Stereochemistry of the Mannich Reaction, Illustrated by the Aminomethylation of Diaziridine

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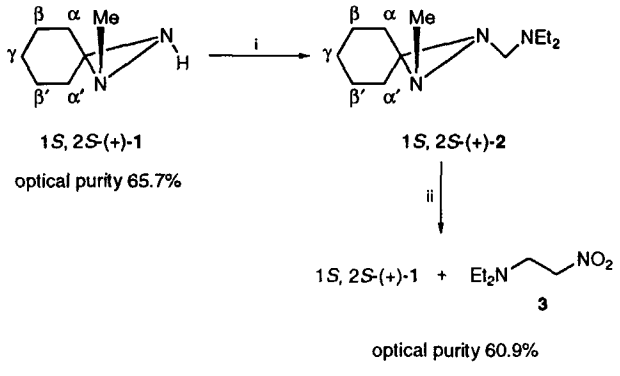
N-Aminomethylation of 1*S*,2*S*-(+)-1-methyl-3,3-pentamethylenediaziridine **1** by methoxymethyldiethylamine was achieved with apparent configuration retention.

The stereochemistry of reactions on the nitrogen atom is a grey area in organic chemistry due to the fast inversion of the atom in normal amines. The possibility of research in this field was opened up following the synthesis of compounds with an asymmetric nitrogen atom for which the absolute configuration was already known.[1,2] Thus, the asymmetric synthesis of diaziridines by reaction of *d*-10-camphorsulfonylketoximes with primary amines is proof of the cyclization mechanism itself.[3,4] It was shown that the Michael reaction with diaziridines was achieved with retention of nitrogen configuration.[5,6] Nucleophilic substitution at nitrogen in *N*-chloroisoxazolidines and the acid-catalysed 1,2-migration of *N*-methoxyisoxazolidine, accompanied with chirality transfer from nitrogen to carbon, took place with retention of optical activity.[7,8]

In this work the stereochemistry of the Mannich reaction was studied based on a model of a configurationally-stable optically-active amine with known absolute configuration, 1*S*,2*S*-(+)-1-methyl-3,3-pentamethylenediaziridine[5] **1**. It is known that diaziridines can readily react with alkoxymethylamines,[9] therefore methoxymethyldiethylamine[10] was used for aminomethylation of **1** (Scheme 1). The reaction was carried out in the presence of molecular sieves for isolating the methanol absorbtion. The optically active aminomethylation product **2** was obtained in high yield. In order to determine its absolute configuration the aminomethyl substituent was removed by treatment with nitromethane in a manner similar to the desoxymethylation of aziridinecarbinol with 2-nitropropane.[11] The initial diaziridine **1** was isolated from solution with negligible loss of optical purity.† Aminomethylation of **1** has therefore been carried out with apparent retention of nitrogen chiral centre configuration.

This unexpected result might be explained by prevention of attack by the aminomethylate reagent on the lone pair of the diaziridine nitrogen of the NH group, followed by deprotonation of intermediate **I** by the action of bases present in the reaction media and more rapid inversion of the aminomethylated nitrogen in comparison with the methylated one in intermediate **II** (Scheme 2). The latter becomes obvious from comparison of the inversion barriers of 1-substituted 2,2-dimethylaziridines (Table 1).

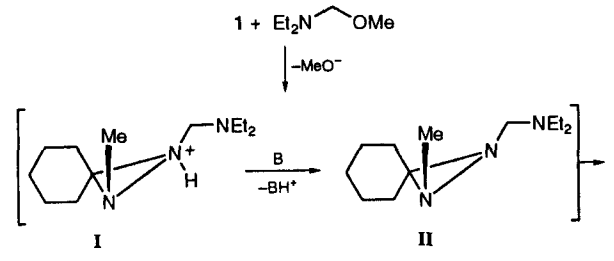


Scheme 1 *Reagents and conditions:* **1**[5], $[\alpha]_D^{20} = 58.7°$ (*c* 2.0 in n-C_7H_{16}), i, three-fold excess of $MeOCH_2NEt_2$ in the presence of molecular sieves (4 Å), 22 h at 20 °C yield of **2** 73.4%, $[\alpha]_D^{20} = 22.0°$ (*c* 2.0 in n-C_7H_{16}), ii, abs. $MeNO_2$, 19 h at 20 °C after evaporation and sublimation at 20 °C/1mm Hg, yield of **1** 17.9%, $[\alpha]_D^{20} = 53.6°$ (*c* 1.6 in n-C_7H_{16}); *in the reaction mixture*, substance **3** was identified by NMR spectroscopy.

† This can be explained by a decrease in the inversion barrier in diaziridines **1**,**2** in polar solvents[12] (MeOH, $MeOCH_2NEt_2$,$MeNO_2$), since in tests using solutions of **1** and **2** in n-C_7H_{16} for 2 days at 20 °C, optical activity decrease was not observed.

Table 1 Inversion barriers for nitrogen atom in aziridines $Me_2\overline{CCH_2NR}$.

R	ΔG_{inv}^{+}/kcal mol^{-1}	Ref.
Me_2NCH_2	15.9	13
Me	17.5	14



Scheme 2 Suggested mechanism of diaziridine **1** aminomethylation.

The structures of all newly-synthesised compounds were confirmed by NMR and elemental analysis data.‡

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‡ Spectroscopic data: ^1H NMR (400 MHz), ^{13}C (100.61 MHz), δ/ppm, *J* and Δν/Hz, $CDCl_3/CCl_4$ (1:1), standard TMS.

For **1**: ^{13}C: 24.46 (t, γ–C, $^1J = 127.9$), 24.74 (t, β–C, $^1J = 126.4$). 25.18 (t, β–C, $^1J = 126.4$). 27.14 (t, α–C, $^1J = 129.3$), 38.49 (t, α–C, $^1J = 127.9$), 39.35 (q, Me, $^1J = 135.2$), 60.59 (s, 3–C).

For **2**: ^1H: 1.11 (t, MeC, $^3J = 7.3$), 1.57 (t) and 1.62 [m, $(CH_2)_5$], 2.48 (s, MeN), 2.70 (m, CCH_2N, ABX_3 system, $\Delta\nu_{AB} = 24.17$, $^2J_{AB} = -12.7$, $^3J_{AX} = {}^3J_{BX} = 7.3$), 3.51 (m, NCH_2N, AB system, $\Delta\nu_{AB} = 148.7$, $^2J_{AB} = -12.7$); ^{13}C: 12.1 (qt, MeC, $^1J = 126.4$, $^2J = 2.9$), 24.38 (tp, γ–C, $^1J = 127.9$, $^2J = 4.4$), 24.73 (t, β–C, $^1J = 128.0$), 25.16 (t, β–C, $^1J = 127.9$), 29.08 (t, α–C, $^1J = 129.3$), 30.13 (t, α–C, $^1J = 127.9$), 38.12 (q, MeN, $^1J = 135.2$), 45.05 (tm, CCH_2N, $^1J = 132.2$, ^2J and $^3J \sim 4.4$), 62.43 (s, 3–C), 69.27 (tp, NCH_2N, $^1J = 143.8$, $^3J = 4.4$).

For **3**: ^1H: 1.04 (t, Me, $^3J = 7.3$), 2.56 (q, CH_2Me), 3.07 (t, CH_2N, $^3J = 6.0$), 4.41 (t, CH_2NO_2).

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