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RECYCLIZATION OF 2-(2,5-DIOXOPYRROLIDIN-1-YL)-GUANIDINE UNDER THE ACTION OF ALIPHATIC AMINES. A NOVEL METHOD FOR THE SYNTHESIS OF 3-(5-AMINO-1H-1,2,4-TRIAZOL-3-YL)PROPANOIC ACID AMIDES

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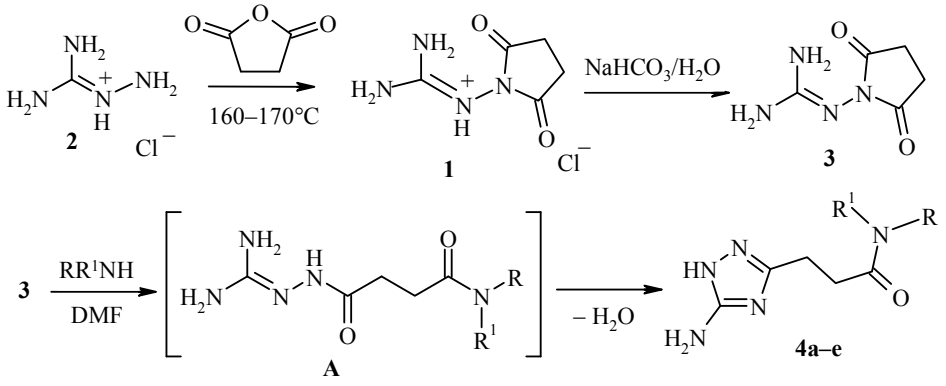
We have previously reported [1] that 2-(2,5-dioxopyrrolidin-1-yl)guanidine hydrochloride (**1**), prepared by fusion of the aminoguanidine hydrochloride (**2**) with succinic anhydride, rearranges to 3-(5-amino-1H-1,2,4-triazol-3-yl)propanoic acid when heated in aqueous alkali solution.

In this work we have shown the action of weak bases on compound **1** gives the free 2-(2,5-dioxopyrrolidin-1-yl)guanidine (**3**). When heated with aliphatic amines in DMF compound **3** undergoes recyclization to give the 3-(5-amino-1H-1,2,4-triazol-3-yl)propanoic acid amides **4a-e** in high yield. The mechanism proposed includes a nucleophilic attack of the amine at the carbonyl group, opening of the pyrrolidin-2,5-dione fragment to form the guanylhydrazide **A**, and its subsequent cyclization to triazole **4**.



4 a R = *i*-Pr, R^1 = H, **b** R = Bn, R^1 = H, **c** R+R^1 = $(CH_2)_4$, **d** R+R^1 = $(CH_2CH_2)_2O$, **e** R+R^1 = $(CH_2)_6$

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^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Unity-300 instrument (300 and 75 MHz respectively) using DMSO-d_6 and with TMS as internal standard. EI mass spectra were recorded on a Finnigan MAT Incos 50 spectrometer with direct introduction of the sample into the ion source and an ionization energy of 70 eV.

2-(2,5-Dioxopyrrolidin-1-yl)guanidine (3). $NaHCO_3$ (2.62 g, 31 mmol) was added to a solution of compound **1** (6.0 g, 31 mmol) in water (9 ml) and stirred at 50-60ºC. The precipitate formed was filtered off and washed with water. Yield 4.11 g (85); mp > 310ºC. ^{1}H NMR spectrum, δ, ppm: 2.50 (4H, s, $2CH_2$); 5.23 (2H, s, NH_2); 5.57 (2H, s, NH_2). ^{13}C NMR spectrum, δ, ppm: 26.90 ($2CH_2$), 160.03, 175.64 (2CO). Mass spectrum, *m/z* (I_{rel}, %): 156 $[M]^+$ (76), 114 (82), 101 (23), 85 (29), 43 (100). Found, %: C 38.72; H 5.12; N 36.11. $C_5H_8N_4O_2$. Calculated, %: C 38.46; H 5.16; N 35.88.

Synthesis of Compounds 4a-e (General Method). A mixture of compound **3** (0.8 g, 5.1 mmol), the aliphatic amine (10.2 mmol), and DMF (1 ml) was heated for 2 h at 130-140ºC with stirring (the synthesis of compounds **4a,c** was carried out in a sealed ampule). The reaction mixture was cooled, benzene (5 ml) was added, and the precipitated solid was filtered off and recrystallized.

3-(5-Amino-1H-1,2,4-triazol-3-yl)-N-isopropylpropanamide (4a). Yield 0.8 g (79%); mp 209-210ºC (water). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.01 (6H, d, *J* = 6.6, 2 CH_3); 2.19-2.33 (2H, m, CH_2); 2.56-2.60 (2H, m, CH_2); 3.76-3.80 (1H, m, CH); 5.73 (2H, br. s, NH_2); 7.68 (1H, d, *J* = 7.2, NH); 11.54 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 197 $[M]^+$ (9), 111 (100), 58 (25), 43 (62). Found, %: C 48.03; H 7.59; N 35.23. $C_8H_{15}N_5O$. Calculated, %: C 48.72; H 7.67; N 35.51.

3-(5-Amino-1H-1,2,4-triazol-3-yl)-N-benzylpropanamide (4b). Yield 1.13 g (90%); mp 208-209ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.59-2.65 (4H, m, 2 CH_2); 4.25 (2H, d, *J* = 5.4, CH_2); 5.77 (2H, br. s, NH_2); 7.22-7.36 (5H, m, Ph); 8.36 (1H, br. s, NH); 11.56 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 245 $[M]^+$ (20), 111 (100), 106 (30), 91 (48), 77 (8), 43 (20). Found, %: C 58.88; H 6.30; N 28.78. $C_{12}H_{15}N_5O$. Calculated, %: C 58.76; H 6.16; N 28.55.

3-(5-Amino-1H-1,2,4-triazol-3-yl)-1-(pyrrolidin-1-yl)propan-1-one (4c). Yield 0.99 g (92%); mp 183-184ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.71-1.83 (4H, m, 2 CH_2); 2.53-2.61 (4H, m, 2 CH_2); 3.25 (2H, t, *J* = 6.8, CH_2); 3.38 (2H, t, *J* = 6.8, CH_2); 5.60 (2H, br. s, NH_2); 11.60 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 209 $[M]^+$ (10), 111 (100), 70 (23), 43 (29). Found, %: C 52.00; H 7.19; N 33.41. $C_9H_{15}N_5O$. Calculated, %: C 51.66; H 7.23; N 33.47.

3-(5-Amino-1H-1,2,4-triazol-3-yl)-1-(morpholin-4-yl)propan-1-one (4d). Yield 0.92 g (80%); mp 177-179ºC (2-propanol). ^{1}H NMR spectrum, δ, ppm: 2.61-2.66 (4H, m, $2CH_2$); 3.41-3.44 (4H, m, $2CH_2$); 3.51-3.55 (4H, m, 2 CH_2); 5.73 (2H, br. s, NH_2); 11.54 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 225 $[M]^+$ (11), 139 (12), 111 (100). Found, %: C 48.21; H 6.51; N 30.82. $C_9H_{15}N_5O_2$. Calculated, %: C 47.99; H 6.71; N 31.09.

3-(5-Amino-1H-1,2,4-triazol-3-yl)-1-(azepan-1-yl)- propan-1-one (4e). Yield 1.08 g (89%); mp 147-148ºC (acetonitrile). ^{1}H NMR spectrum, δ, ppm: 1.45-1.49 (4H, m, $2CH_2$); 1.55-1.60 (2H, m, CH_2); 1.63-1.67 (2H, m, CH_2); 2.59-2.66 (4H, m, $2CH_2$); 3.38-3.43 (4H, m, $2CH_2$); 5.66 (2H, br. s, NH_2); 11.60 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 237 $[M]^+$ (13), 139 (10), 111 (100), 98 (24), 43 (14). Found, %: C 55.82; H 8.20; N 29.67. $C_{11}H_{19}N_5O$. Calculated, %: C 55.68; H 8.07; N 29.51.

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