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PREPARATION OF AMINOTRIAZOLE-THIONE DERIVATIVES FROM N-ARYL-N-CARBOXYETHYL-β-ALANINES

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Depending on the substituents in the aryl moiety, the fusion of N-aryl-N-ethoxycarbonyl-β-alanines with thiocarbohydrazide gives di- or monotriazole derivatives, namely, 4-amino-(2-{[2-(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]anilino}ethyl)-4,5-dihydro-1H-1,2,4-triazole-5-thiones, 1-[2-(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]-2,3-dihydroquinolin-4(1H)-ones, 4-amino-3-[2-(4-methylanilino))ethyl]-4,5-dihydro-1H-1,2,4-triazole-5-thione and 4-amino-3-[2-(4-ethoxyanilino)-ethyl]-4,5-dihydro-1H-1,2,4-triazole-5-thione. A ditriazolethione derivative was also obtained from the diethyl ester of N-ethoxycarbonyl-N-(4-ethoxyphenyl)- β-alanine.

Keywords: dihydroxyquinolone, carboxyalanine, triazole, cyclization.

In previous work on the synthesis of compounds with two identical pyrazole, oxadiazole, or triazole rings [1], we synthesized 4-amino-3-(2-{[2-(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]anilino}-ethyl)-2,4-dihydro-3H-1,2,4-triazole-5-thione (**2a**) and its methyl derivative **2b**, by the action of hydrazine on the corresponding 1,3,4-oxadiazole-2(3H)-thione derivative. In a continuation of this study and searching for a shorter synthetic pathway to the desired products, which hold interest as potential bioactive compounds, we carried out the reaction of carboxylic acids with thiocarbohydrazide already reported by Mekuskiene et al. [2, 3]. In a detailed study of this reaction for N-aryl-N-ethoxycarbonyl-β-alanines (**1**), we established that both the reaction conditions and the substituent in the N-aryl moiety affect the result of this reaction.

The fusion of diacid **1a** with thiocarbohydrazide gave ditriazole derivative **2a** in 80% yield. In the case of N-(4-methylphenyl-N-ethoxycarbonyl-β-alanine (**1b**), 4-amino-3-[2-(4-methylanilino)ethyl]-4,5-di-hydro-1H-1,2,4-triazole-5-thione (**3b**) was obtained as the result of the dealkylation of alanine **1b** along with ditriazolethione **2b**. Triazolethione **3b** was isolated from the filtrate by column chromatography. The dealkylation of N-aryl-N-carboxyethyl-β-alanines in cyclization reactions to give hydroxyquinolinone derivatives has been noted by Kantminene [4].

The alkoxy group in the aryl fragment in carboxylic acids **1c** and **1d** facilitates internal acylation to give 6-alkoxy-1-[2-(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]-2,3-dihydroquinolin-4(1H)-ones **4**. Decarboxylation also occurs in the fusion of alanine **1d** with thiocarbohydrazide to give 4-amino-3-[2-(4-ethoxyanilino)ethyl]-4,5-dihydro-1H-1,2,4-triazole-5-thione (**3d**). The presence of a quinoline system in

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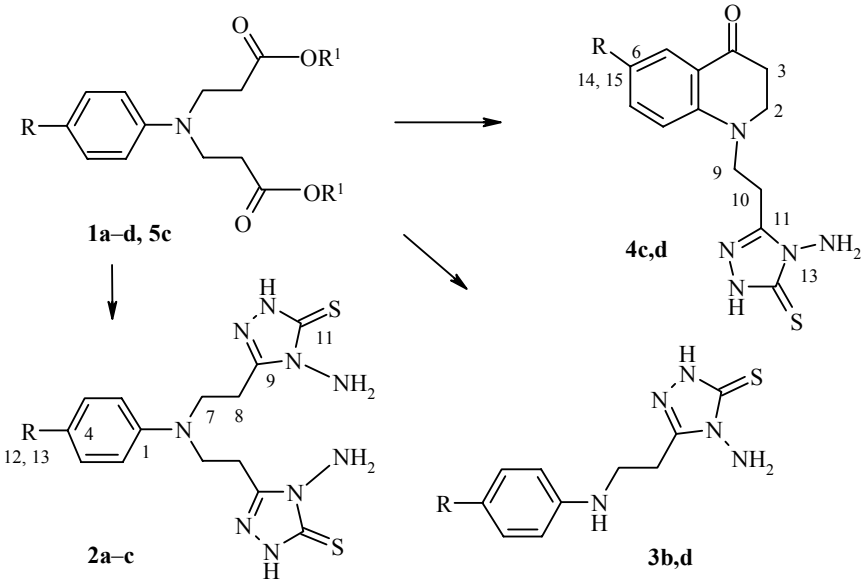
compounds **4** is indicated by the aromatic proton singlet at 6.81-6.83 ppm in the ^{1}H NMR spectra. The ^{1}H NMR spectra of all products **2-4** have signals for the N-NH group as singlets at 13.53 ppm. The primary amino group protons of the dihydroquinoline derivatives of aminotriazolethiones **4** appear as two singlets at 5.56-5.61 ppm.



1, 2 a R = H; **1–3 b** R = Me; **1, 2, 4, 5 c** R= MeO; **1, 3, 4 d** R = EtO; **1a–d** R^1 = H, **5c** R^1 = Et

Triazolethione **2c** was also obtained from the diethyl ester of diacid **5c** by heating this compound at reflux [5] with thiocarbohydrazide in methanolic sodium methylate with subsequent acidification of the reaction mixture.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were taken on a Varian 300 Inova spectrometer at 300 and 75 MHz, respectively, in DMSO-d_6 with TMS as the internal standard. The IR spectra were taken on a Perkin-Elmer Spectrum Bx FT-IR spectrometer for KBr pellets. The chemical ionization mass spectra were taken on a Waters Micromas ZQ 2000 mass spectrometer. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol 254 and Silufol UV-254 plates.

4-Amino-3-(2-{[2-(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]anilino}ethyl)-4,5-dihydro-1H-1,2,4-triazole-5-thione (2a). A mixture of N-ethoxycarbonyl-N-phenyl-β-alanine (**1a**) (2.37 g, 10 mmol) and thiocarbohydrazide (2.12 g, 20 mmol) was heated for 90 min at 160°C. The melt was cooled and dissolved in ethanol (50 ml). The precipitate formed upon cooling was filtered off and crystallized from ethanol to give 1.87 g (79%) **2a**; mp 200-201°C (mp 200-201°C [1]).

4-Amino-3-(2-{[2-(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]-4-methylanilino}ethyl)-4,5-dihydro-1H-1,2,4-triazole-5-thione (2b) and 4-amino-3-[2-(4-methylanilino))ethyl]-4,5-dihydro-1H-1,2,4-triazole-5-thione (3b). A mixture of β-alanine **1b** (5.02 g, 20 mmol) and thiocarbohydrazide (4.25 g, 40 mmol) was heated at 160°C for 90 min. The melt was cooled and dissolved in ethanol (50 ml). The precipitate formed upon cooling was filtered off and crystallized from ethanol to give 4.85 g (62%) **2b**; mp 165-166°C (mp 165-166°C [1]).

The ethanolic filtrate was evaporated and the residue was subjected to chromatography on a silica gel 60 column using 1:1 acetone–hexane as the eluent to give 0.9 g (18%) **3b** as an oil, R_f 0.5 (1:1 acetone–hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.19 (3H, s, 4-CH_3); 2.89 (2H, t, *J* = 7.2, CH_2CN); 3.37 (2H, t, *J* = 7.2, CH_2N); 5.52 (2H, br.s, NH_2); 5.59 (1H, s, NH-Ar); 6.54 (2H, d, *J* = 8.1, H-2,6 Ar); 6.91 (2H, d, *J* = 8.1, H-3,5 Ar); 13.54 (1H, s, NNH). Mass spectrum (20 eV), *m/z* (I_{rel}, %): 250 $[M+H]^+$ (70). Found, %: C 52.85; H 6.12; N 28.10. $C_{11}H_{15}N_5S$. Calculated, %: C 52.99; H 6.06; N 28.09.

4-Amino-3-(2-{[2-(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]-4-methoxyanilino}-ethyl)-4,5-dihydro-1H-1,2,4-triazole-5-thione (2c). Thiocarbohydrazide (13.27 g, 125 mmol) was added to a solution of sodium methylate obtained from metallic sodium (5.35 g, 23.25 mmol) in absolute methanol (50 ml) and heated at reflux for 15 min. Then, diethyl ester **5c** (12.1 g, 41 mmol) was added and heated at reflux for 4 h. The reaction mixture was cooled and 20 ml water was added. Then, acetic acid was added to bring the solution to pH 4. The precipitate formed was filtered off, washed with water, and crystallized from DMF–H_2O to give 10.68 g (64%) **2c**; mp 212-213°C. IR spectrum, ν, cm^{-1}: 1240 (C=S), 3233 (NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.86 (4H, t, *J* = 7.3, CH_2CN); 3.60 (4H, t, *J* = 7.3, CH_2N); 3.68 (3H, s, CH_3O); 5.61 (4H, s, $2NH_2$); 6.83 (4H, s, H Ar); 13.53 (2H, s, 2NH). ^{13}C NMR spectrum, δ, ppm: 22.56 (C-8); 47.64 (C-7); 55.24 (C-11); 114.20 (C-2, C-6); 114.80 (C-3, C-5); 140.97 (C-1); 150.45 (C-9); 151.18 (C-4); 165.93 (C-10). Mass spectrum (20 eV), *m/z* (I_{rel}, %): 408 $[M+H]^+$ (100). Found, %: C 44.59; H 5.34; N 30.95. $C_{15}H_{21}N_9OS_2$. Calculated, %: C 44.21; H 5.19; N 30.93.

1-[2-(4-Amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]-6-methoxy-2,3-dihydroquinolin-4(1H)-one (4c). Analogously to the preparation of triazolethione **2b**, diacid **1c** (2.67 g, 10 mmol) and thiocarbohydrazide (2.65 g, 25 mmol) gave 2.41 g (76%) dihydroquinolone **4c**; mp 142-143°C (2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.81 (2H, t, *J* = 6.3, CH_2CN); 2.85-2.90 (4H, m, $2CH_2$); 3.67 (3H, s, CH_3O); 3.78 (2H, t, *J* = 6.3, CH_2N); 5.56 (1H, s, NH_2); 5.59 (1H, s, NH_2); 6.57 (1H, d, *J* = 8.7, H-8 Ar); 6.72 (1H, d, *J* = 8.7, H-7 Ar); 6.83 (1H, s, H-5 Ar); 13.53 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 18.11, 22.54 (C-2, C-3); 23.85 (C-10); 47.34 (C-9); 55.42 (C-14); 113.25 (C-8); 114.17 (C-5); 115.41 (C-7); 142.37 (C-8a); 149.99, 150.41, 150.63 (C-4a, C-6, C-11); 165.79, 165.86 (C-4, C-13). Mass spectrum (15 eV), *m/z* (I_{rel}, %): 320 $(M+H]^+$ (50). Found, %: C 52.61; H 5.34; N 21.89. $C_{14}H_{17}N_5O_2S$. Calculated, %: C 52.65; H 5.37; N 21.93.

1-[2-(4-Amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)ethyl]-6-ethoxy-2,3-dihydroquinolin-4(1H)-one (4d) and 4-amino-3-[2-(4-ethoxyanilino)ethyl]-4,5-dihydro-1H-1,2,4-triazole-5-thione (3d). Analogously to the preparation of triazolethione **2b**, acid **1d** (1.41 g, 5 mmol) and thiocarbohydrazide (1.06 g, 10 mmol) gave 1.15 g (69%) dihydroquinolone **4d**; mp 92-93°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (3H, t, *J* = 6.9, C<u>H</u>$_3$$CH_2O$); 2.88 (2H, t, *J* = 7.2, CH_2CN); 3.31-3.57 (4H, m, $2CH_2$); 3.61 (2H, m, CH_2N); 3.92 (2H, q, *J* = 6.9, CH_3C<u>H</u>$_2$O); 5.59 (0.67H, s, NH_2); 5.61 (1.33H, s, NH_2); 6.56 (1H, d, *J* = 8.7, H-8 Ar); 6.73 (1H, d, *J* = 8.7, H-7 Ar); 6.81 (1H, s, H-5 Ar); 13.53 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 14.82 (C-15); 18.29, 22.56 (C-2, C-3), 24.56 (C-10), 47.59 (C-9), 63.21 (C-14), 113.22 (C-8), 114.16 (C-5), 115.35 (C-7), 142.35 (C-8a); 149.98, 150.39, 150.65 (C-4a, C-6, C-11); 165.83, 165.85 (C-4, C-13). Mass spectrum (15 eV), *m/z* (I_{rel}, %): 334 $[M+H]^+$ (40). Found, %: C 54.14; H 5.73; N 21.04. $C_{15}H_{19}N_5O_2S$. Calculated, % C 54.04; H 5.74; N 21.01.

Triazolethione **3d** was isolated from the filtrate analogously to **3b**. The yield of **3b** was 0.21 g (15%); mp 179-180°C. IR spectrum, ν, cm^{-1}: 1299 (C=S), 3185 (NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 6.9, C<u>H</u>$_3$$CH_2O$); 2.87 (2H, t, *J* = 7.2, CH_2CN); 3.33 (2H, t, *J* = 7.2, CH_2N); 3.91 (2H, q, *J* = 6.9, CH_3C<u>H</u>$_2$O); 5.31 (2H, s, NH_2); 5.59 (1H, s, NH-Ar); 6.56 (2H, d, *J* = 9.0, H-2, 6 Ar); 6.72 (2H, d, *J* = 9.0, H-3,5 Ar); 13.52 (1H, s, NNH). ^{13}C NMR spectrum, δ, ppm: 14.84 (C-13); 24.57 (C-8); 47.99 (C-7); 63.21 (C-12); 113.24 (C-2, C-6); 115.36 (C-3, C-5); 142.35 (C-1); 150.66 (C-9); 152.10 (C-4); 165.85 (C-11). Mass spectrum (20 eV), *m/z* (I_{rel}, %): 280 $[M+H]^+$ (100). Found, %: C 51.54; H 6.19; N 25.03. $C_{12}H_{17}N_5OS$. Calculated, %: C 51.59; H 6.13; N 25.07.

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