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UNUSUAL AMINO-GROUP ACTIVATION TOWARDS NUCLEOPHILIC SUBSTITUTION: REACTIONS BETWEEN 2-AMINO-5-HALOGENOTHIAZOLES AND NUCLEOPHILES

By

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In a previous article[1] we have shown that 5-halogenothiazoles react with sodium methoxide despite difficult aza-activation in position 5 of the thiazole ring. Here we examine the halogen displacement of 2-amino-5-halogenothiazoles (halogen = Cl, Br) by neutral (piperidine) or anionic (sodium methoxide) nucleophiles.

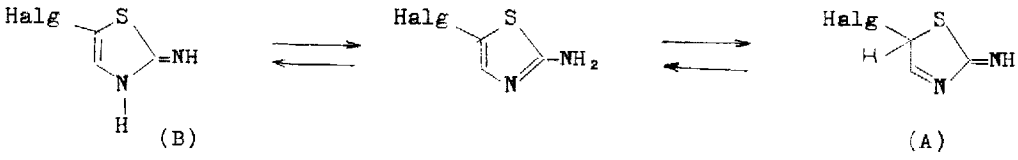
The products of the substitution reactions are obtained in almost quantitative yields: 2-amino-5-methoxythiazole, m.p. 105-106° (benzene) τ_{H_4} = 3.55 ($1H_s$), τ_{CH_3O-} = 6.15 ($3H_s$) (in $CDCl_3$, internal reference Me_4Si); 2-amino-5-N-piperidylthiazole, m.p. 143-44° (benzene), τ_{H_4} = 3.50 ($1H_s$), (in $CDCl_3$, internal reference Me_4Si), elemental analysis in agreement with respective formula. These reaction products are unstable in the presence of large amounts of used nucleophile.

The kinetic runs follow a second order kinetic law and the results are given in Table 1 together with some kinetic values for the same reactions on 5-halogenothiazoles previously reported[1].

The reaction occurs also with sodium benzenethiolate or un-ionised benzenethiols, as reported by C.S. Mahajanshetti[2] but the kinetic feature is complicated by some equilibria.

The presence of the amino group dramatically enhances the reactivity of position 5 of the thiazole ring and the ratio $k_{5\text{-bromo-2-aminothiazole}} / k_{5\text{-bromothiazole}} = 10^4$ emphasize a very unusual amino-activation to nucleophilic substitution. When an $-NEt_2$ group is present in position 2, no reaction is observed. The reaction appears to be enhanced not by some electronic effect[3], but by the presence of a hydrogen atom on the nitrogen bonded in position 2

We have already studied the activation towards nucleophilic substitutions induced by an -OH group in halogenonaphthols[4] and the reactive form of 5-halogeno-2-aminothiazoles can probably be ascribed to similar tautomeric processes:



(B) (A)

The ratio k_{Br}/k_{Cl} (about 1) gives some indication of the slight importance of the breaking of the carbon-halogen bond in the transition state (for 5-halogeno--thiazoles $k_{Br}/k_{Cl} \simeq 1$).

Our present data are not able to distinguish the reactive form (A or B). The relevant importance of the presence of (A) or (B) emphasizes the scarcely aromatic character of the considered thiazole derivatives[5] and makes the present reaction a method of preparation of 5-substituted thiazole derivatives.

Table 1

Reactions between 5-halogeno-2-aminothiazoles and nucleophiles

Halogen	Nucleophile	Solvent	$k(sec^{-1}mol^{-1}l)$[a]	Temp.(°C)
Bromo	MeO^-Na^+	MeOH	0.23	50
Bromo	MeO^-Na^+	MeOH	$0.14\ 10^{-1}$	25
Bromo	Piperidine	Piperidine	$6.6\ 10^{-4}$ [b]	50
Bromo	Piperidine	Piperidine	$1.4\ 10^{-4}$ [b]	25
Bromo	Piperidine	EtOH	$1.8\ 10^{-4}$	50
Chloro	MeO^-Na^+	MeOH	$1.1\ 10^{-2}$	25
5-Bromothiazole	MeO^-Na^+	MeOH	$2.3\ 10^{-5}$ [c]	50
5-Chlorothiazole	MeO^-Na^+	MeOH	$1.9\ 10^{-5}$ [c]	50

a Error: ± 3%; b in S^{-1}; c From ref. 1

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