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CYCLIZATION OF N-ALLYLTHIOUREA DERIVATIVES BY THE ACTION OF α-CHLORONITROSOALKANES

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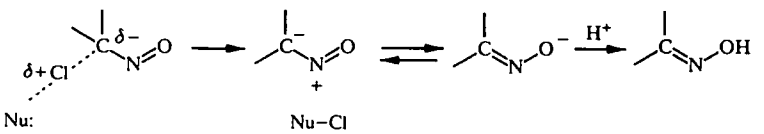
A convenient method is proposed for obtaining difficultly available derivatives of 2-amino-5-chloromethyl-2-thiazoline by the cyclization of N-allylthioureas under the action of α-chloronitrosoalkanes. It is assumed that the reaction proceeds as a halogenophilic process leading to the intermediate formamidinesulfenyl chloride which is rapidly and selectively cyclized with the formation of 2-amino-2-thiazoline derivatives.

The heterocyclization of N-allylthioureas (I) by the action of iodine and bromine leading to the corresponding 2-amino-5-halomethyl-2-thiazoline salts has been known for a long time and is used widely in synthesis to obtain 2-amino-2-thiazoline derivatives and analogs of them [1, 2]. However the 2-amino-5-chloromethyl-2-thiazolines (II) formed initially on chlorinating thioureas (I) are destroyed by the action of chlorine. Subsequently a multistage and nonselective route based on the dihydrothiazine–thiazoline rearrangement has been used to obtain compounds (II) [3].

The aim of the present work was to devise a convenient method for the synthesis of thiazolines (II) which are of interest as physiologically active substances (for example [4]). We therefore investigated the reaction of thioureas with a series of chlorinating agents, including N-chlorosuccinimide, sulfuryl chloride, and tert-butyl hypochlorite. These agents caused oxidative destruction of thioureas (I) leading, as with chlorine, to a whole spectrum of compounds (sulfonic acids, allylurea, elemental sulfur, etc.).

These results stimulated us to broaden the search for milder chlorinating agents, particularly among substances able to participate as substrates in halogenophilic reactions [5]. The α-chloronitrosoalkanes (III) were of particular interest since they react with such mild nucleophiles as trivalent phosphorus compounds [6] (thiourea is also a mild nucleophile). The presence of the strongly electron-accepting NO group in compounds (III) and the significant steric and electrostatic screening of the quaternary carbon center hinders the usual nucleophilic replacement of the chlorine atom (at the carbon atom). These same factors assist halogenophilic reactions to proceed [5], i.e., the nucleophilic replacement at the chlorine atom. In the case of substrates (III) the resonance-stabilized anion is a good leaving group and in a protic solvent is readily converted to an oxime derivative.



In the present work it was in fact shown that the reaction of chloronitrosoalkanes (III) with thioureas (I) leads to the formation of thiazolines (II).

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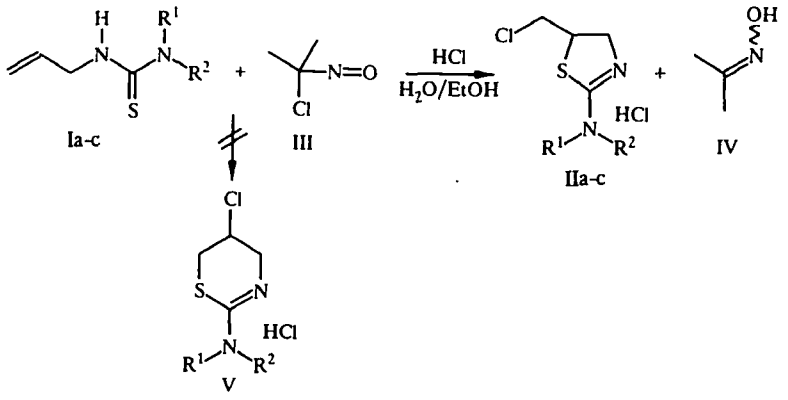
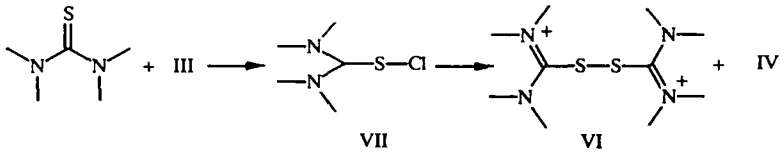


I, II a $R^1 = R^2 = H$; b $R^1 = H$, $R^2 = Ph$; c $R^1 = R^2 = Et$

Reaction occurs smoothly in an acid medium. It is interesting that in no case was the formation detected of even trace amounts of 2-amino-5-chloro-5,6-dihydro-4H-1,3-thiazines (V), isomeric with thiazoline (II). This distinguishes the proposed method from the preparation of the corresponding 2-amino-5-bromomethyl-2-thiazolines which is frequently accompanied by the formation of the isomeric 6-membered heterocycles [2, 7].

The thiazolines (II) were isolated from the reaction mixture practically quantitatively by precipitation from aqueous alcohol solution as picrates or tetraphenylborates. The transformation product of nitrosalkane (III), the corresponding oxime (IV), may also be isolated from the mixture in good yield.

The reaction of chloronitrosoalkanes (III) with thioureas containing no N-allyl substituent proceeds quantitatively in acid medium to the formamidine disulfide (VI). The chloronitrosoalkane (III) is also converted quantitatively into the corresponding oxime (IV).

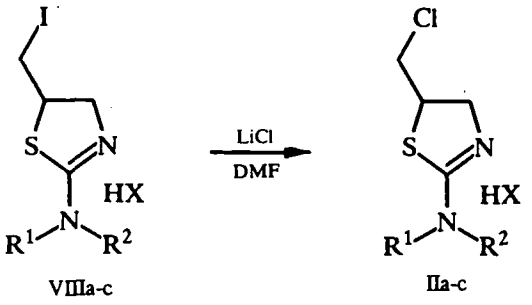


From an analysis of the product composition of these reactions it may be proposed that the mechanism comprises halogenophilic attack by the thiocarbonyl fragment of the thiourea at the chlorine atom of the nitroso derivatives (III) with the formation of an intermediate formamidine-sulfenyl chloride (VII). In the case of N-allyl derivatives (I) the S-chloroisothiourea (VII) cyclizes rapidly. The reaction may be considered as an intramolecular addition of the sulfenyl chloride (VII) at the double bond.

It must be noted that the reactants (III) are extremely passive in relation to the usual olefins, even to such an activated olefin as allylamine, which was shown by special experiments. This, and also the absence from the reaction mixture of the 6-membered heterocycles (V), confirms that the reaction mechanism proposed, comprising halogenophilic attack by the thiocarbamide sulfur at the chlorine atom, is different from traditional representatives of halogen-cyclization reactions and is a conjugated Ad_E process.

However, without special investigations of the nature of the intermediates (VII) it is impossible to exclude the possible occurrence of this process by a radical (or by a chain ion-radical) mechanism, which has a distant analogy to the ter Meer reaction initially mistaken as a trivial S_N2 substitution [8].

To confirm the structure of thiazolines (II) we effected their alternate synthesis starting from the corresponding salts of 2-amino-5-iodomethyl-2-thiazolines (VIII). We discovered that heterocycles (VIII) were readily converted into compounds (II) by the action of an excess of anhydrous lithium chloride in DMF at room temperature. However, the reaction may be complicated by side reactions (for example when R^1 and R^2 are not H).



VIIIa-c IIa-c

II, VIII a $R^1 = R^2 = H$; b $R^1 = H$, $R^2 = Ph$; c $R^1 = R^2 = Et$

EXPERIMENTAL

A check on the composition of reaction products was effected by TLC on Silufol UV 254 plates, developing them in the systems butanol–acetone–formic acid (1:0.8:1) or butanol–0.5% aqueous ammonia (1:1). Chromatograms were visualized with Grote reagent or with iodine vapor. The PMR spectra were recorded on a Bruker CXP 200 spectrometer (internal standard was TMS).

The initial N-allylthioureas (I) were obtained by the known method of [9]. 2-Chloro-2-nitrosopropane, 2-chloro-2-nitrosobutane, and 3-chloro-3-nitrosopentane, obtained according to [6], were used as reactants (III). In all cases the composition of reaction products was analyzed by PMR using a methanol-D_4–36% DCl solution in D_2O (1:1) as reaction mixture. The quantitative formation of thiazolines (II) [or disulfides (VI)] and oximes (IV) was observed from the PMR data.

Thiazolines (II) and formamidine disulfides (VI) were obtained using a 1:1 mixture of ethanol and aqueous acid (36% HCl or 20% H_2SO_4) as solvent. A solution of chloro compound (III) (10 mmole) in alcohol (10 ml) was added dropwise with stirring at 20°C to an acid–alcohol solution (10 ml) of urea (I) (10 mmole). After decolorization the reaction mixture was kept for 1 h and then mixed with a 5-fold excess of aqueous picric acid solution. The precipitated solid was separated after 20 h and recrystallized from aqueous ethanol.

2-Amino-5-chloromethyl-2-thiazoline Picrate (IIa). The yield was 64% after recrystallization, mp 185-186.5°C. PMR spectrum (acetone-D_6): 10.25 (1H, br.s, NH); 9.18 (2H, br.s, NH_2); 8.85 (2H, s, picric acid); 4.68 (1H, m, CH); 4.36 (1H, d.d, ^3J = 7, ^2J = 12 Hz, CH_2N); 4.24 (1H, d.d, ^3J = 3 Hz, CH_2N); 4.09 ppm (2H, m, CH_2Cl). Found, %: C 31.64; H 2.82; N 18.25. $C_4H_7ClN_2S \cdot C_6H_3N_3O_7$. Calculated, %: C 31.63; H 2.65; N 18.44.

5-Chloromethyl-2-phenylamino-2-thiazoline Picrate (IIb). The yield was 60% after recrystallization, mp 160-163°C. PMR spectrum (DMSO-D_6): 10.9 (2H, br.s, NH); 8.60 (2H, s, picric acid); 7.4-7.5 (5H, m, C_6H_5); 4.48 (1H, m, CH); 4.10 (1H, d.d, ^3J = 8, ^2J = 12 Hz); 4.00 (2H, d, ^3J = 6 Hz); 3.95 ppm (1H, d.d, ^3J = 3, ^2J = 12 Hz). Found, %: C 42.40; H 3.00; N 15.12. $C_{10}H_{11}ClN_2S \cdot C_6H_3N_3O_7$. Calculated, %: C 42.16; H 3.10; N 15.36.

5-Chloromethyl-2-diethylamino-2-thiazoline Picrate (IIc). The yield was 89% after recrystallization, mp 150-151°C. PMR spectrum (DMSO-D_6): 9.80 (1H, s, NH); 8.61 (2H, s, picric acid); 4.48 (1H, m, CH); 4.02 (1H, d.d, ^3J = 8. ^2J = 12 Hz, CH_2N); 3.98 (3H, m, [2H CH_2Cl + 1H CH_2N]); 3.50 (4H, m, CH_2); 1.2 ppm (6H, m, CH_3). Found, %: C 38.63; H 4.20; N 16.16. $C_8H_{15}ClN_2S \cdot C_6H_3N_3O_7$. Calculated, %: C 38.58; H 4.16; N 16.07.

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