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Regiospecificity and Conformational Specificity in Oxime Alkylation of a Geometrical Enantiomeric Isomer[1a]

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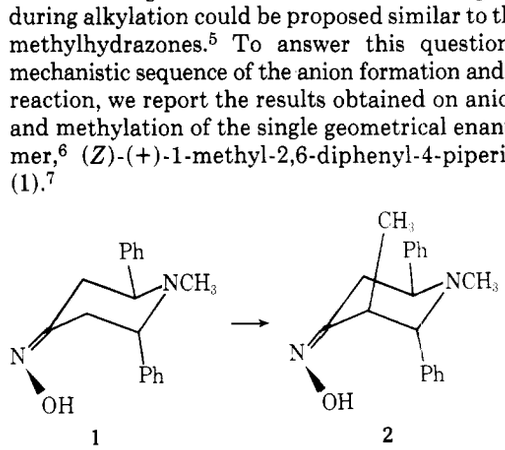
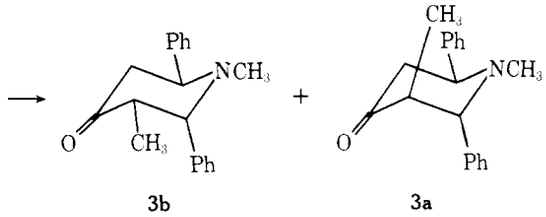
The reactions of electrophiles with the anions of oximes,[1] oxime ethers,[2] dialkylhydrazones,[3] and nitrosamines[1a,4] have been shown to occur with bond formation on the cisoid carbon and perpendicular to the plane of the functional group. This suggests that a cisoid arrangement of four overlapping p orbitals having six electrons produces more stable molecular orbitals than the transoid arrangement. These conclusions are based on structural assignments of the product of electrophilic reactions with the anion, and, although undoubtedly correct, do not provide absolute evidence for the stereochemistry of the reaction pathway. Recently, the dimethylhydrazone anion was shown to be formed by initial removal of the transoid proton with subsequent rearrangement of the stereochemistry to the cisoid anion before alkylation. This observation requires some reevaluation of the stereochemical specificity of the reactions of oximes. A process involving rotation about the carbon–nitrogen bond or inversion at nitrogen prior to or during alkylation could be proposed similar to that of the dimethylhydrazones.[5] To answer this question about the mechanistic sequence of the anion formation and electrophilic reaction, we report the results obtained on anion formation and methylation of the single geometrical enantiomeric isomer,[6] (*Z*)-(+)-1-methyl-2,6-diphenyl-4-piperidone oxime (**1**).[7]



1 **2**



3b **3a**

A sample of **1** ($[\alpha]^{25}_D$ +26.34° (*c* 0.331 g/100 mL); EtOH 95%) was shown to be 87% optically pure by ^1H NMR analysis of the NCH_3 in the presence of the chiral shift reagent Eu(tfc)$_3$.[10] The dianion of **1** was prepared with *n*-butyllithium and alkylated with methyl iodide to give 88% of (*Z*)-(2*R*,3*R*,6*S*)-1,3-dimethyl-2,6-diphenyl-4-piperidone oxime (**2**) ($[\alpha]^{25}_D$ −30.76° (*c* 0.331 g/100 mL); EtOH 95%). The optical purity of **2** was shown to be 86% based on the integration of the NMe signals or 80% based on the CMe signals. Since the singlet of the NCH_3 probably gave a more accurate analysis,

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the alkylation must have occurred with little or no loss of optical purity.

That the reaction of anion formation and alkylation occurred at the syn carbon was demonstrated by determining the absolute configuration of the (−)-1,3-dimethyl-2,6-diphenyl-4-piperidone (**3**) formed by hydrolysis of **2**. Reaction of **2** with pyridinium chlorochromate[11] gave a 56% yield of 1:1 mixture of the two epimers of **3a** and **3b**. This mixture gave a negative Cotton effect at 296 nm which by the ketone sector rule[12] confirmed the absolute configuration to be (−)-(2*R*,3*R*,3*S*,6*S*)-1,3-dimethyl-2,6-diphenyl-4-piperidone (**3a** and **3b**). The optical purity of the ketones was estimated to be 75% by ^{1}H NMR analysis using Eu(Tfc)$_3$.[10] The loss in chirality on hydrolysis of the oxime probably reflects the error in the determination of optical purity of the ketones (**3a** and **3b**).

These results clearly show the regiospecificity of the alkylation of the oximino dianion to be syn to the oximino oxygen and conformationally specific giving an axially substituted oxime. This series of reactions also provides a unique approach to stereochemical control of synthesis of substituted ketones via a chiral oxime.

Experimental Section

Stereospecific Alkylation of (*Z*)-2,6-Diphenyl-1-methyl-4-piperidone Oxime (1). A 0.5 M solution of 1.658 g (5.92 mmol) of (*Z*)-(+)-2,6-diphenyl-1-methyl-4-piperidone oxime, $[\alpha]_D$ +26.34°,[6] in anhydrous tetrahydrofuran was cooled to −80 °C under a stream of dry nitrogen. To the solution was added rapidly 5.918 mL (13.02 mmol) of 2.2 M *n*-butyllithium in hexane. The resulting solution was stirred under nitrogen at −10 °C for 45 min. The solution was cooled again to −80 °C, followed by the rapid addition of 0.379 mL (6.1 mmol) of iodomethane, and stirred between 0 and 5 °C for 2 h. The reaction mixture was hydrolyzed with 20 mL of water, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were dried over sodium sulfate and filtered through magnesium sulfate. Evaporation of the solvent furnished 1.8 g of **1** as a yellow solid. The product was recrystallized from aqueous ethanol to give 1.5 g (88%) of (*Z*)-(−)-(2*R*,3*R*,6*S*)-1,3-dimethyl-2,6-diphenyl-4-piperidone oxime (**2**): mp 187.9 °C; IR ($CHCl_3$) 3750, 3300, 1650, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (d, 3 H), 1.85 (s, 3 H), 2.30 (q, 1 H), 2.56 (t, 1 H), 3.5 (br, 1 H), 3.1–3.3 (m, 2 H); $[\alpha]^{25}_D$ −30.76° (*c* 0.331 g/100 mL, 95% EtOH). Only the product containing the axially oriented 3-methyl was observed.

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.68; H, 7.82; N, 9.55.

(−)-(2*R*,3*R*,3*S*,6*S*)-1,3-Dimethyl-2,6-diphenyl-4-piperidone (3a and 3b). To a suspension of 582 mg (2.7 mmol) of pyridinium chlorochromate in 6 mL of methylene chloride was added finely powdered sodium acetate and a solution of **2** in 15 mL of methylene chloride. The mixture started to turn black within a few seconds, but stirring was continued at room temperature for 35 h. The mixture was diluted with 100 mL of ether and filtered through Florisil. Evaporation of the solvent gave 200 mg of an oily residue. The crude product was chromatographed through silica gel to give 168 mg (56%) of 1:1 **3a** and **3b** as a yellow oil which crystallized: mp 131–132 °C; IR (neat) 1710^{-1}; NMR ($CDCl_3$) δ 0.74 (d, axial C-Me), 1.08 (d, equatorial C-Me), 1.75 (s) and 1.85 (s) (3 H, *N*-methyl), 2.3–3.6 (m, 5 H, Ar), 7.4 (m, 10 H); $[\alpha]^{25}_D$ −34.8° (*c* 0.775 g/100 mL; 95% ethanol), CD [θ] −853° cm^2/g at 296 nm (*c* 0.00755 g/cm^3 in 95% EtOH).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 82.07; H, 7.66; N, 5.00.

The picrate was prepared in ethanol to give a yellow solid, mp 170–171 °C.

Anal. Calcd for $C_{25}H_{24}N_4O_8$: C, 58.99; H, 4.82; N, 11.00. Found: C, 58.25; H, 4.72; N, 11.01.

Determination of the Optical Purity of 1, 2, and 3. To 51 mL of a 0.5 M solution (0.17 mmol) of the amine in deuteriochloroform was added 0.05 mL (0.005 mmol) of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III), Eu(tfc)$_3$, as a 0.1 M solution of deuteriochloroform. The NMR spectra of these solutions exhibited an NCH_3 singlet for the one isomer at δ 2.19 and a singlet at δ 2.00 for the other isomer. The intensities of the peaks showed a composition of 87 and 13% for **1** and 86 and 14% for **2**. The 3-methyl group for the (−)-isomer of **2** appeared as a doublet at δ 1.65 and a doublet at δ 1.85 for the (+)-isomer at a ratio of 80:20% (−:+). The original solution of oxime (**2**), now with 0.2 mL (0.002 mmol) of Eu(tfc)$_3$ in $CDCl_3$ (0.1 M), gave a broad singlet at δ 2.7 for the 3-methyl group of the (−)-isomer and a similar absorption at δ 3.1 for the (+)-isomer. A ratio of 4:1 (−:+) was calculated. The two *N*-methyl groups had collapsed into one broad singlet.

The NMR of the mixture of **3a** and **3b** showed no separation of the signal for the N methyl and the C methyl of **3b**. The axial methyl groups of the isomers of **3a** separated into two collapsed doublets at about δ 0.8. The optical purity was estimated from this ratio to be about 75%. This value is subject to considerable error due to problems in integration. Since **3b** was formed from **3a**, the optical purity of **3b** must be the same as **3a**.

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Registry No.—**1**, 64912-36-3; (−)-**2**, 64912-37-4; (+)-**2**, 64912-38-5; **3a**, 64912-39-6; **3b**, 64912-40-9; **3** picrate, 57162-51-3.

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Reactions of Dichlorobenzenes with Solvated Electrons in Liquid Ammonia[1a]

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Halobenzenes and other monosubstituted benzenes react with solvated electrons from alkali metals in liquid ammonia to give a phenyl radical and the anion of the leaving group.[2] Phenyl radicals can react with another electron and be further reduced to phenyl anions, which upon abstracting protons from ammonia gives, ultimately, benzene.[3]

Dichlorobenzenes were expected to react with solvated electrons step by step as halobenzenes do, and that would imply the formation of *o*-, *m*-, and *p*-chlorophenyl anions at some stage of the reaction. The *o*-chlorophenyl anion generated by other means in liquid ammonia has been shown to eliminate the chloride ion leading to benzyne, but no similar elimination of the chloride ion from the *m*- or *p*-chlorophenyl

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