J. Rokach and P. Hamel*

Merck Frosst Laboratories, P.O. Box 1005, Pointe Claire/Dorval, Quebec H9R 4P8, Canada

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We describe here a novel and general high yield method for the synthesis of 3-alkyl and arylaminoisothiazoles, a previously unknown group of isothiazoles, by the reaction of ammonia with 3-halo-2-alkylisothiazolium salts. The mechanism of the reaction probably involves a ring opening followed by a recyclization to the title compounds.

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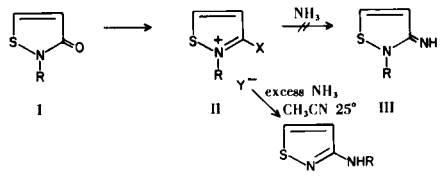
Sir:

We wish to report the discovery of a novel general method of synthesis of 3-alkyl and arylaminoisothiazoles, a previously unknown group of isothiazoles (1).

Attempts to prepare the isothiazoline derivative III (R = CH_3) by reaction of the isothiazolium salt II (R = CH_3, X = Y = Cl) with ammonia were found to lead not to III, the product of direct displacement, but to the rearranged isomer IV (R = CH_3), cleanly and in high yield. (See Scheme I).

Scheme 1



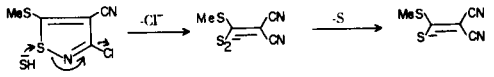
The nmr (deuteriochloroform) of the 3-methylaminoisothiazole (IV, R = CH_3) obtained shows the aromatic protons H_4 and H_5 at 3.61 τ and 1.65 τ, respectively ($J_{4,5}$ = 5), and the *N*-methyl group at 7.00 τ as a doublet (J = 5). On deuterium oxide exchange the doublet collapses to a sharp singlet, thus proving structure IV and eliminating structure III. The mass spectrum (M^+ = 114) confirms the identity of the compound.

A number of selected salts II (X = Y = Cl) were treated in the same way with excess ammonia in acetonitrile, and in all cases a high yield of the rearranged 3-alkyl and arylaminoisothiazoles IV were obtained. Table I contains the relevant data. Again one can see that the coupling of the system -NH-CH collapses on deuterium oxide treatment.

The quaternary salts II were readily prepared in quantitative yields from known I (2). Two types of II were prepared, the first (X = OCH_3, Y = FSO_3) by reaction of I with methyl fluorosulfonate and the second (X = Y = Cl) by reaction of I with phosphoryl chloride. It is interesting to note that all the quaternary methoxy compounds gave lower yields (up to 40%) of IV on treatment with ammonia, and in one instance [II (R = cyclohexyl, X = OCH_3, Y = FSO_3)] no product could be isolated, whereas the chloro compounds gave uniformly high yields (Table I).

Crow and Leonard (3) have found that good nucleophiles (CN^-, RS^-) can readily open the isothiazole ring by attack on the sulfur to yield open chain compounds.

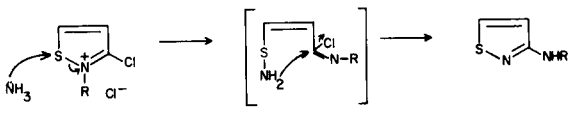
Hatchard (4) observed a similar nucleophilic attack on 3-chloro-4-cyano-5-methylthioisothiazole.



In the case in hand, compounds of type II, the positive charge on the nitrogen renders the sulfur much more susceptible to nucleophilic attack and ammonia, instead of the usually expected attack on the iminium carbon, chooses the sulfur as the main point of attack.

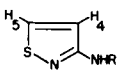
The formation of IV from II can therefore best be rationalized by an initial attack of ammonia at the sulfur site to yield an intermediate *S*-aminoiminoyl chloride which would then cyclize efficiently to yield the observed products. (See Scheme II).

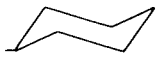
Scheme 2



The formation of III in the reaciton mixture followed by a Dimroth rearrangement to yield IV cannot be completely ruled out and a detailed study of the mechanism as well as further applications of the reaction are under investigation.

Table I



R	M.p. (°C)	Yield	H_4	H_5	Nmr (a) (τ) R
$-CH_3$	oil (fluorosulfonate 86-89)	80%	3.61 $J_{(4,5)} = 5$	1.65	7.00 (CH_3, doublet) J (b) (CH_3-NH) = 5 cps; 5.40 (NH, broad)
$-CH_2CH_3$	oil (fluorosulfonate 91-95)	72%	3.55 $J_{(4,5)} = 5$	1.60	6.57 (CH_2, quintet) J (b) (CH_2-NH) = 7 cps; 5.35 (NH, broad); 8.75 (CH_3, triplet) $J(CH_2\text{-}CH_3)$ = 7 cps
$-CH_2C_6H_5$	74-76	95%	3.55 $J_{(4,5)} = 5$	1.63	5.45 (CH_2, doublet) J (b) (CH_2-NH) = 4 cps; 5.40 (NH, broad); 2.68 (arom.)
$-C_6H_5$	156-158	95%	2.82	0.75	-0.12 (NH); 1.70-2.80 (arom.)
	133-134	95%	3.48	1.59	6.30 (CH, multiplet); 5.62 (NH, broad); 7.60-8.90 $(CH_2)_5$

(a) All spectra were determined in deuteriochloroform except the phenyl compound which was determined in DMSO-d_6. (b) The splitting due to the NH collapses to a singlet in the methyl and benzyl cases and to a quartet in the ethyl case on D_2O exchange.

REFERENCES AND NOTES

(1) For recent reviews of isothiazole chemistry see: (a) K. R. H. Wooldridge, *Advan. Heterocyclic Chem.*, **14**, (1972); (b) R. Slack and K. R. H. Wooldridge, *ibid.*, **4**, 107 (1965).

(2) S. N. Lewis, G. A. Miller, M. Hausman and E. C. Szamborski, *J. Heterocyclic Chem.*, **8**, 571 (1971).

(3) W. D. Crow and N. J. Leonard, *J. Org. Chem.*, **30**, 2660 (1965).

(4) W. R. Hatchard, *ibid.*, **29**, 660, 665 (1964).