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SYNTHESIS OF 1-AZOLYLCYTIZINES

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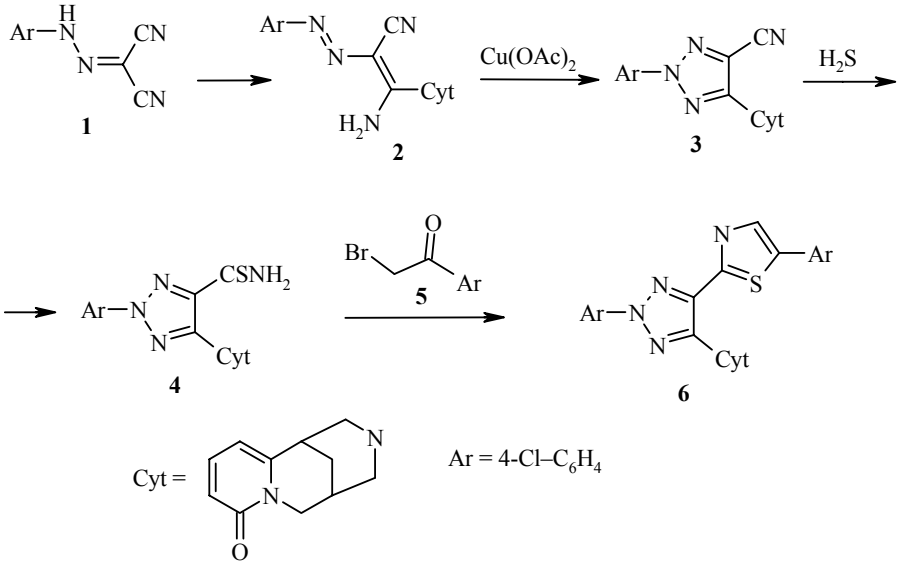
Heterocyclic derivatives of the natural alkaloid cytisine are of interest for medicinal chemistry as potential cholinomimetics [1]. We have for the first time synthesized a heterocyclic esembles, containing in the molecules not only cytisine, but also 1,2,3-triazole and thiazole rings. By the reactions of arylhydrazonomalonodinitrile **1** with cytisine we obtained 3-substituted cytisine **2**, which, on heating in pyridine in the presence of copper(II) acetate, was oxidized to 3-(1,2,3-triazol-4-yl)cytisine **3.**



Subsequent modification of the nitrile groups in thioamide and cyclization in ethanol with bromoacetophenone **5** led to the formation of 5-[thiazol-2-yl(1,2,3-triazol-4-yl]cytisine **6.**

^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded with a Bruker DRX-400 (400 MHz) instrument.

3-Amino-2-(4-chlorophenylhydrazono)-3-(8-oxo-1,5,6,8-tetrahydro-2H,4H-1,5-methanopyrido-[1,2-*a*][1,5]diazocin-3-yl)acrylnitrile (2). Arylhydrazone **1** (0.613 g, 3.0 mmol) and cytisine (0.741 g, 3.9 mmol) in EtOH (30 ml) were stirred for 3 h at 60°C. The mixture was cooled and the precipitate was filtered off. Yield 1.11 g (93%), mp 170-171°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.00 and 2.11 (2H, AB, *J* =15.0, CH_2); 2.61 (1H, s, CH); 3.24 (1H, s, CH); 3.41 (1H, d, *J* = 15.0, CH); 3.56 (1H, dd, *J* = 13.0, *J* = 12.7, CH);

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3.69 (1H, dd, *J* = 15.5, *J* = 14.3, CH); 4.02 (1H, m, CH); 4.31 (1H, d, *J* = 13.5, CH); 4.42 (1H, d, *J* = 15.7, CH), 6.12 (1H, dd, *J* = 6.5, *J* = 1.0, CH); 6.21 (1H, dd, *J* = 9.0, *J* = 1.0, CH); 7.25 (1H, dd, *J* = 9.0, *J* = 6.5, CH); 7.25 and 7.43 (4H, AA'XX', *J* = 8.8, H Ar); 7.41 (2H, s, NH_2). Found, %: C 60.78; H 5.15; Cl 8.98; N 21.40. $C_{20}H_{21}ClN_6O$. Calculated, %: C 60.53; H 5.33; Cl 8.93; N 21.18.

2-(4-Chlorophenyl)-5-(8-oxo-1,5,6,8-tetrahydro-2H,4H-1,5-methanopyrido[1,2-*a*][1,5]diazocin-3-yl)-2H-1,2,3-triazole-4-carbonitrile (3). Compound **2** (0.75 g, 2.0 mmol) and copper(II) acetate (6.6 mmol) in pyridine (30 ml) were stirred at 60°C for 3 h, added to water, and the precipitate was filtered off. Yield 0.53 g (67%), mp 172-173°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.04 (2H, s, CH_2); 2.66 (1H, s, CH); 3.32 (3H, m, CH); 3.78 (1H, dd, *J* = 15.0, *J* =14.0, CH); 4.1 (3H, m, 3CH); 6.16 (2H, d, *J* = 7.5, H Ar); 7.27 (1H, dd, *J* = 7.5, *J* = 8.0, CH); 7.51 and 7.87 (4H, AA'XX', *J* = 8.5, H Ar). Found, %: C 61.33; H 4.16; Cl 9.26; N 21.54. $C_{20}H_{17}ClN_6O$. Calculated, %: C 61.15; H 4.36; Cl 9.02; N 21.39.

2-(4-Chlorophenyl)-5-(8-oxo-1,5,6,8-tetrahydro-2H,4H-1,5-methanopyrido[1,2-*a*][1,5]diazocin-3-yl)-2H-[1,2,3]triazole-4-carbothioamide (4). Hydrogen sulfide was passed through a solution of triazole **3** (0.8 g, 20 mmol) in dry pyridine (10 ml) and TEA (0.8 ml) for 2 h. The mixture was poured into 1 N HCl (50 ml). The precipitate was filtered off. Yield 0.76 g (89%), mp 144-145°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.96 (2H, s, CH_2); 2.57 (1H, s, CH); 3.10 (3H, m, 3CH); 3.75 (2H, m, 2CH); 4.16 (1H, d, *J* = 11.3, CH); 4.30 (1H, d, *J* = 15.5, CH); 6.10 (1H, d, *J* = 6.8, CH); 6.19 (1H, d, *J* = 6.8, CH); 7.27 (1H, dd, *J* = 7.0, *J* = 9.0, CH); 7.47 and 7.94 (4H, AA'XX', *J* = 8.5, H Ar); 9.21 (1H, s, $CSNH_2$); 9.68 (1H, s, $CSNH_2$). Found, %: C 56.35; H 4.56, Cl 8.54; N 19.49. $C_{20}H_{19}ClN_6OS$. Calculated, %: C 56.27; H 4.49; Cl 8.30; N 19.68.

3-{2-(4-Chlorophenyl)-5-[4-(4-chlorophenyl)thiazol-2-yl]-2H-1,2,3-triazol-4-yl}-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (6). Thioamide **4** (0.086 g, 0.2 mmol) and bromoacetophenone **5** (0.047 g, 0.2 mmol) in EtOH (20 ml) were boiled for 3 h. The solvent was evaporated and the residue was recrystallized. Yield 0.088 g (78%), mp 164-165°C (EtOH). ^{1}H NMR spectrum, δ ppm (*J*, Hz): 2.0 (2H, s, CH_2); 2.55 (1H, s, CH); 2.95 (1H, d, *J* = 11.3, CH); 3.28 (1H, s, CH); 3.32 (1H, d, *J* =15.5, CH); 3.93 (2H, m, CH); 4.44 (2H, m, CH); 6.20 (1H, d, *J* = 6.8, CH); 6.34 (1H, d, *J* = 9.2, CH); 7.29 (1H, dd, *J* = 9.0, *J* = 7.0, 2CH), 8.00 (1H, s, CH), 7.53 and 8.04 (4H, AA'XX', *J* = 9.0, H Ar); 7.49 and 7.93 (4H, AA'XX', *J* = 8.8, H Ar). Found: C 60.12, H 4.06, Cl 12.52, N 15.19. Calculated for $C_{28}H_{22}Cl_2N_6OS$, %: C 59.90, H 3.95, Cl 12.63, N, 14.97.

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