Reactivity of Halogenothiazoles towards Nucleophiles. Kinetics of Reactions between 2- and 4-Halogenothiazoles and Nucleophiles

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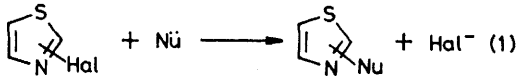
Substitution of halogen by nucleophile in positions 2 and 4 of the thiazole ring is reported. In some cases the reactivity of 4-halogenothiazoles is greater than that of the isomer. For both isomers addition–elimination mechanisms operate and the $k_4 : k_2$ ratios are very sensitive to the experimental conditions. Changes in nucleophile, the counterion of the nucleophile, and solvent are discussed. Evidence of differing steric hindrance in the nucleophiles (for the two positions considered) is presented.

As previously reported,[1,2] nucleophilic substitution of halogen in halogenothiazoles occurs not only at position 2,[3,4] but also at positions 4 and 5. Position 4 was shown[5] to be slightly reactive but few data were collected. Results on the substitution of 4-chlorothiazole by alkoxide ions have also been reported by Metzger and Friedmann.[6] In order to clarify this unexpected reactivity we now report some kinetic data for reactions between 4-halogenothiazoles (and for comparison, 2-halogenothiazoles) and piperidine and benzenethiolate and alkoxide ions.

[1] M. Bosco, L. Forlani, P. E. Todesco, and L. Troisi, *J.C.S. Perkin II*, 1976, 398.
[2] M. Bosco, L. Forlani, P. E. Todesco, and L. Troisi, *Chem. Comm.*, 1971, 1093.
[3] M. Foa', A. Ricci, and P. E. Todesco, *Boll. sci. Fac. Chim. ind. Bologna*, 1965, **23**, 229.
[4] M. Bosco, L. Forlani, V. Liturri, P. Ricci, and P. E. Todesco, *J. Chem. Soc.* (*B*), 1971, 1373.

RESULTS

All reactions for both halogenothiazole isomers followed the stoicheiometry (1) as shown by the isolation of products,



and by titration of halide. Each run followed second-order kinetics (first order in both reactants) up to high conversion and yields were satisfactory. In the reaction between

[5] J. M. Sprague and A. H. Land, ' Heterocyclic Compounds,' ed. R. G. Helderfield, Wiley, New York, 1957, vol. 5, p. 545; M. H. Palmer, ' The Structure and Reactivity of Heterocyclic Compounds,' Arnold, London, 1967, p. 377; A. R. Katritzky and J. M. Lagowsky, ' The Principles of Heterocyclic Chemistry,' Methuen, London, 1967, p. 155.
[6] J. Metzger, ' Recherches recentes dans la serie du Thiazole 1,3,' Congrés International de Chimie Heterocyclique, Montpallier, 1969; A. Friedmann, *Compt. rend.*, 1969, **269C**, 1560.

4-chlorothiazole and t-butoxide ion the product was obtained in low yield because of difficulties in separating the ether from the solvent (see Experimental section). In the reaction of 4-chloro-2-phenylsulphinylthiazole with methoxide the product of substitution at position 4 was obtained in high yield but other products probably arising from substitution at position 2 were formed. In reactions with piperidine in MeOH no methoxy-substitution products were detected [7] and no changes in kinetic constant were observed by adding piperidinium perchlorate. We have investigated the effects of variation of solvent, nucleophile, and counterion. Kinetic data are collected in Table 1.

In order to test the influence of ion pairs in the rate-determining step, several runs were made in the presence of one equiv. of dicyclohexyl-18-crown-6 ether. No effects were observed in the reactions with MeO^- (as the potassium salt, which is more effective in complexing with the crown ether [8]) in MeOH; some results were also obtained for other aza-activated substrates (2-chlorobenzothiazole and 2-chloropyridine). Enhancement of the rates was observed for both chlorothiazole isomers when $Bu^tO^-K^+$ in Bu^tOH was used. The results are collected in Table 2.

TABLE 1

Reactions between halogenothiazoles and nucleophiles at 50 °C

			2-Halogenothiazoles			4-Halogenothiazoles		
Halogen	Nucleophile	Solvent	10^5k [a]	$\Delta H^{\ddagger}$ [b]	$-\Delta S^{\ddagger}$ [c]	10^5k [a]	$\Delta H^{\ddagger}$ [b]	$-\Delta S^{\ddagger}$ [c]
Cl	MeO^-Li^+	MeOH	0.67	20.8 [d]	20.1 [d]	0.046	24.1 [e]	15.3 [e]
Cl	MeO^-Na^+	MeOH	0.81	18.4 [f]	27.1 [f]	0.060	25.5 [g]	10.1 [g]
Cl	MeO^-K^+	MeOH	1.0	21.8 [h]	16.2 [h]	0.11	26.7 [i]	5.4 [i]
Br	MeO^-Na^+	MeOH	1.05			0.13		
Cl	EtO^-Na^+	EtOH	0.44			0.26		
Cl	$Pr^iO^-Na^+$	Pr^iOH	0.74			2.9		
Cl	$Pr^iO^-K^+$	Pr^iOH	1.2			7.0		
Cl	$Bu^tO^-Na^+$	Bu^tOH	0.18	22.0 [l]	19.0 [l]	7.5	19.5 [m]	19.4 [m]
Cl	$Bu^tO^-K^+$	Bu^tOH	0.25	23.2 [n]	14.3 [n]	25	21.8 [o]	9.8 [o]
Cl	MeO^-Na^+	Me_2SO–MeOH (70 : 30) [p]	83					
Cl	MeO^-Na^+	Me_2SO–MeOH (80 : 20) [p]	140			270		
Cl	$Bu^tO^-Na^+$	Me_2SO–Bu^tOH (80 : 20) [p]	120			2 700		
Br	PhS^-Na^+	MeOH	1.76			0.16		
Cl	Piperidine	Piperidine	1.5 [q]			0.26 [q]		
Cl	Piperidine	MeOH	0.10			0.008		

[a] l mol^{-1} s^{-1}. [b] kcal mol^{-1}. [c] cal mol^{-1} K^{-1}. Other temperatures: k/l mol^{-1} s^{-1} (T/°C). [d] 0.24(40), 2.1(60). [e] 0.13(60), 0.41(70). See ref. 3. [g] 0.61(70), 5.0(85). [h] 0.33(40), 2.7(60). [i] 0.41(60), 1.3(70). [l] 0.45(60), 1.32(70). [m] 2.7(40), 18(60). [n] 0.085(40), 2.2(70). [o] 2.4(30), 5.8(40), 60(60). [p] v/v. [q] In s^{-1}.

TABLE 2

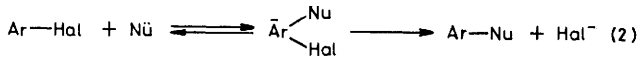
Effect of one equiv. (with respect to the nucleophilic reagent) of crown ether on the reactivity of some chloro-derivatives aza-activated towards RO^-K^+ in ROH

Substrate	T/°C	R	10^5k/l mol^{-1} s^{-1}	
2-Chlorothiazole	50	Me	0.85	1.0 [a]
2-Chlorothiazole	50	Bu^t	2.5	0.25 [a]
4-Chlorothiazole	50	Me	0.15	0.11 [a]
4-Chlorothiazole	50	Bu^t	41	25 [a]
2-Chlorobenzothiazole	25	Me	59	63 [a]
2-Chloropyridine	100	Me	1.3	1.4 [a]

[a] In the absence of crown ether.

DISCUSSION

The reactions of both halogenothiazoles probably proceed by an S_NAr [9] which involves the formation of



a metastable intermediate [reaction (2)]. We have demonstrated the validity of this scheme for 2-halogenothiazoles,[3,4,10] and from the following evidence we assume this mechanism also operates in the case of 4-halogenothiazoles. (i) No element effect is observed in passing from the chloro to the bromo derivative. The ratio $k_{Br} : k_{Cl}$ for 4-halogenothiazoles on reaction with MeO^- in MeOH at 50 °C is 2 : 1. In cases in which the carbon–halogen bond is broken in the rate-determining step, values of this ratio >50 are observed.[11] For 2-halogenothiazoles, with the same reacting system, $k_{Br} : k_{Cl}$ 1.3 is observed. (ii) 2-X- and 5-X-4-chlorothiazoles [2] react at similar rates to that of the unsubstituted 4-chlorothiazole: an elimination–addition mechanism is not present. (iii) No *cine*-substitution products are observed in the reaction mixtures, as expected if an 'aryne' or elimination mechanism was operating.[12]

We can examine our results in the light of the effects expected on changing the nucleophile and/or solvent as follows. Upon increasing the electron donor power of alkyl groups in an alkoxide, the strength of the nucleophile is increased. Decreasing the polarity of a solvent makes stabilisation of a less polar intermediate, with respect to the anionic nucleophile, easier.[13] Steric effects in nucleophiles are important for reactions with an intermediate in which the new bond is largely formed,

[7] J. F. Bunnett, E. W. Garbish, and K. M. Pruitt, *J. Amer. Chem. Soc.*, 1957, **79**, 385; M. Foa', A. Ricci, P. E. Todesco, and P. Vivarelli, *Boll. sci. Fac. Chim. ind. Bologna*, 1965, **23**, 65; N. S. Nudelman and D. Garrido, *J.C.S. Perkin II*, 1976, 1256.

[8] C. J. Pedersen and A. K. Frensdorff, *Angew. Chem. Internat. Edn.*, 1972, 16.

[9] J. F. Bunnett and R. H. Zahaler, *Chem. Rev.*, 1951, **49**, 273.

[10] G. Bartoli, O. Sciaccovelli, M. Bosco, L. Forlani, and P. E. Todesco, *J. Org. Chem.*, 1975, **40**, 1275.

[11] J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, London, 1968; G. Bartoli and P. E. Todesco, *Accounts Chem. Res.*, 1977, **10**, 125.

[12] R. W. Hoffman, 'Dehydrobenzene and Cycloalkynes,' Academic Press, New York, 1967.

[13] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Cornell University Press, New York, 1953, p. 347.

is relatively short (as in the case of C–OR), and depends on the steric requirement of the activated aromatic substrate. An increasing steric effect will decrease the rate. Solvent promotion of the formation of ion pairs, which are less reactive in the classical S_NAr scheme, but which can be more effective if a complex mechanism operates, will decrease the rate.

Thus, for 2-halogenothiazoles steric effects are important. The order $MeO^- > Pr^iO^- > Bu^tO^-$ in the respective solvents is followed (see Table 3). A similar order was found for the reactions between 2-chlorobenzothiazole and alkoxide ions [14] (Table 3). Ion pairs are *not* active for this substrate. This conclusion arises from the preceding sequence and is also indicated by the addition of crown ether which is not significant in methanol (without crown 1.0, with crown 0.85, see Table 2) but is significant for reactions in Bu^tOH (without crown 0.25, with crown 2.5).

TABLE 3

Reactivity ratios for reactions between 2-chlorothiazole, 4-chlorothiazole, and RO^-M^+ at 50°

R	Me	Et	Pr^i	Bu^t	Me	Bu^t
Solvent	MeOH	EtOH	Pr^iOH	Bu^tOH	Me_2SO–MeOH (80 : 20) [a]	Me_2SO–MeOH (80 : 20) [a]
2-Cl M = Na	1	0.54	0.91	0.22	173	147
4-Cl M = Na	1	4.3	48	125	4 500	45 000
4-Cl : 2-Cl M = Na	0.074	0.59	3.9	42	1.9	24.4
2-Cl M = K	1		1.2	0.25		
4-Cl M = K	1		64	277		
4-Cl : 2-Cl M = K	0.11		5.8	100		
2-Chlorobenzothiazole [b] M = Na	1	0.82	0.21	0.072		

[a] v/v. [b] Data from ref. 14.

Steric effects are not important for 4-halogenothiazoles (the order $MeO^- < Pr^iO^- < Bu^tO^-$ is observed). This can be determined by considering the geometry of attack on position 4 relative to position 2, taking into account the geometry of the thiazole system.[16] The dihedral angle formed by the C(4)–halogen bond and p_z orbital of the activating aza-group in the Meisenheimer-like intermediate is larger than that for attack on position 2. Attack by the nucleophile occurs in a direction which yields an intermediate in which both the entering and leaving groups are in a plane perpendicular to the ring plane, which contains the original direction of the carbon–halogen bond. The effect of added crown ether is not relevant. The increase in rate on changing the solvent composition from ROH to Me_2SO–ROH occurs for both MeOH and Bu^tOH. These facts can be explained by assuming that when reaction takes place on

TABLE 4

Yields, physical properties, and n.m.r. spectra of some 2- or 4-substituted thiazoles

Compound	Yield (%)	B.p. (°C) (*p*/mmHg)	Chemical shift τ 2-H	4-H	5-H	Substituent
2-Methoxythiazole	90	133—135 (760)		3.02 (d)	3.45 (d)	5.96 (3 H, s)
2-t-Butoxythiazole	85	57—58 [a]		2.98 (s)	3.46 (d)	8.40 (9 H, s)
2-*N*-Piperidylthiazole	88	120—121 (10)		3.00 (d)	3.64 (d)	6.6 (4 H, m), 8.4 (6 H, m)
4-Methoxythiazole [b]	80	84—86 (15) (picrate, 93—94 [a])	1.58 (d)		3.96 (d)	6.10 (3 H, s)
4-t-Butoxythiazole [c]	40	158—160 (760)	1.52 (d)		3.75 (d)	8.60 (9 H, s)
4-*N*-Piperidylthiazole	75	64—65 (10)	1.54 (d)		4.30 (d)	6.7 (4 H, m), 8.4 (6 H, m)
4-Phenylthiothiazole	70	114—116 (1)	1.29 (d)		2.99 (d)	2.7 (5 H, m)
4-Methoxy-2-phenylsulphinylthiazole	70	59—60 [a]			3.59 (s)	5.89 (3 H, s), 2.9—2.2 (5 H, m)

[a] M.p. [b] Found: C, 41.5; H, 4.2; N, 12.0; S, 27.6. C_4H_4NSO requires C, 41.75; H, 4.35; N, 12.15; S, 27.85%. [c] Found: C, 53.3; H, 7.1; N, 8.8. $C_7H_{11}NSO$ requires C, 53.5; H, 7.0; N, 8.9%.

Moreover the decrease in rate observed on changing from MeO^-–MeOH to Bu^tO^-–Bu^tOH is largely steric in origin. We have also carried out some experiments in the mixed solvent Me_2SO–ROH (80 : 20). When the solvent is MeOH and the alkoxide MeO^- the relative rate is 1. On changing the medium to Me_2SO–MeOH we observed a rate increase of 173 (see Table 3). For the system Bu^tO^- in Me_2SO–Bu^tOH (80 : 20) the rate ratio is 147 (the anion Bu^tO^- can be almost 'naked' or can be more reactive due to the increased electron-donating power of the alkyl groups). The effect of added Me_2SO should be to increase the rate through decreasing the polarity. In fact there is a decrease in rate for Bu^tO^-–Bu^tOH with respect to MeO^-–MeOH, clearly indicating that a steric effect is operating. Proton-releasing ability by the medium is also probably superposed onto the effects discussed.[15]

[14] L. Di Nunno, S. Florio, and P. E. Todesco, *Bull. sci. Fac. Chim. ind. Bologna*, 1969, **27**, 75.

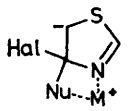
[15] G. Illuminati, G. Marino, and G. Sleiter, *J. Amer. Chem. Soc.*, 1967, 3510; G. Illuminati, G. Sleiter, and M. Speranza, *J. Org. Chem.*, 1971, **36**, 1723.

[16] E. J. Vincent, R. Phan-Tan-Luu, and J. Metzger, *Bull. Soc. chim. France*, 1966, 3530.

C(4) a simultaneous attack is made by the counterion on the aza-group (Scheme).

The effect of changing the counterion gives some evidence for the importance of ion-pairs in the reaction pathway. For the methoxydehalogenation of 2-chlorothiazole in MeOH the ratio $Li^+ : Na^+ : K^+$ 1 : 1.12 : 1.49 is observed. In the other alcohol the ratios $k_{K^+} : k_{Na^+}$ are more than unity. Although the differences observed are modest, though larger than those observed by Reinheimer [17] ($Li^+ : Na^+ : K^+$ 1 : 1.08 : 1.16) for the reactions between 2,4-dinitrochlorobenzene and MeO^- in MeOH, the ratios are the inverse of those expected for ion-pair formation.

For position 4 roughly the same ratios of reactivity



SCHEME

are observed ($Li^+ : Na^+ : K^+$ 1 : 1.30 : 2.39), but ΔS^* (see Table 1) dramatically increases upon decreasing the availability of the cation to ion-pair formation. This is a further indication of the effect of ion pairs on the mechanism of reaction at position 4.

Co-ordination of the ring nitrogen atom with the counterion stabilizes the intermediate to a greater extent than in the absence of this kind of interaction. This is required for attack at position 4 which is not completely ' *ortho* ' to the aza-activating group, *i.e.* there is no double bond between atoms 3 and 4 in the thiazole ring. This also explains the intervention of ion pairs in nucleophilic substitutions in position 4 of the 4-halogenothiazoles.

In summary, 4-halogenothiazoles react with nucleophilics, notwithstanding the conventional assumption that the relative positions of the reaction centre and the aza group should not lead to full activation. In particular cases the reactivity at position 4 is higher than at the apparently more activated position 2. This is fully interpreted by the explanations given here.

[17] J. D. Reinheimer, W. F. Kieffer, S. W. Frey, J. G. Cochran, and E. W. Barr, *J. Amer. Chem. Soc.*, 1958, **80**, 167.

EXPERIMENTAL

Kinetics.—Kinetic measurements were made by following the appearance of halide ion titrimetrically (Volhard) at appropriate concentrations and constant temperature (thermostatted bath, ±0.05°). The estimated error is ±3%. The halogenothiazole concentration was 1—5 × 10^{-2}M. Solvents were purified by standard procedures.[18] Solutions were prepared and analysed by the usual methods.

Halogenothiazoles.—2-Chloro- and 2-bromo-thiazole were prepared and purified as described.[4] 4-Chloro- and 4-bromo-thiazole were prepared from the corresponding 2,4-dihalogenothiazole by dehalogenation with activated zinc.[19]

Products.—These were isolated from reactions under the same conditions as the kinetic runs and identified by their n.m.r. spectroscopic properties (100 MHz; CCl_4; tetramethylsilane as internal standard). Some difficulty arose in separating thiazolyl ethers from the solvent. Solvent was removed under a slow stream of nitrogen, a few drops of water were added, and the thiazole derivative extracted with CCl_4 or CH_2Cl_2. For the reaction with Bu^tO^-–Bu^tOH it was difficult to remove the solvent only, 4-t-butoxythiazole was partially lost, and the yield was not very satisfactory. Nevertheless t.l.c. and g.l.c. analysis indicated that only one product was present in crude reaction mixtures. The purity of the liquid thiazole derivatives was determined by g.l.c. analysis using a 6 ft column (SE 30) in a Hewlett–Packard model 5400 instrument. All thiazole substrates had 98% purity.

Yields, physical properties, and some elemental analyses are reported in Table 4. M.p.s and b.p.s are uncorrected.

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[19] P. Reynaud, M. Robba, and R. C. Moreau, *Bull. Soc. chim. France*, 1962, 173.