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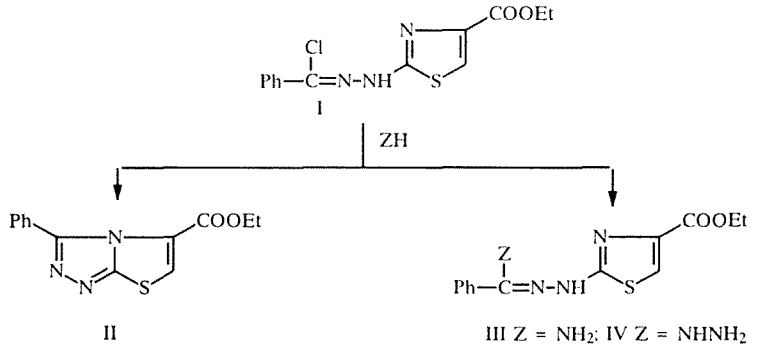
SYNTHESIS AND PROPERTIES OF THIAZOLE HALOHYDRAZONES. 2.* INTERACTION OF 2-α-CHLOROBENZYLIDENEHYDRAZINO-4-ETHOXY-CARBONYLTHIAZOLE WITH NUCLEOPHILES

S. V. Usol'tseva and G. P. Andronnikova

In the interaction of 2-α-chlorobenzylidenehydrazino-4-ethoxycarbonylthiazole with nucleophiles, two competing reactions take place: 1) nucleophilic replacement of the chlorine atom to form the corresponding substitution product; 2) elimination of a hydrogen chloride molecule, concluding in cyclization of the intermediate nitrilimine to form 3-phenyl-5-ethoxycarbonylthiazolo[2,3-c]-1,2,4-triazole. The direction taken by the interaction depends on the nature of the nucleophile and is determined primarily by the ratio of basicity and nucleophilicity of the agent.

Continuing our studies of the reactivity of thiazole halohydrazones [1-3], we have investigated the interaction of 2-α-chlorobenzylidenehydrazino-4-ethoxycarbonylthiazole (I) with nucleophiles.

Upon treatment of the chlorohydrazone I with an alcoholic solution of ammonia, we obtained a mixture of 3-phenyl-5-ethoxycarbonylthiazolo[2,3-c]-1,2,4-triazole (II) and 2-α-aminobenzylidenehydrazino-4-ethoxycarbonylthiazole (III). The use of a concentrated ammonia solution led to the formation of the amidrazone III. Interaction of compound I with hydrazine hydrate followed a course analogous to the reaction with ammonia, forming the triazole II and the substitution product IV. As a result of reaction of the chlorohydrazone I with methylamine, dimethylamine, sodium ethylate, or sodium acetoacetate in ethanol, or with sodium azide in aqueous dioxane, the only reaction product was the triazole II.



ZH NH_3; $N_2H_4 \cdot H_2O$; CH_3NH_2; $(CH_3)_2NH$; C_2H_5ONa; NaN_3; $CH_3C(ONa)=CHCOOEt$

*For preceding communication, see [1].

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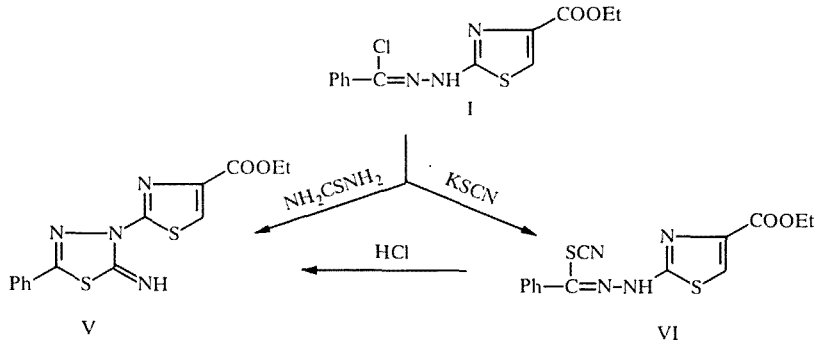
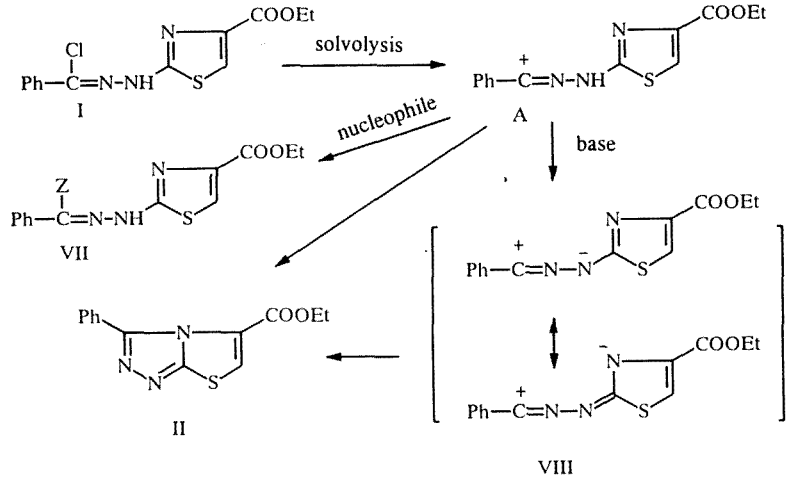
Upon interaction of the chlorohydrazone I with thiourea in ethanol, we obtained 5-phenyl-3-[2-thiazolyl-4-ethoxycarbonyl]-1,3,4-thiadiazolin-2-imine (V). It is known that the formation of this sort of derivative proceeds as a result of intramolecular cyclization of the substitution product involving participation by the NH group of the hydrazone, accompanied by release of an ammonia molecule [4]. Upon interaction of compound I with potassium thiocyanate in ethanol, the reaction stopped in the stage of replacement of the chlorine atom by an SCN group; and the product, 2-α-thiocyanato-benzylidenehydrazino-4-ethoxycarbonylthiazole (VI) was converted to the cyclic product V by heating in acidified ethanol. In the case with potassium thiocyanate, in contrast to the reaction with thiourea, chromatographic analysis of the reaction mass showed that the thiazolotriazole II was also formed.



In our investigation of the conversion of the chlorohydrazone I in various solvents, we found that it is stable in chloroform over an extended period and is not converted to the triazole II. In polar solvents, however, the hydrazone I undergoes solvolysis, leading to the triazole II. Thus, in 96% ethanol at 37°C, compound I was completely converted to the product II in 2.5 h. The solvolysis rate constant, determined by means of UV spectroscopy, was found to be $2.73 \cdot 10^{-4}$ sec^{-1} in ethanol. With increasing polarity of the solvent, the reaction rate increased. In 50% aqueous dioxane, the rate constant was found to be $4.22 \cdot 10^{-3}$ sec^{-1}. In the presence of a base, the reaction was so fast that the rate constant could not be determined spectrophotometrically.

These results are in good agreement with literature data regarding the monomolecular character of the reaction of halohydrazones with nucleophiles, in which an azacarbonium ion appears as an intermediate. Depending on the character of the nucleophile that is used, the reaction of the carbocation A will proceed in either of two directions — formation of the substitution product VII, or elimination of a proton to obtain the nitrilimine VIII [5, 6].



This situation is somewhat complicated by the presence of an additional nucleophilic center, i.e., the nitrogen atom of the thiazole ring, which may compete with the external nucleophile. The observed formation of the thiazolotriazole II can be interpreted as intramolecular 1,5-dipolar cyclization of the nitrilimine VIII, or as intramolecular nucleophilic substitution of the carbocation A. However, our data, indicating a significant increase of the rate of conversion of the chlorohydrazone I to compound II when a base is present, can serve as evidence that the reaction proceeds through the nitrilimine.

Thus, the direction taken in the reaction of the chlorohydrazone I depends on the nature of the nucleophile that is used, and is determined primarily by the ratio of basicity and nucleophilicity of the agent. Thus, ammonia, in the reaction with compound I, plays not only the role of a nucleophile, leading to the substitution product III, but also the role of a base, as indicated by the formation of the triazole II. With more basic agents (methylamine and dimethylamine), and also with anionic nucleophiles (sodium ethylate, sodium azide, sodium acetoacetate), which tend to stabilize the carbocation A, we observe only elimination, concluding in cyclization of the nitrilimine VIII to form the thiazolotriazole II. Upon interaction with thiourea, which is a rather strong nucleophile but a weak base, the substitution reaction takes place.

EXPERIMENTAL

IR spectra were taken on a UR-20 spectrophotometer (KBr tablets), PMR spectra on a Bruker WH-90 instrument (22.62 MHz), solvent DMSO-d_6, internal standard TMS. The individuality of the substances was monitored by means of TLC on Silufol UV-254 plates in a 9:1 chloroform–ethanol system.

The results from elemental analyses of the synthesized compounds matched the calculated values.

The synthesis procedures and characteristics of 2-α-chlorobenzylidenehydrazino-4-ethoxycarbonylthiazole (I) and 3-phenyl-5-ethoxycarbonylthiazolo[2,3-c]-1,2,4-triazole (II) were reported in [1].

Hydrate of 2-α-Aminobenzylidenehydrazino-4-ethoxycarbonylthiazole (III, $C_{13}H_{14}N_4O_2S \cdot H_2O$). A suspension of 0.4 g (1.29 mmoles) of the chlorohydrazone I in 5 ml of concentrated ammonia was stirred for 15 min, after which the product was extracted with 60-80 ml of chloroform. The extract was evaporated under vacuum, and the residue was recrystallized from 50% aqueous ethanol. R_f 0.39; mp 240-243°C. IR spectrum, cm^{-1}: 3415, 3335, 3215, 3100, 2960 (NH); 1680 (C=O), 1670 (NH_2), 1610 (C=N). PMR spectrum, ppm: 10.53 (1H, s, NH); 8.0-7.66 (2H, m, Ph); 7.63 (1H s, 5-H); 7.55-7.23 (3H, m, Ph); 6.35 (2H, s, NH_2); 4.23 (2H, q, CH_2); 1.3 (3H, t, CH_3). Yield 50%.

2-α-Hydrazinobenzylidenehydrazino-4-ethoxycarbonylthiazole (IV, $C_{13}H_{15}N_5O_2S$). To a suspension of 0.4 g (1.29 mmoles) of the chlorohydrazone I in 5 ml of ethanol, 0.3 ml of hydrazine hydrate was added. The solid residue was filtered off and recrystallized from 50% aqueous ethanol. R_f 0.49, mp 204-205°C. IR spectrum, cm^{-1}: 3250, 3150, 3060, 2950 (NH), 1695 (C=O), 1640 (NH_2), 1590 (C=N). PMR spectrum, ppm: 8.03-7.8 (2H, m, Ph); 7.7 (1H, s, 5-H); 7.68-7.4 (3H, m, Ph); 4.25 (2H, q, CH_2); 1.28 (3H, q, CH_3). Yield 53%.

Hydrochloride of 5-Phenyl-3-[4-ethoxycarbonyl-2-thiazolyl]-1,3,4-thiadiazoline-2-imine (V, $C_{14}H_{12}N_4O_2S_2 \cdot HCl$). **A**. To a solution of 0.2 g (0.65 mmole) of the chlorohydrazone I in 5 ml of ethanol, 0.049 g (0.65 mmole) of thiourea was added, and the mixture was refluxed for 5 min. After cooling, the residue was filtered off and recrystallized from ethanol. Yield 54%.

B. A solution of 0.1 g (0.3 mmole) of compound VI in 5 ml of absolute ethanol saturated with hydrogen chloride was refluxed for 10 min. The reaction mass was evaporated down, and the oil was triturated with dry ether. Yield 55%; R_f 0.43; mp 185-186°C. IR spectrum, cm^{-1}: 3345, 3260, 3155 (NH), 1700 (C=O), 1600 (C=N). PMR spectrum, ppm: 10.85 (1H, s, NH); 8.0-7.4 (5H, m, Ph); 7.64 (1H, s, 5-H); 4.23 (2H, q, CH_2); 1.27 (3H, t, CH_3).

2-α-Thiocyanatobenzylidenehydrazino-4-ethoxycarbonylthiazole (VI, $C_{14}H_{12}N_4O_2S_2$). A mixture of 0.1 g (0.32 mmole) of the chlorohydrazone I and 0.03 g (0.32 mmole) of potassium thiocyanate was refluxed in 5 ml of ethanol for 5 min. After cooling, the residue was filtered off and recrystallized from 50% aqueous ethanol. R_f 0.43; mp 170-173°C. IR spectrum, cm^{-1}: 2045 (SCN), 1715 (C=O), 1605 (C=N). PMR spectrum, ppm: 10.5 (1H, s, NH); 8.0-7.62 (2H, m, Ph); 7.62 (1H, s, 5-H); 7.56-7.25 (3H, m, Ph); 4.25 (2H, q, CH_2); 1.25 (3H, t, CH_3). Yield 55%.

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