Chemistry of Heterocyclic Compounds, Vol. 48, No. 11, February, 2013 (Russian Original Vol. 48, No. 11, November, 2012)

NOVEL STRATEGY FOR THE SYNTHESIS OF THE PYRROLO[3,4-*d*][1,2]DIAZEPINE HETEROCYCLIC SYSTEM

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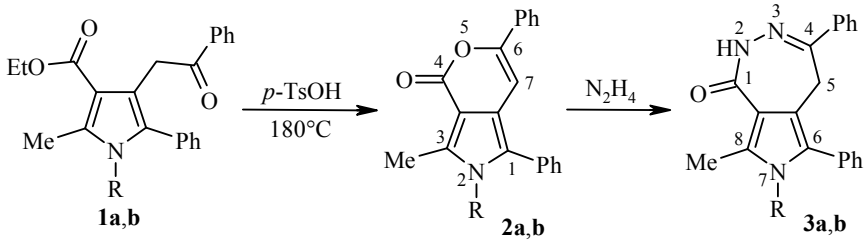
Keywords: hydrazine, pyrano[3,4-*c*]pyrrol-4(2*H*)-one, pyrrole, pyrrolo[3,4-*d*][1,2]diazepine, cyclization, recyclization.

Pyrrolo[3,4-*d*][1,2]diazepines are heterocyclic analogs of the 2,3-benzodiazepine structure, but remain rare and little studied to this time. Their synthesis consists of the stepwise addition of a tosylmethylisocyanide dianion to 1,2-diazepines and has been reported only once [1]. At the same time, the interest in these compounds is linked to the search for convenient methods of synthesis for heterocyclic analogs of tofisopam [2] and talampanel [3], and to broadening of the range of lead compounds for design of medicinal compounds.

The aim of our work was the development of a simple method for preparing pyrrolo[3,4-*d*]-[1,2]diazepines by the cyclization of pyrrole polycarbonyl compounds using hydrazine.

We developed a novel general method for the preparation of the 5,7-dihydropyrrolo[3,4-*d*]-[1,2]diazepin-1(2*H*)-ones **3a**,**b** by recylization of the pyrano[3,4-*c*]pyrrol-4(2*H*)-ones **2a**,**b** using hydrazine. The pyrano[3,4-*c*]pyrrol-4(2*H*)-ones **2a**,**b** were formed in quantitative yields by fusing the pyrroles **1a**,**b** in the presence of catalytic amounts of toluenesulfonic acid. Pyrroles **1a**,**b** were obtained by an addition reaction with simultaneous cyclization using acetoacetate enamines and dibenzoylethylene [4].



a R = H, **b** R = Me

The ^{1}H NMR spectra of the obtained diazepinones **3a**,**b** had characteristic signals for the NH protons at 9.81-9.86 ppm and the CH_2 protons at 3.69-3.96 ppm. The ^{13}C NMR spectra showed the presence of carbonyl carbon signals at 164.5-164.7 ppm and methylene group carbon signals at 26.2-26.5 ppm.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1849-1850, November, 2012. Original article submitted May 27, 2012.

Considering the availability of the starting reagents and the high yields of the final product, we propose that this method can be used for the synthesis of 5,7-dihydropyrrolo[3,4-*d*][1,2]diazepin-1-ones.

IR spectra were recorded on an IR-75 instrument for KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 instrument (400 and 100 MHz, respectively) using DMSO-d_6 with HMDS as internal standard. Elemental analysis was carried out on an Elementar Vario EL Cube. The melting points for the synthesized compounds were determined on a Boetius hot stage apparatus, and were not corrected.

Pyrano[3,4-*c*]pyrrol-4(2*H*)-ones 2a,b (General Method). *p*-Toluenesulfonic acid (0.1 g, 0.6 mmol) was added to a melt of the 3-ethoxycarbonyl-2-methyl-4-(2-oxo-2-phenylethyl)-5-phenyl-1*H*-pyrrole (**1a**) or the 3-ethoxycarbonyl-1,2-dimethyl-4-(2-oxo-2-phenylethyl)-5-phenyl-1*H*-pyrrole (**1b**) (5.0 g, 14.0 mmol) at 185°C. The mixture was maintained with stirring for 10 min, cooled to 80°C, and the solidified crystalline mass was recrystallized from ethyl cellosolve.

3-Methyl-1,6-diphenylpyrano[3,4-*c*]pyrrol-4(2*H*)-one (2a). Yield 4.0 g (93%). Colorless, fine crystals; mp 285-286°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.10 (1H, s, NH); 7.83 (2H, d, *J* = 8.4, H Ph); 7.64 (2H, d, *J* = 8.4, H Ph); 7.43 (2H, t, *J* = 7.6, H Ph); 7.40 (2H, t, *J* = 7.6, H Ph); 7.31 (1H, t, *J* = 7.6, H Ph); 7.25 (1H, t, *J* = 7.6, H Ph); 7.16 (1H, s, H-7); 2.66 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 165.6 (CO); 158.7; 149.8; 134.5; 133.2; 131.8; 128.5; 128.1; 127.9; 125.9; 125.5; 124.2; 122.9; 118.3; 96.7; 11.8. Found, %: C 79.80; H 5.01; N 4.62. $C_{20}H_{15}NO_2$. Calculated, %: C 79.72; H 5.02; N 4.65.

2,3-Dimethyl-1,6-diphenylpyrano[3,4-*c*]pyrrol-4(2*H*)-one (2b). Yield 3.4 g (78%). Colorless, fine crystals; mp 218-219°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.74 (2H, d, *J* = 7.6, H Ph); 7.52 (2H, t, *J* = 7.6, H Ph); 7.48-7.33 (5H, m, H Ph); 7.33 (1H, t, *J* = 7.6, H Ph); 6.84 (1H, s, H-7); 3.64 (3H, s, NCH_3); 2.69 (3H, s, 3-CH_3). ^{13}C NMR spectrum, δ, ppm: 165.9 (CO); 158.8; 149.7; 134.5; 133.0; 130.1; 129.4; 128.5; 128.1; 127.9; 127.3; 126.0; 124.0; 119.2; 95.8; 31.9; 11.0. Found, %: C 80.02; H 5.51; N 4.38. $C_{21}H_{17}NO_2$. Calculated, %: C 79.98; H 5.43; N 4.44.

5,7-Dihydropyrrolo[3,4-*d*][1,2]diazepin-1(2*H*)-ones (3a,b) (General Method). A mixture of compound **2a**,**b** (2 mmol), hydrazine hydrate (0.5 g, 10 mmol), and ethyl cellosolve (5 ml) was refluxed for 16 h. The crystals precipitated were filtered off and washed with ethyl cellosolve.

8-Methyl-4,6-diphenyl-5,7-dihydropyrrolo[3,4-*d*][1,2]diazepin-1(2*H*)-one (3a). Yield 0.6 g (95%). Colorless crystals; mp 233-234°C. IR spectrum, ν, cm^{-1}: 3400 (NH), 1640 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.40 (1H, s, 7-NH); 9.81 (1H, s, 2-NH); 7.60 (2H, dd, *J* = 7.2, *J* = 1.6, H Ph); 7.39 (4H, d, *J* = 4.4, H Ph); 7.33-7.22 (4H, m, H Ph); 3.96 (2H, s, 5-CH_2); 2.48 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 164.7 (CO); 158.1; 136.5; 134.3; 131.8; 129.0; 128.3; 128.0; 126.5; 126.2; 125.0; 123.8; 115.2; 113.6; 26.5 (CH_2); 11.0. Found, %: C 76.21; H 5.42; N 13.28. $C_{20}H_{17}N_3O$. Calculated, %: C 76.17; H 5.43; N 13.32.

7,8-Dimethyl-4,6-diphenyl-5,7-dihydropyrrolo[3,4-*d*][1,2]diazepin-1(2*H*)-one (3b). Yield 0.5 g (82%). Colorless crystals; mp 236-237°C. IR spectrum, ν, cm^{-1}: 1640 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.86 (1H, s, NH); 7.55-7.36 (5H, m, H Ph); 7.36-7.20 (5H, m, H Ph); 3.69 (2H, s, 5-CH_2); 3.43 (3H, s, NCH_3); 2.53 (3H, s, 8-CH_3). ^{13}C NMR spectrum, δ, ppm: 164.5 (CO); 158.1; 138.4; 136.1; 134.0; 130.3; 130.0; 129.3; 128.2; 127.9; 127.4; 126.9; 126.1; 116.0; 112.5; 31.1; 26.2 (CH_2); 10.6. Found, %: C 76.59; H 5.86; N 12.64. $C_{21}H_{19}N_3O$. Calculated, %: C 76.57; H 5.81; N 12.76.

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