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LETTERS TO THE EDITOR

SYNTHESIS OF DERIVATIVES OF PYRAZOLE WITH CHIRAL SUBSTITUENTS AT THE NITROGEN ATOM

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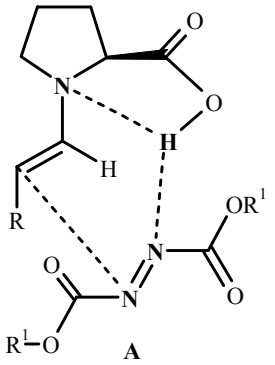
The stereoselective creation of C–N bonds with the use of simple and accessible reagents is one of the most important problems of organic chemistry. Among the substances synthesized annually with the objective of discovering medicinal substances, all have a large number of chiral structures, while at the same time there is a tendency to develop enantiomeric purity, but not racemic substances. This tendency applies in full measure to pyrazole derivatives, the biological activity of which is well known [1, 2]. In this work we have used for the first time for the synthesis of pyrazoles with chiral substituents at the nitrogen atom the recently described [3] reaction of directed stereoselective α-amination of aldehydes using azadicarboxylates as the source of nitrogen, catalyzed by L-proline. This reaction leads to the formation of optically active α-hydrazino aldehydes which are suitable chiral synthons, among others for the construction of the pyrazole ring. The observed stereochemistry may be explained by the initial formation of an enamine from proline and the aldehyde with subsequent coordination to the azadicarboxylate *via* hydrogen bonds (intermediate **A**).



A

The stereoselective formation of the C–N bond facilitates the *anti* position of the substituent R relative to the carboxyl group of proline and the formation energetically favorable six-membered transition state.

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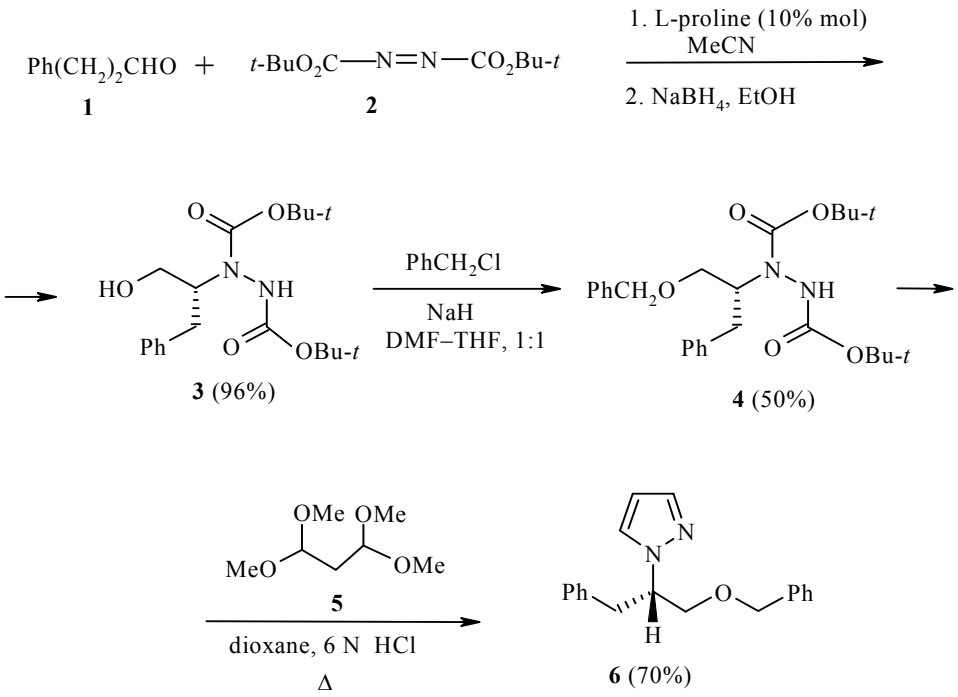
An original method for the introduction of an asymmetric carbon into the pyrazole ring was developed based on this reaction.



For example, interaction of di-*tert*-butyl azadicarboxylate (**2**), catalyzed by L-proline, with 3-phenylpropanal (**1**) at 0°C in acetonitrile with subsequent reduction with $NaBH_4$ *in situ* led to the formation of di-*tert*-butyl 1-[1-benzyl-2-hydroxy)ethyl]hydrazine-1,2-dicarboxylate (**3**). Reduction of the aldehyde group is necessary to prevent racemization in subsequent cyclization to pyrazole in acid medium.

A series of consecutive reactions: introduction of the benzyl protecting group at the hydroxy group, removal of the *tert*-butoxy protecting groups in acid medium, and, finally, cyclization *in situ* with the tetramethyl acetal of malonaldehyde led to the formation of the desired 1-[1-benzyl-2-benzyloxy)ethyl]pyrazole (**6**) in 70% yield and an enantiomeric purity of >99% (according to HPLC on a column with a chiral stationary phase).

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 spectrometer (400 and 100 MHz respectively) with TMS as internal standard. Specific rotations were measured on a Jasco DIP-360 (589 nm) polarimeter. Chromatospectral studies were carried out with Carlo Erba/Kratos Fractovap Series 4200, Hewlett Packard Ultra-1 column, 25 m×mm, 0.33 μ thick layer, helium carrier gas (1 ml/min), split of flow 1:10, evaporation temperature 280°C, temperature gradient from 150 to 280°C (5 C/min). Control of the course of reactions and purity of products was carried out by TLC on Silufol UV-254 plates and gas chromatography with detector by mass spectrometry. Enantiometric purity of substrates by HPLC using a chiral stationary phase: Chiralpak AD-RH 4.6x250 mm, 5 μ, eluent hexane-2-propanol 75:25, 1.0 ml/min, temperature 20°C.

Di-*tert*-butyl 1-[(1-Benzyl-2-hydroxy)ethyl]hydrazine-1,2-dicarboxylate (3). L-Proline (0.06 g, 0.5 mmol) was added to a solution of di-*tert*-butyl azadicarboxylate (**2**) (1.15 g, 5 mmol) in acetonitrile (50 ml), the mixture was cooled to 0°C, and 3-phenylpropanal **1** (0.99 ml, 7.5 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 2 h and then for 1 h at room temperature. After this the solution was decolorized, cooled to 0°C again, ethanol (50 ml) and $NaBH_4$ (0.19 g, 5 mmol) were added, and the mixture was stirred for 5-10 min at 0°C. The reaction mixture was washed with 50% aqueous NH_4Cl and extracted with ethyl acetate.

The organic phase was dried with $MgSO_4$ and the solvent was removed in vacuum to give a white crystalline substance (2.64 g, 96%), mp 110-111°C (acetonitrile). ^{1}H NMR spectrum, δ, ppm: 1.28 and 1.36 (9H in total, both s, $C(CH_3)_3$); 1.52 (9H, s, $C(CH_3)_3$); 2.48-2.79 (2H, m, CH_2Ph); 3.41-3.68 (2H, m, CH_2OH); 4.49-4.92 (1H, m, CHN); 5.95 and 6.07 (1H in total, both s, NH); 7.08-7.39 (5H, m, Ph). ^{13}C NMR spectrum, δ, ppm: 28.01 (6C, $(CH_3)_3C$); 35.88 (CH_2Ph); 51.25 (CH); 62.21 (CH_2OH): 82.12 (2C, $C(CH_3)_3$); 126.67 (C, CH); 129.07 (2C, CH); 130.86 (2C, CH); 135.02 (C); 164.23 (C=O); 167.15 (C=O). $[\alpha]^{21}_D$ +34.3 ($CHCl_3$, *c* 0.05). Found, %: C 62.39; H 8.15; N 7.58. $C_{19}H_{30}N_2O_5$. Calculated, %: C 62.27; H 8.25; N 7.64.

Di-*tert*-butyl 1-[1-benzyl-2-(benzyloxy)ethyl]hydrazine-1,2-dicarboxylate (4). NaH (0.3 g, 12.6 mmol) was added with stirring to solution of compound **3** (2.64 g, 7.2 mmol) in 1:1 THF-DMF (40 ml), stirring was continued for 30 min, then benzyl chloride (0.91 ml, 7.9 mmol) was added dropwise. When addition of benzyl chloride was completed, the mixture was heated to 80°C and kept at this temperature for 6-8 h (TLC monitoring). The solvent was removed in vacuum, methanol (5 ml) was added to the residue, the solution was diluted with water and extracted with CH_2Cl_2 (2×300 ml). The extract was dried over $MgSO_4$ and the solvent removed in vacuum to give a light-yellow oil (1.6 g, 50%). ^{1}H NMR spectrum, δ, ppm: 1.30-1.48 (18H, m, $C(CH_3)_3$); 2.46-2.60 (2H, m, CH_2Ph); 3.28-3.25 (4H, m, CH_2OCH_2Ph); 4.98-5.12 (1H, m, CHN); 6.75 and 6.87 (1H in total, both s, NH); 7.17-7.48 (10H, m, C_6H_5). Found, %: C 67.89; H 7.82; N 5.98. $C_{26}H_{36}N_2O_5$. Calculated, %: C 68.40; H 7.95; N 6.14.

1-[(1-Benzyl-2-benzyloxy)ethyl]-1H-pyrazole (6). Tetramethylacetal of malonic dialdehyde **5** (0.03 ml, 0.16 mmol) was added to a solution of compound **4** (0.07 g, 0.16 mmol) in 6 N HCl (20 ml) and the mixture was stirred at room temperature, until evolution of gas had ceased, and then for further 2-4 h at 70-80°C. The reaction mixture was poured into cold water and extracted with CH_2Cl_2 (3×50 ml). The organic layer was separated, washed with water, dried over Na_2SO_4, the solvent was removed in vacuum, and the residue chromatographed on a silica gel column with 15:1 petroleum ether–ethyl acetate as eluent. A thick dark-brown oil was isolated (0.032 g, 70%). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 3.13-3.18 (2H, m, $CHCH_2Ph$); 3.27 and 3.37 (2H, m and m, $CHCH_2O$); 4.39 (1H, m, CH); 5.10 (2H, s, OCH_2Ph); 6.05 (1H, br. s, H-$4_{pyrazole}$); 6.89 (2H, dd, J = 7.6, J = 2.4, C_6H_5); 7.04 (1H, d, J = 2.4, H-$3_{pyrazole}$); 7.15 (3H, m, C_6H_5); 7.32 (5H, m, C_6H_5); 7.54 (1H, m, H-$5_{pyrazole}$). $[\alpha]^{21}_D$ +3.8 ($CHCl_3$, *c* 0.055), *ee* >99% (according to HPLC on a column with a chiral stationary phase).

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