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TECHNOLOGY OF ORGANIC AND INORGANIC CHEMISTRY

Synthesis of New Substituted Thiazoles Containing Aminooxadiazole Ring

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Abstract—Synthesis of biheterocyclic thiazole–amonooxadiazoles, the potential biologically active compounds is developed. Regularities of transformations and physico-chemical characteristics of intermediates and final compounds are revealed.

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The heterocycles of thiazole series are known to possess biological activity; some representatives of this class compounds are well-known medicine preparations [1, 2]. Compounds containing simultaneously thiazole and aminooxadiazole fragments merit special mentioning. Synthesis of these potentially biologically active compounds practically has not been described. We developed a few-step procedure for the synthesis of thiazole–aminooxadiazoles and studied conditions of the process and its technological parameters.

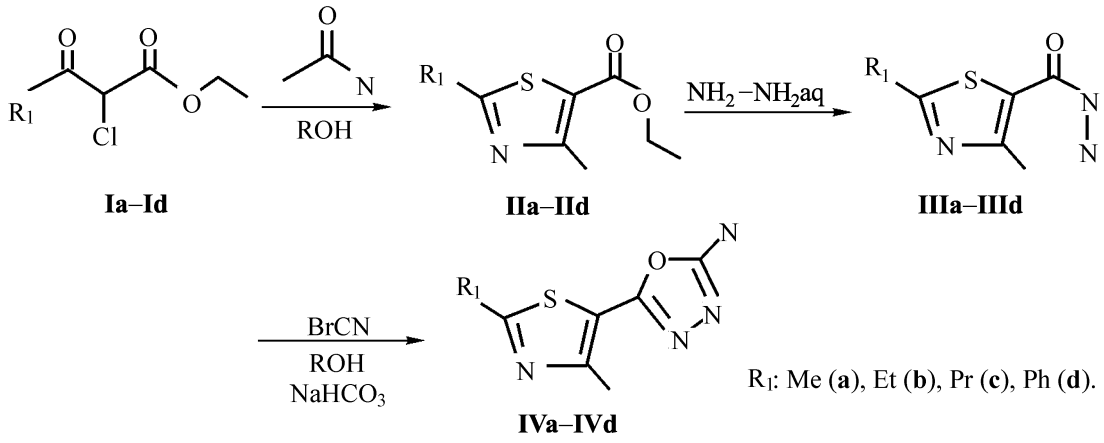
Substituted thiazoles **IIa**–**IId** were prepared by reaction of chloroacetoacetic esters prepared in correspondence with the procedure in [3] with thioacetamide in alcohol medium (like Hanch reaction [4, 5]) at 80–90°C, duration period 7–12 h, yield up to 75–80%.

Compounds **IIa**–**IId** are crystalline substances melting in the temperature range from 56 to 65°C.

Note that at the synthesis of compounds **IIa**–**IIc** the process duration increases for the series of substituents a to c, probably in connection with steric properties of these substituents. The process duration for compound **IId** increases probably due to strong electromeric effect of conjugated system that includes phenyl group. Introduction of triethylamine to the reaction zone allows accelerate the process considerably and increase yield of compound **IId** to 75%.

The process conditions for the synthesis of the thiazoles and some of their characteristics are listed in Table 1.

Synthesis of corresponding hydrazines **IIIa**–**IIId** has been poorly illuminated in literature. We prepared hydra-



Ia–Id **IIa–IId** **IIIa–IIId** **IVa–IVd**

Table 1. Process conditions for the synthesis of compounds **IIa–IId**

Compd. no.	Process duration, h	Process temperature, °C	Yield, %	mp, °C
IIa	5	80 7	8	56
IIb	7	82 7	7	65
IIc	8.5	85 7	0	61
IId	12.3 9	0	73 5	5

Table 2. Conditions of synthesis of compounds **IIIa–IIId**

Compd. no.	Process duration, h	Process temperature, °C	Yield, %	mp, °C
IIIa	10	77–83	82 1	01
IIIb	11	80–85	80 1	05
IIIc	13	84–88	77 1	14
IIId	16	90–95	74 1	58

Table 3. The process conditions for the synthesis of compounds **IVa-IVd**

Compd. no.	Process duration, h	Process temperature, °C	Yield, %	mp, °C
IVa	6	28 8	0	235
IVb	8.5	31 7	7	224
IVc	9	35 7	3	243
IVd	10	40	68 2	30

zides **IIIa–IIId** by reaction of thiazoles **IIa–IId** with 3–5-fold excess of 64% hydrazine hydrate in absolute ethnol at 90–100°C, reaction duration was 10 to 20 h, yield is as high as 95%. The compounds obtained are characterized by high melting point; they are well crystallizing from water–alcohol solutions. Results of the synthesis of compounds **IIIa–IIId** are shown in Table 2.

Aminooxadiazole derivatives **IVa–IVd** were obtained in 65–80% yield by cyclization of the prepared hydrazides [6, 7] with bromocyane in the presence of anhydrous potassium carbonate at equimolar ratio of reagents in ethanol medium at 20–40°C for 6–10h. IR spectra of the obtained compound do not contain adsorption bands of carbonyl and hydrazide groups while adsorption of aminooxadiazole NH_2 group appears in the spectra.

Structure, purity and nature of compounds **IVa–IVd** were revealed using 1H NMR spectroscopy. The NMR data obtained showed that amine fragment in compounds **IVa–IVd** is considerably less basic as compared with related unsubstituted aminooxazoles. The most probably this is defined by the presence of conjugated system thiazole–aminooxadiazole, in the case of **IVd** in particular, due to presence of phenyl group expanding conjugation. Spectral characteristics of the synthesized compounds are listed in Table 4.

CONCLUSIONS

A series of new potentially biologically active biheterocyclic compounds containing thiazole and aminooxazole rings is synthesized, optimal conditions of the synthesis are studied and revealed.

Structure of the obtained compounds is proved and they are characterized by means of ^{1}H NMR spectroscopy.

EXPERIMENTAL

The ^{1}H NMR spectra are recorded on a e Bruker AM 500 spectrometer, internal reference TMS, solvent DMSO-d_6. Melting points are measured on a PTP unit.

Synthesis of R-substituted ethyl esters of thiazolecarboxylic acids IIa–IId. Mixture of preliminary prepared R-substituted chloroacetoacetic ester **Ia–Id** (0.236 mol) and thioacetamide (0.236 mol) in 100 ml of ethanol or isopropyl alcohol was refluxed on water bath with stirring for 7–12 h. After cooling the reaction mixture was diluted with 200 ml of dichloromethane. Precipitate formed was removed by filtration and filtrate was washed with 20% solution of sodium hydrocarbonate (100 ml) to neutral reaction and then by solution (100 ml) of sodium chloride. The layers were separated, and from organic layer dicloromethane was distilled off after drying over magnesium sulfate, and then compounds **IIa–IId** were isolated in 85–90% yield.

Spectral characteristics of compounds **IIa–IId** obtained are listed in Table 4.

Synthesis of hydrazides of R-substituted thiazolecarboxylic acids IIIa–IIId. To a solution of the obtained by above procedure R-substituted ethyl ester of thiazolecarboxylic acid **IIa–IId** (0.5 mol) in 125 ml of ethanol or isopropyl alcohol was dozed at 20–30°C 100 ml of 64% hydrazine hydrate (0.236 mol) and the raction mixture obtained was refluxed with stirring for 10–20 h. Then reaction mixture was concentrated in a vacuum to 60–75%. The crystals dropped are soluble in water. They were recryctallized from ethanol, and compounds **IIIa–IIId** were obtained in 85–93% yield.

Table 4. 1H NMR spectral data of compounds **II–IV** (solutions in DMSO–*d*6)

Compound	^{1}H NMR spectra, δ, ppm
IIa	2.55 s (3H, CH_3); 2.47 s (3H, CH_3); 1.31 t (3H, CH_3); 4.27 q (2H, CH_2)
IIb	1.31 t (3H, CH_3); 1.37 t (3H, CH_3); 2.47 s (3H, CH_3); 2.9 q (2H, CH_2); 4.27 q (2H, CH_2)
IIc	0.91 t (3H, CH_3); 1.32 t (3H, CH_3); 1.6 m (2H, CH_2); 2.4 s (3H, CH_3); 2.91 t (2H, CH_2); 4.25 d (2H, CH_2)
IId	1.33 t (3H, CH_3); 2.55 s (3H, CH_3), 4.28 d (2H, CH_2); 7.72–7.8 m (5H $_{arom}$)
IIIa	2.32 s (3H, CH_3); 2.38 s (3H, CH_3); 5.68 s (3H, NH, NH_2)
IIIb	1.39 t (3H, CH_3); 2.39 s (3H, CH_3); 3.35 d (2H, CH_2); 5.68 s (3H, NH, NH_2)
IIIc	0.92 t (3H, CH_3); 1.61 m (2H, CH_2); 2.29 s (3H, CH_3); 3.35 t (2H, CH_2); 5.7 s (3H, NH, NH_2)
IIId	2.47 s (3H, CH_3); 5.4 s (3H, CH_3); 7.62–7.7 m (5H_{arom}); 5.81 s (3H, NH, NH_2)
IVa	2.37 s (3H, CH_3); 2.55 s (3H, CH_3); 7.4 s (2H, NH_2)
IVb	1.36 t (3H, CH_3); 2.38 s (3H, CH_3); 2.98 d (2H, CH_2); 7.32 s (2H, NH_2)
IVc	0.9 t (3H, CH_3); 1.64 m (2H, CH_2); 2.29 s (3H, CH_3); 2.97 t (2H, CH_2); 7.6 s (2H, NH_2)
IVd	2.46 s (3H, CH_3); 7.62–7.72 m (5H_{arom}); 7.33 7.6 s (2H, NH_2)

Spectral characteristics of compounds **IIIa–IIId** obtained are listed in Table 4.

Synthesis of R-substituted thiazoloaminooxazoles IVa–IVd. To a suspension of hydrazide **IIIa–IIId** (0.07 mol) and sodium hydrocarbonate (0.07 mol) in water (50 ml) at cooling by ice was dozed solution of brmocyane (0.07 mol) in ethanol. The reaction mixture was kept at 20–25°C for 6–12 h. Then for few hours it was cooled to 3–5°C and crystals dropped were filtered off, washed with water for removing sodium bromide, and dried. Compounds **IVa-IVd** were obtained in 65–80% yield.

Spectral characteristics of compounds **IVa–IVd** obtained are listed in Table 4.

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