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Regio- and Stereoselectivity of the Formation of 1,3-Oxazolidines in the Reaction of *l*-Ephedrine with Phenylglyoxal. Unexpected Rearrangement of 2-Benzoyl-3,4-dimethyl-5-phenyl-1,3-oxazolidine to 4,5-Dimethyl-3,6-diphenylmorpholin-2-one.

Felix Polyak*,[1] Tatiana Dorofeeva, Gunars Zelchans, and Gennady Shustov[2]

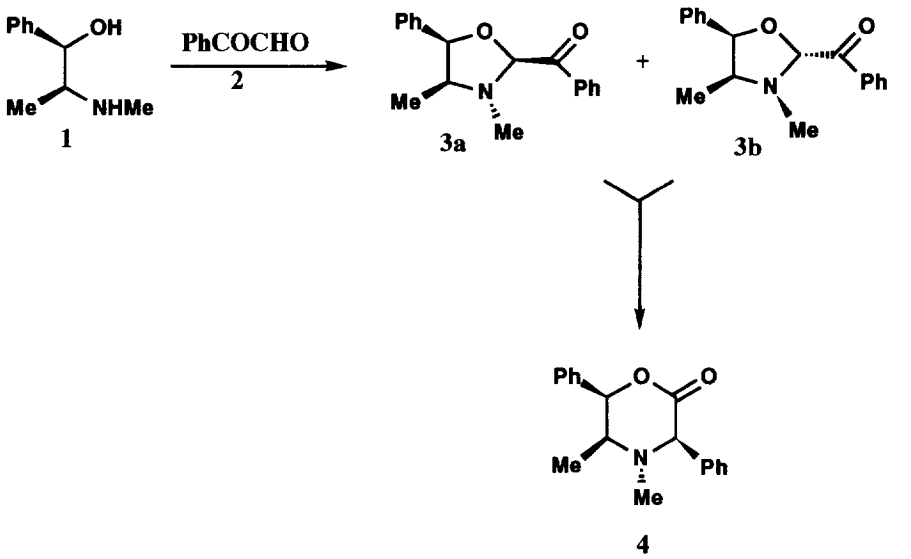
Institute of Organic Synthesis, Latvian Acad. Sci., 21 Aizkraukles str., Riga, LV-1006, Latvia

Abstract: *Optically active 2-benzoyl-3,4-dimethyl-5-phenyl-1,3-oxazolidines, obtained by the reaction of l-ephedrine with phenylglyoxal, after keeping without solvent undergo a spontaneous stereospecific rearrangement to 4,5-dimethyl-3,6-diphenylmorpholin-2-one.*

Optically active 1,3-oxazolidines, possessing a reactive functional group at the C-2 atom, are prospective intermediates for the resolution of racemic compounds[3] and in asymmetric reactions which take place under the control of the chiral centres of the oxazolidine ring.[4] As a rule these intermediates are easily obtained by the reaction of a carbonyl compound (or its acetal) with an optically active β-amino alcohol (i.e. ephedrine, norephedrine, amino alcohols derived from α-amino acids). Asymmetric reactions of this type are widely used and are characterised by a moderate to high optical yield. The variety of these reactions includes alkylation of aliphatic carbon[5], reactions of C=C bonds (oxidation[6], cycloaddition[7], addition of alkylcuprates[8], Diels-Alder reactions[9], addition of trimethylsilyl ether[10], intramolecular radical-mediated cyclization[11]), aldol addition[12] and reduction of α–carbonyl group[13]. Due to our interest in the asymmetric reduction of the carbonyl group[14] we tried to obtain a few 2-acyloxazolidines by the reaction of α–dicarbonyl compounds with *l*-ephedrine.[15]

The reaction of *l*-ephedrine with phenylglyoxal was carried out under the following conditions: **A.** A solution of *l*-ephedrine (1.65g, 10mmol) and phenylglyoxal-monohydrate (1.52g, 10mmol) in absolute ether (80ml) was kept in the presence of molecular sieves 4Å for 12 hours at 20°C. Then the reaction mixture was filtered and evaporated. **B.** A solution of the reagents in toluene (100ml) was boiled in the presence of a catalytic amount of Amberlyst-15 for 2 hours with azeotropic removal of water. **C.** A solution of the reagents in ethanol (80ml) was kept in the presence of molecular sieves 4Å for 2 hours at 20°C.

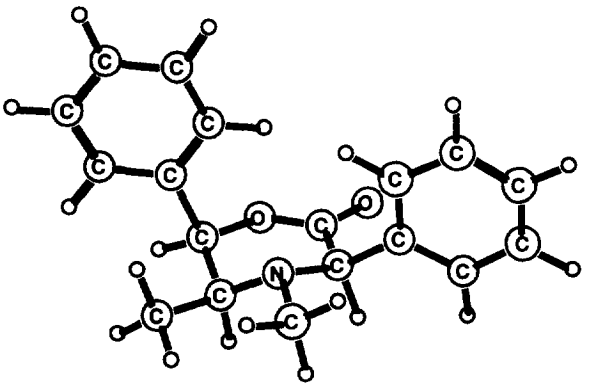
We found that in all cases the reaction was regiospecific and only 2-benzoyloxazolidine was obtained with a quantitative yield. It is a product of the condensation of *l*-ephedrine with the more electrophilic and therefore more reactive aldehyde group of phenylglyoxal.



2-Benzoyloxazolidine **3** was obtained as two diastereomers **3a** and **3b**.[16] The absolute configuration of **3a** - 2S,4S,5R and **3b**-2R,4S,5R was determined by ^{1}H NMR criteria.[17] The isomer with a substituent at C-2 cis to C4-Me and C5-Ph groups of the oxazolidine cycle has an upfield shift of the signals of C2-H (singlet at 4.92 ppm) and C5-H (doublet at 5.23 ppm); the isomer with a trans-substituent at C-2 has a downfield shift of these protons (5.57 and 5.44 ppm respectively) and their positions are interchanged.

In conditions **A** and **B** diastereomers **3a** and **3b** were obtained in a ratio ca.3/1 approximately, as in the case of the reaction of *l*-ephedrine with aromatic aldehydes.[17] This ratio is the result of thermodynamic control. Indeed, according to ^{1}H NMR spectra this ratio of diastereomers was observed only at the end of the reaction (in conditions **A** equilibrium was reached after 6 days), but at the beginning we observed the formation of the diastereomer **3b** only. At the same time in EtOH the diastereomer **3b** is predominant not only kinetically but also thermodynamically. This diastereomer was obtained as a single compound in the conditions **C**, and after keeping the solution in EtOH for 4 days at ambient temperature the ratio **3a**/**3b** is 12.5 : 87.5.

The viscous mixture of the diastereomers **3a** and **3b** becomes crystalline by keeping at ambient temperature for 12 days. The crystalline compound unexpectedly differs from oxazolidines **3a** and **3b** by its ^{1}H NMR spectra.[18] Its structure was established by X-Ray analysis as 4,5-dimethyl-3,6-diphenylmorpholin-2-one **4**.[19] This compound was found as a single (3R,5S,6R)-isomer. All attempts to detect another isomer by chromatographic or spectral methods failed. A small quantity (~ 6% by GC) of morpholinone **4** was found in the reaction product in conditions **B**. When we tried to observe the transformation of pure oxazolidine **3b** to **3a** and/or **4** in the different conditions, we noted that in the solution of EtOH or $CDCl_3$ only slow isomerisation to **3a** takes place (faster in $CDCl_3$), but after 4 days **3b** was predominant in the mixture and no traces of **4** were detected. In contrast, when pure **3b** was kept without solvent at ambient temperature, we observed both



X-ray structure of 4

processes. The equilibrium state **3a** / **3b** was achieved after 4 days and at this time 35% of **4** was observed in the mixture. The reasons for the formation of the morpholinone **4** by rearrangement of oxazolidines **3** and its stereospecifity are not clear to us, a study of the kinetics and mechanism of this rearrangement is in progress.

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1. Current address - Department of Chemistry, Technion - Israel Institute of Technology, Haifa 32000, Israel.

2. On leave from the Institute of Chemical Physics, Russian Academy of Sciences, Moscow, Russia. Present address: Department of Chemistry, University of Prince Edward Island, Charlottetown, P.E.I., Canada C1A 2R3.

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15. Chiral 2-acetyloxazolidine was obtained in the 3 steps from N-tosylnorephedrine and methacroleine[13].

16. Compound **3a**: ^{1}H NMR (200 MHz, $CDCl_3$, TMS), δ (ppm): 0.76 (3H, d, C4-Me, J= 6.4 Hz), 2.44 (3H, s, N-Me), 2.99 - 3.12 (1H, dq, C4-H, J_1= 6.4 Hz, J_2= 6.9 Hz), 4.92 (1H, s, C2-H), 5.23 (1H, d, C5-H, J= 6.9 Hz), 7.21 - 7.64 (8H, m) and 8.16 (2H, d, J= 8.9Hz) (protons of 2 benzene rings). Mass-spectrum (m/z; rel.int.,%): 281 (1.7) (M), 147 (25.7), 146 (55.3), 118 (100).
Compound **3b**: ^{1}H NMR (200 MHz, $CDCl_3$, TMS), δ(ppm): 0.73 (3H, d, C4-Me, J= 6.4 Hz), 2.47 (3H, s, N-Me), 3.64 - 3.77 (1H, dq , C4-H, J_1= J_2= 6.5 Hz), 5.44 (1H, d, C5-H, J= 6.6 Hz), 5.57 (1H, s, C2-H), 7.13 - 7.60 (8H, m) and 8.13 (2H, d, J= 8.8 Hz) (protons of 2 benzene rings). Mass-spectrum (m/z; rel.int., %): 281(2.3) (M), 147 (25.7), 146 (44.3), 118 (100).

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18. Compound **4**: Mp 144-145°C, $[\alpha]_D^{20}$ = - 40.5 (C1, EtOH). ^{1}H NMR (200 MHz, CDCl3, TMS), δ(ppm): 1.02 (3H, d, C5-Me, J= 6.8 Hz), 2.23 (3H, s, N-Me), 3.09 - 3.21 (1H, dq, C5-H, J_1= 6.8 Hz, J_2= 3.7 Hz), 4.11 (1H, s, C3-H), 5.44 (1H, d, C6-H, J= 3.7 Hz), 7.11 - 7.67 (10H, m, 2Ph). Mass-spectrum (m/z; rel.int., %): 281 (1.8) (M), 147 (25.5), 146 (45.5), 118 (100).

19. The X-Ray analysis of **4** : Empirical formula $C_{18}H_{19}NO_2$, orthorombic, $P2_12_12_1$, a = 7.278 (1), b = 11.269 (2), c = 18.433 (3) Å, V = 1511.8 (3) Å^3, Z = 4, D_x = 1.17 g cm^{-3}, Mo K_α radiation (grafite monochromator), λ = 0.70926 Å, μ = 0.5 cm^{-3}, F(000) = 568, room temperature, R = 0.062 for 1119 reflections.

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