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CYCLIZATION OF CHALCONES TO ISOXAZOLE AND PYRAZOLE DERIVATIVES

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A series of pyrazole and isoxazole derivatives were obtained by the condensation of the chalcones with hydrazine, phenylhydrazine, and hydroxylamine. All compounds were characterized using NMR, IR, and MS techniques.

Keywords: β-alanines, chalcones, isoxazoles, pyrazoles, pyrazolines.

Chalcones are convenient intermediate compounds for the synthesis of five-, six-, and seven-membered heterocycles often exhibiting biological activity. Pyrazole and isoxazole derivatives constitute an interesting class of heterocycles due to their synthetic versatility and effective biological activities. Isoxazole derivatives represent a unique class of nitrogen- and oxygen-containing five-membered heterocycles, and they are associated with a wide spectrum of biological effects such as antiviral [1], anthelmintic [2], anti-inflammatory [3], anticonvulsant [4], anticancer [5], etc. Pyrazolines display various biological activities such as antimicrobial [6], antifungal [7], antidepressant [8], immunosuppressive [9], anticonvulsant [10], antitumor [11], antiamoebic [12], antibacterial [13], and anti-inflammatory [14]. β-Aminopropionic acid (β-alanine) is the simplest β-amino acid. It is the most important component of numerous biologically active compounds such as vitamin B_5 (pantothenic acid), penicillins, cephalosporins, and peptides [15]. The synthetic N-substituted β-alanines are growth stimulators for agricultural crops [16-18]. It is probable that the new compounds containing fragments of the above-mentioned compounds exhibit biological activity themselves.

We continue our study of the chemistry of N-substituted amino acids and their derivatives. The starting compounds **1-3** were synthesized by condensation of N-(4-acetylphenyl)-β-alanine with aromatic aldehydes [19]. In this work, heating chalcones **1** and **2** under reflux with hydroxylamine in ethanol in the presence of sodium ethoxide gave disubstituted dihydroisoxazoles **5** and **6**. Under different conditions, when pyridine was used as a base, we succeeded in synthesizing isoxazole derivative **7**.

In the IR spectrum of compound **7**, the absorption band of the C=N group appeared at 1563 cm^{-1}. The ^1H NMR spectrum for compound **6** showed proton signals of the isoxazoline moiety as an ABX type spin system, and the proton signals were observed as double doublets due to the spin coupling. The signal of heterocyclic proton in compound **7** was observed at 7.02 ppm.

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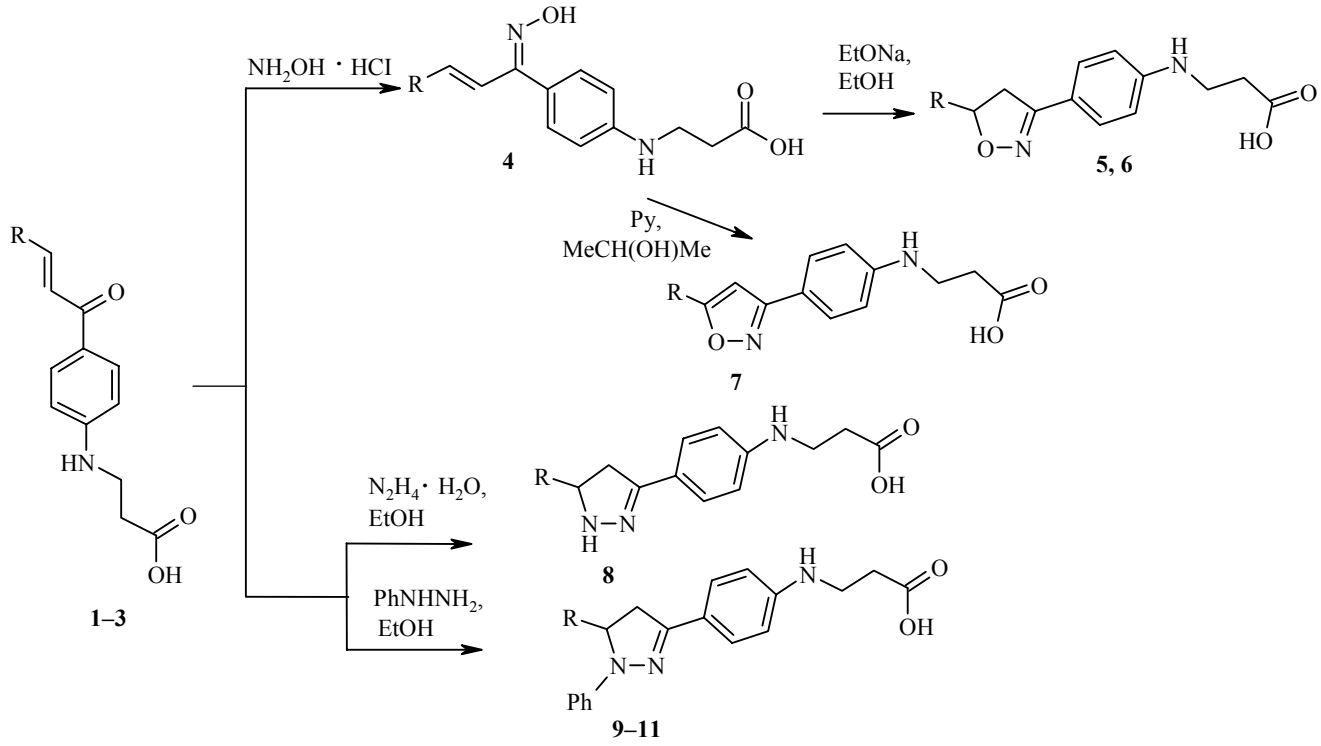

1, 5, 10 R = Ph; **2, 6-9** R = 4-$MeOC_6H_4$; **3, 11** R = 4-ClC_6H_4

One of the most convenient methods for the synthesis of pyrazolines is the reaction of α,β-unsaturated ketones or aldehydes with hydrazine hydrate and its derivatives [20]. In this work, condensation of N-(styrylcarbonylphenyl)-β-alanines **1-3** with hydrazine hydrate and phenylhydrazine was carried out in alcohol under reflux. It was noticed that in the reaction with hydrazine hydrate pyrazoline ring **8** was formed already after 4 h, while the reaction with phenylhydrazine lasted for 12-20 h. When ethanol was used as a solvent in this reaction the yield of pyrazolines **9-11** was lower (30-61%), but they were more pure, and there was no need to purify them by column chromatography.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Varian Unity Inova 300 spectrometer (300 and 75 MHz respectively) in DMSO-d_6 operating in the Fourier transform mode with TMS as an internal standard. Melting points were determined on an automatic melting point apparatus APA1 and are uncorrected. The IR spectra were determined in potassium bromide pellets on a Perkin-Elmer FT-IR system spectrum GX spectrometer. Mass spectra were obtained on a Waters (Micromas) ZQ 2000 spectrometer, APCI, 20 V. Silica gel plates (Silufol UV-254) were used for analytical purposes. Elemental analysis was carried out on the CHN analyzer CE 440.

3-[4-(5-Aryl-4,5-dihydroisoxazol-3-yl)phenylamino]propanoic Acids 5, 6. (General Method). To a freshly prepared sodium alkoxide solution (0.30 g, 13 mmol of sodium metal in 20 ml of absolute ethanol) 4.6 mmol of the corresponding chalcone (**1**, **2**) and hydroxylamine (0.32 g, 4.6 mmol) were added. The mixture was heated under reflux for 6 h, then diluted with 20 ml of water and acidified with acetic acid to pH 6. The precipitate was filtered off and washed with water. The crude product was purified by twice-repeated precipitation from 10% NaOH solution with acetic acid to pH 6.

3-[4-(5-Phenyl-4,5-dihydroisoxazol-3-yl)phenylamino]propanoic Acid (5). Yield 0.86 g (60%); mp 167-168°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.50 (2H, t, *J* = 6.7, CH_2CO); 3.25 (1H, dd, J_{AX} = 8.3, J_{AB} = 16.8, H_A-4); 3.28 (2H, t, *J* = 6.7, NHC$\underline{H}_2$); 3.75 (1H, dd, J_{BX} = 10.6, J_{AB} = 16.8, H_B-4); 5.60 (1H, dd, J_{AX} = 8.2, J_{BX} = 10.6, H_X-5); 6.19 (1H, br. s, NH); 6.59-7.44 (9H, m, H Ar); 11.95 (1H, br. s, COOH). Found, %: C 69.81; H 5.77; N 9.11. $C_{18}H_{18}N_2O_3$. Calculated, %: C 69.66; H 5.85; N 9.03.

3-{4-[5-(4-Methoxyphenyl)-4,5-dihydroisoxazol-3-yl]phenylamino}propanoic Acid (6). Yield 0.97 g (61%); mp 146-147°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.50-2.53 (2H, m, CH_2CO); 3.30-3.31 (3H, m, NHC$\underline{H}_2$; H_A-4); 3.70 (1H, dd, J_{BX} = 10.5, J_{AB} = 16.8, H_B-4); 3.74 (3H, s, CH_3); 5.54 (1H, dd, J_{BX} = 10.3, J_{AX} = 8.8, H_X-5); 6.21 (1H, br. s, NH); 6.61, 7.43 (4H, two d, *J* = 8.8, H Ar); 6.93, 7.30 (4H, two d, *J* = 8.7, H Ar); 12.18 (1H, br. s, COOH). Mass spectrum, *m/z* (*I*, %): 341 $[M+H]^+$ (100). Found, %: C 67.39; H 5.76; N 8.09. $C_{19}H_{20}N_2O_4$. Calculated, %: C 67.05; H 5.92; N 8.23.

3-{4-[5-(4-Methoxyphenyl)isoxazol-3-yl]phenylamino}propanoic Acid (7). A mixture of chalcone **2** (1.2 g, 3.7 mmol) and hydroxylamine (0.77 g, 11 mmol) was dissolved in 8 ml of 2-propanol, then 2 ml of pyridine was added and the mixture was heated under reflux for 6 h. The solvent was evaporated under reduced pressure. The precipitated product was washed with water (3×20 ml) and purified by twice-repeated precipitation from 10% NaOH solution with acetic acid to pH 5-6. Yield 0.52 g (42%); mp 258-259°C. IR spectrum, ν, cm^{-1}: 1513 (C=N), 1614 (C=O), 3121 (NH), 3393 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32-2.35 (2H, m, CH_2CO); 3.27-3.31 (2H, m, NCH_2); 3.79 (3H, s, CH_3); 6.34 (1H, br. s, NH); 6.66, 7.55 (4H, two d, *J* = 8.1, H Ar); 7.02, 7.76 (4H, two d, *J* = 8.7, H Ar); 7.02 (1H, s, CH). Mass spectrum, *m/z* (*I*, %): 339 $[M+H]^+$ (100). Found, %: C 67.52; H 5.40; N 8.17. $C_{19}H_{18}N_2O_4$. Calculated, %: C 67.45; H 5.36; N 8.28.

3-{4-[5-(4-Methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl]phenylamino}propanoic Acid (8). A solution of chalcone **2** (1.0 g, 3.1 mmol) and hydrazine hydrate (0.62 g, 12 mmol) in ethanol (10 ml) was refluxed for 4 h, then left at room temperature for 12 h. The resulting precipitate was filtered off and washed with ethanol and ether. Yield 0.88 g (85%); mp 101-102°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.41-2.53 (2H, m, CH_2CO); 2.71 (1H, dd, J_{AX} = 10.6, J_{AB} = 16.1, H_A-4); 3.23-3.34 (3H, m, H_B-4, NHC$\underline{H}_2$); 3.73 (3H, s, CH_3); 4.68 (1H, t, J_{AX} = 10.4, H_X-5); 6.55-7.75 (10H, m, H Ar, NNH, N$\underline{H}CH_2$). Mass spectrum, *m/z* (*I*, %): 340 $[M+H]^+$ (100). Found, %: C 67.39; H 6.41; N 12.13. $C_{19}H_{21}N_3O_3$. Calculated, %: C 67.24; H 6.24; N 12.38.

3-{4-[5-(4-Methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]phenylamino}propanoic Acid (9). A solution of chalcone **2** (1.0 g, 3,1 mmol) and phenylhydrazine (0,49 g, 4,5 mmol) in methanol (15 ml) was refluxed for 20 h. After cooling, the resulting precipitate was filtered off and washed with methanol and ether. Yield 0.78 g (61%); mp 175-176°C (methanol). IR spectrum, ν, cm^{-1}: 1600 (C=N), 1713 (C=O), 3343–3288 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51-2.53 (2H, m, CH_2CO); 2.96 (1H, dd, J_{AX} = 6.2, J_{AB} = 17.2, H_A-4); 3.29 (2H, t, *J* = 6.4, NCH_2); 3.70 (3H, s, CH_3); 3.78 (1H, dd, J_{BX} = 11.9, J_{AB} = 17.2, H_B-4); 5.27 (1H, dd, J_{AX} = 6.2, J_{BX} = 11.7, H_X-5); 6.06 (1H, br. s, NH); 6.59-7.50 (13H, m, H Ar); 12.25 (1H, br. s, COOH). ^{13}C NMR spectrum, δ, ppm: 33.55 ($\underline{C}H_2COO$); 38.46 (NH$\underline{C}H_2$); 43.32 (C-4); 54.91 (CH_3); 62.24 (C-3); 111.66; 112.54, 114.17, 117.57, 119.78, 126.99, 127.03, 128.62, 134.73, 144.83, 149.17, 158.27 (C Ar); 148.02 (C=N); 173.04 (COO). Found, %: C 72.54; H 6.26; N 9.87. $C_{25}H_{25}N_3O_3$. Calculated, %: C 72.27; H 6.06; N 10.11.

3-[4-(1,5-Diphenyl-4,5-dihydro-1H-pyrazol-3-yl)phenylamino]propanoic acid (10). A solution of chalcone **1** (1.0 g, 3 mmol) and phenylhydrazine (0.49 g, 4.5 mmol) in methanol (15 ml) was refluxed for 12 h. After cooling, 30 ml of water was added and the resulting precipitate filtered off and washed with water. The obtained crude material was chromatographed over a silica gel column (acetone–hexane, 1:1.5). R_f 0.65. Yield 0.6 g (46%); mp 147-148°C. IR spectrum, ν, cm^{-1}: 1596 (C=N), 1713 (C=O), 3362 (NH), 3275 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51 (2H, t, *J* = 6.7, CH_2CO); 2.99 (1H, dd, J_{AX} = 6.3, J_{AB} = 17.3, H_A-4); 3.29 (2H, t, *J* = 6.7, NCH_2); 3.82 (1H, dd, J_{BX} = 12.0, J_{AB} = 17.2, H_B-4); 5.32 (1H, dd, J_{AX} = 6.3, J_{BX} = 11.9, H_X-5); 6.07 (1H, br. s, NH); 6.59-7.51 (14H, m, H Ar); 12.25 (1H, br. s, COOH). ^{13}C NMR spectrum, δ, ppm: 33.54 ($\underline{C}H_2COOH$);

38.46 (NCH_2); 43.32 (C-4); 62.73 (C-5); 111.67, 112.49, 117.66, 119.67, 125.79, 127.09, 127.17, 128.69, 128.86, 142.90, 144.81, 149.22 (C Ar); 148.06 (C=N); 173.05 (COO). Found, %: C 74.83; H 6.28; N 10.76. $C_{24}H_{23}N_3O_2$. Calculated, %: C 74.78; H 6.01; N 10.90.

3-{4-[5-(4-Chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]phenylamino}propanoic acid (11). A solution of chalcone **3** (1.0 g, 3.2 mmol) and phenylhydrazine (0.43 g, 4 mmol) in ethanol (15 ml) was refluxed for 18 h. After cooling the resulting precipitate was filtered off and washed with ethanol and ether. Yield 0.4 g (30%); mp 172-173°C (ethanol). IR spectrum, ν, cm^{-1}: 1596 (C=N), 1713 (C=O), 3344 (NH), 3254 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.63 (2H, t, J = 6.6, CH_2CO); 3.06 (1H, dd, J_{AX} = 6.6, J_{AB} = 17.2, H_A-4); 3.46 (2H, t, J = 6.7, NCH_2); 3.88 (1H, dd, J_{BX} = 12.0, J_{AB} = 17.2, H_B-4); 5.34 (1H, dd, J_{AX} = 6.6, J_{BX} = 12.0, H_X-5); 6.65-7.58 (13H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 35.04 ($\underline{C}H_2COO$); 40.73 ($NH\underline{C}H_2$); 45.26 (C-4); 64.87 (C-5); 114.01, 114.79, 119.99, 122.88, 129.12, 129.69, 130.53, 130.80, 134.27, 144.17, 149.84, 151.22 (C Ar); 147.23 (C=N); 174.32 (COO). Found, %: C 68.72; H 5.44; N 10.26. $C_{24}H_{22}ClN_3O_2$. Calculated, %: C 68.65; H 5.28; N 10.01.

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