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HALOGEN MIGRATION IN REACTIONS OF HALOGENOISOTHIAZOLES WITH POTASSIUM AMIDE IN LIQUID AMMONIA

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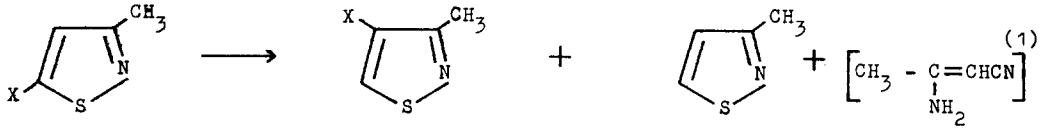
In this laboratory extensive investigations have been carried out on reactions of halogeno monoaza- and diazahetarenes with potassium amide in liquid ammonia (1). Several reaction types have been established: substitutions according to AE- and EA mechanisms, sometimes combined with halogen migration, ring transformations and ring coupling reactions. Extending our work on the π-deficient pyrimidines (2) to the π-excessive five-membered heterocycles we started an investigation on the reactivity of 5-halogenoisothiazoles towards potassium amide in liquid ammonia at -33°. It was found that under these conditions halogen migration occurs and that amination, if any, only takes place to a small extent.

Treatment of 5-bromo-3-methylisothiazole (I, X = Br) with the fourfold molar amount of potassium amide in liquid ammonia at -33° for 5 min. yields the isomeric 4-bromo-3-methylisothiazole (II, X = Br). As by-product a small amount of 3-methylisothiazole (III) is obtained. When I (X = Br) is allowed to react for 15 min. the yield of II (X = Br) is increased (see table). In both reactions no indication was obtained for the formation of 4- and 5-amino-3-methylisothiazole even when the reaction time was enhanced to 2 hrs. So the occurrence of 4,5-dehydro-3-methylisothiazole can be excluded.



I II III IV (1)

Similar results are obtained when reacting the 5-chloro compound (I, X = Cl); the rate of the isomerisation, however, appeared to be lower than that of the 5-bromo compound (see table).

The reaction of the 5-iodo compound (I, X = J) with potassium amide gives quite

different results. Deiodination of I (X = J) into III is now the main process (3), while the product resulting from iodine migration is only present in a small quantity. However, in this reaction a reasonable amount of β-aminocrotononitril IV is obtained which product as we have shown, can originate from primarily formed 5-amino-3-methylisothiazole. No indication for the presence of 4-amino-3-methylisothiazole is obtained.

Reaction of 5-halogenoisothiazoles with potassium amide at -33° [a]

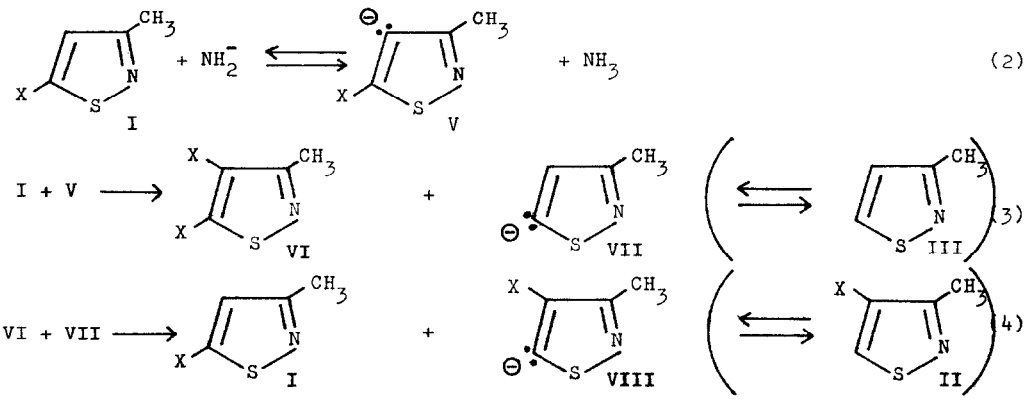
Substrate I	Reaction time (min)	Unreacted substrate (I)	Products [b]		
			II	III	IV
X = Br	5	X = Br; 26%	X = Br [c]; 70%	1 - 2%	absent
X = Br	15	X = Br; 5%	X = Br ; 85%	6%	absent
X = Cl	5	X = Cl; 41%	X = Cl ; 26%	2%	absent
X = J	3	X = J ; 0%	X = J ; 15%	34%	7%

a. In all reactions the ratio of substrate to potassium amide is 1 : 4, conc.potassium amide = 0.25.

b. The products II and III, isolated by preparative gaschromatography, gave satisfactory elemental analyses and consistent spectral properties (infrared, ultraviolet and nmr).

c. see reference 4.

The halogen migration in basic medium, which has also been observed in benzenes(5), pyridines(6) and thiophenes(7), is suggested to take place according to the following mechanism:



On the basis of this mechanism it is evident that the 5-chloro compound will react more slowly than the 5-bromo compound, assuming that the rate determining step in this sequence of reactions is the transhalogenation reaction. Chlorine, being less electropositive than bromine, will be less inclined to migrate in this intermolecular process from the 5-position in I to the 4-position in V.

Further support for this mechanism is obtained from the experimental finding that an equimolar mixture of 4,5-dibromo-3-methylisothiazole (VI, X = Br) and 3-methylisothiazole (III) (8) is converted into II (X = Br) in nearly quantitative yield. It indicates that the occurrence of the reaction takes place much faster than the replacement of the 5-bromine atom by an amino group, 5-amino-4-bromo-3-methylisothiazole being formed in only very small yields ($< 1\%$).

An equimolar mixture of 4-bromo-5-chloro-3-methylisothiazole and 3-methylisothiazole gives equal amounts of 4-bromo-3-methylisothiazole (30%) and 5-chloro-3-methylisothiazole (30%) together with some 5-amino-4-bromo-3-methylisothiazole (9) (5%) and unreacted 3-methylisothiazole (60%). This result is in accordance with the mechanism given and confirms that chlorine has a rather low reactivity in this transchlorination reaction.

Acknowledgement

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References

1. H.J.den Hertog and H.C.van der Plas, Adv.Het.Chem.volume 4, p.121. Ed. A.R.Katritzky (Acad.Press, New York, London).

2. See for the XIth Communication from this Laboratory on the reactivity of pyrimidines, H.C.van der Plas, P.Smit and A.Koudijs, Tetrahedron Letters p.9 (1968).

3. The formation of product III can possibly be compared with the deiodination of 2-iodobenzothiazole found in reactions with nucleophilic reagents. Cf. G.Bartoli, L. di Nunno, P.E. Todesco, Tetrahedron Letters p. 2369 (1968).

4. For reference purpose this compound was prepared by treating 3-methylisothiazole with bromine in fuming sulphuric acid (yield 80%). This procedure was found to be far superior to the reported one. Cf. D.Buttimore, D.H.Jones, R.Slack, K.R.H. Wooldridge, J.Chem.Soc. p.2032 (1963).

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5b. J.F.Bunnett, D.J.McLennan, J.Am.Chem.Soc. 90, 2190 (1968).

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8. It has been proved that in a basic medium 3-methylisothiazole (III) readily loses its proton from position 5, yielding VII. Cf. R.A.Olofson, J.M.Landesberg, K.N.Houk and J.S.Michelman, J.Am.Chem.Soc. 88, 4265 (1966).

9. This compound appears to be unstable towards potassium amide in liquid ammonia; the decomposition products have not been identified thus far.