Synthesis of 3,4,5-Trisubstituted-2(3*H*)-thiazolethiones via Metallation of 3,4-Disubstituted-2(3*H*)-thiazolethiones

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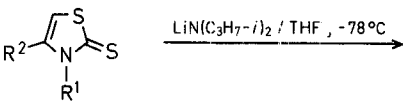
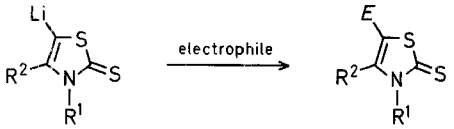
Thiazoles lacking a 2-substituent readily undergo metallation in the 2-position[1]. Scattered examples are known of metallation of thiazoles at the 4- and 5-positions, e.g. 2-methylthiazoles undergo ring- or α-metallation, depending on the nature of the other substituents[2].

2(3*H*)-Thiazolethiones have not been previously ring metallated: we now report that direct lithiation in the 5-position (to give **2**) of 3,4-disubstituted-2(3*H*)-thiazolethiones **1**, followed by reaction with electrophiles, provides a convenient method for the synthesis of 3,4,5-trisubstituted-2(3*H*)-thiazolethiones **3**.

Treatment of **1a** with 1 equivalent of lithium diisopropylamide in tetrahydrofuran led to the specific formation of the 5-lithiated derivative, which reacted smoothly with acid chloride, aldehyde, ketone, alkyl halide, carbon dioxide, or deuterium oxide electrophiles, as summarised in the Table.



1a $R^1 = C_6H_5CH_2$, $R^2 = C_6H_5$
b $R^1 = C_6H_5CH_2$, $R^2 = CH_3$
c $R^1 = CH_3$, $R^2 = C_6H_5$
d $R^1 = C_2H_5$, $R^2 = C_6H_5$



2 **3**

The generality of the reaction was shown by using the substrate **1b**, having a 4-methyl substituent, and also by substrates **1c-d**, which possess *N*-methyl and *N*-ethyl substituents, respectively.

Competing α-lithiation of the *N*-alkyl substituent R^1 might be expected, since this derivative would enjoy dipole stabilisation[3]. Ring 5-substitution is the only reaction observed, however, even when $R^1 = C_6H_5CH_2$. ^{1}H-N.M.R. shows in all cases the full retention of the methylene or methyl signals from R^1, and the removal of H-5, which appears at

Table. Trisubstituted-2(3*H*)-thiazolethiones **3** from 3,4-Disubstituted-2(3*H*)-thiazolethiones **1a–d**

Substrate	Electrophile	*E* in **3**	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
1a[4]	4-H_3C—C_6H_4—CO—Cl	4-H_3C—C_6H_4—CO—	52	129° (C_2H_5OH)	$C_{24}H_{19}NOS_2$ (401.5)	2.28 (s, 3H); 5.40 (s, 2H); 6.8–7.6 (m, 14H)
1a[4]	4-Cl—C_6H_4—CHO	4-Cl—C_6H_4—CH(OH)—	65	50° (C_2H_5OH)	$C_{23}H_{18}ClNOS_2$[b] (423.9)	3.2 (br s, 1H); 5.25 (s, 2H); 5.5 (s, 1H); 6.7–7.5 (m, 14H)
1a[4]	$(H_3C)_2CO$	$(H_3C)_2C(OH)$—	40	103–105° (C_2H_5OH)	$C_{19}H_{19}NOS_2$ (341.5)	1.25 (s, 6H); 2.3 (br s, 1H); 5.15 (s, 2H); 6.7–7.5 (m, 10H)
1a[4]	H_3C—J	H_3C—	71	98° (C_2H_5OH)	$C_{17}H_{15}NS_2$ (297.4)	2.52 (s, 3H); 5.85 (s, 2H); 7.3–8.2 (m, 10H)
1a[4]	D_2O	D	80	98° (C_2H_5OH)	$C_{16}H_{12}DNS_2$ (284.4)	5.45 (s, 2H); 6.8–7.6 (m, 10H)
1a[4]	CO_2	HOOC—	68	210–220° (dec) (HCOOH)	$C_{17}H_{15}NO_2S_2$ (327.4)	5.40 (s, 2H); 6.8–7.7 (m, 5H)[d]
1b[c]	D_2O	D	83	131° (C_2H_5OH)	$C_{11}H_{10}DNS_2$ (222.3)	2.1 (s, 3H); 5.5 (s, 2H); 7.25 (s, 5H)
1c[c]	H_3C—J	H_3C—	46	61–62° (C_2H_5OH)	$C_{11}H_{11}NS_2$ (221.3)	2.02 (s, 3H); 3.4 (s, 3H); 7.2–7.6 (m, 5H)
1c[c]	D_2O	D	79	128–129° (C_2H_5OH)	$C_{10}H_8DNS_2$ (208.3)	3.55 (s, 3H); 7.3–7.7 (m, 5H)
1c[c]	CO_2	HOOC—	45	258–260° (HCOOH)	$C_{11}H_9NO_2S_2$ (251.3)	3.45 (s, 3H); 7.4–7.8 (m, 5H)[d]
1d[c]	D_2O	D	78	83–84° (C_2H_5OH)	$C_{11}H_{10}DNS_2$ (222.3)	1.15 (t, 3H); 4.15 (q, 2H); 7.3–7.7 (m, 5H)
1d[c]	CO_2	HOOC	65	230° (dec) (HCOOH)	$C_{12}H_{11}NO_2S_2$ (265.3)	1.0 (t, 3H); 3.9 (q, 2H); 7.3–7.6 (m, 5H)[d]

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.4, H ±0.24, N ±0.15, S ±0.19); exceptions: entry 3, N ±0.07, H ±0.24, S ±0.19 %.

[b] M.S.: *m/e* = 423.0527 (M^+, calculated: 423.0518).

[c] Advantageously prepared by addition of the amine to CS_2, reaction with haloketone, and thermal cyclisation, analogously to **1a** (Ref.[4]).

[d] Recorded in D_2O/NaOD.

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$\delta = 6.5$ ppm in the starting materials. Thus, the 5-proton in 2(3*H*)-thiazolethiones of type **1** is readily removed to give a stable, but reactive 5-lithio derivative **2**. The reactions of organometallic reagents of this type should be of general utility in thiazole chemistry.

5-Substitution of 3,4-Disubstituted-2(3*H*)-thiazolethiones 1; General Procedure:

The 3,4-disubstituted-2(3*H*)-thiazolethione **1** (2.0 mmol) in dry tetrahydrofuran (2 ml) is added under nitrogen to a stirred solution of lithium diisopropylamide (2.0 mmol) in tetrahydrofuran (5 ml) cooled to −78 °C. The resulting deep yellow solution is stirred for 15 min, after which the electrophile (2.0 mmol, or excess if deuterium oxide or carbon dioxide) is added, causing immediate discharge of the colour. After warming to 25 °C, and stirring for several hours, solvent is removed (40 °C/15 torr). The residue is taken up in chloroform (10 ml), the solution washed with water (10 ml), dried with sodium sulphate, and evaporated to give a yellow solid, which is crystallised from ethanol or formic acid to give the substitution product **3**.

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