LETTERS
TO THE EDITOR

Synthesis of 4-Aryl-2-hydroxy-4-oxo-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}but-2-enamides

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Abstract—The reaction of methyl aroylpyruvates with 2-(4-aminobenzenesulfamido)thiazole (norsulfazole) in glacial acetic acid in the presence of anhydrous sodium acetate furnished 4-aryl-2-hydroxy-4-oxo-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}but-2-enamides.

Keywords: 4-aryl-2-hydroxy-4-oxo-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}but-2-enamides, 2-(4-aminobenzene-sulfamido)thiazole, norsulfazole

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N-Substituted amides of 4-aryl-2-hydroxy-4-oxobut-2-enoic (aroylpyruvic) acids are polycarbonyl compounds having several reaction sites in their structure, which allows their application in a targeted synthesis of various organic compounds. In addition, compounds with hypoglycemic, antiviral, anticonvulsant, analgesic, anti-inflammatory, antimicrobial, and other activities have been found among amides of aroylpyruvic acids and their derivatives [1–6].

The reaction the most frequently used for the preparation of amides is the treatment of 5-aryl-2,3-dihydrofurane-2,3-dione with amines in anhydrous benzene, dioxane, toluene or other solvents [1, 7, 8], which has a number of drawbacks [9, 10]. We have developed a simple and more suitable method of the synthesis of *N*-arylamides of aroylpyruvic acids where it is not necessary to use anhydrous solvents and toxic reagents [10–12]. A distinctive feature of this method is the direct interaction of arylamines with methyl esters of aroylpyruvic acids.

In order to synthesize new derivatives of aroylpyruvic acids with potential biological activity it is of interest to obtain 4-aryl-2-hydroxy-4-oxobut-2-enoic acid *N*-arylamides containing the 2-(4-aminobenzene-sulfamido)thiazole moiety in the amide fragment, which is a component of the known sulfatiazole (norsulfazole) drug. Norsulfazole is one of the chemotherapeutic (antibacterial) drugs and is effective for the

treatment of infections caused by hemolytic streptococcus, pneumococcus, gonococcus, staphylococcus, and *E. coli* [13].

We found that the reaction of methyl aroylpyruvates with 2-(4-aminobenzenesulfamido)thiazole in glacial acetic acid in the presence of an equivalent amount of anhydrous sodium acetate under reflux afforded (2*Z*)-4-aryl-2-hydroxy-4-oxo-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}but-2-enamides **1–7** in good yields (65–93%) (Scheme 1).

Compounds **1–7** are colored crystalline substances soluble in DMF, DMSO, as well as in dioxane, acetonitrile, and acetic acid (with heating), and insoluble in water.

In the IR spectra of compounds **1–7** there were absorption bands of stretching vibrations of amino (3450–3200 cm^{−1}), hydroxyl (3216–3104 cm^{−1}), amide and ketone carbonyl groups (1704–1685, 1672–1616 cm^{−1}), as well as of SO₂ moiety (1360–1324, 1148–1140 cm^{−1}).

The ¹H NMR spectra of compounds **1–7** contained the signals of aromatic protons (6.87–8.08 ppm), methine proton (6.64–7.14 ppm), C⁵H and C⁴H protons of the thiazole ring (6.36–6.77 and 6.85–7.19 ppm, respectively, *J*_{5,4} = 4.60–4.64 Hz), CONH (10.25–10.81 ppm) and SO₂NH groups (12.70–12.73 ppm). The proton signals from other groups were observed in the expected areas.

Scheme 1.

R = 4-Cl (**1**), 3,4-(MeO)₂ (**2**), 4-Me (**3**), 3-MeO (**4**), 4-MeO (**5**), H (**6**), 4-F (**7**).

According to ¹H NMR data compounds **1–7** exist in two tautomeric forms **A** and **B**. Thus, in the ¹H NMR spectra of compounds **1–5** a weak signal appeared at 4.53–4.59 ppm characteristic of the β-methylene group of the diketone form. According to the ratio of the values of the integral intensity of the signals of β-methylene group and CH= proton enol **A** (≈90%) is the predominate form, which exists as *Z*-isomer. Compounds **6** and **7** in the DMSO-*d*₆ solution are completely enolized and contain 100% of the enol form **A**. The absence of the proton signal of the enol hydroxy group in the ¹H NMR spectra is apparently due to its considerable broadening as a result of exchange processes [10–12, 14]. All compounds obtained give an intense cherry color at adding an alcohol solution of ferric chloride.

The exclusive formation of 4-aryl-2-hydroxy-4-oxobut-2-enoic acid amides seems to be caused by the fact that sodium acetate directly added to the reaction

mixture [10–12] or formed during the reaction course (in the case of sodium sulfacetamide) [14] enters into an exchange reaction with aroylpyruvic acid ester to form a sodium derivative. In the latter, carbonyl group in the α-position is deactivated, therefore an attack of the ester carbonyl moiety by the primary amino group of arylamine is probable (Scheme 2).

It was of interest to study the way in which the sodium acetate formed during the reaction course affects the reaction of methyl esters of aroylpyruvic acids with 2-(4-aminobenzenesulfamido)thiazole (norsulfazole). For this purpose, compound **1** was prepared in three ways using the above method (*a*), and without the addition of sodium acetate. The reaction was carried out in glacial acetic acid using sodium norsulfazole (method *b*) or sodium salt of methyl 4-chlorobenzoylpyruvate (method *c*) (see below). The obtained data indicated that the method *a* is somewhat more effective, which is apparently due to more accurate amount of sodium cation in the reaction medium when it is added as acetate.

Scheme 2.

(2*Z*)-2-Hydroxy-4-oxo-*N*-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-4-(4-chlorophenyl)but-2-eneamide (1**).**

a. A solution of 2.40 g (0.01 mol) of methyl 4-chlorobenzoylpyruvate and 0.82 g (0.01 mol) of anhydrous sodium acetate in 10 mL of glacial acetic acid was added to a solution of 2.55 g (0.01 mol) of 2-(4-aminobenzenesulfamido)thiazole in 15 mL of glacial acetic acid. The reaction mixture was refluxed for 20 min. After cooling the precipitate was filtered off and recrystallized from acetic acid–dioxane (1 : 1). Yield 4.17 g (90%), mp 211–213°C (AcOH–dioxane,

1 : 1). IR spectrum, ν , cm^{-1} : 3360 (NH), 3130 (OH), 1696 (CONH), 1660 (C=O), 1360, 1148 (SO_2). ^1H NMR spectrum, δ , ppm: 4.59 s (2H, COCH_2CO), 6.77 d (1H, $\text{C}^5\text{H}_{\text{thiazole}}$, $J = 4.6$ Hz), 7.14 s (1H, CH=), 7.19 d (1H, $\text{C}^4\text{H}_{\text{thiazole}}$, $J = 4.6$ Hz), 7.46–8.04 m (8H, CH_{Ar}), 10.81 s (1H, CONH), 12.71 br.s (1H, SO_2NH). Mass spectrum, m/z : 463 $[\text{M}]^+$. Found, %: C 49.04; H 3.08; N 8.97; S 13.92. $\text{C}_{19}\text{H}_{14}\text{ClN}_3\text{O}_5\text{S}_2$. Calculated, %: C 49.19; H 3.04; N 9.06; S 13.82.

b. A solution of 2.40 g (0.01 mol) of methyl 4-chlorobenzoylpyruvate in 10 mL glacial acetic acid was added to a solution of 3.85 g (0.01 mol) of 2-(4-aminobenzenesulfamido)thiazole sodium hexahydrate in 20 mL of glacial acetic acid. The reaction mixture was refluxed for 20 min. After cooling the precipitate was filtered off and recrystallized from acetic acid–dioxane (1 : 1). Yield 3.61 g (78%), mp 210–212°C (AcOH–dioxane, 1:1). Found, %: C 49.29; H 3.10; N 9.14; S 13.71. $\text{C}_{19}\text{H}_{14}\text{ClN}_3\text{O}_5\text{S}_2$. Calculated, %: C 49.19; H 3.04; N 9.06; S 13.82.

c. A solution of 2.62 g (0.01 mol) of sodium methyl 4-chlorobenzoylpyruvate in 15 mL of glacial acetic acid was added to a solution of 2.55 g (0.01 mol) of 2-(4-aminobenzenesulfamido)thiazole in 15 mL of glacial acetic acid. The reaction mixture was refluxed for 20 min. After cooling the precipitate was filtered off and recrystallized from acetic acid–dioxane (1 : 1). Yield 3.01 g (65%), mp 210–212°C (AcOH–dioxane, 1 : 1). Found, %: C 49.06; H 3.09; N 9.00; S 13.75. $\text{C}_{19}\text{H}_{14}\text{ClN}_3\text{O}_5\text{S}_2$. Calculated, %: C 49.19; H 3.04; N 9.06; S 13.82.

Compounds **2–7** were obtained similarly according to procedure *a*.

(2Z)-2-Hydroxy-4-(3,4-dimethoxyphenyl)-4-oxo-N-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}but-2-enamide (2). Yield 3.86 g (79%), mp 147–149°C (AcOH–dioxane, 1 : 1). IR spectrum, ν , cm^{-1} : 3328, 3232 (NH), 3104 (OH), 1700 (CONH), 1672 (C=O), 1360, 1144 (SO_2). ^1H NMR spectrum, δ , ppm: 3.87 s (6H, 2MeO), 4.53 s (2H, COCH_2CO), 6.61 d (1H, $\text{C}^5\text{H}_{\text{thiazole}}$, $J = 4.6$ Hz), 6.97 s (1H, CH=), 7.01 d (1H, $\text{C}^4\text{H}_{\text{thiazole}}$, $J = 4.6$ Hz), 7.01–7.97 m (7H, CH_{Ar}), 10.56 s (1H, CONH), 12.70 br.s (1H, SO_2NH). Found, %: C 51.40; H 3.95; N 8.52; S 13.02. $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_7\text{S}_2$. Calculated, %: C 51.52; H 3.91; N 8.58; S 13.10.

(2Z)-2-Hydroxy-4-(4-methylphenyl)-4-oxo-N-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}but-2-enamide (3). Yield 4.12 g (93%), mp 210–212°C (AcOH–

dioxane, 1 : 1). IR spectrum, ν , cm^{-1} : 3352, 3232 (NH), 3104 (OH), 1696 (CONH), 1660 (C=O), 1348, 1148 (SO_2). ^1H NMR spectrum, δ , ppm: 2.36 s (3H, Me), 4.56 s (2H, COCH_2CO), 6.76 d (1H, $\text{C}^5\text{H}_{\text{thiazole}}$, $J = 4.6$ Hz), 7.10 s (1H, CH=), 7.14 d (1H, $\text{C}^4\text{H}_{\text{thiazole}}$, $J = 4.6$ Hz), 7.19–8.08 m (8H, CH_{Ar}), 10.78 s (1H, CONH), 12.70 br.s (1H, SO_2NH). Found, %: C 54.07; H 3.81; N 9.56; S 14.36. $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_5\text{S}_2$. Calculated, %: C 54.16; H 3.86; N 9.47; S 14.46.

(2Z)-2-Hydroxy-4-(3-methoxyphenyl)-4-oxo-N-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}but-2-enamide (4). Yield 3.67 g (80%), mp 174–176°C (AcOH–dioxane, 1:1). IR spectrum, ν , cm^{-1} : 3352, 3200 (NH), 3180 (OH), 1696 (CONH), 1668 (C=O), 1324, 1144 (SO_2). ^1H NMR spectrum, δ , ppm: 3.79 s (3H, MeO), 4.58 s (2H, COCH_2CO), 6.75 d (1H, $\text{C}^5\text{H}_{\text{thiazole}}$, $J = 4.6$ Hz), 7.06 s (1H, CH=), 7.18 d (1H, $\text{C}^4\text{H}_{\text{thiazole}}$, $J = 4.6$ Hz), 7.24–7.92 m (8H, CH_{Ar}), 10.77 s (1H, CONH), 12.73 br.s (1H, SO_2NH). Found, %: C 52.40; H 3.76; N 9.08; S 13.87. $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_6\text{S}_2$. Calculated, %: C 52.28; H 3.73; N 9.14; S 13.96.

(2Z)-2-Hydroxy-4-(4-methoxyphenyl)-4-oxo-N-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}but-2-enamide (5). Yield 3.44 g (75%), mp 208–210°C (AcOH). IR spectrum, ν , cm^{-1} : 3380 (NH), 3110 (OH), 1704 (CONH), 1664 (C=O), 1352, 1144 (SO_2). ^1H NMR spectrum, δ , ppm: 3.82 s (3H, MeO), 4.54 s (2H, COCH_2CO), 6.76 d (1H, $\text{C}^5\text{H}_{\text{thiazole}}$, $J = 4.6$ Hz), 7.07 s (1H, CH=), 7.14 d (1H, $\text{C}^4\text{H}_{\text{thiazole}}$, $J = 4.6$ Hz), 6.87–8.02 m (8H, CH_{Ar}), 10.77 s (1H, CONH), 12.70 br.s (1H, SO_2NH). Found, %: C 52.18; H 3.68; N 9.22; S 14.00. $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_6\text{S}_2$. Calculated, %: C 52.28; H 3.73; N 9.14; S 13.96.

(2Z)-2-Hydroxy-4-oxo-N-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-4-phenylbut-2-enamide (6). Yield 3.17 g (74%), mp 258°C (decomp.) (AcOH). IR spectrum, ν , cm^{-1} : 3450 (NH), 3216 (OH), 1685 (CONH), 1616 (C=O), 1328, 1140 (SO_2). ^1H NMR spectrum, δ , ppm: 6.64 s (1H, CH=), 6.69 d (1H, $\text{C}^5\text{H}_{\text{thiazole}}$, $J = 4.6$ Hz), 7.09 d (1H, $\text{C}^4\text{H}_{\text{thiazole}}$, $J = 4.6$ Hz), 7.37–7.92 m (9H, CH_{Ar}), 10.32 s (1H, CONH), 12.70 br.s (1H, SO_2NH). Found, %: C 53.27; H 3.49; N 9.84; S 15.02. $\text{C}_{19}\text{H}_{15}\text{N}_3\text{O}_5\text{S}_2$. Calculated, %: C 53.14; H 3.52; N 9.78; S 14.93.

(2Z)-2-Hydroxy-4-oxo-N-{4-[(1,3-thiazol-2-yl)sulfamoyl]phenyl}-4-(4-fluorophenyl)but-2-enamide (7). Yield 3.98 g (89%), mp 274°C (decomp.) (AcOH–dioxane, 1 : 1). IR spectrum, ν , cm^{-1} : 3328 (NH), 3145 (OH), 1685 (CONH), 1648 (C=O), 1344, 1144 (SO_2).

^1H NMR spectrum, δ , ppm: 6.36 d (1H, $\text{C}^5\text{H}_{\text{thiazole}}$, $J = 4.6$ Hz), 6.82 s (1H, CH=), 6.85 d (1H, $\text{C}^4\text{H}_{\text{thiazole}}$, $J = 4.6$ Hz), 6.95–7.92 m (8H, CH_{Ar}), 10.25 s (1H, CONH), 12.71 br.s (1H, SO_2NH). Found, %: C 50.88; H 3.10; N 9.46; S 14.23. $\text{C}_{19}\text{H}_{14}\text{FN}_3\text{O}_5\text{S}_2$. Calculated, %: C 51.00; H 3.15; N 9.39; S 14.33.

^1H NMR spectra were registered on a Bruker AM-300 spectrometer (300 MHz) in $\text{DMSO}-d_6$, internal reference TMS. IR spectra were recorded on a Specord M-80 spectrometer from KBr pellets. Mass spectra (ESI+) were obtained on a Waters ACQUITY UPLC I-Class spectrometer with Xevo TQD detector. Elemental analysis was performed using a Perkin Elmer 2400 analyzer. Melting points were determined on a Melting Point M-565 apparatus.

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