Polycyclic heterocycles with acidic N-H groups VIII [1] The synthesis of some binuclear N-H acids with free rotary 1,2,4-triazole, 6-azauracil and pyrazole ring

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Abstract

4-(2-Aminobenzyl)-3-phenyl-4,5-dihydro[1,2,4]triazol-5-one (**3**) was prepared by catalytic hydrogenation of the corresponding 1-benzoyl-4-(2-nitrobenzyl)semicarbazide (**2**). The cyclization of **3** in alkaline medium led to the 4-(2-aminobenzyl)-3-phenyl-4,5-dihydro[1,2,4]triazol-5-one (**4**) which was the key intermediate for the synthesis of target bicyclic heterocyclic NH acids. By the diazotation of **4** and coupling of the resulting diazonium salt with ethyl cyanoacetylcarbamate or malonodinitrile, the hydrazones **5a** and **5b,** respectively, were prepared. These arylhydrazones were then transformed into [1,2,4]triazine (**5c**) and 1,3-diaminopyrazole (**5d**).

Keywords: 1,2,4-Triazole, 6-azauracil, 1,3-diaminopyrazole

Introduction

Polycyclic heterocyclic NH acids with free rotary cycles can form a large number of conformations which enables them to shape different at interaction with substrate. Such compounds are able to bind at two different centres of a substrate molecule (e.g. through intermolecular hydrogen bonds) and this type of interaction can cause the change of conformation of substrate molecule.

The above discussed interaction is one of possible mechanisms of interference in conformations of prion proteins. This topic is under intensive study at present[2] and some compounds like *Congo red*[3] or *suramin*[4], which show antiprion activity, seem to operate by this mechanism. Recently antiprion activity has been found in some more simple compounds like *N*-benzylidenebenzohydrazide derivatives[5].

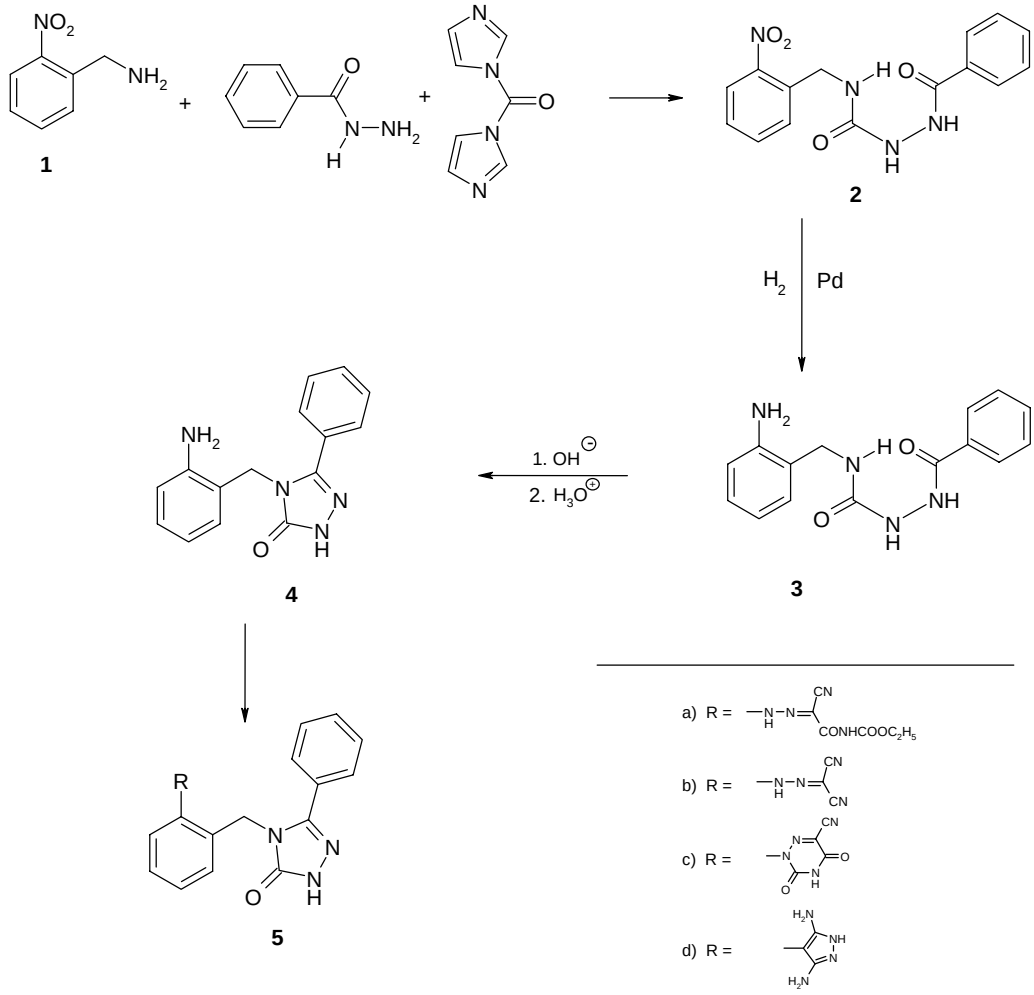
The activity of the last mentioned compound type inspired us to focus on the synthesis of compounds where the benzohydrazide unit is part of 1,2,4-triazole ring. The topic of this article

is therefore the synthesis of some compounds which bear beside the 1,2,4-triazole ring also pyrazole or 6-azauracil rings which are bound together by a 2-substituted benzyl group. This type of bond offers a large number of conformations.

Results and Discussion

The starting 2-nitrobenzylamine (**1**)[6] was treated in the first step with 1,1´-carbonyldiimidazole and in the second step with benzhydrazide resulting in the 1-benzoyl-4-(2-nitrobenzyl)semicarbazide (**2**). The catalytic hydrogenation of the nitrogroup gave the corresponding aminoderivative **3**. The cyclization of aminoderivative **3** in alkaline medium led to the 4-(2-aminobenzyl)-3-phenyl-4,5-dihydro[1,2,4]triazol-5-one (**4**) which was the key intermediate for the synthesis of target bicyclic heterocyclic NH acids. The diazotisation of aminoderivative **4** and coupling of resulting diazonium salt with ethyl cyanoacetylcarbamate or malonodinitrile gave the hydrazones **5a** and **5b**, respectively.

At most, we were interested in the preparation of bicyclic heterocyclic compounds **5c** and **5d** which were synthetised by the cyclization of the corresponding hydrazones **5a** and **5b**, respectively. The compound **5c** was prepared by cyclization reaction of **5a** with aqueous sodium carbonate. The cyclization of hydrazone **5b** was achieved by treatment with hydrazine hydrate and resulted in formation of **5d** which contains both 1,2,4-triazolo and 3,5-diaminopyrazole rings. This compound could be also interesting as a CDK inhibitor because some similar more simple compounds of this group have shown this activity[7].



Scheme

Experimental Section

1-Benzoyl-4-(2-nitrobenzyl)semicarbazide (2). 2-Nitrobenzylamine hydrochloride[6] (1.50 g; 7.95 mmol) was dissolved in 10% sodium hydroxide solution (10.0 ml) and the oil was extracted twice with 15 ml of dichloromethane. The organic phase was then dried with anhydrous sodium sulphate for 1 hour and evaporated *in vacuo*. The residue (1.09 g, 7.17 mmol) was dissolved in dry dichloromethane (15 ml) and 1,1´-carbonyldiimidazole (1.16 g, 7.17 mmol) was added. The reaction mixture was stirred in a closed flask at room temperature for 3 hours and evaporated *in vacuo*. The residue was dissolved in dry tetrahydrofuran and benzoic acid hydrazide (0.98 g, 7.17 mmol) was added. The reaction mixture was refluxed for 2 hours. After cooling to room temperature the reaction mixture was evaporated *in vacuo*. The residue was suspended in 20 ml of ethanol and the white solid was filtered off with suction and washed twice with 15 ml of cold

ethanol. Yield: 69 %. The crude product was crystallized from ethanol. Recovery: 1.21 g (48 % overall), M/S (ESI, m/z (rel. %)): 315.09 $(M+1)^+$, mp: 201-202 °C, IR (KBr) ν: 1666, 1643, 1520, 1334, 1252, 1059, 858, 790, 688. Anal. Calcd. For $C_{15}H_{14}N_4O_4$ (314.30): C 57.32; H 4.49; N 17.83. Found: C 57.31, H 4.47, N 17.74.

1-Benzoyl-4-(2-aminobenzyl)semicarbazide (3). The 1-benzoyl-4-(2-nitrobenzyl)-semicarbazide (**2**) (0.32 g; 1.00 mmol) was dissolved in ethanol (150 ml) and 10% palladium on a charcoal (40 mg) was added. The hydrogenation was performed in a Parr hydrogenation apparatus under atmospheric pressure. After consumption of hydrogen (3.00 mmol, 68 ml) was the catalyst filtered off and the filtrate was evaporated *in vacuo*. The white crystalline compound was suspended in water (25 ml) and filtered off with suction. Yield: 99 %. The crude product was pure enough for further synthesis. M/S (ESI, m/z (rel. %)): 285.00 $(M+1)^+$, mp: 204-205 °C, IR (KBr) ν: 3355, 1680, 1646, 1568, 1499, 1251, 740, 689. ^{1}H NMR (DMSO) δ: 4.09(d, J=6.3, 2H, CH_2), 5.11(s, 2H, NH_2), 6.48(t, J=7.5, 1H, ArH), 6.59 (d, J=7.8, 1H, ArH), 6.94(t, J=7.2, 2H, ArH), 7.02(d, J=7.8, 1H, ArH), 7.52(m, 3H, NH, ArH), 7.90(d, J=7.2, 2H, ArH), 7.98(s, 1H, NH), 10.16(s, 1H, NH). Anal. Calcd. For $C_{15}H_{16}N_4O_2$ (284.32): C 63.37, H 5.67, N 19.71. Found: C 63.31, H 5.59, N 19.80.

4-(2-Aminobenzyl)-3-phenyl-4,5-dihydro[1,2,4]triazol-5-one (4). The 1-benzoyl-4-(2-aminobenzyl)semicarbazide (**3**) (1.00 g; 3.52 mmol) was refluxed in 80 ml of 5% potassium carbonate water solution. After cooling to room temperature was the solution neutralized with acetic acid. The precipitate was filtered off with suction and washed with water. Yield: 75 %. The crude product was crystallized from mixture of ethanol-toluene (1:1). M/S (ESI, m/z (rel. %)): 267.00 $(M+1)^+$, mp: 176-177 °C, IR (KBr) ν: 3334, 1699, 1495, 1456, 766, 740, 696. ^{1}H NMR (DMSO) δ: 4.72(s, 2H, CH_2), 5.20(s, 2H, NH_2), 6.34(m, 2H, ArH), 6.63(d, J=7.8, 1H, ArH), 6.93(t, J=7.8, 1H, ArH), 7.49(m, 5H, ArH), 12.13(s, 1H, NH). Anal. Calcd. For $C_{15}H_{14}N_4O$ (266.31): C 67.65, H 5.30, N 21.04. Found: C 67.63, H 5.31, N 20.95.

Ethyl 2-[(5-oxo-3-phenyl-4,5-dihydro-1,2,4-triazol-4-yl)methyl]-phenylhydrazono cyano acetylcarbamate (5a). To a stirred ice-cooled suspension of compound (**4**) (0.51 g; 1.92 mmol) in a mixture of water (35 ml) and conc. hydrochloric acid (3.0 ml) was slowly added a solution of sodium nitrite (140 mg; 2.02 mmol) in water (4 ml) so that the temperature was maintained between 0-5°C. The suspension dissolved slowly during 35 minutes of stirring. Ethyl cyanoacetylcarbamate (0.42 g; 2.691 mmol) was dissolved in warm water (110 ml), cooled on an ice bath and sodium acetate (5 g) was added. To this ice-cooled solution the solution of diazonium salt was slowly added so that the temperature was maintained between 0-5 °C. The reaction mixture was allowed to stand at 0 °C overnight. The crystalline precipitate was collected with suction, washed with water and dried on air. Yield: 90 %. The crude product was crystallized from mixture of ethanol and water (1:1 v/v). M/S (ESI, m/z (rel. %)): 434.3 $(M+1)^+$, mp: 141-143 °C, IR (KBr) ν: 3229, 2213, 1769, 1702, 1496, 1367, 1273, 1197, 1031, 922, 760, 700. ^{1}H NMR (DMSO) δ: 1.24(t, 3H, J=7.1, CH_3), 4.09(q, 2H, J=7.0, CH_2), 5.07 (s, 2H, CH_2), 6.71(d, 1H, J=8.0, ArH), 7.08(m, 3H, ArH), 7.49(m, 5H, ArH), 12.21 (s, 1H, NH). Anal. Calcd. For $C_{21}H_{19}N_7O_4$ (433.43): C, 58.19; H, 4.42; N, 22.62. Found: C, 58.25; H, 4.17; N, 22.43.

2-[(5-Oxo-3-phenyl-4,5-dihydro-1,2,4-triazol-4-yl)methyl]-phenylhydrazono malono-nitrile (5b). This compound was prepared analogously to (**5a**) from amino derivative (**4**) (0.51 g; 1.92 mmol), conc.hydrochloric acid (3.0 ml), water (45 ml), sodium nitrite (140 mg, 2.02 mmol) and malonodinitrile (127 mg, 1.92 mmol) in the yield 90 %. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid. M/S (ESI, m/z (rel. %)): 344.3 $(M+1)^+$, mp = 199-200 °C, IR (KBr) ν: 2211, 1698, 1553, 1496, 1455, 1343, 1275, 984, 762, 701. ^{1}H NMR (DMSO) δ: 5.04 (s, 2H, CH_2), 6.72(d, 1H, J=7.8, ArH), 7.14(t, 1H, J=7.8, ArH), 7.35(m, 2H, ArH), 7.52(m, 5H, ArH), 12.26 (s, 1H, NH). Anal. Calcd. For $C_{18}H_{13}N_7O$ (343.35): C, 62.97; H, 3.82; N, 28.56. Found: C, 62.83; H, 3.86; N, 28.58.

4-[2-(5-Cyano-6-azauracil-1-yl)-benzyl]-3-phenyl-4,5-dihydro-1,2,4-triazol-5-one (5c). A mixture of hydrazone (**5a**) (433 mg; 1.00 mmol), Na_2CO_3 (120 mg) and water (10 ml) was heated on a boiling water bath until a solution formed and then for an additional 15 minutes. The solution was then allowed to cool down and acidified with HCl (37 %) to pH1. After several hours, the crystalline solid was collected with suction, washed with water and dried in air. Yield: 79 %. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid. M/S (ESI, m/z (rel. %)): 388.13 $(M+1)^+$, mp = 158-160 °C, IR (KBr) ν: 2246, 1712, 1549, 1497, 1320, 1180, 767,701, ^{1}H NMR (DMSO) δ: 4.83(s, 2H, CH_2), 6.39(m, 2H, ArH), 6.68(d, J=8.0, 1H, ArH), 6.96(t, J=7.9, 1H, ArH), 7.48(m, 2H, ArH); 7.51(m, 3H, ArH), 12.13 (s, 1H, NH). Anal. Calcd. For $C_{19}H_{13}N_7O_3$ (387.36): C, 58.91; H, 3.38; N, 25.31. Found: C, 58.99; H, 3.52; N, 25.16.

4-[2-(3,5-Diaminopyrazole-4-yl-azo)-benzyl]-3-phenyl-4,5-dihydro-1,2,4-triazol-5-one (5d). A mixture of hydrazone (**5b**) (346.37; 1 mmol), hydrazine hydrate (0.1 ml; 2.0 mmol; 99 %) and methanol (35 ml) was refluxed for 10 minutes. The solution was then allowed to cool down and acidified with acetic acid (0.3 ml). The reaction mixture was crystalized from ethanol with a charcoal. The filtrate was evaporated (40 °C; 20 mm Hg) and the solid residue was triturated with water (20 ml). The crystalline compound was collected with suction, washed with water and dried in air. Yield 94 %, M/S (ESI, m/z (rel. %)): 348.3 $(M+1)^+$, mp = 279-280 °C, IR (KBr) ν: 1703, 1611, 1557, 1504, 1453, 1406,1330, 1125, 924, 766, 695, 600. ^{1}H NMR (DMSO) δ: 4.12(s, 2H, NH_2), 4.74(s, 2H, CH_2), 5.21(s, 2H, NH_2), 6.42(m, 2H, ArH), 6.70(d, J=7.9, 1H, ArH), 7.01(t, J=7.9, 1H, ArH), 7.52(m, 5H, ArH), 12.23(s, 1H, NH). Anal. Calcd. For $C_{18}H_{17}N_7O$ (347.38): C, 62.24; H, 4.93; N, 28.22. Found: C, 62.21; H, 4.99; N, 28.19.

Melting points were determined on a Boetius stage and are not corrected. ^{1}H NMR *spectra were measured in DMSO-d_6 at 300 K on a Bruker Avance 300 spectrometer (300* MHz) with TMS as an internal standard; chemical shifts are reported in ppm and coupling constants in Hz. Mass spectra were recorded using an LCQ ion trap mass spectrometer (Finnigan MAT, San Jose, CA, USA). Elemental analyses were performed using an EA 1108 Elemental Analyzer (Fison Instruments).

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References

1. Buchtík R., Slouka J., Hlaváč J. *Arkivoc* **2006**, (*v*), 78-85.
2. Forloni G. *et al*. *Curr.Med.Chem.Immun.Endoc.Metab. Agents* **2003**, *3*, 185.
3. Ingrosso L., Ladogana A., Pochiari M. *J.Virol.* **1995**, *69*, 506.
4. Gilch S. *et al*. *EMBO J.* **2001**, *20*, 3957.
5. Bertsch U. *J.Virol.* **2005**, *79*, 7785.
6. Stodola F. H. *J.Org.Chem.* **1972**, *37*, 178.
7. Cankar P.*et al*. PCT Int. Appl 2006, WO 2006024858 A1.