

Synthesis of Pyrrolo[2, 1-*b*]thiazolines Using *N*-(Trimethylsilylmethyl)-2- methylthiothiazolinium Trifluoromethanesulfonate

Shinya KOHRA and Kazuo UEDA

(Received July 31, 1996)

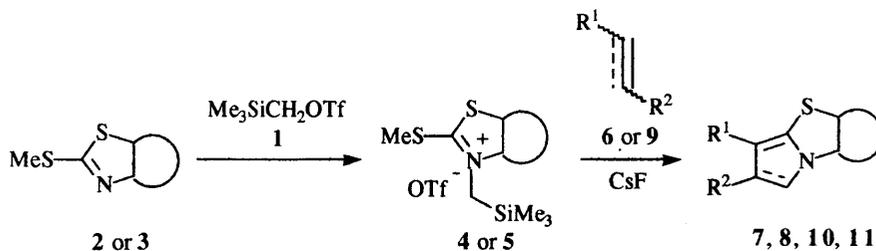
Abstract

N-(Trimethylsilylmethyl)-2-methylthiothiazolinium trifluoromethanesulfonate (**4**), readily prepared from 2-methylthiothiazoline (**2**) and trimethylsilylmethyl trifluoromethanesulfonate (**1**), reacted with activated alkenes (**5**) and alkynes (**6**) in the presence of cesium fluoride in acetonitrile to give the corresponding 4, 5-dihydropyrrolo[2, 1-*b*]thiazoline and pyrrolo[2, 1-*b*]thiazoline derivatives.

The 1, 3-dipolar cycloaddition reaction is one of the most important reaction to construct five-membered heterocycles. We have reported that tailor-made azomethine and thiocarbonyl ylids can be generated by the 1, 3-elimination reaction of trimethylsilylmethyl-substituted ketene *N,S*- or *S,S*-acetals promoted by fluoride ion and react with dipolarophiles to give five-membered heterocycles.¹⁻³⁾ As an unpublished result, we have recognized that the reaction of 3-trimethylsilylmethylamino-3-methylthio-2-cyanoacrylonitrile with dipolarophiles in the presence of a fluoride ion gives five-membered heterocycles but the reaction of 3-trimethylsilylmethylamino-2-cyanoacrylonitrile with dipolarophiles gives no cycloadducts. These facts have shown that the elimination of a methylthio group following cleavage of carbon-silicon bond is a useful tool for the generation of 1,3-dipolar. Here we describe the reaction of *N*-(trimethylsilylmethyl)-2-methylthiothiazolinium trifluoromethanesulfonate, which has a Me₃SiCH₂-N=C-SMe system, with dipolarophiles gives 4,5-dihydropyrrolo[2, 1-*b*]thiazoline derivatives.

Trimethylsilylmethyl trifluoromethanesulfonate (**1**)⁴⁾ is an interesting compound to the preparation of silicon-containing sulfonium, nitrogen and other ylids.⁵⁻¹⁵⁾ Starting material **1** was prepared according to the literature.⁴⁾

A solution of 2-methylthiothiazoline (**2**) in dichloromethane was treated with **1** and stirred at room temperature for over night. After the solvent was removed *N*-(trimethylsilylmethyl)-2-methylthiothiazolinium trifluoromethanesulfonate (**4**) was afforded¹⁶⁾. The crude salt **4** was used in the next step without purification.



Scheme 1.

A solution of **4**, thus obtained, and dimethyl fumarate (**6b**) in the presence of cesium fluoride in acetonitrile was stirred at room temperature for 24h. The usual work-up after treatment with aqueous ammonium chloride and separation by preparative t. l. c. gave dimethyl 4, 5-dihydropyrrolo[2, 1-*b*]thiazoline-5, 6-dicarboxylate (**7b**), formal [3+2] cycloaddition product, in 53% yield. The cycloaddition behavior of an unsymmetrically substituted dipolarophile was studied to determine the regioselectivity of the reaction. The reaction of **4** and methyl acrylate (**6a**) under the similar conditions gave methyl 4, 5-dihydropyrrolo[2,1-*b*]thiazoline-6-carboxylate (**7a**) in 57% yield, exclusively. When methyl cinnamate (**6d**) was used as a dipolarophile, cycloadduct **7d** was obtained as a single product. The representative results are listed in Table 1. *N*-(Trimethylsilylmethyl)-2-methylthiobenzothiazolium trifluoromethanesulfonate (**5**) was also prepared and reacted with activated alkenes (**6a-6d**) to give the corresponding [3+2] cycloadducts (**8a-8d**) in a manner similar to that described for **7a**. The reaction also shows complete regioselectivity in the cycloaddition with unsymmetrically substituted olefins. However the reactions of **4** and **5** with *N*-methylmaleimide was unsuccessful under the present reaction conditions.

Salt **4** and **5** reacted with alkynes (**9a** and **9b**) under the similar conditions to give [3+2] cycloaddition products, pyrrolo[2, 1-*b*]thiazoline derivatives (**10a** and **10b**) and pyrrolo[2, 1-*b*]benzothiazole derivatives (**11a** and **11b**). (see Table 2)

This work demonstrates a mild and simple procedure for the preparation of pyrrolo[2, 1-*b*]thiazoline and pyrrolo[2, 1-*b*]benzothiazole derivatives.

Table 1. Reactions of **4** and **5** with activated alkenes(**6**)^{a)}

entry	starting material	alkene(6)		product (7 or 8)	Yield(%) ^{b)}	
		R ¹	R ²			
1	4	CO ₂ Me	H	(6a)	7a	57
2	4	CO ₂ Me	CO ₂ Me	trans-(6b)	7b	53
3	4	CO ₂ Me	CO ₂ Me	cis-(6b)	7b	73
4	4	CN	CN	trans-(6c)	7c	81
5	4	CO ₂ Me	C ₆ H ₅	trans-(6d)	7d	51
6	5	CO ₂ Me	H	(6a)	8a	60
7	5	CO ₂ Me	CO ₂ Me	trans-(6b)	8b	55
8	5	CN	CN	trans-(6c)	8c	64
9	5	CO ₂ Me	C ₆ H ₅	trans-(6d)	8d	53

a) All reactions were carried out using **4** or **5** (0.5 mmol) and **6**(0.5 mmol) in the presence of CsF(1.0 mmol) in acetonitrile(4 ml) at room temperature for 24 h. b) Yield after isolation by preparative t.l.c..

Table 2. Reactions of **4** and **5** with alkynes(**9**)

entry	starting material	alkyne(9)		product (10 or 11)	Yield(%)	
		R ¹	R ²			
1	4	CO ₂ Me	H	(9a)	10a	63
2	4	CO ₂ Me	CO ₂ Me	(9b)	10b	78
3	5	CO ₂ Me	H	(9a)	11a	49
4	5	CO ₂ Me	CO ₂ Me	(9b)	11b	60

a) All reactions were carried out using **4** or **5** (0.5 mmol) and **9**(0.5 mmol) in the presence of CsF(1.0 mmol) in acetonitrile(4 ml) at room temperature for 24 h. b) Yield after isolation by preparative t.l.c..

Experimental

All melting points were determined in a open capillary tube on a MP-21 Yamato melting point apparatus and are uncorrected. Infrared (ir) spectra were recorded in potassium bromide pellets on a JASCO IRA-2 spectrophotometer and ultraviolet (uv) absorption spectra were determined in 95% ethanol on a Hitachi EP-S2 spectrophotometer. ¹H Nuclear magnetic resonance (nmr) spectra were obtained on Varian Gemini-200 (200MHz), Gemini-300 (300-MHz), and UNITY plus 500 (500MHz) spectrometers with tetramethylsilane as an internal standard. Mass spectra (ms) were recorded on a JEOL JMS-DX303 mass spectrometer.

Typical Procedure: Synthesis of Methyl 4, 5-dihydropyrrolo[2,1-*b*]thiazoline-6-carboxylate (7a): To a solution of 2-methylthiazoline (2) (67mg, 0.5 mmol) in dichloromethane (5ml) was added trimethylsilylmethyl trifluoromethanesulfonate (1) (118mg, 0.5mmol) and the resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure to give *N*-(trimethylsilylmethyl)-2-methylthiothiazolium trifluoromethanesulfonate (4). The crude salt was used next step further purification.

A 50 ml, two-necked flask was fitted with a magnetic stirring bar and gas inlet tube. The flask was charged with CsF (152mg, 1.0mmol) and was heated at 120-140°C under reduced pressure with a hot plate stirrer for 2h. The apparatus was cooled under purging with nitrogen. A solution of 4a (0.5mmol) and methyl acrylate (6a) (43mg, 0.5mmol) in acetonitrile (4ml) was introduced *via* a syringe with stirring. The reaction mixture was stirred at room temperature for 20h. Ethyl acetate (20ml) and saturated ammonium chloride solution (5ml) were then added and the mixture was stirred for 10min. The resulting mixture was separated and the aqueous layer was extracted with ethyl acetate (2x10ml). The combined organic layer was washed with water (2x20ml) and brine (20ml). After drying over anhydrous MgSO₄, the solvent was removed to give oily residue. The crude product was purified by preparative t.l.c. using a 1:2 mixture of hexane and ethyl acetate as an eluent to give 7a (53mg, 0.286 mmol) as an oil in 57% yield.

Methyl 4, 5-dihydropyrrolo[2, 1-*b*]thiazolin-6-carboxylate (7a) : yield 57%; pale yellow oil; ir (KBr) ν max: 2950, 2850, 1740, 1670, 1560, 1435, 1235, 1105 cm⁻¹; uv (EtOH) λ max nm (log ϵ) : 304 (4.11), 237 (3.61) ; ¹H-nmr (CDCl₃) δ : 3.03 (2H, td, *J*=8.3 and 1.4Hz, H-5), 3.20 (2H, t, *J* = 6.4Hz, H-2), 3.30 (2H, td, *J* = 8.3 and 1.4Hz, H-4), 3.51 (2H, t, *J* = 6.4Hz, H-3), 3.70 (3H, s, OMe) ; ms *m/z* (%) : 185 (M⁺, 28), 154 (19), 126 (12), 86 (65), 84 (100). HR-ms Calcd for C₈H₁₁NO₂S *m/z*=243.0565. Found *m/z*=185.0411

Dimethyl 4, 5-dihydropyrrolo[2, 1-*b*]thiazoline-5, 6-dicarboxylate (7b) : yield 53%; pale yellow oil; ir (KBr) ν max: 2950, 1740, 1695, 1560, 1435 cm⁻¹; uv (EtOH) λ max nm (log ϵ) : 295 (3.63) ; ¹H-nmr (CDCl₃) δ : 3.14 (1H, td, *J*=8.6 and 6.9Hz, H-2), 3.28-3.40 (1H, m, H-2), 3.46-3.51 (2H, m, H-3 and H-4), 3.53-3.59 (1H, m, H-3), 3.63 (1H, dd, *J*=9.4 and 5.3Hz, H-4), 3.70 (3H, s, OMe), 3.73 (3H, s, OMe), 4.15 (1H, dd, *J*=9.5 and 5.4Hz, H-5) ; ms *m/z* (%) : 243 (M⁺, 26), 185 (12), 184 (100), 183 (15), 152 (38). HR-ms Calcd for C₁₀H₁₃NO₄S *m/z*=243.0565. Found *m/z*=243.0565

5, 6-Dicyano-4, 5-dihydropyrrolo[2, 1-*b*]thiazoline (7c) : yield 81%; colorless needles, mp 121-122°C (hexane-ethyl acetate) ; ir (KBr) ν max: 2970, 2170, 1545, 1270 cm⁻¹; uv (EtOH) λ max nm (log ϵ) : 285 (5.18), 233 (4.81) ; ¹H-nmr (CDCl₃) δ : 3.23 (1H,

td, $J=8.6$ Hz, H-2), 3.40-3.53 (1H, m, H-4), 3.58-3.75 (4H, m, H-2, H-3 x 2 and H-4), 4.15 (1H, dd, $J=9.5$ and 5.4 Hz, H-5) ; ms m/z (%) : 177 (M^+ , 89), 176 (47), 151 (33), 149 (56), 121 (21). *Anal.* Calcd for $C_8H_7N_3S$: C, 54.22; H, 3.98; N, 23.71; S, 18.09. Found; C, 54.33; H, 4.02; N, 23.79; S, 17.96.

Methyl 4, 5-dihydro-5-phenylpyrrolo[2, 1-b]thiazoline-6-dicarboxylate (7d) : yield 51%; pale yellow oil; ir (KBr) ν max: 2950, 2840, 1670, 1565, 1240, 1190 1110cm^{-1} ; uv (EtOH) λ max nm ($\log \epsilon$) : 302 (4.20), 236 (3.86) ; $^1\text{H-nmr}$ (CDCl_3) δ : 3.08 (1H, td, $J=9.0$ and 6.7Hz, H-2), 3.30-3.70 (8H, m, H-2, H3x2, H-4x2 and OMe), 4.50 (1H, dd, $J=9.6$ and 3.9 Hz, H-5), 7.15-7.35 (5H, m, aromatic-H) ; ms m/z (%) : 261 (M^+ , 13), 133(15). HR-ms Calcd for $C_{14}H_{15}NO_2S$ $m/z=$ 261.0824. Found $m/z=$ 261.0820

Methyl 1, 2-dihydropyrrolo[2, 1-b]benzothiazole-3-carboxylate (8a) : yield 60%; pale yellow prisms, mp 155-157°C (hexane-ethyl acetate) ; ir (KBr) ν max:2948, 1644, 1558, 1478, 1430cm^{-1} ; uv (EtOH) λ max nm ($\log \epsilon$) : 352 (4.55), 234 (4.09) ; $^1\text{H-nmr}$ ($\text{DMSO-}d_6$) δ : 3.14 (2H, t, $J=9.0$ Hz, H-2x2), 3.60 (3H, s, OMe), 4.13 (2H, t, $J=9.0$ Hz, H-1x2), 6.97-7.04 (2H, m, H-8 and H-6 or H-7), 7.28 (1H, td, $J=8.0$ and 1.0 Hz, H-6 or H-7), 7.60 (8.2Hz, H-5) ; ms m/z (%) : 233 (M^+ , 100), 202 (38), 174 (41). *Anal.* Calcd for $C_{12}H_{11}NO_2S$:C, 61.78;H, 4.75; N, 6.00;S, 13.74. Found;C, 61.53 ;H, 4.80;N, 5.80;S, 13.68.

Dimethyl 1, 2-dihydropyrrolo[2, 1-b]benzothiazole-2, 3-dicarboxylate (8b) : yield 55%;pale yellow needles, mp 151-152°C (hexane-ethyl acetate) ; ir (KBr) ν max:3000, 2950 , 1740, 1660, 1555, 1470, 1435cm^{-1} ; uv (EtOH) λ max nm ($\log \epsilon$) :346 (4.65), 233 (4.26) ; $^1\text{H-nmr}$ ($\text{DMSO-}d_6$) δ : 3.60 (3H, s, OMe), 3.66 (3H, s, OMe), 4.24-4.50 (3H, m, H-1x2 and H-2), 7.06 (2H, td, $J=8.2$ and 1.1Hz, H-8 and H-6 or H7), 7.32 (1H, td, $J=8.2$ and 1.1Hz, H-6 or H-7), 7.66 (1H, d, $J=7.5$ Hz, H-5) ; ms m/z (%) : 291 (M^+ , 33), 232 (100), 173 (34). *Anal.* Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81; S, 11.01. Found; C, 57.44; H, 4.48; N, 4.82; S, 10.96.

2, 3-Dicyano-1,2-dihydropyrrolo[2, 1-b]benzothiazole (8c) : yield 64%; pale yellow prisms, mp 251-253°C (benzene-ethanol) ; ir (KBr) ν max: 2190, 1585, 1555, 1480, 1465cm^{-1} ; uv (EtOH) λ max nm ($\log \epsilon$) : 333(-), 231(-) ; $^1\text{H-nmr}$ ($\text{DMSO-}d_6$) δ : 4.42 (1H, t, $J=11.0$ Hz, H-1), 4.55 (1H, dd, $J=11.0$ and 5.6Hz, H-1), 4.94 (1H, dd, $J=11.0$ and 5.6Hz, H-2), 7.05-7.18 (2H, m, H-8 and H-6 or H-7), 7.36 (1H, td, $J=7.5$ and 1.0Hz, H-6 or H-7), 7.72 (1H, d, $J=7.2$ Hz, H-5) ; ms m/z (%) : 225 (M^+ , 100), 224 (51), 199 (48), 198 (26). *Anal.* Calcd for $C_{12}H_7N_3S$: c, 63.98; H, 3.13; N, 18.65 ; S, 14.23. Found; C, 64.1 ; H, 3.39; N, 18.37; S, 14.09.

Methyl 1, 2-dihydro-2-phenylpyrrolo[2, 1-b]benzothiazole-3-carboxylate (8d) : yield 53%; pale yellow needles, mp 175-176°C (hexane-ethyl acetate) ; ir (KBr) ν max: 2875, 1650, 1580, 1550, 1460, 1435cm^{-1} ; uv (EtOH) λ max nm ($\log \epsilon$) : 349 (4.65), 233

(4.29) ; $^1\text{H-nmr}$ ($\text{DMSO-}d_6$) δ : 3.50 (3H, s, OMe), 4.00 (1H, dd, $J=10.6$ and 4.0 Hz, H-1), 4.51 (1H, t, $J=10.7$ Hz, H-1), 4.68 (1H, dd, $J=10.7$ and 4.0 Hz, H-2), 7.0-7.38 (8H, m, aromatic-H), 7.66 (1H, d, $J=8.2$ Hz, H-5) ; ms m/z (%) : 309 (M^+ , 69), 250 (43), 232 (39), 151 (22). *Anal.* Calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_2\text{S}$: C, 69.90; H, 4.9; N, 4.53; S, 10.37. Found; C, 69.63; H, 4.99; N, 4.59; S, 10.28.

Methyl pyrrolo[2,1-b]thiazoline-6-carboxylate (10a) : yield 63%; pale yellow oil; ir (KBr) ν max: 2950, 1700, 1525, 1495, 1240cm^{-1} ; uv (EtOH) λ max nm ($\log \epsilon$) : 284 (3.90), 218 (4.23) ; $^1\text{H-nmr}$ (CDCl_3) δ : 3.73 (2H, t, $J=7.3$ Hz, H-2), 3.81 (3H, s, OMe), 4.17 (2H, t, $J=7.3$ Hz, H-3), 6.57 (1H, d, $J=3.1$ Hz, H-5), 6.62 (1H, d, $J=3.1$ Hz, H-4) ; ms m/z (%) : 243 (M^+ , 26), 185 (12), 184 (100), 183 (15), 152 (38). HR-ms Calcd for $\text{C}_8\text{H}_9\text{NO}_2\text{S}$ $m/z=183.0354$. Found $m/z=183.0352$.

Dimethyl pyrrolo[2,1-b]thiazoline-5,6-dicarboxylate (10b) : yield 78%; pale yellow oil; ir (KBr) ν max: 3145, 2950, 1725, 1490, 1440, 1275cm^{-1} ; uv (EtOH) λ max nm ($\log \epsilon$) : 291 (4.01), 229 (4.07) ; $^1\text{H-nmr}$ (CDCl_3) δ : 3.71 (2H, t, $J=7.3$ Hz, H-2), 3.80 (3H, s, OMe), 3.83 (3H, s, OMe), 4.22 (2H, t, $J=7.3$ Hz, H-3), 7.26 (1H, s, H-4) ; ms m/z (%) : 241 (M^+ , 17), 210 (11), 88 (10), 86 (65), 84 (100). HR-ms Calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_4\text{S}$ $m/z=241.0409$. Found $m/z=241.0411$

Methyl pyrrolo[2,1-b]benzothiazole-3-carboxylate (11a): yield 49%; pale yellow needles mp $120\text{-}121^\circ\text{C}$ (hexane) ; ir (KBr) ν max: 3120, 2940, 1685, 1530,1490, 1285, 1250cm^{-1} ; uv (EtOH) λ max nm ($\log \epsilon$) : 307 (4.20), 243 (4.52), 205 (4.58) ; $^1\text{H-nmr}$ (CDCl_3) δ : 3.90 (3H, s, OMe), 6.98 (1H, d, $J=3.2$ Hz, H-2), 7.38 (2H, td, 7.5 and 7.6Hz, H-6 and H-7), 7.42 (1H, d, $J=3.2$ Hz, H-1), 7.68 (2H, dd, $J=7.2$ and 7.4 Hz, H-5 and H-8) ; ms m/z (%) : 231 (M^+ , 87), 200 (100), 172 (16). *Anal.* Calcd for $\text{C}_{12}\text{H}_9\text{NO}_2\text{S}$: C, 62.32; H, 3.92; N, 6.06; S, 13.86. Found; C, 62.03; H, 3.96; N, 6.02; S, 13.79.

Dimethyl pyrrolo[2,1-b]benzothiazole-2,3-dicarboxylate (11b) : yield 60%; pale yellow mp $145\text{-}146^\circ\text{C}$ (hexane-ethyl acetate) ; ir (KBr) ν max: 3125, 3050, 2950, 1740, 1710, $1510, 1275\text{cm}^{-1}$; uv (EtOH) λ max nm ($\log \epsilon$) : 290 (4.15), 241 (4.67), 201 (4.45) ; $^1\text{H-nmr}$ ($\text{DMSO-}d_6$) δ : 3.81 (3H, s, OMe x 2), 7.407.63 (2H, m, H-6 and H-7), 8.04 (1H, dd, $J=8.0$ and 1.0 Hz, H-8), 8.23 (1H, dd, $J=7.5$ and 1.0 Hz, H-5), 8.65 (1H, s, H-1) ; ms m/z (%) : 289 (M^+ , 100), 258 (75), 228 (17). *Anal.* Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_4\text{S}$: C, 58.12; H, 3.83; N, 4.84; S, 11.08. Found; C, 58.08; H, 3.86; N, 4.78; S, 11.08.

References and Notes

1. S. Kohra, K. Ueda, Y. Tominaga, *Chem. Pharm. Bull.*, 1995, **43**, 204-209.
2. Y. Tomiaga, K. Ogata, H. Ueda, S. Kohra, A. Hosomi, *ibid.*, 1995, **43**, 1425-1434.
3. Y. Tominaga, S. Takada, S. Kohra, *ibid.*, 1996, **44**, 653-660.
4. S. Ambasht, S. K. Chiu, *Synthesis*, **1980**, 318-320.
5. E. Vedeis, G. R. Madnez, *J. Am. Chem. Soc.*, 1979, **101**, 6452-6454.
6. *idem.*, *ibid.*, 1980, **102**, 7993-7994.
7. Y. Terao, N. Imai, K. Achiwa, M. Sekiya, *Chem. Pharm. Bull.*, 1982, **30**, 3167-3171.
8. A. Padwa, G. Haffmanns, M. Tomas, *Tetrahedron Lett.*, 1983, **24**, 4303-4306.
9. O. Tsuge, S. Kanemasa, S. Kuraoka, S. Takenaka, *Chem. Lett.*, **1984**, 279-280.
10. *idem.*, *ibid.*, **1984**, 281-284.
11. A. Padwa, G. Haffmanns, M. Tomas, *J. Org. Chem.*, 1985, **49**, 3314-3322.
12. A. Padwa, Y. Y. Chen, U. Chiacchio, W. Dent, *Tetrahedron*, 1985, **41**, 3529-3535.
13. A. Padwa, Y. Y. Chen, U. Chiacchio, H. Nimmesgern, *J. Org. Chem.*, 1985, **50**, 4006-4014.
14. O. Tsuge, S. Kanemasa, K. Matsuda, *J. Org. Chem.*, 1986, **51**, 1997-2004.
15. O. Tsuge, S. Kanemasa, T. Yamada, K. Matsuda, *ibid.*, 1987, **52**, 2523-2530.
16. Compound 4: ¹H-nmr (CDCl₃) δ: 0.23 (9H, s, SiMe₃), 2.87 (3H, s, SMe), 3.51 (2H, s, CH₂SiMe), 3.90 (2H, t, J=8.6Hz, SCH₂), 4.59 (2H, t, J=8.6Hz, NCH₂).