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A NEW ROUTE TO 8-SUBSTITUTED PYRROLIZIDINES[1]

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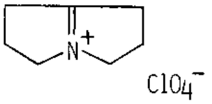
Abstract - A new route to 8-substituted pyrrolizidines starting with $\Delta^{4(8)}$-dehydropyrrolizidinium perchlorate is described.

Whereas one route to 8-substituted pyrrolizidines has been known, it suffered from disadvantages particularly of limited scope of the reaction, low overall yields, and use of high pressure hydrogenation devices[2,3]. Starting with $\Delta^{4(8)}$-dehydropyrrolizidinium perchlorate (1) which is now available in this laboratory[4], we have successfully developed a new general route to 8-substituted pyrrolizidines.

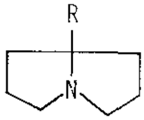

(1)

Thus, 8-cyanopyrrolizidine (2)[4], easily prepared from 1 and KCN in water, was converted to a new pyrrolizidinecarboxylate (3)[5], bp 106-110° C/ 22 mmHg, by refluxing in 20 % hydrogen chloride in ethanol containing 1 equiv. of water for 13 h. The yield was 82 %. Treatment of the carboxylate (3) with $LiAlH_4$ in anhydrous ether afforded 8-hydroxymethylpyrrolizidine (4)[2] in 75 % yield as a colorless oil. The direct reduction of the compound (2) with $LiAlH_4$ in anhydrous ether gave a new diamine; 8-aminomethylpyrrolizidine (5) in good yield. In these results, it is noteworthy that the reduction of 2 with $LiAlH_4$ gave the diamine (5) in contrast to the fact that the reduction of the higher congeners, 10-cyanoquinolizidine[6] and 9-cyanoindolizidine[7] , only resulted in the formation of quinolizidine and indolizidine, respectively, with splitting of the cyano group. The Grignard reaction of the iminium perchlorate (1) with benzylmagnesium bromide gave 8-benzylpyrrolizidine (6) in 83 % yield.

$$\begin{tikzcd}
(\underline{1}) \arrow[r, "KCN"] \arrow[d, "PhCH_2MgBr"] & (\underline{2}) \arrow[r, "HCl/EtOH", "H_2O\ (1\ equiv.)"'] \arrow[d, "LiAlH_4"] & (\underline{3}) \arrow[d, "LiAlH_4"] \\
(\underline{6}) & (\underline{5}) & (\underline{4})
\end{tikzcd}$$

Scheme 1

Table. 8-Substituted Pyrrolizidines.



Compound	R	Yield (%)^a	Bp (°C)[mmHg]	Mp (°C)
2	CN^b	83 (1)	93-94 [5]	225-226 (dec.)^d
3	COOEt	82 (2)	106-110 [22]	———
4	CH_2OH^c	75 (3)	76-77 [3]	249-253 (dec.)^e
5	CH_2NH_2	76 (2)	103-104 [30]	216-218 (dec.)^f
6	CH_2Ph	83 (1)	172 [43]	171-172^e
8	CH_2CN	65 (7)	143-144 [32]	227-231^e
9	CH_2COOMe	80 (8)	92-93 [7]	100-103^g
10	CH_2CH_2OH	88 (9)	93.5-94.5 [5]	208-211^e
11	$CH_2CH_2NH_2$	84 (8)	87-88 [6]	200^{h,i}

a Yields were based on the compounds in brackets.

b Values are from Ref. 4 .

c Known compound, see Ref. 2 .

d As methiodide.

e As picrate.

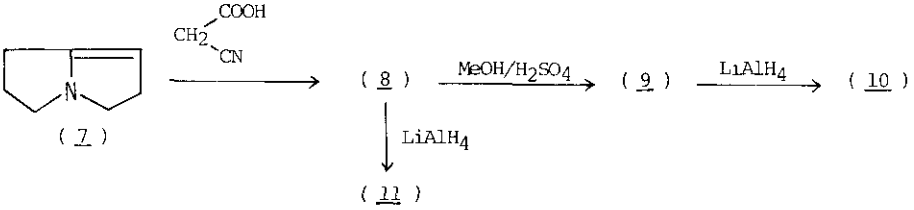
f As dipicrate.

g As hydrochloride.

h As dihydrochloride.

i With sublimation.

On the other hand, $\Delta^{1(8)}$-dehydropyrrolizidine (7)[4,8] liberated on treatment of the iminium perchlorate (1) with sodium hydroxide in ether is of potential reactivity. Refluxing the enamine (7) with cyanoacetic acid in dioxane afforded 8-cyanomethylpyrrolizidine (8) in 65 % yield, which in turn gave 9 , 10 , and 11 according to the conventional processes as shown in Scheme 2 .



Scheme 2

Thus, in terms of easily available starting materials, high overall yields, and variety of substituents, a convenient route to various 8-substituted pyrrolizidines is now provided.

References and Notes

1. Part IV in the series of studies on pyrrolizidines and related compounds. For Part III, see S. Miyano, S. Fujii, O. Yamashita, N. Toraishi, K. Sumoto, F. Satoh, and T. Masuda, *J. Org. Chem.*, in press.

2. N.J. Leonard and G.L. Shoemaker, *J. Am. Chem. Soc.*, **71**, 1762 (1949).

3. N.J. Leonard and K.M. Beck, *J. Am. Chem. Soc.*, **70**, 2504 (1948); N.J. Leonard, L.R. Hruda, and F.W. Long, *ibid.*, **69**, 690 (1947).

4. S. Miyano, T. Somehara, M. Nakao, and K. Sumoto, *Synthesis*, 701 (1978); K. Sumoto, S. Fujii, O. Yamashita, T. Somehara, and S. Miyano, *J. Het. Chem.*, in press.

5. I.R. (liq. film) : 1740 cm^{-1}(ester C=O), N.M.R. (CDCl$_3$, TMS as an internal standard) : δ 4.18 (q, 2H, J=7.0 Hz, -OC$\underline{H_2}$CH$_3$), 1.26 (t, 3H, J=7.0 Hz, -OCH$_2$C$\underline{H_3}$), and 1.4-3.3 ppm (m, 12H, pyrrolizidine ring protons), Mass(m/e) 183 (M$^+$), Anal. Calcd. for $C_{10}H_{17}NO_2$: C,65.54 ; H,9.35 ; N,7.64. Found : C,65.35 ; H,9.43 ; N,7.89.
The other new products listed in Table were adequately characterized by elemental analysis and spectroscopic methods.

6. N.J. Leonard and R.R. Sauers, *J. Am. Chem. Soc.*, **79**, 6210 (1957); N.J. Leonard and A.S. Hay, *ibid.*, **78**, 1984 (1956).

7. M.G. Reinecke and R.G. Daubert, *J. Org. Chem.*, **38**, 3281 (1973); M.G. Reinecke and R.F. Francis, *ibid.*, **37**, 3494 (1972), and also see reference 4. The reduction of 9-cyanoindolizidine with

LiAlH$_4$ in anhydrous ether gives indolizidine in quantitative yield (unpublished work in this laboratory).

8. Y. Arata, K. Tanaka, S. Yoshifuji, and S. Kanatomo, Chem. Pharm. Bull., **27**, 981 (1979).

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