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Synthesis of 1,2-Diphenylpyrazolidin-4-ol and its Derivatives

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Summary. A synthesis of 1,2-diphenylpyrazolidin-4-ol *via* direct heterocyclization of 1,2-diphenylhydrazine with 1-chloro-2,3-epoxypropane, its *O*-epoxypropyl-, *O*-ethyl-, and *O*-benzylderivatives are described. Novel hydrazone derivatives with pyrazolidine units were also synthesized. The compounds were characterized by spectroscopic methods as well as elemental analyses.

Keywords. 1,2-Diphenylhydrazine; 1,2-Diphenylpyrazolidin-4-ol; Hydrazone; 1-Chloro-2,3-epoxypropane; Cyclocondensation.

Introduction

Among the hydroxy and hydrazinopyrazolidines some are found to possess biological activity [1]. Compounds, and particularly 1,2-diphenylpyrazolidin-4-ol, are not widely investigated. It is known [2, 3] that 1,2-dimethyl- and 1-methyl-2-phenylhydrazines with α,β-unsaturated carbonyl compounds usually form 3-pyrazolines. Only in special cases [4, 5] the formation of hydroxypyrazolidines, *i.e.* cyclic semihydrazynales, was observed. In contrary, when cyclic hydrazides of dicarboxylic acids (diethylmalonic, succimic, maleic, phthalic) react with unsaturated aldehydes derivatives of pyrazolidin-3-oles as the main products are obtained. Formation of the pyrazolidin-5-ol derivatives was observed also in the cyclocondensation of 1-formyl-2-isopropylhydrazine with acetaldehyde [6], or by cyclocondensation of 1-benzoyl-2-benzylhydrazine with acrylaldehyde [7] in non(-)polar solvents such as CCl_4 or $CDCl_3$. *L. Balbiano* [8] and *F. Gerhardt* [9] have found that by refluxing phenylhydrazine with 1-chloro-2,3-epoxypropane (*CEP*) in benzene formation of 1,3-diphenylamino-2-propanol hydrochloride is observed. During its distillation the hydrochloride of phenylhydrazine splits off and 1-phenyl-pyrazolidin-4-ol is formed. However, the yield of 1-phenyl-pyrazolidin-4-ol has not been determined since it was not isolated from the reaction mixture, instead $ZnCl_2$ was added and it was converted to 1-phenylpyrazole. The formation of *N,N*-diphenylpyrazolidin-4-ol by reaction of 1,2-diphenylhydrazine (*DPH*) with an excess of *CEP* at room temperature is described in Ref. [10]. However, the conditions of this reaction have not been reported. Herein we report on the synthesis and characterization of 1,2-diphenylpyrazolidin-4-ol and its derivatives.

Results and Discussion

First we investigated the course of the reaction of *DPH* with *CEP* in presence of acetic acid [11] using methanol as the solvent. The reaction was carried out at 45–50°C for 32 h. Under these reaction conditions the formation of two products was observed on TLC. 1,2-Diphenylpyrazolidin-4-ol (**1**) and azobenzene were isolated by column chromatography, using acetone:*n*-hexane = 1:7 as eluent in yields of 53 and 23%. The elemental analysis and mass spectral data of the first compound supported the molecular formula $C_{15}H_{16}N_2O$. The structure of **1** was confirmed by the characteristical for pyrazolidinoles chemical shifts of carbon atoms at 59.6 and

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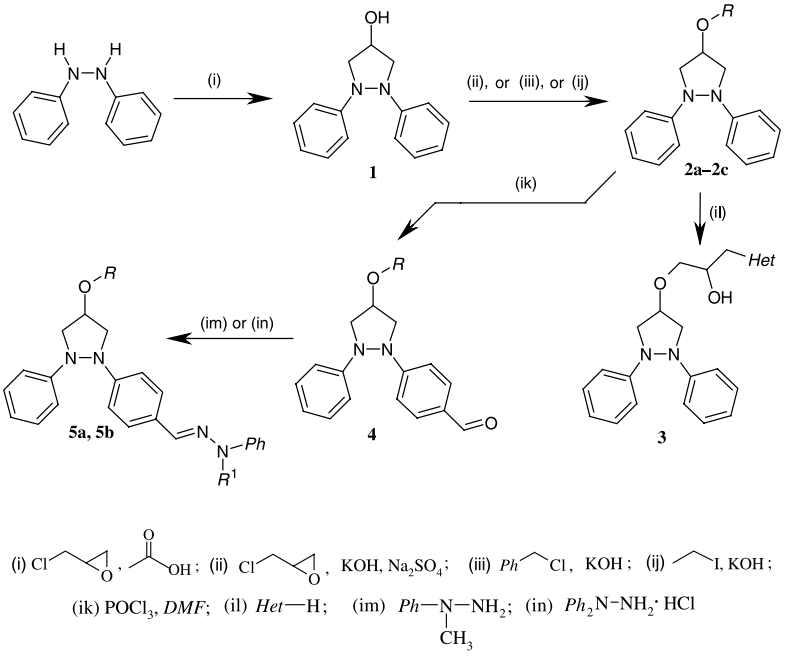

R = **2a** epoxy methyl group; **2b** ethyl; **2c, 4, 5a** and **5b** benzyl; *Het* = carbazol-9-yl

Scheme 1

74.7 ppm in the ^{13}C NMR spectrum, OH bond at $\bar{\nu} = 3555\,\mathrm{cm}^{-1}$ in the IR spectrum, and the molecular ion peak $[M+H]^+$ at $m/z = 241.4$ in the mass spectrum. The cleavage of N–N and C–C bonds with the formation of $[C_6H_5NCH_2+H]^+$dominant (100%) in the fragmentation process of **1**. The azobenzene was identified by its melting point. Formation of the latter may be explained by the oxidation of the part of the starting material under these conditions. When we repeated the reaction *via* direct heterocyclization under Ar atmosphere the amount of oxidation product decreased to 2–3%, and the yield of **1** was 69%. In order to confirm the structure of **1** some alkylation reactions were carried out. By the reaction of **1** with *CEP* in the presence of powdered KOH and Na_2SO_4 O-epoxypropylated derivative **2a** was obtained. O-Ethylated and O-benzylated derivatives **2b** and **2c** were obtained by the reaction of **1** with iodoethane and benzyl chloride in the presence of powdered KOH. The nucleophilic opening of the oxirane ring in **2a** was carried out by treating it with carbazole according to Ref. [11] to give **3**. *Vilsmeier* formylation of **2c** followed by condensation of the resulting aldehyde **4** with hydrazine derivatives yields hydrazones **5a** and **5b**. A singlet signal in the ^{1}H NMR spectrum at $\delta = 9.81$ ppm and the presence of a carbonyl band and C–H bands in the IR spectrum at about $\bar{\nu} = 1676$ and $1353\,\mathrm{cm}^{-1}$ refers to an aromatic aldehyde group in **4**.

The IR, MS, and NMR spectral data of all synthesized compounds are in accordance with the assigned structures and are given in the experimental part. The newly synthesized hydrazones **5a** and **5b** were preliminary investigated as hole transporting materials. They exhibit good compatibility with polycarbonate and homogenic films could be prepared. The hole drift mobility, measured by the xerographic time of flight technique [12–14], exceeded $10^{-7}\,\mathrm{cm}^2/\mathrm{Vs}$ at an electric field of $10^6\,\mathrm{V/cm}$.

In conclusion, the conditions of alkylation-heterocyclization of *DFH* with *CEP* were derived and novel derivatives of **1** were synthesized. They can be used as intermediates in the synthesis of hole transporting materials.

Experimental

Melting points: Electrothermal melting temperature apparatus. ^{1}H, ^{13}C NMR spectra: Varian Unity Inova Instrument (300/75 MHz) in $CDCl_3$ at room temp, *TMS* as internal standard. The IR spectra (KBr) were recorded on Perkin Elmar Spectrum BX II FT-IR system spectrophotometer. Mass spectra were recorded on Waters (Micromass) ZQ 2000 (20 V). The

course of the reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates and development with I_2 or UV light. Silica gel (grade 62, 60–200 mesh, 150 Å, Aldrich) was used for column chromatography. Microanalyses were performed at the Microanalytical Laboratory – Organic Chemistry Department, Kaunas University of Technology, and the results agreed with the calculated values within experimental errors.

1,2-Diphenylpyrazolidin-4-ol (**1**, $C_{15}H_{16}N_2O$)

A. A mixture of 18.4 g *DPH* (0.1 mol), 30.1 g *CEP* (0.325 mol), 25 cm^3 methanol, and 5 cm^3 acetic acid was stirred at 50–55°C for 32 h. After termination of the reaction the excess of *CEP*, methanol, and acetic acid was removed by rotary evaporation. The residue was purified by column chromatography on silica gel using acetone:*n*-hexane = 1:7 as eluent. Two products were obtained. The yield of **1** was 13 g (54%); mp 111–112°C; the yield of azobenzene (mp 65–68°) – 4 g (23%). For **1**: MS (APCI, 20 V): m/z (%) = 241.4 ($[M+H]^+$, 9), 223.4 ($[M+H]^+$-H_2O, 19), 136.2 ($[PhNHCH_2CHO+H]^+$, 28), 120.1 ($[PhNCH_2CH+H]^+$, 18), 106.0 ($[PhNCH_2+H]^+$, 100); IR (KBr): $\bar{\nu}$ = 3555 (OH), 3087, 3057, 3048, 3035, 3023 (CH_{arom}), 2936, 2917, 2874, 2783 (CH_{aliph}), 1592, 1497, 1460, 1454 (C=C, C–N), 747, 697, 658 (CH=CH of monosubstituted benzene) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.41–6.55 (m, 10H, *Ph*), 4.51 (s, C*H*(OH)), 3.91–3.18 (m, NCH_2CHCH_2N), 1.77 (split s, OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.9 (arom C), 129.4, 120.4, 114.3 (arom CH), 74.7 (C-4), 59.6 (C-3, C-5) ppm.

B. The mixture of 55.3 g *DFH* (0.3 mol), 89.7 g *CEP* (0.975 mol), 75 cm^3 methanol, and 15 cm^3 acetic acid was stirred at 50–55°C for 32 h under Ar. After termination of the reaction the excess of CEP, methanol, and acetic acid was removed by rotary evaporation. The residue was dissolved in the mixture of butanone:*n*-hexane = 1:3. The formed crystals were filtered off, washed with the same mixture and recrystallized from butanone:*n*-hexane = 1:3 to afford colorless needles. Yield 50 g (69%); mp 111–112°C.

4-(2,3-Epoxypropoxy)-1,2-diphenylpyrazolidine (**2a**, $C_{18}H_{20}N_2O_2$)

A mixture of 5.1 g **1** (0.02 mol), 19.4 g *CEP* (0.21 mol), 4.2 g 85% powdered KOH (0.064 mol), and 3 g anhydrous Na_2SO_4 (0.02 mol) was stirred at 50°C until **1** was completely consumed. Then the mixture was extracted with diethyl ether, washed with distilled H_2O until neutral, dried ($MgSO_4$), and the solvents were removed by rotary evaporation. The residue was left at room temperature. The crystals formed upon standing were filtered off, washed with 2-propanol, and dried. Yield 5 g (79%); mp 66–67°C. IR (KBr): $\bar{\nu}$ = 3088, 3057, 3020, 3003 (CH_{arom}), 2933, 2914, 2854 (CH_{aliph}), 1595, 1493, 1459, 1452 (C=C, C–N), 1262 (cycle of oxyrane), 755, 748, 696, 653 (CH=CH of monosubstituted benzene) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.28–6.78 (m, 10H, *Ph*), 4.44–4.36 (m, 1H, CH_2OCH), 3.92–3.20 (m, 6H, NCH_2CHCH_2N, OCH_2CH), 2.92–2.84 (m, 1H, CH_2 of epoxy group), 2.63–2.56 (m, 1H, CH_2 of epoxy group), 2.33–2.22 (m, 1H, OCH_2CH) ppm.

4-Ethoxy-1,2-diphenylpyrazolidine (**2b**, $C_{17}H_{20}N_2O$)

To a solution of 8.7 g **1** (0.036 mol) in 20 cm^3 butanone 7.3 g 85% powdered KOH (0.11 mol) and 1.9 g K_2CO_3 (0.014 mol) were added and the mixture was stirred at 50°C for 9 h. Then 5.9 g (3.9 cm^3) ethyl iodide (0.038 mol) were added and the mixture was stirred for 2 h. The same amounts of ethyl iodide were added after 2, 4, and 6 h. Then 2 g of 85% powdered KOH (0.03 mol) were added and the mixture was stirred at 40°C for 70 h. After termination of the reaction (eluent: acetone:diethyl ether:*n*-hexane = 3:2:18), the mixture was extracted with diethy ether, washed with distilled H_2O until neutral. The organic layer was dried ($MgSO_4$), and the solvent was evaporated by rotary evaporation. The crude product was purified by column chromatography on silica gel using acetone:*n*-hexane (1:7) as eluent. The product was recrystallized from ethanol and dried. Yield 5 g (52%); mp 65–67°C. IR (KBr): $\bar{\nu}$ = 3086, 3062, 3040, 3025 (CH_{arom}), 2972, 2945, 2914, 2873 (CH_{aliph}), 1597, 1506, 1466, 1441 (C=C, C–N), 745, 691, 667 (CH=CH of monosubstituted benzene) cm^{-1}.

4-Benzyloxy-1,2-diphenylpyrazolidine (**2c**, $C_{23}H_{22}N_2O$)

A mixture of 7.2 g **1** (0.03 mol), 22.8 g benzylchloride (0.18 mol), 5.9 g 85% powdered KOH (0.09 mol), and 2.1 g Na_2SO_4 (0.015 mol) was stirred at 70°C for 3 h (eluent: acetone:*n*-hexane = 7:18). Then the mixture was left at room temperature. The crystals formed upon standing were filtered off, washed with distilled H_2O until neutral, and dried. The product was recrystallized from $CHCl_3$, dried, and used for synthesis of the aldehyde. Yield 4 g (43%); mp 121–122°C. IR (KBr): $\bar{\nu}$ = 3084, 3064, 3050, 3032, 3019, 3009 (CH_{arom}), 2945, 2920, 2899, 2856, 2779 (CH_{aliph}, C–H combination frequency of aldehyde group), 1596, 1494, 1470, 1461, 1452 (C=C, C–N), 751, 714, 697, 667 (CH=CH of monosubstituted benzene) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.47–6.78 (m, 15H, *Ph*), 4.42–4.29 (m, $CHOCH_2$), 3.90–3.40 (m, 4H, NCH_2CHCH_2N) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.9 (arom C), 129.4, 120.4, 114.3 (arom CH), 74.7 (C-4), 59.6 (C-3, C-5) ppm.

1-(1,2-Diphenylpyrazolidin-4-oxy)-3-(carbazol-9-yl)-2-propanol (**3**, $C_{30}H_{29}N_3O_2$)

To a solution of 3 g **2a** (0.01 mol) and 1.7 g carbazole (0.01 mol), 2 g 85% powdered KOH (0.03 mol), and 0.7 g anhydrous Na_2SO_4 (0.005 mol) were added. The mixture was stirred at room temperature for 4 h (eluent: acetone:*n*-hexane = 7:18). Then the mixture was extracted with ethyl acetate as described above for **2b**. The solid residue was purified by column chromatography using acetone:*n*-hexane = 3:22 as eluent. Yield 4 g (86%) **3**; mp 134–136°C. IR (KBr): $\bar{\nu}$ = 3553 (OH), 3045, 3022, 3003 (CH_{arom}), 2936, 2911, 2870 (CH_{aliph}), 1625, 1594, 1491, 1461, 1452 (C=C, C–N), 756, 734, 726, 698, 667 (CH=CH monosubstituted benzene) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.03 (d, 2H, J = 7.7 Hz, 4-H *Het*), 7.65–6.68 (m, 16H, Het, *Ph*), 4.20–3.60 (m, 5H, NCH_2CHCH_2N, CH_2OCH), 3.50–3.00 (m, 5H, OCH_2CHCH_2N), 1.78 (s, OH) ppm.

4-Benzyloxy-1-phenyl-2-(4-formylphenyl)pyrazolidine (**4**, $C_{23}H_{22}N_2O_2$)

To a 100 cm^3 3-neck round bottom flask equipped with thermometer, magnetical stirrer, and additional funnel 3.3 cm^3 *DMF* (0.0432 mol) were added. The content was cooled in a NaCl/ice bath. When the temperature inside the flask reached 0°C, 2 cm^3 $POCl_3$ (0.0216 mol) were added slowly. During the addition of $POCl_3$, the temperature of the mixture was not allowed to rise above 5°C. When the addition was completed, the reaction mixture was allowed to warm to room temperature. A solution of 6 g **2c** (0.018 mol) in 15 cm^3 *DMF* was added and the mixture was heated to 70–75°C for 3 h. The hot reaction mixture was poured into a 250 cm^3 beaker containing 100 g ice. The mixture was neutralized by adding the solution of 6.42 g CH_3COONa in 16 g H_2O and allowed to stand at 5°C for 24 h. The formed greenish solid was filtered off, washed repeatedly with H_2O followed by 2-propanol, and dried. The crude product was recrystallized from methanol:ethyl acetate = 1:1. The crystals formed upon standing were filtered off and washed with 2-propanol. Yield 2.5 g (39%); mp 145–148°C. IR (KBr): $\bar{\nu}$ = 3086, 3065, 3033, 3009 (CH_{arom}), 2942, 2922, 2899, 2859 (CH_{aliph}), 1599, 1493, 1469, 1454 (C=C, C–N), 748, 710, 695, 678 (CH=CH of monosubstituted benzene); ^{1}H NMR ($CDCl_3$): δ = 9.81 (s, CHO), 7.86–7.69 (m, 2H, *Ph*), 7.40–6.80 (m, 12H, *Ph*), 4.53–4.31 (m, 3H, $CHOCH_2$), 3.95–3.53 (m, 4H, NCH_2CHCH_2N).

4-(4-Benzyloxy-2-phenylpyrazolidin-1-yl)benzaldehyde N-methyl-N-phenylhydrazone (**5a**, $C_{30}H_{30}N_4O$)

To a solution of 1 g **4** (2.9 mmol) in 1 cm^3 toluene:2-propanol = 1:1, 0.34 cm^3 *N*-methyl-*N*-phenylhydrazine (2.9 mmol) were added and the reaction mixture was refluxed for 4 h. After termination of the reaction (TLC; eluent: ethyl acetate:*n*-hexane = 7:18), the mixture was cooled. Formed crystals were filtered off, washed with 2-propanol, and dried. The product was purified by column chromatography using ethyl acetate:*n*-hexane = 3:22 as eluent. Yield 2.5 g (39%); mp 145–148°C. IR (KBr): $\bar{\nu}$ = 3083, 3059, 3028, 3006 (CH_{arom}), 2987, 2954, 2926, 2009, 2889, 2859 (CH_{aliph}), 1598, 1498, 1461, 1454 (C=C, C–N), 751, 696, 664 (CH=CH monosubstituted benzene) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.58 (d, 2H, *J*=8.8 Hz, *Ph*), 7.48 (s, CH=N), 7.40–7.19 (m, 11H, *Ph*), 7.01–6.82 (m, 8H, *Ph*), 4.49–4.38 (m, OCH), 4.41 (s, OCH_2), 3.92–3.46 (m, 4H, NCH_2CHCH_2N), 3.37 (s, CH_3) ppm.

4-(4-Benzyloxy-2-phenylpyrazolidin-1-yl)benzaldehyde N,N-diphenylhydrazone (**5b**, $C_{35}H_{32}N_4O$)

Compound **5b** was prepared according to the procedure described above for **5a**, except that to a solution of 2.8 g **4** (7.8 mmol) in 30 cm^3 toluene:2-propanol = 1:1, the hot solution of 1.7 g *N*,*N*-diphenylhydrazine hydrochloride (0.0078 mol) in 10 cm^3 methanol was added. The time of the reaction was 1 h (eluent: acetone:*n*-hexane = 1:4). The mixture was extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$), filtered, and solvents were removed by rotary evaporation. The residue was purified by column chromatography using acetone:*n*-hexane = 3:22 as eluent. Fractions containing resulting product were collected and the eluent was evaporated. Then the 20% solution of **5b** in 14 cm^3 toluene was poured with intensive stirring into a 10-fold excess of *n*-hexane to obtain 2.8 g (69%) **7**; mp 168–170°C. ^{1}H NMR ($CDCl_3$): δ = 7.47–7.07 (several m, 25H, *Ph*, CH=N), 6.74–6.69 (m, 1H, 4-H CH_2-*Ph*), 6.55–6.52 (m, 4H, 1,4-disubstituted benzene), 4.61 (s, OCH_2), 3.91–3.89 (m, OCH), 3.45–3.22 (m, 4H, NCH_2CHCH_2N) ppm.

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