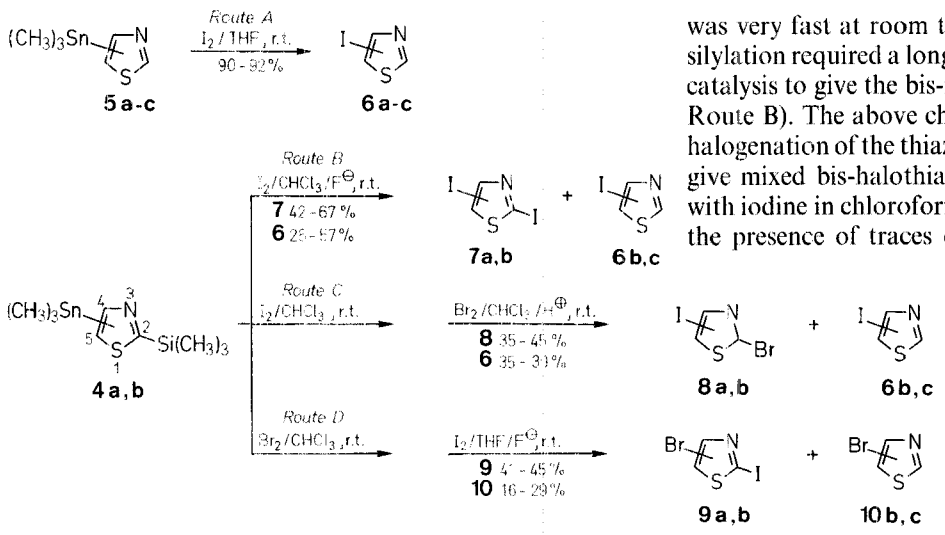
Product No.	Yield [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[a]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]	M.S. *m/e* (M^+)
3a	86	80–85/2	$C_6H_{10}BrNSSi$ (236.2)	0.41 s, 9H); 7.40 (s, 1H)	235
4a	75	51–55/0.5	$C_9H_{19}NSSiSn$ (320.1)	0.36 (s, 9H); 0.40 (s, 9H); 7.55 (s, 1H)	319
4b	90	75–77	$C_9H_{19}NSSiSn$ (320.1)	0.40 (s, 9H); 0.41 (s, 9H); 8.08 (s, 1H)	319
5a	96	91–93/17	$C_6H_{11}NSSn$ (247.9)	0.48 (s, 9H); 7.55 (d, 1H, J = 2.9 Hz); 8.16 (d, 1H, J = 2.9 Hz)	247
5b	96	90–93/16	$C_6H_{11}NSSn$ (247.9)	0.41 (s, 9H); 7.91 (s, 1H); 9.08 (s, 1H)	247
5c	93	102–105/14	$C_6H_{11}NSSn$ (247.9)	0.39 (s, 9H); 7.44 (d, 1H, J = 1.6 Hz); 9.01 (d, 1H, J = 1.6 Hz)	247

[a] Satisfactory microanalyses obtained: C ±0.19, H ±0.21.

Table 2. Halothiazoles **6–9** Prepared.

Product No.	Yield [%]	m.p. [°C]	Molecular Formula[a]	I.R. (CCl_4) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]	M.S. *m/e* (M^+)
6b	90	oil	C_3H_2INS (211.0)	1435, 1330	8.73 (d, 1H, J = 2.2 Hz); 7.50 (d, 1H, J = 2.2 Hz)	211
6c	92	79–81	C_3H_2INS (211.0)	1475, 1375	8.88 (s, 1H); 7.95 (s, 1H)	211
7a	42	110–112	C_3HI_2NS (337)	1440, 1375	7.34 (s)	337
7b	67	103–105	C_3HI_2NS (337)	1470, 1365	7.27 (s)	337
8a	45	93–95	$C_3HBrINS$ (289.9)	1445, 1395	7.42 (s)	289
8b	35	110–112	$C_3HBrINS$ (289.9)	1480, 1390	7.66 (s)	289
9a	45	80–82	$C_3HBrINS$ (289.9)	1455, 1380	7.24 (s)	289
9b	41	oil	$C_3HBrINS$ (289.9)	1480, 1375	7.44 (s)	289

[a] Satisfactory microanalyses obtained: C ±0.17, H ±0.28.



Scheme **B**

4/7/8/9	Substituent in position	**5/6/10**	Substituent in position
a	4-C	**a**	2-C
b	5-C	**b**	4-C
		c	5-C

was very fast at room temperature (TLC) whereas iododesilylation required a longer reaction time and the fluoride ion catalysis to give the bis-iodothiazoles **7a** and **7b** (Scheme **B**, Route B). The above chemoselectivity allowed the stepwise halogenation of the thiazole ring by two different halogens to give mixed bis-halothiazoles. Thus, treatment of **4a** or **4b** with iodine in chloroform and subsequently with bromine in the presence of traces of trichloroacetic acid produced 4-iodo-2-bromo- or 5-iodo-2-bromothiazole (**8a**) and (**8b**) respectively (Scheme **B**, Route C). Similarly, by reversing the halogenation order, the regioisomers 4-bromo-2-iodo- and 5-bromo-2-iodothiazole (**9a**) and (**9b**) were obtained (Scheme **B**, Route D) (Table 2). In all cases, the yields of products **7**, **8** and **9** were not higher than 50% (see experimental) nor could these be improved by changing the solvent (tetrahydrofuran) and catalyst. This appears to be due to the protodesilylation at C-2 competing with the halodesilylation reaction, as indicated by the formation of

comparable amounts of mono-halothiazoles **6** and **10**. Nevertheless, this method is the only one available for the direct one-pot bis-halogenation of the thiazole ring and for the preparation of mixed halothiazoles.

All reactions were carried out under nitrogen using anhydrous solvents. 2,4-Dibromothiazole **(2)** was prepared according to the literature method[4]. 2 Trimethylsilylthiazole **(3b)** was prepared as described[5]. Chromatography was carried out on silica gel (eluent petroleum ether/diethyl ether 9:1).

2-Trimethylsilyl-4-bromothiazole (3a):
To a stirred solution of *n*-butyllithium (49.4 mmol) in diethyl ether (150 ml), cooled at −78 °C, is added dropwise in 1 h a solution of 2,4-dibromothiazole (**2**; 10 g, 41.1 mmol) in diethyl ether (70 ml). The mixture is stirred at −78 °C for 1 h, then a solution of trimethylsilyl chloride (4.91 g, 45.2 mmol) in diethyl ether (30 ml) is added dropwise in 15 min. After 1 h at −78 °C, the reaction mixture is washed with saturated aqueous sodium hydrogen carbonate (20 ml), and extracted with diethyl ether (2 × 50 ml). The organic layer is dried with sodium sulfate and the solvent removed under vacuum. The residue is distilled to give **3a**; yield: 8.4 g (86%); b.p. 80–85 °C/2 torr (Table 1).

2-Trimethylsilyl-4-trimethylstannylthiazole (4a); Typical Procedure:
To a stirred solution of *n*-butyllithium (22.2 mmol) in diethyl ether (100 ml) at −78 °C, is added dropwise in 1 h a solution of **3a** (3.5 g, 14.8 mmol) in diethyl ether (50 ml). The mixture is stirred at −78 °C for 1 h, and then a solution of trimethyltin chloride (4.42 g, 22.2 mmol) in diethyl ether (30 ml) is added dropwise in 15 min. After an additional 1 h at −78 °C, the reaction mixture is washed with saturated aqueous sodium hydrogen carbonate (30 ml) and extracted with diethyl ether (2 × 50). The organic layer is dried with sodium sulfate and the solvent is removed under vacuum. The residue is distilled to give **4a**; yield: 3.6 g (75%); b.p. 51–55 °C/0.5 torr (Table 1).

2-Trimethylsilyl-5-trimethylstannylthiazole (4b):
Compound **4b** is prepared as described above for **4a** starting from *n*-butyllithium (30.5 mmol) in diethyl ether (120 ml), 2-trimethylsilylthiazole **(3b)** (4.0 g, 25.5 mmol) in diethyl ether (50 ml) and trimethyltin chloride (6.0 g, 30.5 mmol) in diethyl ether (40 ml). The crude mixture is filtered and the solvent removed under vacuum to give **4b**; yield 7.32 g (90%); m.p. 75–77 °C (from petroleum ether).

2-Trimethylstannylthiazole (5a):
Compound **5a** is prepared as described above for **4a** starting from *n*-butyllithium (22 mmol) in diethyl ether (80 ml), thiazole (1.7 g, 20.0 mmol) in diethyl ether (50 ml) and trimethyltin chloride (4.4 g, 22.0 mmol) in diethyl ether (30 ml). The crude mixture is filtered and the solvent removed under vacuum to give **5a**; yield: 4.46 g (96%); b.p. 91–93 °C/17 torr (Lit.[8], 86 °C/10 torr) (Table 1).

4- and 5-Trimethylstannylthiazoles (5b) and (5c):
To a stirred solution of **4a** or **4b** (1 g, 3.1 mmol) in tetrahydrofuran (10 ml), at room temperature, is added 5% aqueous hydrochloric acid (1 ml). After 1 h the reaction mixture is extracted with diethyl ether (2 × 20 ml) and washed with saturated aqueous sodium hydrogen carbonate (20 ml). The organic layer is dried with sodium sulfate and the solvent removed under vacuum to give **5b** and **5c** respectively.
5b: yield: 0.73 g (96%); b.p. 90–93 °C/16 torr. (Table 1)
5c: yield: 0.71 g (93%); b.p. 102–105 °C/14 torr. (Table 1)

2-, 4- and 5-Iodothiazoles 6a–c:

Route A: To a stirred solution of **5a–c** (0.49 g, 2.0 mmol) in tetrahydrofuran (20 ml) at room temperature, is added dropwise a solution of iodine (0.51 g, 2.0 mmol) in tetrahydrofuran (30 ml). After 30 min the solution is washed with saturated aqueous sodium hydrogen carbonate (40 ml) and sodium thiosulfate (30 ml), extracted with diethyl ether (3 × 30 ml) and the solvent removed under vacuum. The residue is chromatographed to give **6a–c**.

6a: yield: 0.38 g (90%); b.p. 117–118 °C/40 torr (Lit.[1], b.p. 118 °C/40 torr).
6b: yield: 0.38 g (90%) (Table 2).
6c: yield: 0.39 g (92%) (Table 2).

Route B: *By the Reaction of* ***4a*** *or* ***4b*** *with Iodine:* To a stirred solution of **4a** or **4b** (0.51 g, 1.6 mmol) in chloroform (10 ml) is added dropwise a solution of iodine (0.81 g, 3.2 mmol) in chloroform (20 ml), containing cesium fluoride (10 mg). The reaction mixture is stirred overnight at room temperature, then treated with saturated aqueous sodium hydrogen carbonate (20 ml) and sodium thiosulfate (15 ml). The organic layer is dried with sodium sulfate and the solvent removed under vacuum. The residue is chromatographed to give **7a** [yield: 0.22 g (42%)], **6b** [yield: 0.18 g (57%)] from **4a**; **7b** [yield: 0.36 g (67%)],**6c** [yield: 84 mg (25%)] from **4b** (Table 2).

Route C: *By the Reaction of* ***4a*** *or* ***4b*** *with Iodine and then Bromine:* To a stirred solution of **4a** or **4b** (0.51 g, 1.6 mmol) in chloroform (10 ml) is slowly added an equimolar amount of iodine (0.4 g, 1.61 mmol) in chloroform (20 ml). The reaction mixture is allowed to stand at room temperature for 30 min, then treated with saturated aqueous sodium hydrogen carbonate (20 ml) and sodium thiosulfate (20 ml). The organic layer is dried with sodium sulfate and the solvent removed under vacuum. The residue is dissolved in chloroform (20 ml) and a solution of bromine (0.51 g, 3.2 mmol) in chloroform (20 ml) containing trichloroacetic acid (10 mg) is added dropwise. The reaction mixture is stirred overnight at room temperature and then worked-up as described above. Chromatography of the residue gives **8a** [yield: 0.2 g (45%)], **6b** [yield: 0.13 g (39%)] from **4a**; **8b** [yield: 0.16 g (35%)], **7b** [yield: 43 mg (8%)] and **6c** [yield: 0.12 g (35%)] from **4b**.

Halothiazoles 9 and 10:

Route D: *Reaction of* ***4a*** *or* ***4b*** *with Bromine and then Iodine:* To a stirred solution of **4a** or **4b** (0.51 g, 1.6 mmol) in chloroform (10 ml) is added dropwise an equimolar amount of bromine (0.26 g) in chloroform (20 ml). The reaction mixture is allowed to stand at room temperature for 30 min then treated with saturated aqueous sodium hydrogen carbonate (20 ml) and sodium thiosulfate (20 ml). The organic layer is dried with sodium sulfate and the solvent removed under vacuum. The crude mixture is dissolved in tetrahydrofuran (20 ml) and a solution of iodine (0.48 g, 1.9 mmol) in tetrahydrofuran (20 ml) containing cesium fluoride (10 mg) is added dropwise. The reaction mixture is stirred at room temperature for 4 h, then worked-up as described above, Chromatography of the residue gives **9a** [yield: 0.2 g (45%)], **10b** [yield: 76 mg (29%); b.p. 188–190 °C/760 torr (Lit.[1], 190 °C/760 torr)] from **4a**; **9b** [yield: 0.19 g (41%)] and **10c** [yield: 42 mg (16%); b.p. 80–81 °C/18 torr (Lit.[1], 81 °C/18 torr)] from **4b**.

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