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LETTERS TO THE EDITOR

CYCLIZATION OF δ-[(*S*)-1-PHENYLETHYL]-AMINO ALCOHOLS TO FORM CHIRAL 1,3-DISUBSTITUTED PHTHALANES

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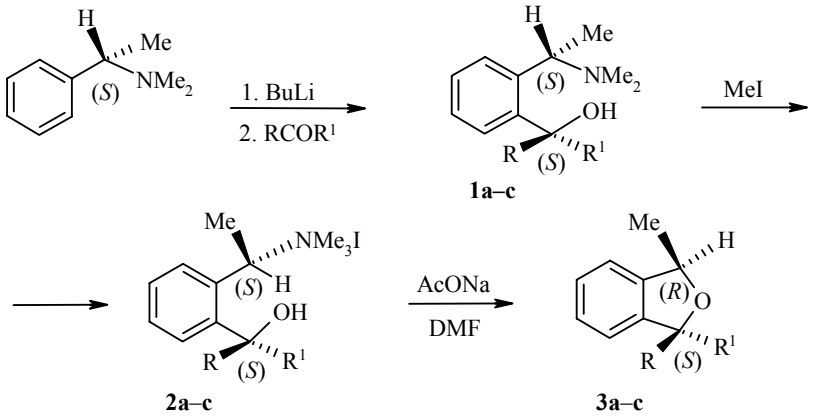
In studying the possibility of replacing the dimethylamino group in chiral δ-(1-phenylethyl)amino alcohols **1a-c** [1-3] by reaction of their iodomethylates **2a-c** with morpholine in the presence of sodium acetate, we observed that cyclization occurs with formation of optically active 1,3-disubstituted 1,3-dihydroisobenzofurans (phthalanes) **3a-c**. The dihydroisobenzofuran moiety is encountered in molecules of some natural and synthetic biologically active compounds [4], but there is almost no data available on chiral phthalanes. Further study of this reaction showed that it occurs similarly in DMF and DMSO, and in the presence of a number of salts (sodium and copper acetates, NaCl, NaCN, Na_2S) and NaOH, its rate increases considerably.



1a–c **2a–c** **3a–c**

1-3 a R = R^1 = Ph; **b** R+R^1 = C_5H_{10}; **c** R = 2,4-$Me_2C_6H_3$, R^1 = Ph

In cyclization of iodomethylates **2a,b** the optically active phthalanes **3a,b** are formed, i.e., the reaction occurs stereoselectively. In order to estimate the stereoselectivity, we conducted the cyclization of the iodomethylate of amino alcohol **2c** with two chiral centers. We obtained only one (according to ^{1}H NMR

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spectral data) out of the two possible diastereomeric 3-methyl-1-(2,4-dimethylphenyl)-1-phenyl-1,3-dihydroisobenzofurans (**3c**), which is evidence for stereospecificity of the reaction.

We assume that cyclization of iodomethylates **2a-c** occurs as an intramolecular nucleophilic substitution according to an S_N2 mechanism, i.e., with inversion of the configuration of the site that is attacked (the chiral center of the starting amine, which had an (*S*)-configuration). Thus in the phthalanes **3a-c** obtained, the C-3 atom should have an (*R*)-configuration. In the literature, (+)-3-methyl-1,3-dihydroisobenzofuran is described [5], for which an (*R*)-configuration has been established. The positive rotation we observed ($[\alpha]_D$ 131°) for phthalane **3a** may be confirmation for the (*R*)-configuration of the C-3 atom in this compound and consequently for the proposed mechanism. It is also likely that phthalanes **3b,c** are formed with inversion of the configuration of the center.

The increase in the reaction rate in the presence of salts and NaOH may be explained by the fact that the anions, having properties of bases, to some extent promote ionization of the hydroxyl group and its conversion to a good nucleophile, which intramolecularly attacks the benzyl carbon atom on the side opposite to the leaving trimethylammonium group.

We also isolate a small amount of the corresponding amino alcohol **1a-c** from the reaction mixture (1-2%, if the reaction is carried out in the presence of salts; and 10% in the absence of salts), the formation of which may be assumed to be the result of nucleophilic attack on the methyl group.

The ^{1}H NMR spectra were taken on a Varian XL-400 (400 MHz) in $CDCl_3$, internal standard TMS.

3-Methyl-1,1-diphenyl-1,3-dihydroisobenzofuran (3a). MeI (0.02 mmol) at 0°C was added to a solution of amino alcohol **1a** (5 mmol) in dry acetone (50 ml). The precipitated iodomethylate **2a** was filtered out and washed with dry ether; mp 232°C (decomposes). $[\alpha]_D$ -84° (*c* 1, ethanol).

A mixture of iodomethylate **2a** (5 mmol), sodium acetate (25 mmol) in freshly distilled DMF (20 ml) was refluxed for 5 h and then the DMF was driven off under vacuum; the residue was dissolved in water, alkalinized to pH 10-11, and extracted with ether. The ether extracts were washed with 1 N HCl solution and dried with $MgSO_4$. The ether was distilled off and the phthalane **3a** obtained (98% yield) was recrystallized from alcohol; mp 92°C, $[\alpha]_D$ 131° (*c* 1, ethanol). ^{1}H NMR spectrum, δ, ppm: 1.62 (3H, d, CH_3–CH); 5.30 (1H, q, C<u>H</u>–CH_3); 7.10-7.40 (14H, m, arom.). Found, %: C 87.79; H 6.43. $C_{21}H_{18}O$. Calculated, %: C 88.08; H 6.33.

3'-Methyl-3'-H-spiro[cyclohexane-1,1'-isobenzofuran] (3b) was obtained similarly from iodomethylate **2b**; mp 204°C (decomposes), $[\alpha]_D$ 10° (*c* 1, ethanol), and was purified chromatographically on a column with silica gel (Silica gel 60) in a benzene–acetone system, 10:1, R_f 0.8. Yield 50%. $[\alpha]_D$ -8° (*c* 2, ethanol). ^{1}H NMR spectrum, δ, ppm: 1.50 (3H, d, CH_3–CH); 1.60-1.90 (10H, m, C6H10); 5.28 (1H, q, C<u>H</u>–CH_3); 7.08-7.30 (4H, m, arom.).

3-Methyl-1-(2,4-dimethylphenyl)-1-phenyl-1,3-dihydroisobenzofuran (3c) was obtained similarly from the corresponding iodomethylate **2c**; mp 232°C (decomposes); $[\alpha]_D$ 33° (*c* 1, ethanol), yield 70%; mp 75°C; $[\alpha]_D$ -257° (*c* 1, ethanol). ^{1}H NMR spectrum, δ, ppm: 1.38 (3H, d, CH_3–CH); 1.95 (3H, s, *p*-CH_3); 2.30 (3H, s, *o*-CH_3); 5.45 (1H, q, C<u>H</u>–CH_3); 6.75-7.30 (12H, m, arom.).

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