Reaction of 2-Amino-5-bromo-1,3-thiazoles with Sodium 2-Hydroxyethoxide; Preparation of 2-Amino-3a,5,6,7a-tetrahydro[1,3]thiazolo[1,4]dioxins

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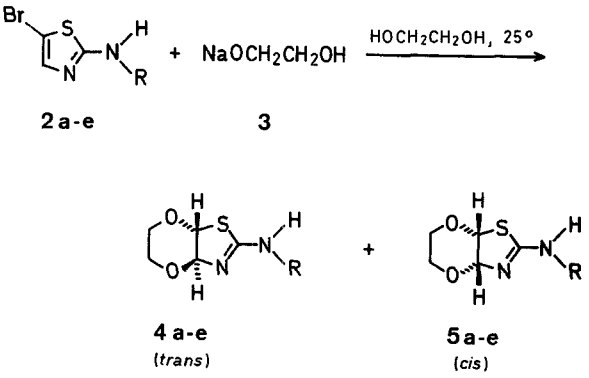
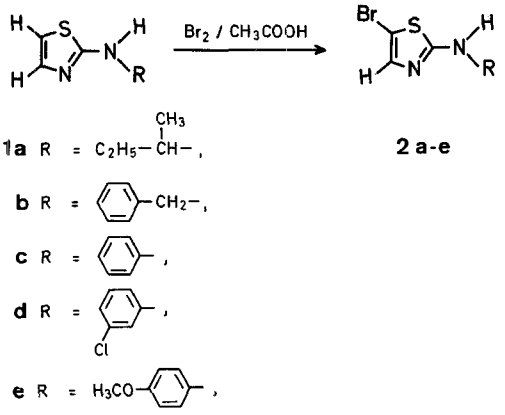
Although the synthesis of dihydrothiazoles by cyclisation reactions is well-known[1], no examples of the preparation of dihydrothiazoles from 1,3-thiazole derivatives have been reported in the literature. We have previously reported[2] that 2-amino-5-halothiazoles react with nucleophiles to give 5-substituted thiazoles. We now present some results for reactions between 2-alkyl-(or aryl)-amino-5-bromo-1,3-thiazoles (**2a–e**) with sodium 2-hydroxyethoxide (**3**) in ethylene glycol at 25°.

The formation of the 2-amino-3a,5,6,7a-tetrahydro[1,3]thiazolo[1,4]dioxins **4** and **5** presumably proceeds via nucleophilic expulsion of the bromine in position 5 by the 2-hydroxyethoxy group and subsequent cyclisation by base-catalysed intramolecular addition on the C=C-double bond.



The starting thiazoles, **2a–e**, were prepared by bromination of the 2-aminothiazoles **1a–e** with bromine in acetic acid and were purified by column chromatography on silica gel and subsequent recrystallisation (see Table 1). The thiazoles **1a–e** were prepared by cyclisation of acetaldehyde and *N*-substituted thioureas with bromine (see Table 1).



The structure of 2-benzylamino-1,3-thiazole (**1b**) was confirmed by two independent syntheses from (a) 2-bromo-1,3-thiazole and benzyl bromide in methanol and (b) from 2-amino-1,3-thiazole and benzyl bromide in methanol. However the yields from these syntheses were low.

The ^{1}H-N.M.R. spectra of compounds **4** and **5** (see Table 2) show the presence of two protons in positions 4 and 5 of the ring. The signals of these protons are shifted to higher field as compared to those for the protons in positions 4 and 5 of the unsubstituted 2-aminothiazoles (e.g. for 2-aminothiazole, δ ($CDCl_3$/TMS) = 6.50, (d, 1H, H-5), 7.03

Table 1. Preparation of 2-Alkyl-(or aryl)-amino-1,3-thiazoles (**2a–e**)

	R	m.p. of **1**[a] (solvent)	Yield [%] of **2**	m.p. of **2**[a] (solvent)	Molecular formula[b]
a	C_2H_5—$CH(CH_3)$—	72–73° (CH_3OH/H_2O)	60	65–66° (CH_3OH/H_2O)	$C_7H_{11}BrN_2S$ (235.1)
b	C_6H_5—CH_2	131–132° (CCl_4)	65	123–124° (C_6H_6)	$C_{10}H_9BrN_2S$ (269.2)
c	C_6H_5	128–129° (CCl_4)	75	125–126° (CH_2Cl_2)	$C_9H_7BrN_2S$ (255.1)
d	3-Cl—C_6H_4	101–102° (C_2H_5OH/H_2O)	65	123–124° (C_6H_6)	$C_9H_6ClBrN_2S$ (289.6)
e	4-H_3CO—C_6H_4	126–127° (C_2H_5OH/H_2O)	70	144–145° (c-C_6H_{12})	$C_{10}H_9BrN_2OS$ (285.2)

[a] M.p.'s are uncorrected.

[b] All products gave satisfactory microanalysis (C ±0.25%, H ±0.21%, N ±0.18%). N.M.R. and I.R. spectral data are in agreement with the structures.

Table 2. Preparation of 2-Amino-3a,5,6,7a-tetrahydro[1,3]thiazolo[1,4]dioxins **4** and **5**

Product	Overall yield [%]	Ratio **4**:**5**	m.p. (solvent)[a]	Molecular formula[b]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm] H-4 (d, 1H)	H-5 (d, 1H)	$J_{4,5}$ [Hz]	OCH_2CH_2O (4H)	alkyl or aryl	others
4a			110–111° (C_6H_6)	$C_9H_{16}N_2O_2S$ (216.3)	4.97	4.76	8	3.87 (s)	0.8–1.7 (m, 9H)	—
	54	80:20[c]								
5a			—	—	5.61	5.17	4	3.4–4.1 (m)	0.8–1.7 (m, 9H)	—
4b			184–185° (C_6H_6)	$C_{12}H_{14}N_2O_2S$ (250.2)	4.97	4.76	8	3.84 (s)	7.16 (s, 5H)	4.40 (s, 2H, $C_6H_5C\underline{H}_2$)
	68	73:27								
5b			90–91° (CH_2Cl_2/pet. ether)	$C_{12}H_{14}N_2O_2S$ (250.2)	5.61	5.16	4	3.4–4.1 (m)	7.29 (s, 5H)	4.41 (s, 2H, $C_6H_5CH_2$)
4c			138–140° (CCl_4)	$C_{11}H_{12}N_2O_2S$ (236.3)	5.04	4.87	8	3.91 (s)	7.18 (s, 5H)	
	60	66:34								
5c			136–137° (CH_2Cl_2/pet. ether)	$C_{11}H_{12}N_2O_2S$ (236.3)	5.79	4.97	3	3.4–4.1 (m)	7.1–7.2 (m, 5H)	
4d			182–183° (C_6H_6)	$C_{11}H_{11}ClN_2O_2S$ (270.7)	5.01	4.82	8	3.92 (s)	6.9–7.3 (m, 4H)	
	74	70:30								
5d			132–133° (C_6H_6/C_6H_{12})	$C_{11}H_{11}ClN_2O_2S$ (270.7)	5.83	4.95	4	3.6–4.1 (m)	6.8–7.4 (m, 4H)	
4e			162–163° ($CHCl_3$)	$C_{12}H_{14}N_2O_3S$ (266.3)	4.99	4.81	8	3.87 (s)	6.7–7.2 (m, 4H)	3.68 (s, 3H, OCH_3)
	65	60:40								
5e			106–107° (CH_2Cl_2/pet. ether)	$C_{12}H_{14}N_2O_3S$ (266.3)	5.76	4.97	4	3.4–4.1 (m)	6.7–7.1 (m, 4H)	3.76 (s, 3H, OCH_3)

[a] Not corrected.
[b] All compounds gave satisfactory microanalyses (C ±0.29%, H ±0.24%, N ±0.25%).
[c] Determined from N.M.R. spectra of crude mixture.

Table 3. ^{13}C-N.M.R. ($CDCl_3$/TMS) Data for Selected Products

Product	Chemical Shifts δ [ppm] C-2 (s)	C-4 (d)	C-5 (d)	$OCH_2—CH_2—O$	aryl or 2-butyl	$C_6H_5\underline{C}H_2$
4b	156.20	101.64	90.65	68.20 (t), 66.36 (t)	137.27 (s), 128.35 (d), 127.56 (d), 127.36 (d)	47.25 (t)
5b	106.8	93.24	86.40	62.07 (t), 60.55 (t)	137.53 (s), 127.95 (d), 127.17 (d), 126.86 (d)	49.26 (t)
4a	156.20	102.07	90.63	68.50 (t), 66.58 (t)	51.23 (d), 29.74 (t), 20.37 (q), 10.33 (q)	—
3a	170.30	137.88	104.33	—	53.51 (d), 29.05 (t), 19.58 (q), 9.81 (q)	—
2a	170.30	137.88	92.65	—	53.51 (d), 29.05 (t), 19.58 (q), 9.81 (q)	—

(d, 1H, H-4). This shift is caused by a change of hybridisation of the carbon atoms 4 and 5 (from sp^2 to sp^3).

The I.R. spectra of **4** and **5** do not show signals for OH groups as might be expected from a simple nucleophilic substitution reaction of **2** with **3**. The mass spectra of **4** and **5** are identical, e.g. when $R = C_6H_5CH_2$, $m/e = 250$, 205, 191, 164, 148, 118, 106, 91. Compound **4** and **5** are thus isomeric species arising from partial saturation of the thiazole ring.

In the ^{13}C-N.M.R. spectra of **4** and **5** (see Table 3), the expected signal for C-2 (~160 ppm) is seen whereas the signals for C-4 and C-5 are shifted (with regard to the unsubstituted 2-aminothiazole) to higher field (the oxygen atoms as electron-withrawing functions cause a simultaneous shift in the opposite direction). Conformational studies of dihydro-1,3-thiazoles made by Wilson and Bazzone[3] on the basis of ^{1}H-N.M.R. spectra showed the possibility of relating the coupling constant with the structure and concluded that $J_{trans} > J_{cis}$.

In the present case, however, complications arise from the presence of the second condensed ring. To avoid these difficulties, Chanon and Metzger[4] considered the anisotropy effects given by the substituents present on the chemical shifts of H-4 and H-5 in the two isomeric species. Substituents such as methyl or hydroxy deshield the proton on the opposite side of the thiazole ring.

On the basis of the evidence presented above we consider the structural assignments of **4** *(trans)* and **5** *(cis)* to be correct, with $J_{trans} > J_{cis}$. It is also probable that tautomeric isomers of the aminothiazoles are the reactive species for the formation of **4** and **5**.

Preparation of 2-Amino-3a,5,6,7a-tetrahydro[1,3]thiazolo[1,4]-dioxins 4 and 5; General Procedure:

The 2-amino-5-bromo-1,3-thiazole **2** (1 mol) is dissolved in ethylene glycol (~40 ml) and this solution is added to a 1 normal solution of sodium 2-hydroxyethoxide in ethylene glycol (1 mol of **3**). After 24–48 h, T.L.C. analysis indicates the absence of the starting materials. The crude mixture is poured into ice/water and extracted with dichloromethane. The extract is dried (Na_2SO_4), the solvent is removed to leave a solid which is chromatographed through a column of silica gel (cyclohexane/ethyl acetate as eluent). The products **4** and **5** are collected separately and recrystallised. Yields and physical properties of the products are given in Table 2. When an excess of nucleophile to thiazole is used the yield is lower and some other unidentified products are present in the reaction mixture.

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[1] F. Kurzer, in *Organic Compounds of Sulphur, Selenium, and Tellurium* Vol. 3, Chap. 13., Chem. Soc., London, 1975.

[2] L. Forlani, A. Medici, P. E. Todesco. *Tetrahedron Lett.* **1976**, 201.

[3] G. E. Wilson, J. J. Bazzone, *J. Am. Chem. Soc.* **96**, 1465 (1974).

[4] M. Chanon, J. Metzger. *Bull. Soc. Chim. Fr.* **1968**, 2885.