

REGIOSELECTIVITY IN BASE-PROMOTED IMINE FORMATION^{1,2}

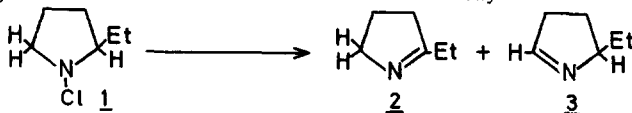
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Abstract. Specific base-solvent combinations control orientation in eliminations from N-chloro-2-ethylpyrrolidine to give substantial proportions of previously-unreported 5-ethyl-1-pyrroline.

In recent years, the influence of the base-solvent combination upon orientation in alkene formation by base-promoted 1,2-elimination reactions has been extensively investigated³. We now report the use of specific base-solvent systems to alter the regioselectivity of imine-forming elimination allowing for the preparation of a heretofore unreported cyclic imine.

In order to probe the regioselectivity of base-promoted imine formation, N-chloro-2-ethylpyrrolidine, 1, was selected as a model substrate. Dehydrochlorination of 1 can conceivably



produce the more substituted imine 2 and the less substituted imine 3. Although 2-alkyl-1-pyrrolines may be prepared by several methods^{4,5}, 5-alkyl-1-pyrrolines are unreported.

2-Ethyl-1-pyrroline, 2, was prepared by the method of Etienne and Correia⁴ and was reduced to 2-ethylpyrrolidine with NaBH₄ in MeOH⁶. The 2-ethylpyrrolidine (0.5-1.0 mmole) was stirred with a two-fold excess of N-chlorosuccinimide (NCS) in pentane (10 ml.) for 1 hour⁷. The mixture was filtered to remove succinimide and excess NCS and 1.0 ml. of MeOH or *t*-BuOH was added to the filtrate. The volume was reduced to 0.5 ml. *in vacuo*. To this solution of 1 was added MeONa-MeOH or *t*-BuOK-*t*-BuOH. Although the rapid formation of a precipitate was noted, the mixture was stirred at room temperature for 1 hour. Alternatively, the preparation of 1 from 2-ethylpyrrolidine was carried out in hexane. After filtration, *t*-BuOK was added to the hexane solution of 1 and the mixture was stirred at room temperature for 15-24 hours (the reaction appeared to be complete in about 3 hours). After the desired reaction periods, the reaction mixtures were clarified by centrifuging, anisole was added as an internal standard, and the solutions were analyzed by gas chromatography (20' x 1/8" column of 10% Carbowax 400 on Chromosort W at 90°C).

Relative proportions of 2 and 3 which result from reactions of 1 with MeONa-MeOH, *t*-BuOK-*t*-BuOH, and *t*-BuOK-hexane are recorded in the Table. In all cases, quantitative imine yields were realized. When the reaction mixture of 1 with *t*-BuOK-*t*-BuOH was stirred at room temperature for 3 days, the relative imine proportions and the imine yield were the same as those found after 24 hours. Since *t*-BuOK-*t*-BuOH was the most reactive base-solvent combination employed, this

Table. Orientation^a in Reactions of 1 with Various Base-Solvent Combinations

%2/%3	Base-Solvent		
	MeONa-MeOH ^b	t-BuOK-t-BuOH ^c	t-BuOK-Hexane
	96/4	73/27	58/42

^aRelative imine percentages were reproducible to +1%. ^bIdentical results were obtained with [1] = 0.20 M., [MeONa] = 0.25 M. and [1] = 0.39 M., [MeONa] = 1.66 M. ^cIdentical results were obtained with [1] = 0.02 M., [t-BuOK] = 0.25 M. and [1] = 0.20 M., [t-BuOK] = 0.25 M.

^dHeterogeneous base-solvent combination. Ratio of 1 to t-BuOK = 1.0 : 1.3-3.0.

result demonstrates kinetically controlled formation of 2 and 3 in all three base-solvent systems.

Eliminations from 1 induced by MeONa-MeOH exhibit high regioselectivity for the more substituted imine 2. However, the relative proportion of 3 was enhanced when MeONa-MeOH was replaced by the associated³ base-solvent system of t-BuOK-t-BuOH. An even higher percentage of 3 was obtained with the heterogeneous combination of t-BuOK-hexane. Fortunately, the ease of carbon-nitrogen double bond-forming elimination allows such selective base-solvent systems to be utilized.

From a larger scale reaction of 1 with t-BuOK-hexane, 3 was separated by preparative gas chromatography (20' x 1/4" column of 10% Carbowax 400 on Chromosorb W at 90-110°C). The isolated 3 gave a parent ion at m/e = 97. The infrared spectrum of 3 in CCl₄ showed C=N stretching absorption at 1630 cm⁻¹ (compared with 1651 cm⁻¹ for 2). The proton magnetic resonance spectrum of 3 in CCl₄ exhibited absorptions at 1.00 δ (triplet, 3H, -CH₂CH₃), 1.20-2.70 δ (unresolved, 6H, C-3 H, C-4 H, and -CH₂CH₃), 3.85 δ (multiplet, 1H, C-5 H) and 7.53 δ (unresolved, 1H, C-2 H).

The orientation data presented in the Table clearly establishes the utility of base-promoted elimination reactions for the preparation of previously-unavailable cyclic imines. Extension of this work to the synthesis of other 5-alkyl-1-pyrrolines and related larger ring heterocycles is in progress.

References and Notes

- 1) Partial support by The Robert A. Welch Foundation, Grant D-638, is gratefully acknowledged.
- 2) Taken in part from the MS thesis of GJB, Washington State University, 1974.
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(Received in USA 23 January 1979)