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Stereochemical Features of the Condensation of Lithiated (*S*)-*N*,*N*-Dimethyl-1-phenylethylamine with *o*-Methoxybenzophenones

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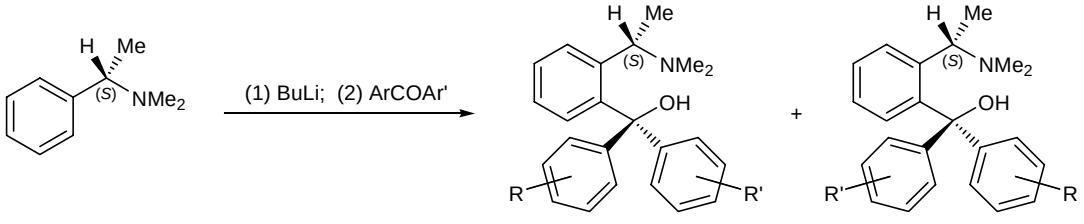
Abstract—The condensation of lithiated (*S*)-*N*,*N*-dimethyl-1-phenylethylamine with *o*-methoxybenzophenones occurs in a nonstereoselective fashion due to possible coordination of lithium not only at the carbonyl group but also at the oxygen atom of the *ortho*-methoxy group.

Lithiation of *N*,*N*-dialkylbenzylamines is known to involve the *ortho* position, leading to *o*,*o*'-disubstituted benzenes which cannot be obtained by other methods [1]. Lithiation of optically active *N*,*N*-dimethyl-1-phenylethylamine (**I**) at the *ortho* position, followed by condensation with carbonyl compounds, opens the way to chiral δ-amino alcohols; these compounds are promising difunctional reagents which, unlike β- and γ-amino analogs [2], have been studied poorly. δ-Amino alcohols attract interest as chiral ligands for asymmetric synthesis [3] and initial compounds for the preparation of chiral heterocycles [4].

We previously showed that the stereochemical result of the condensation of lithiated amine **I** (lithium derivative **II**) with unsymmetrical ketones strongly depends on the structure of the latter and that both steric and electronic factors of the carbonyl component are significant. The presence of a bulky alkyl group, e.g., *tert*-butyl, in alkyl phenyl ketone [5] or of two or three methyl groups in the *ortho* and *para* positions of benzophenone [6] makes the condensation highly stereoselective. We also found [6] that the high diastereoselectivity in the condensation of lithium derivative **II** with di- and trimethyl-substituted benzophenones is determined by joint action of steric (the presence of a methyl group in the *ortho* position) and electronic factors (positive inductive effect of the two methyl groups in positions *2* and *4*, regardless of whether they are located in the same or different rings). The importance of electronic factor is confirmed by 100% diastereoselectivity in the reaction of **II** with 3,4-dimethoxybenzophenone [7].

In the present work we examined reactions of lithiated amine **II** with 2-methoxybenzophenone and a number of dimethoxybenzophenones ArCOAr', analogs of 2,4-di-, 2,5-di-, and 2,4,6-trimethylbenzophenones which are known to react with **II** with high diastereoselectivity [6] to give the corresponding



I **III**–**VIII**

III, R = H, R' = 2,4-$(MeO)_2$; **IV**, R = H, R' = 2,5-$(MeO)_2$; **V**, R = H, R' = 2,6-$(MeO)_2$; **VI**, R = H, R' = 2-MeO; **VII**, R = H, R' = 2-MeO-4,6-Me_2; **VIII**, R = 2-Me, R' = 4-MeO.

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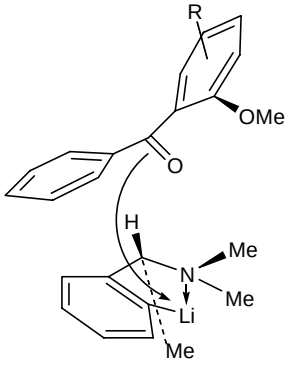
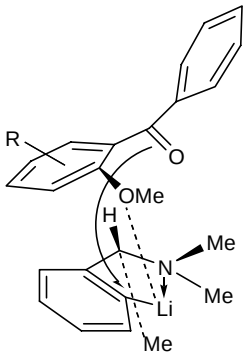
δ-amino alcohols having (*S*)-configuration of the new chiral (carbinol) center. The presence of a methoxy group in the *ortho* position implies increased number of potential coordination centers in the resulting amino alcohols which can be used as ligands for chiral complexes in asymmetric syntheses. In addition, methoxy groups could affect biological activity of amino alcohols; it is known that many biologically active substances contain a methoxy group which increases their lipophilicity.

The condensation of lithiated amine **II** with methoxy-substituted benzophenones was performed according to the procedure described previously [5–7], in a diethyl ether–hexane mixture at –70 and 20°C under argon. As a result, δ-amino alcohols **III**–**VIII** were obtained; their structure was proved by the IR and ^{1}H NMR spectra. The hydroxy group in the triarylmethanol fragment gives rise to IR absorption at 3200–2400 cm^{-1}, and the ^{1}H NMR spectra contain signals from the methoxy protons at δ 3–4 ppm and hydroxy proton at δ 9–10 ppm. The position and shape of the OH absorption band in the IR spectra and downfield shift of the hydroxy proton signal in the ^{1}H NMR spectra indicate formation of a strong intramolecular hydrogen bond in all amino alcohols **III**–**VIII**.

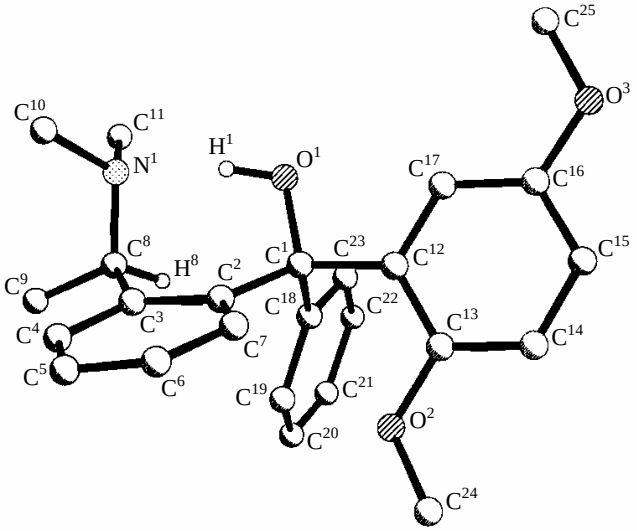
Diastereoisomeric δ-amino alcohols **III**–**V** were formed at a ratio of 1:1 (according to the intensity ratio of the NMe_2 and C**H**CH_3 signals in the ^{1}H NMR spectra). This result was unexpected, for we supposed that steric electronic effects of even one methoxy group in the *ortho* position of benzophenone would be sufficient to ensure stereoselective reaction. Therefore, one more factor should be taken into account, namely possible coordination of the lithium atom in **II** at the oxygen atom of the *ortho*-methoxy group. Such coordination could change mutual orientation of the reacting species in the transition state. We thus presumed two possible condensation schemes **A** and **B**. In



A



B



Structure of the molecule of (*R*,*R*)-2,5-dimethoxyphenyl-[*o*-(1-dimethylaminoethyl)phenyl]phenylmethanol (*R*,*R*)-(**IV**) according to the X-ray diffraction data.

the condensation of lithium derivative **II** with 2,4-dimethylbenzophenone, reported previously, the coordination of lithium occurred only at the carbonyl oxygen atom (scheme **A**), and the stereochemical outcome of the reaction depended on steric and electronic properties of the carbonyl compound [6]. In the reactions of **II** with 2-methoxy- and 2,4-, 2,5-, and 2,6-dimethoxybenzophenones, additional coordination of the lithium atom at the oxygen atom of the *ortho*-methoxy group in benzophenone is possible. As a result, orientation of the carbonyl compound with respect to the lithiated amine molecule changes, so that the substituted benzene ring of benzophenone appears closer to molecule **II** (scheme **B**).

The absence of stereoselectivity in the formation of amino alcohols **III**–**V** indicates that both schemes, **A** and **B** are equiprobable, i.e., the contribution of the coordination factor is approximately equal to the joint effect of the steric and electronic factors of two methoxy groups. Analysis of molecular models showed the lithium atom can coordinate only to an *ortho*-substituent having a heteroatom with a lone electron pair. This is supported by the lack of stereoselectivity in the condensation of lithium derivative **II** with benzophenones having a methoxy group in the *ortho* position and by 100% stereoselectivity in the condensation of **II** with 3,4-dimethoxybenzophenone. In the latter case, only one diastereoisomeric amino alcohol with *S*-configuration of the chiral center is obtained; i.e., approach of the reactants follows scheme **A** [7]. If a benzophenone molecule contains only one *ortho*

substituent (*o*-MeO) capable of coordinating lithium atom, its approach by the substituted ring may become predominating, and the stereoisomer ratio should differ from equimolar. In fact, the condensation of **II** with 2-methoxybenzophenone gave a mixture of diastereoisomeric amino alcohols **VI** at a ratio of 3:2.

We failed to separate diastereoisomeric δ-amino alcohols **III**–**V** by chromatography, but in the reaction with 2,5-dimethoxybenzophenone we isolated pure amino alcohol (*R*,*R*)-**IV** which partially crystallized from the mixture. The (*R*)-configuration of the new chiral center (C^1) was established by X-ray analysis taking into account the known (*R*)-configuration of the C^8 center in the initial amine (see figure) [amino alcohol **IV** was obtained from (*R*)-*N*,*N*-dimethyl-1-phenylethylamine, $[\alpha]_D^{20} = 69°$ (neat)].

A high stereoselectivity was observed in the condensation of **II** with 4-methoxy-2'-methylbenzophenone: diastereoisomeric alcohols **VIII** were formed at a ratio of 6:1. Here, the situation is analogous to the previously described reaction with 2,4'-dimethylbenzophenone (diastereoisomer ratio 9:1) [6].

We made an attempt to estimate the contributions of steric, electronic, and coordination factors using 2-methoxy-4,6-dimethylbenzophenone as carbonyl substrate. As a result, a mixture of diastereoisomeric amino alcohols **VII** was obtained at a ratio of 4:1. As shown in [6], the condensation of **II** with 2,4,6-trimethylbenzophenone is completely diastereoselective, i.e., it occurs according to scheme **A**. Replacement of one *ortho*-methyl group by methoxy reduces the stereoselectivity, indicating an appreciable contribution of scheme **B** due to coordination of lithium at the *ortho*-methoxy group. We cannot still conclude which approach, **A** or **B**, is preferred.

EXPERIMENTAL

The IR spectra were recorded in hexachloro-1,3-butadiene on a UR-20 spectrometer. The ^{1}H NMR spectra were obtained on a Varian XR-400 spectrometer (400 MHz) from solutions in $CDCl_3$ using tetramethylsilane as internal reference. The optical rotations ($[\alpha]_D^{20}$) were measured on an EPO-1 polarimeter (VNIEKIPRODMASh) from solutions in ethanol using 2.5- and 1-cm cells.

X-Ray diffraction study of a single crystal of amino alcohol (*S*)-**IV** was performed on an Enraf–Nonius CAD-4 diffractometer (MoK_α irradiation, graphite monochromator) at room temperature. Monoclinic crystals with the following unit cell parameters: a = 9.268(2), b = 8.802(2), c = 13.175(3) Å; β = 94.01(3)°, V = 1072.1(4) Å^3; d_{calc} = 1.21 g/cm^3; z = 2; space group $P2_1$. The structure was solved by the direct method and was refined by the least-squares procedure in full-matrix approximation. All hydrogen atoms were visualized by the difference synthesis of electron density. The position of the hydroxy hydrogen atom was refined in isotropic approximation, and the positions of the other hydrogen atoms were refined using the *rider* model. In the calculations, 2287 reflections with $I > 2\sigma(I)$ were used. The final divergence factors were $R(F) = 0.037$ and $\omega R(F^2) = 0.097$, GOF = 1.04.

Amino alcohols III–VIII (*general procedure*). A solution of 0.01 mol of lithium derivative **II** {obtained from amine (*S*)-**I**, $[\alpha]_D^{20} = -69°$ (neat)} in a 1:1 hexane–diethyl ether mixture was added dropwise with stirring under dry argon to a solution of 0.011 mol of the corresponding substituted benzophenone in 20–30 ml of dry diethyl ether. The mixture was stirred for 12 h and treated with 5–10 ml of water, and the aqueous phase was separated and extracted with diethyl ether (3×20 ml). The extracts were combined with the organic phase and washed with water and dilute (1:1) hydrochloric acid, the acid solution was made alkaline and extracted with diethyl ether, the extract was dried over $MgSO_4$, and the solvent was distilled off. Unreacted amine **I** was removed by vacuum distillation, bp 65°C (10 mm), and the residue was crystallized from appropriate solvent. The diastereoisomer ratio in the resulting amino alcohols **III**–**VIII** was determined from the ^{1}H NMR spectra of the reaction mixtures.

2,4-Dimethoxyphenyl[(*S*)-*o*-(1-dimethylaminoethyl)phenyl]phenylmethanol (III). Diastereoisomer ratio 1:1, yield 79%, mp 131°C (from ethanol), $[\alpha]_D^{20} = -91.9°$ (*c* = 1, ethanol). IR spectrum: ν_{OH} 3200–2700 cm^{-1}. ^{1}H NMR spectrum, δ, ppm: 1.08 d and 1.15 d (3H, C**H**$_3$CH), 2.04 s and 2.09 s [6H, N(CH$_3$)$_2$], 3.30 s and 3.47 s (3H, *o*-CH$_3$O), 3.78 s and 3.80 s (3H, *p*-CH$_3$O), 3.89 q and 3.94 q (1H, C**H**CH$_3$), 6.37–7.42 m (12H, H$_{arom}$), 9.23 s (1H, OH). Found, %: C 76.69; H 7.63; N 3.42. $C_{25}H_{29}NO_3$. Calculated %: C 76.69; H 7.47; N 3.58.

2,5-Dimethoxyphenyl[(*R*)-*o*-(1-dimethylaminoethyl)phenyl]phenylmethanol (IV) was synthesized from (*R*)-*N*,*N*-dimethyl-1-phenylethylamine (*R*)-(**I**), $[\alpha]_D^{20} = 69°$ (neat). Diastereoisomer ratio 1:1. Oily substance, yield 77%, $[\alpha]_D^{20} = 97.1°$ (*c* = 1, ethanol). IR spectrum: ν_{OH} 3200–2470 cm^{-1}. ^{1}H NMR spectrum, δ,

ppm: 0.95 d and 1.10 d (3H, C**H**$_3$CH), 1.95 s and 2.05 s [6H, N(CH$_3$)$_2$], 3.11 s and 3.20 s (3H, *o*-CH$_3$O), 3.55 s and 3.62 s (3H, *m*-CH$_3$O), 3.91 q (1H, C**H**CH$_3$), 6.61–8.23 m (12H, H$_{arom}$).

(*R*,*R*)-2,5-Dimethoxyphenyl-*o*-(1-dimethylaminoethyl)phenyl]phenylmethanol (*R*,*R*)-(IV) was isolated by recrystallization of diastereoisomer mixture **IV** from hexane, mp 146°C (from ethanol), $[\alpha]_D^{20}$ = 113.1° (*c* = 1, ethanol). ^{1}H NMR spectrum, δ, ppm: 1.09 d (3H, C**H**$_3$CH, *J* = 6.78 Hz), 2.08 s [6H, N(CH$_3$)$_2$], 3.40 s (3H, *o*-CH$_3$O), 3.69 s (3H, *m*-CH$_3$O), 3.96 q (1H, C**H**CH$_3$, *J* = 6.74 Hz), 6.77–7.42 m (12H, H$_{arom}$), 9.40 s (1H, OH). Found, %: C 76.80; H 7.58; N 3.53. $C_{25}H_{29}NO_3$. Calculated, %: C 76.69; H 7.47; N 3.58.

2,6-Dimethoxyphenyl[(*S*)-*o*-(1-dimethylaminoethyl)phenyl]phenylmethanol (V). Diastereoisomer ratio 1:1, yield 75%, $[\alpha]_D^{20}$ = –18.4° (*c* = 1, ethanol), mp 152°C (from ethanol). IR spectrum: ν$_{OH}$ 3200–2470 cm^{-1}. ^{1}H NMR spectrum, δ, ppm: 1.10 d and 1.32 d (3H, C**H**$_3$CH), 1.94 s and 2.09 s [6H, N(CH$_3$)$_2$], 3.33 s and 3.35 s (3H, *o*-CH$_3$O, *o*'-CH$_3$O), 3.93 q and 4.12 q (1H, C**H**CH$_3$), 6.40–7.52 m (12H, H$_{arom}$), 8.43 s (1H, OH). Found, %: C 76.64; H 7.69; N 3.69. $C_{25}H_{29}NO_3$. Calculated, %: C 76.69; H 7.47; N 3.58.

[(*S*)-*o*-(1-Dimethylaminoethyl)phenyl]-2-methoxyphenyl(phenyl)methanol (VI). Diastereoisomer ratio 3:2, yield 59%, oily substance, $[\alpha]_D^{20}$ = –85.1° (*c* = 2, ethanol). IR spectrum: ν$_{OH}$ 3200–2450 cm^{-1}. ^{1}H NMR spectrum, δ, ppm: 1.12 d and 1.17 d (3H, C**H**$_3$CH), 2.08 s and 2.13 s [6H, N(CH$_3$)$_2$], 3.31 s and 3.52 s (3H, *o*-CH$_3$O), 3.86 q and 4.01 q (1H, C**H**CH$_3$), 6.72–7.61 m (13H, H$_{arom}$), 10.2 s (1H, OH). Picrate, mp 201°C (from ethanol). Found, %: C 61.37; H 5.17; N 9.88. $C_{24}H_{27}NO_2 \cdot C_6H_3N_3O_7$. Calculated, %: C 61.01; H 5.12; N 9.49.

[(*S*)-*o*-(1-Dimethylaminoethyl)phenyl]-2,4-dimethyl-6-methoxyphenyl(phenyl)methanol (VII). Diastereoisomer ratio 4:1, yield 59%, $[\alpha]_D^{20}$ = –84.9° (*c* = 2, ethanol). IR spectrum: ν$_{OH}$ 3300–2900 cm^{-1}. ^{1}H NMR spectrum, δ, ppm: 1.07 d and 1.09 d (3H, C**H**$_3$CH), 2.08 s and 2.14 s [6H, N(CH$_3$)$_2$], 2.21 s and 2.22 s (3H, *p*-CH$_3$), 2.27 s and 2.22 s (3H, *o*-CH$_3$), 3.70 s and 3.71 s (3H, *o*-CH$_3$O), 3.93 q and 3.81 q (1H, C**H**CH$_3$), 6.50–8.05 m (11H, H$_{arom}$), 10.11 s (1H, OH). Found, %: C 79.98; H 8.24. $C_{26}H_{31}NO_2$. Calculated, %: C 80.17; H 8.02.

4-Methoxyphenyl[(*S*)-*o*-(1-dimethylaminoethyl)phenyl]-2-tolylmethanol (VIII). Diastereoisomer ratio 6:1, yield 59.5%, oily substance, $[\alpha]_D^{20}$ = –102.5° (*c* = 1, ethanol). IR spectrum: ν$_{OH}$ 3200–2400 cm^{-1}. ^{1}H NMR spectrum, δ, ppm: 1.10 d and 1.15 d (3H, C**H**$_3$CH), 2.08 s and 2.23 s [6H, N(CH$_3$)$_2$], 2.35 s and 2.26 s (3H, *o*-CH$_3$), 3.60 s and 2.99 s (3H, *p*-CH$_3$O), 4.03 q and 3.90 q (1H, C**H**CH$_3$), 6.40–8.02 m (12H, H$_{arom}$), 9.52 s (1H, OH). Picrate, mp 187°C (from ethanol). Found, %: C 61.80; H 5.27; N 9.53. $C_{25}H_{29}NO_2 \cdot C_6H_3N_3O_7$. Calculated, %: C 61.58; H 5.34; N 9.27.

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