SYNTHESIS OF 2-AMINOTHIAZOLE DERIVATIVES

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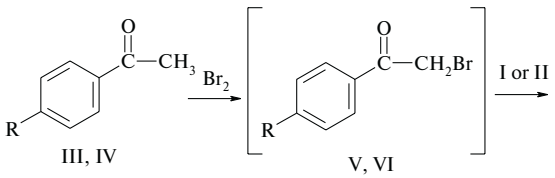
2-Aminothiazole derivatives were reported to possess antibacterial [1], antiviral [2], and psychotropic activity [3]. These compounds are usually obtained using a two-stage scheme, including bromination of the initial ketones in ether in the presence of $AlCl_3$ [4] or in a MeOH–$(MeO)_3$ mixture [5] followed by cyclocondensation of the intermediate α-bromoketones with thiourea (I) in ethanol or methanol [4, 6, 7]. It was also reported that 2-aminothiazole derivatives can be synthesized via a single-stage interaction of ketones with a mixture of N-bromosuccinimide, thiourea, and benzoyl peroxide in boiling benzene [8].

The two-stage character and the need to isolate the intermediate α-bromoketones possessing lacrimatory properties are obvious drawbacks of the first method. The disadvantages of the second method are the use of toxic and explosive solvent (benzene) and the absence of data concerning the synthesis of 2-aminothiazole derivatives from allylthiourea (II) and related compounds.

In the search for a simple and effective means of obtaining 2-aminothiazole derivatives, we have studied the possibility of selective monobromination of ketones in a mixture of urea and DMF, followed by cyclocondensation of the monobromoketones in the same solvent. An indication of the possibility to ensure the selective monobromination of ketones in the presence of urea and DMF was the fact that carboxylic acid amides are capable of forming complexes with Br_2, thus inhibiting the undesired dibromination process [9, 10].

Indeed, it was established that acetophenone (III) and *p*-bromoacetophenone (IV) are subject to selective monobromination in a mixture of urea and DMF to form phenacyl bromide (V) and *p*-bromophenacyl bromide (VI) with a yield above 70%.

Our experiments showed that the target 2-aminothiazole derivatives can be obtained "in one flask," by initially conducting monobromination of the initial ketones in a mixture of urea and DMF followed by cyclocondensation of the intermediate bromoketones *in situ* with thiourea (I) or allylthiourea (II).



VII – X

R = H (III, V, VII, VIII), Br (IV, IV, IX, X)

R′ = H (VII, IX), CH_2–CH=CH_2 (VIII, X)

This process yields 2-aminothiazole derivatives in the form of hydrobromides, which convert into free bases when treated with an aqueous K_2CO_3 solution.

Using the method outlined above and proceeding from the initial ketones III and IV and thioureas I and II, we obtained the following 2-aminothiazole derivatives: 2-amino-4-phenylthiazole (VII), 2-allylamino-4-phenylthiazole (VIII), 2-amino-4-(*p*-bromophenyl)thiazole (IX), and 2-allylamino-4-(*p*-bromophenyl)thiazole (X). The reaction pathways are depicted in the scheme below; the yield and characteristics of the products are listed in Table 1.

Using the same scheme to brominate ethyl acetoacetate (EAA), we obtained an α-bromine derivative (XI) that reacted with I and II to yield 2-amino-4-methyl-5-ethoxycarbonylthiazole (XII) and 2-allylamino-4-methyl-5-ethoxycarbonylthiazole (XIII). By the same token, bromination of compound X in an ether solution led to an isomer bromide XIV which reacted with thiourea to yield 2-amino-4-(ethoxycarbonylmethyl)thiazole (XV) [8, 13].

Our experience showed that this scheme can also be used for the synthesis of 2-amino-4,5-tetramethylenethiazole

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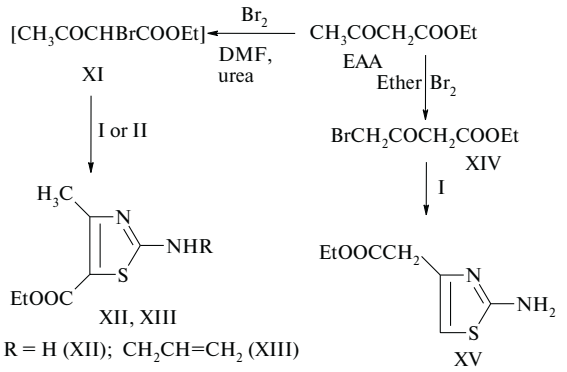
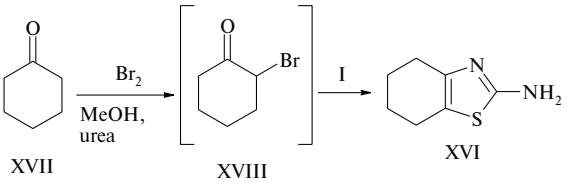
(XVI) from cyclohexanone (XVII), but more stable results in this case are obtained when DMF is replaced by methanol.



This synthesis is also conducted in one flask without isolating intermediate bromocyclohexanone (XVIII).



The synthesized 2-aminothiazole derivatives were identified by comparing their melting points and TLC patterns with those of known samples. For compound XII, the ^{1}H NMR spectra were compared as well (see the experimental part below).

Being relatively simple and offering satisfactory yields, the proposed method may compete with those described previously for the synthesis of 2-aminothiazole derivatives [4 – 8].

EXPERIMENTAL PART

The ^{1}H NMR spectra were measured on a Bruker AM-300 spectrometer using samples dissolved in DMSO-d_6. The course of reactions was monitored and purity of the reaction products was checked by TLC on Silufol UV-254 plates eluted in a benzene – ethyl acetate (1 : 1) system; the spots were visualized under UV illumination. The yields and physicochemical characteristics of the synthesized compounds are listed in Table 1. When necessary, the obtained 2-aminothiazole derivatives can be purified by recrystallization from aqueous ethanol.

Phenacyl bromide (V). To a mixture of 12 g (0.1 mole) of acetophenone and 6 g urea in 60 ml of DMF was gradually (over ~15 min) added, with stirring and cooling in ice, 16 g (0.1 mole) of bromine. Upon termination of the bromination process (20 – 30 h at ~20°C), the reaction mixture was diluted with water. The precipitated oily product exhibited crystallization within a short period of time, after which the crystalline deposit was separated by filtration and washed with water to obtain 17 g (85%) of compound V; m.p., 57 – 59°C. When necessary, bromoketone V can be distilled under reduced pressure (water-jet pump) [5].

Bromophenacyl bromide (VI). Compound VI was obtained using a procedure analogous to that described above. Yield, 71%; m.p., 107 – 108°C (ethanol) [5].

2-Aminothiazole derivatives (VII – X). To a solution of 0.1 mole of acetophenone or *p*-bromoacetophenone and 0.1 mole urea in 60 ml of DMF was gradually added, with stirring and cooling in ice, 0.1 mole of bromine. The mixture was allowed to stand at ~20°C until complete discoloration of bromine (~24 h). Then 0.1 mole of thiourea or allylthiourea were added and the mixture was stirred for 24 h at ~20°C and 2 h at 70 – 80°C (here and below, on a bath). Upon cooling, the mixture was treated with an excess of aqueous K_2CO_3 solution. The precipitate was separated by filtration and washed with water to obtain 2-amino-4-phenylthiazole (VII), 2-allylamino-4-phenylthiazole (VIII), 2-amino-4-(*p*-bromophenyl)thiazole (IX), and 2-allylamino-4-(*p*-bromophenyl)thiazole (X).

2-Amino-4-methyl-5-ethoxycarbonylthiazole (XII). To a mixture of 1.3 g (10 mmole) of ethyl acetoacetate and 0.6 g (10 mmole) urea in 4 ml of DMF was gradually added, with stirring and cooling in ice, 1.6 g (10 mmole) of bromine. Upon complete discoloration of bromine (~5 min), 0.76 g (10 mmole) of thiourea was added and the mixture was stirred for 24 h at ~20°C. Then the process was terminated by diluting the reaction mixture with ethyl acetate. The precipitate was separated by filtration and washed with ethyl acetate to obtain the salt XII · HBr; ^{1}H NMR spectrum (δ, ppm): 1.23 (t, 3H, J 7.2 Hz), 2.45 (s, 3H, CH_3), 4.21 (q, 2H, J 7.2 Hz, CH_2), 7.20 (bs, 2H, NH_2).

In order to obtain compound XII in the base form, the reaction mixture upon treatment with thiourea has to be diluted with an excess of aqueous K_2CO_3 solution (instead of ethyl acetate), after which the precipitated product is separated by filtration and washed with water.

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds VII – X, XII, XIII and XVI

Initial compounds		Target compound	Yield, %	M.p., °C	Empirical formula	Ref.
Ketone	Thiourea					
III	I	VII	73	148 – 150	$C_9H_8N_2S$	[6]
III	II	VIII	75	72 – 73	$C_{12}H_{12}N_2S$	[11]
IV	I	IX	77	180 – 182	$C_9H_7BrN_2S$	[6]
IV	II	X	71	108 – 110	$C_{12}H_{11}BrN_2S$	[12]
EAA	I	XII	80	174 – 176	$C_7H_{10}N_2O_2S$	[8]
EAA	I	XII · HBr	70	225 – 228 (decomp.)	$C_7H_{10}N_2O_2S \cdot HBr$	[8]
EAA	II	XIII	55	70 – 73	$C_{10}H_{14}N_2O_2S$	[14]
XVII	I	XVI · HBr	53	234 – 236	$C_7H_{10}N_2S \cdot HBr$	[15]
XVII	I	XVI	42	86 – 87	$C_7H_{10}N_2S$	[15]

2-Allylamino-4-methyl-5-ethoxycarbonylthiazole (XIII). Compound XIII was obtained using a procedure analogous to that described above for XII in the base form. Upon adding allylthiourea, the reaction mixture was kept for 12 h at ~20°C and heated for 3 h at 70 – 80°C.

2-Amino-4,5-tetramethylenethiazole (XVI). To a mixture of 10 g (0.1 mole) of cyclohexanone and 12 g (0.2 mole) of urea in 25 ml of MeOH was gradually (over ~10 min) added, with stirring and cooling in ice, 16 g (0.1 mole) of bromine. Upon termination of the bromination process (10 – 15 min at ~20°C), thiourea (7.8 g, 0.1 mole) was added immediately and the reaction mixture was allowed to stand for 72 h at ~20°C with periodic stirring. The precipitated hydrobromide was filtered and washed with methanol.

In order to obtain compound XVI in the free base form, the hydrobromide was treated with an excess of aqueous K_2CO_3 solution, after which the precipitated product was separated by filtration and washed with water.

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