ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 2, pp. 264–267. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © V.L. Gein, I.V. Kovtonogova, O.V. Bobrovskaya, M.I. Vakhrin, 2014, published in Zhurnal Obshchei Khimii, 2014, Vol. 84, No. 2, pp. 271–274.

Synthesis of 5-Aryl-4-aroyl-3-hydroxy-1-(4-guanidylsulfonylphenyl)-3-pyrrolin-2-ones

V. L. Gein, I. V. Kovtonogova, O. V. Bobrovskaya, and M. I. Vakhrin[†]

Perm State Pharmaceutical Academy, ul. Polevaya 2, Perm, 614990 Russia
e-mail: geinvl48@mail.ru

Received March 25, 2013

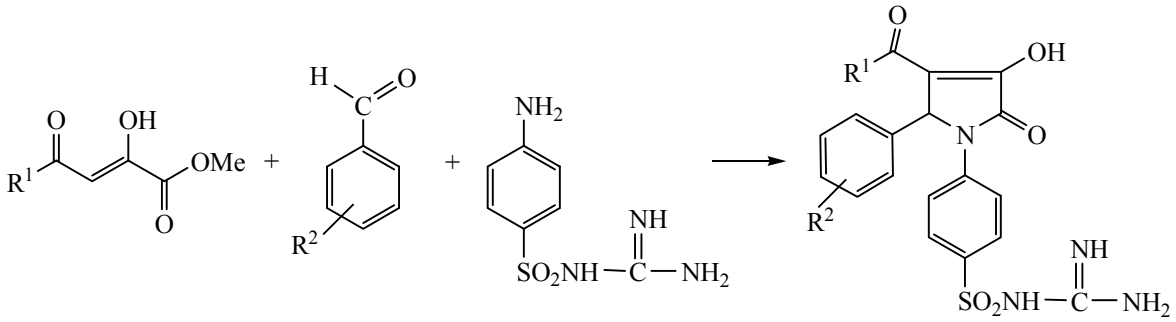
Abstract—Three-component reaction of methyl aroylpyruvate with aromatic aldehyde and 4-aminobenzenesulfonylguanidine resulted in 5-aryl-4-aroyl-3-hydroxy-1-(4-guanidylsulfonylphenyl)-3-pyrrolin-2-ones.

DOI: 10.1134/S1070363214020170

The substituted 3-hydroxy-3-pyrrolin-2-ones and their derivatives are of interest as substances possessing a broad spectrum of biological activity [1].

Three-component reaction of acylpyruvates with a mixture of an aromatic aldehyde and an amine is the most frequently used method for the synthesis of substituted 3-hydroxy-3-pyrrolin-2-ones [2]. Aiming to create new functionally substituted pyrrolidine-2,3-diones we first introduced 4-aminobenzenesulfonylguanidine (sulgin) into the reaction with methyl aroylpyruvate and aromatic aldehyde. The choice of 4-aminobenzenesulfonylguanidine as an amine component was due to the fact that it contains two nucleophilic groups and is used as a drug for treating intestinal infections [3].

Three-component reaction was performed by refluxing equimolar amounts of the starting reactants for 3–5 min in glacial acetic acid to give 5-aryl-4-aroyl-3-hydroxy-1-(4-guanidylsulfonylphenyl)-3-pyrrolin-2-ones **I–VIII**.



I–VIII

$R^1 = C_6H_5$, $R^2 = H$ (**I**); $R^1 = C_6H_5$, $R^2 = 4\text{-Br}$ (**II**); $R^1 = C_6H_5$, $R^2 = 4\text{-Cl}$ (**III**); $R^1 = 4\text{-}CH_3C_6H_4$, $R^2 = 4\text{-OH}$ (**IV**); $R^1 = 4\text{-}CH_3C_6H_4$, $R^2 = 4\text{-}(CH_3)_2CH$ (**V**); $R^1 = 4\text{-}ClC_6H_4$, $R^2 = 2\text{-F}$ (**VI**); $R^1 = 4\text{-}ClC_6H_4$, $R^2 = 4\text{-}NO_2$ (**VII**); $R^1 = 4\text{-}ClC_6H_4$, $R^2 = 3\text{-F}$ (**VIII**).

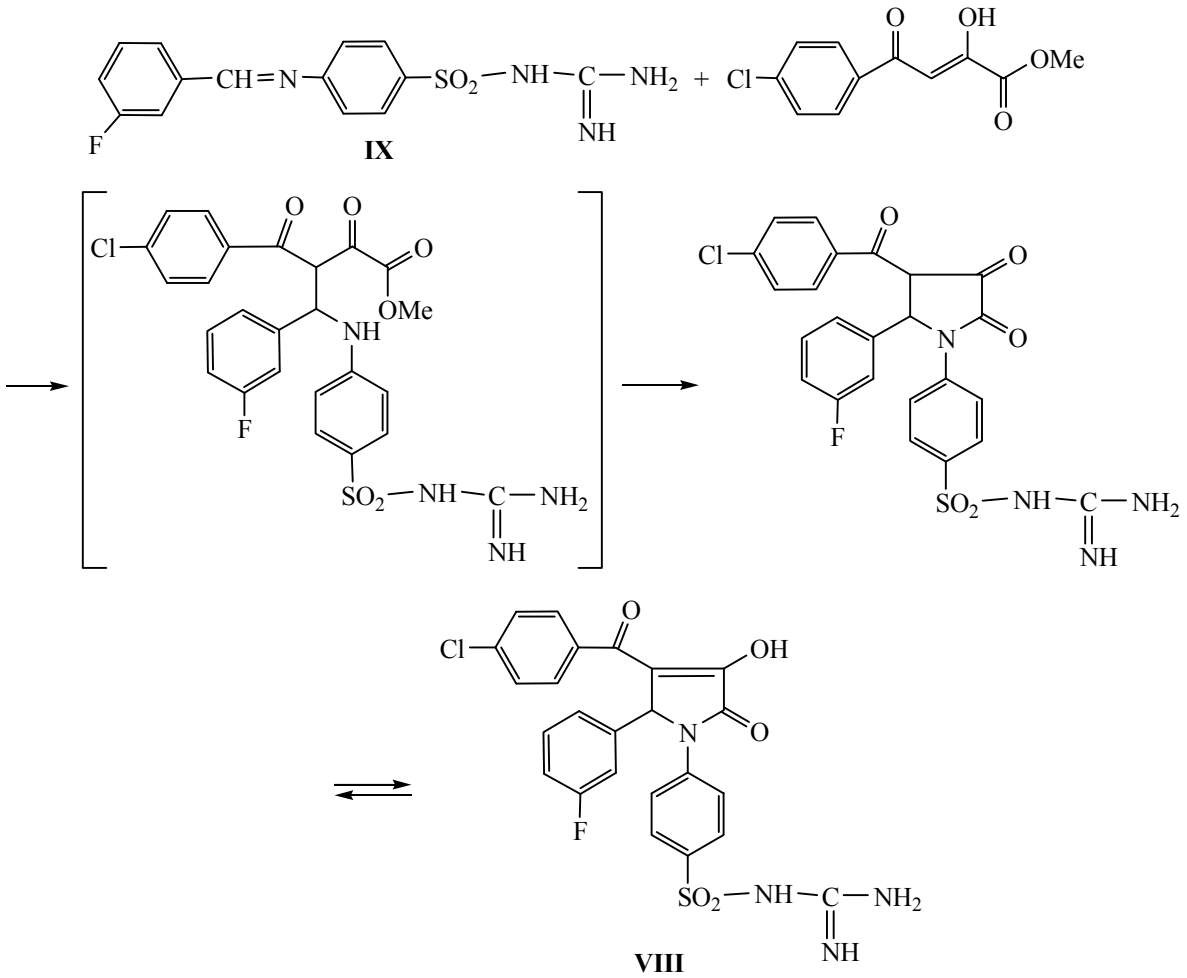
Compounds **I–VIII** are crystalline substances soluble in DMF, DMSO, in ethanol and acetic acid at heating, and insoluble in water.

Along with the signals of aromatic protons, the ^1H NMR spectra of compounds **I–VIII** contained the proton singlet signals of C^5H (6.12–6.46 ppm), NHC (=NH)NH_2 (6.55–6.64 ppm), and OH group in position 3 of the ring (11.00–12.18 ppm).

The absence of the proton signal of enolized carbonyl group in position 3 of the heterocycle in the spectra of some compounds is caused by its strong broadening due to intensive proton exchange [2].

[†] Deceased.

Scheme 1.



The IR spectra of compounds **I**–**VIII** contained the absorption bands of stretching vibrations of NH and NH_2 (3448–3280 cm^{-1}), hydroxyl (3208–3136 cm^{-1}), lactam carbonyl (1696–1680 cm^{-1}), ketone (1636–1624 cm^{-1}) and SO_2 groups (1392–1365, 1144–1135 cm^{-1}).

In order to establish the proposed mechanism of the reaction Schiff base **IX** was obtained by reacting 3-fluorobenzaldehyde with sulgin and its interaction with methyl 4-chlorobenzoylpyruvate was studied (see Scheme 1).

The result of this reaction indicates that the formation of compounds **I**–**VIII** proceeds apparently via the intermediate formation of Schiff bases, which react with the starting ester followed by cyclization of the intermediate ester of 4-amino-2-oxobutanoic acid into the corresponding pyrrolidine-2,3-dione.

Therefore the spectral data and the reaction with Schiff base allow a conclusion that a primary aromatic amine group is the most reactive nucleophilic center in sulgin. The basicity and nucleophilicity of amino group in the guanidine moiety is reduced apparently due to the nature of the electron-withdrawing effect of sulfo group.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were registered on a Bruker AM- 300 spectrometer (300 and 75 MHz, respectively) in DMSO-d_6 relative to internal TMS. IR spectra were obtained on a Specord M-80 instrument for the samples in paraffin oil. Elemental analysis was performed on a Perkin Elmer 2400 instrument. Melting points were measured on Melting Point 565-M instrument.

4-Benzoyl-3-hydroxy-1-(4-guanidylsulfonylphenyl)-5-phenyl-3-pyrrolin-2-one (I). A mixture of equimolar amounts of benzaldehyde and 4-aminobenzenesulfonylguanidine in 10 mL of glacial acetic acid was

added to a solution of 0.01 mol of methyl benzoylpyruvate in 10 mL of glacial acetic acid. The reaction mixture was refluxed for 3–5 min. After cooling, the precipitate formed was treated with ethanol, filtered off and recrystallized from glacial acetic acid. Yield 3.43 g (72%), mp 298–300°C. IR spectrum, ν, cm^{-1}: 3376, 3344, 3280 [NHC(=NH)NH_2], 3152 (OH), 1692 (CON), 1628 (C=O), 1388, 1144 (SO_2). ^1H NMR spectrum, δ, ppm: 6.34 s (1H, C^5H), 6.64 s [4H, NHC(=NH)NH_2], 7.06–7.64 m (14H, CH_{Ar}), 11.72 br.s (1H, OH). Found, %: C 60.60, 60.38; H 4.15, 4.31; N 11.66, 11.86; S 6.64, 6.82. $C_{24}H_{20}N_4O_5S$. Calculated, %: C 60.49; H 4.23; N 11.76; S 6.73.

4-Benzoyl-5-(4-bromophenyl)-3-hydroxy-1-(4-guanidylsulfonylphenyl)-3-pyrrolin-2-one (II) was prepared similarly. Yield 3.66 g (66%), mp 244–246°C. IR spectrum, ν, cm^{-1}: 3416, 3288 [NHC(=NH)NH_2], 3192 (OH), 1692 (CON), 1628 (C=O), 1384, 1144 (SO_2). ^1H NMR spectrum, δ, ppm: 6.26 s (1H, C^5H), 6.56 s [4H, NHC(=NH)NH_2], 7.28–7.60 m (13H, CH_{Ar}). Found, %: C 52.01, 51.79; H 3.38, 3.52; N 10.00, 10.18; S 5.69, 5.85. $C_{24}H_{19}BrN_4O_5S$. Calculated, %: C 51.90; H 3.45; N 10.09; S 5.77.

4-Benzoyl-3-hydroxy-1-(4-guanidylsulfonylphenyl)-5-(4-chlorophenyl)-3-pyrrolin-2-one (III) was prepared similarly. Yield 3.83 g (75%), mp 255–257°C. IR spectrum, ν, cm^{-1}: 3416, 3344 [NHC(=NH)NH_2], 3200 (OH), 1696 (CON), 1632 (C=O), 1380, 1144 (SO_2). ^1H NMR spectrum, δ, ppm: 6.29 s (1H, C^5H), 6.57 s [4H, NHC(=NH)NH_2], 7.09–7.72 m (13H, CH_{Ar}). Found, %: C 56.29, 56.56; H 3.69, 3.83; N 10.87, 11.06; S 6.20, 6.37. $C_{24}H_{19}ClN_4O_5S$. Calculated, %: C 56.42; H 3.75; N 10.97; S 6.28.

3-Hydroxy-5-(4-hydroxyphenyl)-1-(4-guanidylsulfonylphenyl)-4-(4-methylbenzoyl)-3-pyrrolin-2-one (IV) was prepared similarly. Yield 3.45 g (68%), mp 262–264°C. IR spectrum, ν, cm^{-1}: 3448, 3344 [NHC(=NH)NH_2], 3176 (OH), 1692 (CON), 1628 (C=O), 1388, 1144 (SO_2). ^1H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 6.12 s (1H, C^5H), 6.56 s [4H, NHC(=NH)NH_2], 7.02–7.59 m (12H, CH_{Ar}), 9.12 s (1H, OH, phenol), 11.1 br.s (1H, OH, enol). Found, %: C 59.12, 59.40; H 4.30, 4.45; N 10.95, 11.16; S 6.24, 6.41. $C_{25}H_{22}N_4O_6S$. Calculated, %: C 59.28; H 4.38; N 11.06; S 6.33.

3-Hydroxy-1-(4-guanidylsulfonylphenyl)-5-(4-isopropylphenyl)-4-(4-methylbenzoyl)-3-pyrrolin-2-one (V) was prepared similarly. Yield 3.78 g (71%), mp 255–257°C. IR spectrum, ν, cm^{-1}: 3420, 3340 [NHC(=NH)NH_2], 3180 (OH), 1680 (CON), 1624 (C=O), 1365, 1135 (SO_2). ^1H NMR spectrum, δ, ppm: 1.10, 1.05 d [6H, $(C\underline{H}_3)_2CH$, *J* 5.57 Hz], 2.33 s (3H, 4-$C\underline{H}_3C_6H_4CO$), 2.58–2.90 m [1H, $(CH_3)_2C\underline{H}$], 6.21 s (1H, C^5H), 6.56 s [4H, NHC(=NH)NH_2], 6.93–7.63 m (12H, CH_{Ar}), 11.00 br.s (1H, OH). Found, %: C 63.02, 63.27; H 5.23, 5.38; N 10.43, 10.64; S 5.94, 6.11. $C_{28}H_{28}N_4O_5S$. Calculated, %: C 63.14; H 5.30; N 10.52; S 6.02.

3-Hydroxy-1-(4-guanidylsulfonyl)-5-(2-fluorophenyl)-4-(4-chlorobenzoyl)-3-pyrrolin-2-one (VI) was obtained similarly. Yield 4.23 g (80%), mp 273–275°C. IR spectrum, ν, cm^{-1}: 3424, 3336 [NHC(=NH)NH_2], 3192 (OH), 1692 (CON), 1636 (C=O), 1384, 1144 (SO_2). ^1H NMR spectrum, δ, ppm: 6.43 s (1H, C^5H), 6.58 s [4H, NHC(=NH)NH_2], 6.78–7.86 m (12H, CH_{Ar}), 11.80 br.s (1H, OH). Found, %: C 54.37, 54.62; H 3.37, 3.50; N 10.50, 10.70; S 5.98, 6.15. $C_{24}H_{18}ClFN_4O_5S$. Calculated, %: C 54.50; H 3.43; N 10.59; S 6.06.

3-Hydroxy-1-(4-guanidylsulfonylphenyl)-5-(4-nitrophenyl)-4-(4-chlorobenzoyl)-3-pyrrolin-2-one (VII) was obtained similarly. Yield 4.34 g (78%), mp 244–246°C. IR spectrum, ν, cm^{-1}: 3416, 3376 [NHC(=NH)NH_2], 3208 (OH), 1696 (CON), 1632 (C=O), 1376, 1144 (SO_2). ^1H NMR spectrum, δ, ppm: 6.46 s (1H, C^5H), 6.59 s [4H, NHC(=NH)NH_2], 7.34–8.00 m (12H, CH_{Ar}), 12.1 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 60.18 (C^5H), 119.13, 121.88, 123.64, 126.46, 128.44, 129.32, 130.71, 136.58, 137.73, 138.34, 141.25, 144.24, 147.37, 151.28 (=C–OH), 158.15 [NHC(=NH)NH_2], 164.87 (N–C=O), 187.89 (C=O). Found, %: C 51.74, 51.95; H 3.19, 3.31; N 12.51, 12.7; S 5.69, 5.85. $C_{24}H_{18}ClN_5O_7S$. Calculated, %: C 51.85; H 3.26; N 12.60; S 5.77.

3-Hydroxy-1-(4-guanidylsulfonylphenyl)-5-(3-fluorophenyl)-4-(4-chlorobenzoyl)-3-pyrrolin-2-one (VIII) was prepared similarly. *a*. Yield 4.07 g (77%), mp 279–281°C. IR spectrum, ν, cm^{-1}: 3432, 3344 [NHC(=NH)NH_2], 3136 (OH), 1692 (CON), 1632 (C=O), 1392, 1144 (SO_2). ^1H NMR spectrum, δ, ppm: 6.28 s (1H, C^5H), 6.55 s [4H, NHC(=NH)NH_2], 6.81–7.68 m (12H, CH_{Ar}). Found, %: C 54.39, 54.61; H 3.35, 3.50; N 10.49, 10.68; S 5.99, 6.13. $C_{24}H_{18}ClFN_4O_5S$. Calculated, %: C 54.50; H 3.43; N 10.59; S 6.06.

b. A solution of equimolar amount of methyl 4-chlorobenzoylpyruvate in 10 mL of glacial acetic acid was added to a solution of 0.01 mol of Schiff base **IX**

in 10 mL of glacial acetic acid. The reaction mixture was refluxed for 3–5 min. After cooling, the precipitate was treated with ethanol, filtered off, and recrystallized from glacial acetic acid. Yield 3.23 g (61%), mp 279–281°C. Mixing test showed no melting point depression.

4-(3-Fluorophenylmethyleneamino)benzenesulfonylguanidine (IX). An equimolar amount of 3-fluorobenzaldehyde was added to 0.01 mol of 4-aminobenzenesulfonylguanidine dissolved under heating in 10 mL of glacial acetic acid. The reaction mixture was heated for 2 min. After cooling, the precipitate was filtered off and recrystallized from glacial acetic acid. Yield 2.53 g (79%), mp 220–222°C. IR spectrum, ν, cm^{-1}: 3432, 3328, 3250 [NHC(=NH)NH_2], 1632 (C=N), 1376, 1136 (SO_2). ^{1}H NMR spectrum, δ, ppm: 6.41 s (1H, =NH), 6.49 s (1H, SO_2NH), 6.59 s (2H, NH_2), 7.17–7.74 m (8H, CH_{Ar}), 8.51 s (1H, CH=N). Found, %: C 52.38, 52.60; H 4.04, 4.16; N 17.39, 17.58; S 9.92, 10.09. $C_{14}H_{13}FN_4O_2S$. Calculated, %: C 52.49; H 4.09; N 17.49, S 10.01.

REFERENCES

1. Gein, V.L., *Tetragidropirrol- i tetragidrofuran-2,3-diones* (Tetrahydropyrrole- and Tetrahydrofurane-2,3-diones), Perm: PGFA, 2004.
2. Andreichikov, Yu.S., Gein, V.L., and Anikina, I.N., *Zh. Org. Khim*., 1986, vol. 22, no. 8, p. 1749.
3. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: RIA "Novaya Volna," 2012.