Chemistry of Heterocyclic Compounds, Vol. 41, No. 7, 2005

USE OF A METALLATION REACTION TO OBTAIN SUBSTITUTED 2-(5-METHYL-2-THIAZOLYL)ETHANOLS

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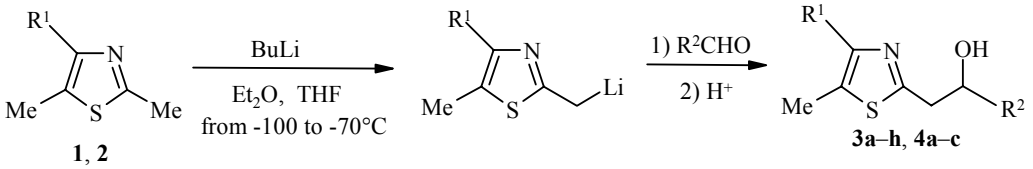
The interaction of anions, obtained by treating 2,4,5-trimethylthiazole and 2,5-dimethyl-4-phenylthiazole with butyllithium, with aliphatic and aromatic aldehydes leads to substituted 2-thiazolyl-1-ethanols. It was established that the metallation reaction occurs at the 2-methyl group of the thiazoles.

Keywords: butyllithium, 2,5-dimethyl-4-phenylthiazolide anion, 2-thiazolylethanols, metallation.

Metallation of alkyl- and aryl-substituted thiazoles with butyllithium is a key reaction for obtaining various functional derivatives of these compounds. The interaction of 2-methylbenzothiazole with butyllithium and the reaction of the resulting anion with acid chlorides and esters of carboxylic acids, aldehydes, and other electrophiles has been studied in detail [1].

A very small number of studies has been devoted to the metallation of aryl- and alkyl-2,4,5-substituted thiazoles. It was shown that in the case of 2-methyl-4-phenylthiazole the presence of a stabilizing anion of the phenyl substituent in position 4 of the thiazole increases the acidity of the hydrogen atom in position 5 and precisely this position is subject to electrophilic attack. On the other hand, in the case of 2,4-dimethylthiazole the acidity of the hydrogen atom in position 5 of the thiazole is less than the acidity of the hydrogen atom of the methyl group in position 2, consequently electrophilic attack is effected at the 2-CH_3 group [2].

There are no data in the literature on the metallation of 2,5-dimethyl-4-substituted thiazoles. To establish the effect of the nature of the substituent at position 4 of the thiazole on the conditions and direction of the metallation of 2,5-dimethylthiazoles with butyllithium, we have studied the condensation of anions obtained from 2,5-dimethylthiazoles, containing a methyl or phenyl substituent in position 4 with a fairly representative selection of aldehydes.



1, **2** **3a–h**, **4a–c**

1, **3** R^1 = Me, **3 a** R^2 = *i*-Pr, **b** R^2 = *i*-Bu, **c** R^2 = Ph, **d** R^2 = 2-$CF_3C_6H_4$, **e** R^2 = 3-$CF_3C_6H_4$, **f** R^2 = 4-$MeSC_6H_4$, **g** R^2 = 4-F-3-$MeOC_6H_3$, **h** R^2 = 2-F-4-$MeOC_6H_3$; **2**, **4** R^1 = Ph; **4 a** R^2 = Ph, **b** R^2 = 2-FC_6H_4, **c** R^2 = 3-FC_6H_4

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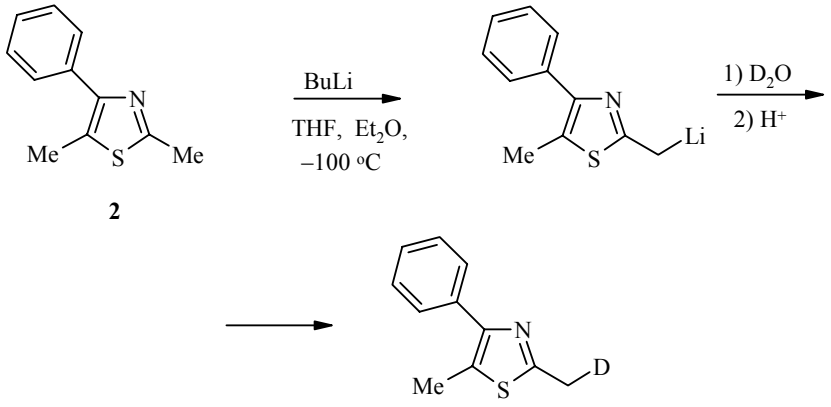
We have obtained 2-thiazolyl-1-ethanols **3a-h** and **4a-c** for the first time (Table 1). Metallation of thiazole **1** and treatment of the anion with aldehydes was carried out at -70°C. The yields of compounds **3a-h** were 20-60%. Metallation of thiazole **2** and subsequent treatment of the anion with aldehydes was carried out at -100°C. On increasing the temperature of the reaction of thiazole **2** with butyllithium to -70°C the yields of compounds **4a-c** were reduced.

In the ^{1}H NMR spectra of compounds **3a-h** and **4a-c** the signals of the protons of the methylene group at position 2 of the thiazole were not equivalent and were a doublet of doublets with different coupling constants (Table 2). The signal of the CH group proton for compounds **3c-h** and **4a-c**, in which R^2 is a substituted or unsubstituted phenyl radical lies at 5.00-5.50 ppm. In the case of compounds **3a** and **3b**, in which R^2 is an isopropyl or an isobutyl radical respectively, the signal is displaced towards high field and is observed at 3.69 (for compound **3a**) and 4.02 ppm (for compound **3b**).

To confirm the course of the metallation reaction at the 2-methyl group of the thiazole under the usual conditions the 2,5-dimethyl-4-phenylthiazolide anion was synthesized and treated with D_2O. The obtained compound **6** was purified chromatographically and its ^{13}C NMR spectrum was recorded. As additional standard the ^{13}C NMR spectrum of 2-methyl-5,6,7,8-tetrahydro-4H-cyclohepta[*d*]-1,3-thiazole (**5**) [3] was used for reliable identification of the signal of the 2-methyl group of the thiazoles.



2 **6**

In the ^{13}C NMR spectrum of compound **2** a signal was present at 12.05 ppm which was absent from this region in the spectrum of compound **5**. This permits assignment of the signal at 12.38 ppm in the spectrum of compound **6** to the carbon atom of the methyl group at position 5 of the thiazole. Signals were present in the ^{13}C NMR spectra of compounds **2**, **5**, and **6** in the region of 18 ppm (18.57 for **2**, 18.00 for **5**, and 18.56 for **6**). In the case of the undeuterated thiazoles **1**, **2**, and **5** this signal is a singlet, but in the case of the deuterated thiazole **6**, it was a triplet (J = 88.8 Hz). This enables assignment of the signal near 12 ppm to the carbon atom of the methyl group at position 2 of thiazoles **2** and **5**. Since in the spectrum of deuterated compound **6** the signal near 12 ppm is split into a triplet, it may be suggested that in the case of 2,5-dimethyl-substituted thiazoles the presence of a phenyl substituent at position 4 of the thiazole has no effect on the acidity of the hydrogen of the 5-methyl group and the metallation reaction occurs at the 2-methyl group.

The mass spectra of the obtained 2-thiazolylethanols were poorly informative due to the instability of compounds in the electron beam. In the spectrum of compound **4a** a low-intensity peak was present with *m/z* 295 for the molecular ion. The most intense peak with *m/z* 276 corresponds presumably with the 5-methyl-4-phenyl-(2-phenylvinyl)thiazolium cation with a conjugated system of double bonds. An intense peak was also present in the spectrum with *m/z* 189, which corresponds to the mass of the initial thiazole **2**.

TABLE 1. Physicochemical Characteristics of Compounds **3a-h**, **4a-c**

Compound	Empirical formula	Found, %* / Calculated, %				R_f (TLC)*[2]	mp, °C	Yield, %
		C	H	N	S			
3a	$C_{10}H_{17}NOS$	63.77 / 60.26	6.48 / 8.60	6.94 / 7.03	13.67 / 16.09	0.45	Oil	60
3b	$C_{11}H_{19}NOS$	59.51 / 61.93	8.76 / 8.98	6.94 / 6.57	13.50 / 15.03	0.35	Oil	40
3c	$C_{13}H_{15}NOS$	65.05 / 66.92	6.48 / 6.48	6.94 / 6.00	13.51 / 13.74	0.35	90-92	55
3d	$C_{14}H_{14}F_3NOS$	55.88 / 55.80	4.71 / 4.68	4.71 / 4.65		0.25	117-119	50
3e	$C_{14}H_{14}F_3NOS$	55.39 / 55.80	4.64 / 4.68	4.89 / 4.65		0.27	98-99	50
3f	$C_{14}H_{17}NOS_2$	59.96 / 60.18	6.19 / 6.13	5.50 / 5.01	21.54 / 22.95	0.24	95-97	53
3g	$C_{14}H_{16}FNO_2S$	59.79 / 59.77	5.70 / 5.73	5.02 / 4.98		0.16	94-95	51
3h	$C_{14}H_{16}FNO_2S$	59.93 / 59.77	5.76 / 5.73	5.05 / 4.98		0.45	68-70	25
4a	$C_{18}H_{17}NOS$	73.21 / 73.19	5.85 / 5.80	4.65 / 4.74	10.71 / 10.86	0.45	95	60
4b	$C_{18}H_{16}FNOS$	68.81 / 68.99	5.28 / 5.15	4.56 / 4.47		0.50	108-110	55
4c	$C_{18}H_{16}FNOS$	68.89 / 68.99	5.45 / 5.15	4.64 / 4.47		0.50	87-90	55

* Samples of substances **3a-h** and **4a-c** for elemental analysis were obtained by recrystallization from hexane.

*[2] Benzene–acetone, 10:1 (compounds **3f,g**, **4a-c**); 4:1 (compounds **3a-c,h**); 19:1 (compounds **3d,e**).

The structure of compound **4a** was confirmed by data of X-ray structural analysis in [4]. In the crystal molecules of **4a** are linked by intermolecular hydrogen bonds OH···N, and the thiazole ring and the phenyl ring at position 4 are disposed in one plane due to conjugation (Fig. 1).

It has therefore been shown that metallation of 2,5-dimethylthiazoles containing a methyl or phenyl group in position 4 leads to the formation of anions at the methyl group in position 2. Subsequent reaction of the anions with aldehydes leads to the preparation of 2-thiazolyl-1-ethanols.

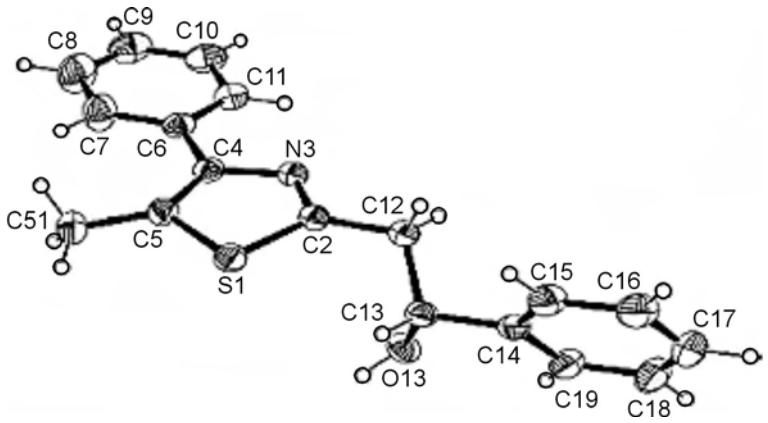


Fig. 1. Structure of the 2-thiazolyl-1-ethanol **4a** molecule and numbering of the atoms.

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds **3a-h**, **4a-c**

Com-pound	Chemical shifts, δ, ppm. (*J*, Hz)				
	CH_2	CH (m)	CH_3 (s)	other signals	OH (1H, br. s)
3a	2.95 (1H, m); 2.85 (1H, dd, ^3J = 7.5, ^2J = 15.4)	3.69	2.24 (3H); 2.21 (3H)	1.63-1.75 (1H, m); 0.90-1.0 (6H, m)	4.00
3b	2.98 (1H, dd, ^3J = 2.5, ^2J = 16.4); 2.82 (1H, dd, ^3J = 8.5, ^2J = 16.4)	4.02	2.27 (6H)	1.76-1.86 (1H, m); 1.44-1.52 (2H, m); 1.18-1.26 (2H, m); 0.93 (3H, m), 0.89 (3H, m)	
3c	3.21 (1H, dd, ^3J = 2.5, ^2J = 15.4); 3.14 (1H, dd, ^3J = 8.3, ^2J = 15.4)	5.07	2.23 (6H)	7.38 (2H, m); 7.32 (2H, m); 7.26 (1H, m)	
3d	3.18 (1H, dd, ^3J = 2.0, ^2J = 15.0); 3.04 (1H, dd, ^3J = 9.0, ^2J = 15.0)	5.46	2.27 (6H)	7.88 (1H, d, *J* = 8.5); 7.62 (1H, m, *J* = 8.5); 7.57 (1H, m, *J* = 7.8); 7.38 (1H, m, *J* = 7.8)	5.10
3e	3.22 (1H, dd, ^3J = 2.0, ^2J = 13.3); 3.11 (1H, dd, ^3J = 7.5, ^2J = 13.3)	5.16	2.23 (6H)	7.67 (1H, br. s); 7.58 (1H, m); 7.52 (1H, m); 7.44 (1H, m)	4.97
3f	3.17 (1H, dd, ^3J = 3.0, ^2J = 15.2); 3.11 (1H, dd, ^3J = 8.5, ^2J = 15.2)	5.03	2.27 (6H)	7.35 (2H, d, *J* = 8.4); 7.22 (2H, d, *J* = 8.4); 2.45 (3H, s, CH_3S)	4.65
3g	3.16 (2H, m)	5.03	2.27 (3H); 2.26 (3H)	7.04 (1H, m); 6.98 (1H, m); 6.81-6.89 (1H, m); 3.80 (3H, s, CH_3O)	
3h	3.25 (1H, dd, ^3J = 2.5, ^2J = 15.0); 3.13 (1H, dd, ^3J = 8.7, ^2J = 15.0)	5.31	2.24 (6H)	7.42 (1H, m); 6.68 (1H, m); 6.57 (1H, m); 3.79 (3H, s, CH_3O)	
4a	3.30 (1H, dd, ^3J = 4.5, ^2J = 15.0); 3.25 (1H, dd, ^3J = 8.5, ^2J = 15.0)	5.19	2.53 (3H)	7.64 (2H, m); 7.43 (4H, m); 7.35 (3H, m); 7.28 (1H, m)	
4b	3.38 (1H, dd, ^3J = 3.0, ^2J = 15.2); 3.23 (1H, dd, ^3J = 9.0, ^2J = 15.2)	5.44	2.25 (3H)	7.64 (2H, m); 7.12-7.66 (7H, m)	
4c	3.20 (1H, dd, ^3J = 3.0, ^2J = 15.1); 3.11 (1H, dd, ^3J = 8.8, ^2J = 15.1)	5.02	2.27 (3H)	7.60 (1H, m); 7.52 (5H, m); 7.43 (1H, m); 7.31 (1H, m); 7.11 (1H, m)	

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 instrument (400 and 100 MHz respectively), internal standard was TMS. Melting points were determined on a Boetius hot stage (heating rate 4 deg/min). The mass spectrum of compound **4a** was obtained on a Kratos MS-890A, energy of ionizing electrons was 70 eV, temperature of ionization chamber 200°C. Solvents were used after careful purification and drying. Thiazoles **1** and **2** were obtained by the method of Hantzsch [5] by the interaction of thioacetamide and 3-bromo-2-butanone [6] and phenyl 1-bromoethyl ketone [7].

2-Thiazolyl-1-ethanols 3a-h and 4a-c (General Procedure). A solution of thiazole **1** (1 g, 7.87 mmol) in a mixture of ether (20 ml) and THF (4 ml) was cooled to -70°C (toluene, dry ice, liquid nitrogen) with stirring in a current of argon. A 1.6-fold excess of a solution of BuLi (1.6 M) in hexane (8 ml, 12.6 mmol) was added during 10 min with a syringe. The mixture was stirred for 30 min, and the colorless solution became red-black. A 1.2-fold excess of aldehyde dissolved in THF (2 ml) was added to the solution during 10 min and maintained for 20-30 min, after which aqueous 1 M citric acid solution (20 ml) was added and the reaction mixture left to heat to room temperature. The mixture was washed with water (2 × 20 ml) and with saturated NaCl solution (10 ml), dried over Na_2SO_4, the solvent evaporated, and the residue dried in the vacuum of an oil pump.

2-Thiazolyl-1-ethanols 4a-c were obtained according to the procedure given above from thiazole **2** (1 g, 5.29 mmol), butyllithium (2.6 ml, 9.5 mmol), the butyllithium was added at -100°C.

2-(2-Hydroxy-3-methylbutyl)-4,5-dimethyl-1,3-thiazole (3a). Yellow oil, yield 1 g.

2-(2-Hydroxy-4-methylpentyl)-4,5-dimethyl-1,3-thiazole (3b) was purified by steam distillation and a yellow oil (0.7 g, 40%) was obtained.

2-(2-Hydroxy-2-phenylethyl)-4,5-dimethyl-1,3-thiazole (3c). The red oil was rubbed in a mixture of ether–hexane, 1:1 cooled to +5°C. A yellow powder (1 g) was obtained.

2-[2-Hydroxy-2-(2-trifluoromethylphenyl)ethyl]-4,5-dimethyl-1,3-thiazole (3d). The white powder was washed with hexane, and dried. Yield 1.2 g.

2-[2-Hydroxy-2-(3-trifluoromethylphenyl)ethyl]-4,5-dimethyl-1,3-thiazole (3e). After rubbing with hexane a white powder (1.17 g) was obtained.

2-{2-Hydroxy-2-[4-(methylthio)phenyl]ethyl}-4,5-dimethyl-1,3-thiazole (3f). The orange crystals were washed with hexane and dried. Yield 1.75 g.

2-[2-Hydroxy-2-(4-fluoro-3-methoxyphenyl)ethyl]-4,5-dimethyl-1,3-thiazole (3g). The oil crystallized spontaneously in a matter of week, the fine yellow crystals were washed with hexane, and dried. Yield 1.2 g.

2-[2-Hydroxy-2-(2-fluoro-4-methoxyphenyl)ethyl]-4,5-dimethyl-1,3-thiazole (3h) was purified by chromatography on silica gel (eluent $CHCl_3$). The obtained oil crystallized spontaneously during 3 days. The crystals were separated, and washed with cold hexane. Yield 0.5 g.

2-(2-Hydroxy-2-phenylethyl)-5-methyl-4-phenyl-1,3-thiazole (4a). After recrystallization from hexane a white powder (0.5 g) was obtained.

2-[2-Hydroxy-2-(2-fluorophenyl)ethyl]-5-methyl-4-phenyl-1,3-thiazole (4b). After rubbing with hexane a yellowish powder (0.9 g) was obtained.

2-[2-Hydroxy-2-(3-fluorophenyl)ethyl]-5-methyl-4-phenyl-1,3-thiazole (4c). After rubbing with hexane a yellowish powder (0.9 g) was obtained.

2-Deuteromethyl-5-methyl-4-phenyl-1,3-thiazole (6). The anion of thiazole **2** was generated analogously to the procedure described above based on initial thiazole **2** (0.1 g, 0.53 mmol). Butyllithium (1 ml, 1.6 mmol) was added at -100°C. After 30 min D_2O (0.1 ml, 5.2 mmol) was added, and the mixture was maintained at -100°C for 30 min. A 1 M aqueous solution of citric acid (20 ml) was then added, and the reaction mixture allowed to warm to room temperature. The reaction mixture was washed with water (2 × 20 ml), and with saturated NaCl solution (10 ml), dried over Na_2SO_4, the solvent evaporated, and the residue dried in an oil pump vacuum. The yellow oil obtained was purified chromatographically (SiO_2, 1% acetone in benzene). Yield 0.05 g (49%) of a colorless oil.

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