

SHORT  
COMMUNICATIONS

## Synthesis of Some Oxa- and Thiazolidine-1,3-diones and Their Oxiranyl and Thiiranyl Derivatives

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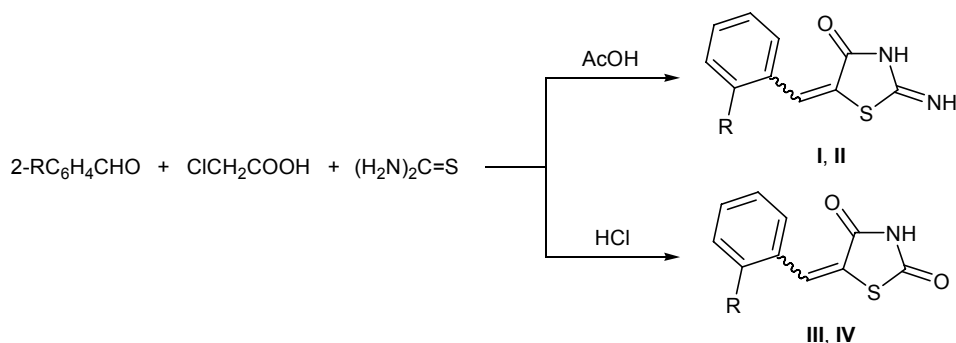
Azolidinediones and their various derivatives exhibit high physiological activity and are widely used in pharmacology [1]. In addition, they can be used as ligands for the synthesis of some transition metal complexes which catalyze formation of oxiranes from alkenes [2]. In continuation of our studies in the field of synthesis and application of azolidinediones, we synthesized thiazolidinediones by three-component condensations of various aldehydes or amines, chloroacetic acid, and thiourea or urea [3, 4].

The present communication reports on convenient methods for the preparation of substituted oxa- and

thiazolidine-1,3-diones from readily accessible starting compounds.

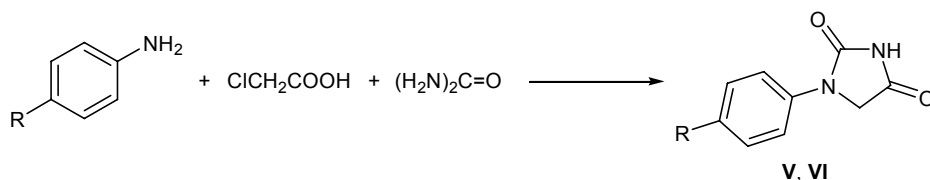
Thiazolidinediones were synthesized in one step by three-component condensation of aromatic aldehydes with chloroacetic acid and thiourea. The reaction performed in acetic acid gave 5-benzylidene-2-imino-1,3-thiazolidin-4-ones **I**, and **II**, while 5-benzylidene-1,3-thiazolidine-2,4-diones **III** and **IV** were obtained on heating in boiling hydrochloric acid (Scheme 1). The condensation of 4-chloro- or 4-bromoaniline with chloroacetic acid and urea at 120–130°C (reaction time 0.5 h) afforded 60–65% of 1-(4-halophenyl)imidazoli-

Scheme 1.



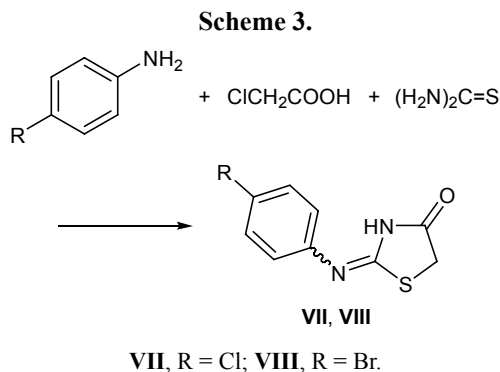
**I, III**, R = H; **II, IV**, R = HO.

Scheme 2.



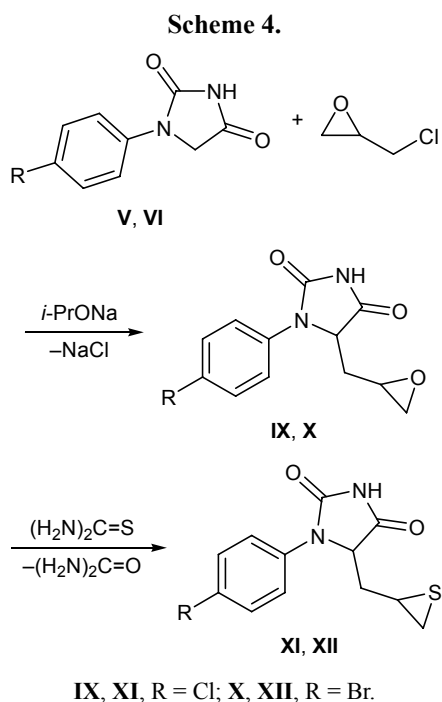
**V**, R = Cl; **VI**, R = Br.

dine-2,4-diones **V** and **VI** (Scheme 2). 4-Chloro- and 4-bromoanilines reacted with chloroacetic acid and thiourea under analogous conditions to form 2-(4-halophenylimino)-1,3-thiazolidin-4-ones **VII** and **VIII** (Scheme 3).



It is known that protons in the activated methylene group in the  $\alpha$ -position with respect to the carbonyl group in imidazolidine-2,4-dione can be replaced by the action of various nucleophiles [3]. By treatment of compounds **V** and **VI** with 2-chloromethylloxirane in the presence of sodium isopropoxide we obtained 1-(4-halophenyl)-5-(oxiran-2-ylmethyl)imidazolidine-2,4-diones **IX** and **X**, and the latter were converted into thiiranyl-substituted derivatives **XI** and **XII** by thioepoxidation with thiourea in alcohol (Scheme 4).

Azolidinediones **I–XII** were isolated as colorless crystalline substances. Their structure was confirmed



by IR and  $^1\text{H}$  NMR spectra and elemental analysis. The IR spectra of **I–XII** contained absorption bands at 3136 and 3048  $\text{cm}^{-1}$  due to stretching vibrations of the N–H bond in the CONHCO fragment, and stretching vibrations of the exocyclic double C=N bond in **I**, **II**, **VII**, and **VIII** gave rise to absorption at 1655  $\text{cm}^{-1}$ . The doublet band at 1520  $\text{cm}^{-1}$  in the IR spectra of **II–IV** may be assigned to bending vibrations of the imino group and probably endocyclic NH group. Unlike initial compounds **VII** and **VIII**, oxiranyl-substituted derivatives **IX** and **X** displayed in the IR spectra strong absorption bands at 825–865, 1115–1135, and 1225–1290  $\text{cm}^{-1}$ , belonging to antisymmetric and symmetric vibrations of the oxirane ring. The carbonyl group was characterized by a strong absorption band in the region 1720–1725  $\text{cm}^{-1}$ , and stretching vibrations of aromatic C=C bonds appeared at 1592–1464  $\text{cm}^{-1}$ .

The  $^1\text{H}$  NMR spectra of thiazolidinediones **VII** and **VIII** contained upfield signals at  $\delta$  4.4 ppm from protons in the methylene group. Aromatic protons resonated in the region  $\delta$  7.1–7.7 ppm, and a broadened downfield signal at  $\delta$  11.1–11.3 ppm was assigned to the NH proton. In the  $^{13}\text{C}$  NMR spectra of these compounds we observed 7 signals, two of which corresponded to  $sp^3$ -hybridized carbon atoms ( $\delta_{\text{C}}$  40 and 51 ppm,  $\text{CH}_2$ ). Three downfield signals at  $\delta_{\text{C}}$  118, 129, and 139 ppm belong to aromatic carbon atoms, and carbonyl carbon atoms resonated in the weakest field, at  $\delta_{\text{C}}$  155 and 171 ppm.

In the  $^1\text{H}$  NMR spectra of oxiranes **IX** and **X**, signals from protons in the methylene groups appeared as two doublets at  $\delta$  2.1–2.3 and 2.3–3.0 ppm (*cis* and *trans* isomers). The signal from the CH proton in the oxirane ring was located at  $\delta$  2.7–3.1 ppm. Carbon nuclei in the  $\text{CH}_2\text{CHCH}_2$  fragment were characterized by chemical shifts of  $\delta_{\text{C}}$  41.0, 41.5, 42.0, and 42.5 ppm in the  $^{13}\text{C}$  NMR spectra, aromatic carbon atoms resonated at  $\delta_{\text{C}}$  119.8, 120, and 122 ppm, and signals from the carbonyl carbon atoms were located most downfield ( $\delta_{\text{C}}$  179.5 ppm).

Thiirane derivatives **XI** and **XII** showed in the IR spectra a strong absorption band at 645–655  $\text{cm}^{-1}$ , which is typical of stretching vibrations of C–S bond in three-membered ring. In the  $^1\text{H}$  NMR spectra of **XI** and **XII**, signals from the methylene protons appeared as doublets at  $\delta$  1.8–2.2 and 2.1–1.8 ppm, i.e., in a stronger field relative to the corresponding signals of oxirane derivatives **IX** and **X**. This may be explained by lower electronegativity of sulfur atom as compared to oxygen.

**5-Benzylidene-2-imino-1,3-thiazolidin-4-one (I).**

A mixture of 32 g (0.4 mol) of thiourea, 9.5 g (0.1 mol) of chloroacetic acid, 10.6 g (0.1 mol) of benzaldehyde, and 30 ml of glacial acetic acid was heated for 4 h under reflux. The mixture was cooled and made alkaline by adding a solution of sodium carbonate, and the precipitate was filtered off, washed with water, and dried. Yield 80%, mp 248°C,  $R_f$  0.39. Found, %: C 58.93; H 3.81; N 13.65; S 15.82.  $C_{10}H_8N_2S$ . Calculated, %: C 58.80; H 3.95; N 13.72; S 15.70.

**5-(2-Hydroxybenzylidene)-2-imino-1,3-thiazolidin-4-one (II)** was synthesized in a similar way from salicylaldehyde. Yield 15.2 g (69%), mp 276°C,  $R_f$  0.63. Found, %: C 54.71; H 3.72; N 12.61; S 14.33.  $C_{10}H_8N_2O_2S$ . Calculated, %: C 54.63; H 3.66; N 13.72; S 14.56.

**5-Benzylidene-1,3-thiazolidine-2,4-dione (III).**

A mixture of 9.1 g (0.1 mol) of chloroacetic acid, 10.6 g of benzaldehyde, 32 g (0.4 mol) of thiourea, and 250 ml of 33% hydrochloric acid was heated under reflux. After cooling, the mixture was diluted with water, and the precipitate was filtered off, washed with water, and dried. Yield 13.5 g (60%), mp 233°C,  $R_f$  0.57. Found, %: C 58.34; H 3.59; N 6.93; S 15.46.  $C_{10}H_7NO_2S$ . Calculated, %: C 58.52; H 3.44; N 6.82; S 15.62.

**5-(2-Hydroxybenzylidene)-1,3-thiazolidine-2,4-dione (IV).** Yield 16.1 g (73%), mp 285°C,  $R_f$  0.45. Found, %: C 54.42; H 4.47; N 6.19; S 14.28.  $C_{10}H_7N_2O_3S$ . Calculated, %: C 54.29; H 3.19; N 6.33; S 14.49.

**1-(4-Chlorophenyl)imidazolidine-2,4-dione (V).**

A mixture of 5.6 g (0.1 mol) of urea, 9.5 g (0.1 mol) of chloroacetic acid, and 12.8 g (0.1 mol) of *p*-chloroaniline was heated at 120–130°C on an oil bath. After 1 h, exothermic reaction was over, and the mixture solidified. It was treated first with boiling water and then with boiling methanol and filtered. A colorless solid separated from the methanol filtrate on cooling. Yield 62%, mp 231°C,  $R_f$  0.36. Found, %: C 51.49; H 3.17; Cl 16.74; N 13.52.  $C_9H_7ClN_2O_2$ . Calculated, %: C 51.32; H 3.35; Cl 16.83; N 13.30.

**1-(4-Bromophenyl)imidazolidine-2,4-dione (VI)** was synthesized in a similar way. Yield 16.62 g (65%), mp 235°C,  $R_f$  0.58. Found, %: C 42.52; H 2.44; Br 31.12; N 10.63.  $C_9H_7BrN_2O_2$ . Calculated, %: C 42.38; H 2.77; Br 31.33; N 10.98.

**2-(4-Chlorophenylimino)-1,3-thiazolidin-4-one (VII).** A mixture of 7.6 g (0.1 mol) of thiourea, 9.5 g (0.1 mol) of chloroacetic acid, and 12.8 g (0.1 mol) of

4-chloroaniline was heated for 1 h at 120–130°C (oil bath). The mixture solidified and was treated with 18% hydrochloric acid on heating for 1 h under reflux. After cooling, the precipitate was filtered off and recrystallized from methanol. Yield 62%, mp 265°C,  $R_f$  0.42. Found, %: C 47.38; H 3.37; N 12.12; S 14.35.  $C_9H_7ClN_2O_2S$ . Calculated, %: C 47.69; H 3.11; N 12.36; S 14.14.

**2-(4-Bromophenylimino)-1,3-thiazolidin-4-one (VIII)** was synthesized in a similar way from 4-bromoaniline. Yield 18.6 g (73%), mp 279°C,  $R_f$  0.54. Found, %: C 39.62; H 2.87; Br 29.28; N 10.17.  $C_9H_7BrN_2OS$ . Calculated, %: C 39.87; H 2.60; Br 29.47; N 10.33.

**1-(4-Chlorophenyl)-5-(oxiran-2-ylmethyl)imidazolidine-3,5-dione (IX).** Metallic sodium, 4.6 g (0.2 mol), was added in small portions under stirring to 5 ml of isopropyl alcohol. The mixture was cooled, 42 g (0.2 mol) of compound V was added, the mixture was vigorously stirred at 70–75°C, and 18.7 g (0.2 mol) of 2-chloromethyloxirane was added dropwise over a period of 20 min. The mixture was heated for 3 h on a water bath, cooled, and filtered, and the solvent was distilled off under reduced pressure. Yield 70%, mp 172°C,  $R_f$  0.54. Found, %: C 54.26; H 4.06; Cl 13.48; N 10.37.  $C_{12}H_{11}ClN_2O_3S$ . Calculated, %: C 54.05; H 4.16; Cl 13.29; N 10.50.

**1-(4-Bromophenyl)-5-(oxyran-2-ylmethyl)imidazolidine-2,4-dione (X)** was synthesized in a similar way from compound VI. Yield 65%, mp 181°C,  $R_f$  0.62. Found, %: C 46.17; H 3.72; Br 25.41; N 9.13.  $C_{12}H_{11}BrN_2O_3$ . Calculated, %: C 46.32; H 3.56; Br 25.68; N 9.00.

**1-(4-Chlorophenyl)-5-(thiiran-2-ylmethyl)imidazolidine-2,4-dione (XI).** Thiourea, 7.6 g (0.1 mol), was added to a solution of 25 g (0.1 mol) of compound IX in 30 ml of ethanol, and the mixture was stirred at 60–70°C. When the initial oxirane derivative disappeared, the mixture was cooled, washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. Yield 72%, mp 199°C,  $R_f$  0.34. Found, %: C 51.12; H 3.85; N 9.82; S 11.45.  $C_{12}H_{11}ClN_2O_2S$ . Calculated, %: C 50.98; H 3.92; N 9.91; S 11.34.

**1-(4-Bromophenyl)-5-(thiiran-2-ylmethyl)imidazolidine-2,4-dione (XII)** was synthesized in a similar way from compound X. Yield 22.5 g (75%), mp 224°C,  $R_f$  0.47. Found, %: C 44.17; H 3.18; N 8.36; S 9.67.  $C_{12}H_{11}N_2O_2S$ . Calculated, %: C 44.05; H 3.39; N 8.56; S 9.80.

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker spectrometer (300 MHz). The IR spectra were measured on a Specord 75IR instrument from samples dispersed in mineral oil. Thin-layer chromatography was performed on Silufol UV-254 plates using isopropyl alcohol–hexane (3:5) as eluent.

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