SYNTHESIS AND TRANSFORMATIONS OF 4-SUBSTITUTED 2-AMINOTHIAZOLES

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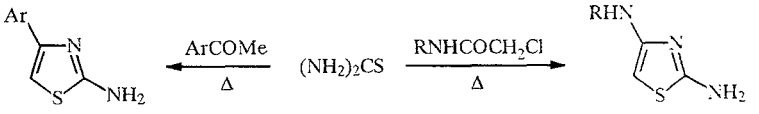
4-Substituted 2-aminothiazoles were synthesized and some of the transformations of these compounds at the amino group were studied. A number of new thiazole derivatives were obtained.

2-Aminothiazoles are known mainly as biologically active compounds with a broad range of activity [1, 2], intermediates in the synthesis of antibiotics [3, 4], and dyes [5]. The extensive synthetic possibilities of these heterocycles due to the presence of several reaction sites hold promise for the preparation of new thiazole derivatives and expansion of the range of application of these compounds.

In the present work, we studied the transformations of 4-substituted 2-aminothiazoles (I-V) at the exocyclic nitrogen atom.

2-Aminothiazoles I-V were obtained by the condensation of thiourea with methyl aryl ketones in the presence of iodine or with previously synthesized ω-bromoketones as well as with N–R-chloroacetamides (see Scheme 1).

Scheme 1



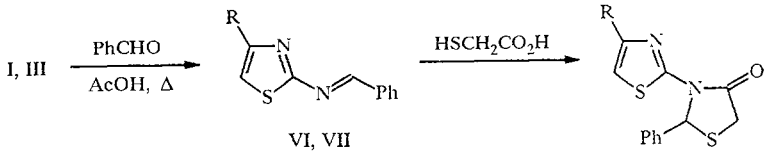
I, II III-V

I Ar = Ph; II Ar = C_6H_4Br-*p*; III R = $C_6H_4NO_2$-*p*; IV R = $C_6H_4NO_2$-*m*; V R = cyclo-C_6H_{11}

Aminothiazoles I and II were obtained in 40-50% yield and their physical constants corresponded to literature values [6, 7]. The structures of III-V were indicated by their PMR spectra, which display signals for aromatic protons at 7.0-8.0 ppm, primary and secondary amino groups at 5.0-6.0 ppm, and, in the case of V, cyclohexyl protons at 1.0-2.0 and 3.7 ppm.

We should note that the expected 4-substituted 2-aminothiazoles could not be isolated when N-arylchloroacetamides containing electron donor substituents such as *m*-OH, *m,m*-(*t*-Bu)$_2$, and *p*-OH are present in the aromatic ring. The most likely reason for this finding is the reduction in the electrophilicity of the carbonyl group in the N–R-chloroacetamide although the reaction with the cyclohexyl derivative proceeds in the ordinary manner and leads to thiazole V.

Scheme 2



VI, VII VIII

VI, VIII R = Ph, VII R = $HNC_6H_4NO_2$-*p*

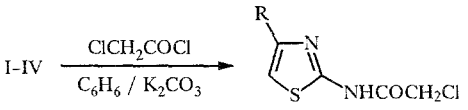
Bashkir State University, Ufa 450074. Latvian Institute of Organic Synthesis, Riga LV-1006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 715-718, May, 1993. Original article submitted December 16, 1992.

0009-3122/93/2905-0612$12.50

Aminothiazoles I and III react with benzaldehyde to give Schiff bases VI and VII, respectively. Product VI reacts with thioglycolic acid to give 2-phenyl-3-(4-phenylthiazol-2-yl)thiazolidone-4 (VIII) (see Scheme 2).

The acylation of thiazoles I-IV by chloroacetyl chloride leads to the corresponding chloroacetamides IX-XII (Scheme 3).

Scheme 3



IX-XII

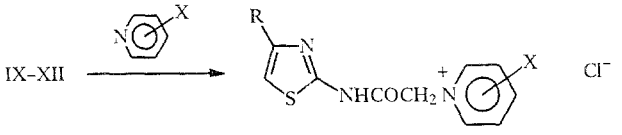
IX R = Ph; X R = C_6H_4Br-*p*; XI R = $HNC_6H_4NO_2$-*p*; XII R = $HNC_6H_4NO_2$-*m*

An attempt to introduce a second chloroacetyl group at the 4-NH group attached to the aromatic substituent in III and IV was unsuccessful due to its low nucleophilicity.

The PMR spectra of chloroacetamides IX-XII have signals for methylene group protons at 4.2-4.7 ppm and an amide proton at 10.0-11.5 ppm as well as aromatic proton signals.

The chlorine atom in IX-XII is extremely labile and is readily replaced by pyridine and its derivatives to give the corresponding quaternary salts (XIII-XXVI) (Scheme 4).

Scheme 4



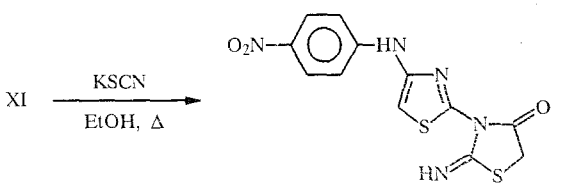
XIII-XXVI

XIII—XVI X = H, XIII R = Ph, XIV R = C_6H_4Br-*p*, XV R = $HNC_6H_4NO_2$-*p*, XVI R = $HNC_6H_4NO_2$-*m*, XVII—XVIII X = *m*-CHO, XVII R = Ph, XVIII R = $HNC_6H_4NO_2$-*p*, XIX X = *p*-CHO, R = $HNC_6H_4NO_2$-*p*, XX—XXII X = *p*-CH = NOH, XX R = Ph, XXI R = $HNC_6H_4NO_2$-*p*, XXII R = $HNC_6H_4NO_2$-*m*, XXIII—XXVI X = 1,3 dioxanyl-*m*, XXIII R = Ph, XXIV R = C_6H_4Br-*p*, XXV R = $HNC_6H_4NO_2$-*p*, XXVI R = $HNC_6H_4NO_2$-*m*

The PMR spectra of salts XIII-XXVI contain signals characteristic for the starting chloroacetamides as well as for the pyridine ring (8.0-9.7 ppm) and functional groups present.

The reaction of XI with KSCN is accompanied by cyclization to give 2-imino-3-[4-(4-nitrophenylamino)thiazol-2-yl]thiazolidone-4 (XXVII) (Scheme 5).

Scheme 5



XXVII

The indices of the products obtained are given in Table 1.

EXPERIMENTAL

The PMR spectra were taken on a Tesla BS-487C spectrometer in DMSO-d_6 with HMDS as the internal standard. The IR spectra were taken on a UR-20 spectrometer in Vaseline mull.

TABLE 1. Indices of Compounds Synthesized

Compound	Chemical formula	mp, °C	Yield, %	Compound	Chemical formula	mp, °C	Yield, %
III	$C_9H_8N_4O_2S$	144	77	XVI	$C_{16}H_{14}ClN_5O_3S$	200	85
IV	$C_9H_8N_4O_2S$	110	77	XVII	$C_{17}H_{14}ClN_3O_2S$	200	71
V	$C_9H_{15}N_3S$	134	65	XVIII	$C_{17}H_{14}ClN_5O_4S$	123	75
VI	$C_{16}H_{12}N_2S$	192	67	XIX	$C_{17}H_{14}ClN_5O_4S$	195	51
VII*	$C_{16}H_{11}N_3O_2S$	182	58	XX	$C_{17}H_{15}ClN_4O_2S$	>200	69
VIII	$C_{18}H_{14}N_2OS_2$	123	45	XXI	$C_{17}H_{15}ClN_6O_4S$	>200	44
IX	$C_{11}H_9ClN_2OS$	155	72	XXII	$C_{17}H_{15}ClN_6O_4S$	>200	72
X	$C_{11}H_8BrClN_2OS$	195	51	XXIII	$C_{20}H_{20}ClNO_3S$	>200	71
XI	$C_{11}H_9ClN_3O_3S$	165	78	XXIV	$C_{20}H_{19}BrClNO_3S$	>200	58
XII	$C_{11}H_9ClN_3O_3S$	79	73	XXV	$C_{20}H_{20}ClN_5O_5S$	>200	65
XIII	$C_{16}H_{16}ClN_3OS$	>200	84	XXVI	$C_{20}H_{20}ClN_5O_5S$	>200	73
XIV	$C_{16}H_{13}BrClN_3OS$	122	69	XXVII	$C_{12}H_9N_5O_3S_2$	>200	29
XV	$C_{16}H_{14}ClN_5O_3S$	>200	85				

2-Amino-4-phenylthiazole I was synthesized according to Dodson and King [6]. **2-Amino-4-(*p*-bromophenyl)thiazole II** was obtained from *p*-bromophenacyl bromide, which was synthesized according to a reported procedure [8] and cyclized to give thiazole II as described previously [9]. The yield of II was 41%, mp 178°C [7].

The elemental analysis data of the compounds synthesized for C, H, halide, N, and S corresponded to the calculated values.

2-Amino-4-arylaminothiazoles (III and IV) and 2-Amino-4-cyclohexylaminothiazole (V). A mixture of 2.5 g (0.012 mole) N-4-nitrophenylchloroacetamide, 0.92 g (0.012 mole) thiourea, and 50 ml absolute ethanol was heated at reflux for 8 h. After evaporation of ethanol, the residue was treated with 60 ml 20% aqueous Na_2CO_3. The precipitate was filtered off, washed with water, and crystallized from 50% aqueous ethanol. The yield of III was 2.5 g. Thiazoles IV and V were synthesized analogously using the corresponding N-substituted chloroacetamide.

4-Aryl-2-benzylideneaminothiazoles (VI and VII) were obtained from thiazoles I and III and benzaldehyde according to Mangi and Dash [10]. PMR spectrum of VII (δ, ppm): 7.7-8.9 (11H, m, H_{arom} and CH=N).

2-Phenyl-3-(4-phenylthiazol-2-yl)thiazolidone-4 (VIII) was obtained by the reaction of thiazole VI with thioglycolic acid according to Tierney [11]. IR spectrum: 1705 (C=O), 1600, 1150, 730 (arom) cm^{-1}. PMR spectrum (δ, ppm): 4.1 (2H, s, CH_2), 6.1 (1H, s, CH), 7.0-9.0 (11H, m, H_{arom}).

4-R-2-Acetylaminothiazoles (IX-XII). A sample of 1.4 ml (0.012 mole) chloroacetyl chloride was added dropwise with stirring to a mixture of 3.2 g (0.012 mole) 4-(N-4-nitrophenylamino)-2-aminothiazole III, 1.7 g (0.012 mole) potassium carbonate, and 15 ml benzene. After 4 h, the precipitate of XI was filtered off, washed with water, and crystallized from isooctane. Products IX, X, and XII were obtained analogously from 4-substituted 2-aminothiazoles I, II, and IV, respectively.

Only starting amide XI was isolated after heating equimolar amounts of chloroacetamide XI, chloroacetyl chloride, and potassium carbonate in benzene at reflux for 6 h.

1-[2-(4-R-Thiazolyl-2-amino)-2-oxoethyl]pyridinium chlorides (XIII-XXVI). A mixture of 0.5 g (0.002 mole) thiazole XI and 1.6 g (0.02 mole) pyridine was maintained for 48 h at 25°C. Then, 30 ml ether was added and the precipitate formed was filtered off and crystallized from ethyl acetate to give 0.6 g salt XV. Analogously, XIII, XIV, XVI-XIX, and XXIII-XXVI were synthesized from thiazoles IX, X, and XII and pyridine derivatives.

Products XX-XII were obtained by heating equimolar amounts of chloroacetamide and 4-pyridinaldoxime in a minimal amount of ethanol at reflux for 8 h.

2-Imino-3-[4-(N-4-nitrophenylamino)thiazol-2-yl]thiazolidone-4 (XXVII) was synthesized from chloroacetamide XI and potassium thiocyanate according to our previous procedure [12]. PMR spectrum (δ, ppm): 4.3 (2H, s, CH_2), 7.5-8.3 (5H, m, H_{arom}), 8.5 (1H, s, =NH). IR spectrum: 1725 (C=O), 3315 (=NH, NH) cm^{-1}.

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