The Preparation of N-Methylpyrrolidine Rings by 1,3-Dipolar Cycloaddition Reaction

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The 1,3-dipolar cycloaddition reaction has been studied from synthetic and mechanistic viewpoints, and is known to be strongly affected by the substituents of aziridines and olefins.¹⁾ But these works have not dealt with aziridines with a small N-substituent such as N-methyl group. As a preliminary approach to a new synthetic method of N-methylpyrrolidine rings which is a key step of nicotine synthesis, 1-methyl-2-phenylaziridine was synthesized and its photochemical and thermal 1,3-dipolar cycloadditions to olefins were studied.

FIG. 1.

Formylation of *dl*-phenylglycine methyl ester, using the procedure described by Sugi and Mitsui,²⁾ gave *dl*-methyl 2-formylamino-2-phenylacetate: NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 3.79 (3H, s), 5.71 (1H, d), 6.79 (1H, broad), 7.41 (5H, s), 8.27 (1H, s). The ester was reduced by lithium aluminum hydride in ether to give 2-methylamino-2-phenylethanol: 88.8%; bp 126~128°C (6 mmHg); NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 2.27 (3H, s), 3.40~3.85 (5H, m), 7.29 (5H, s). 1-Methyl-2-phenylaziridine was obtained by a method similar to that used for the preparation of arylaziridines³⁾: 68.1%; bp 67.5~68°C (6 mmHg); MS *m/e* 133 (*M*⁺); NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.57 (1H, d), 1.86 (1H, d), 2.26 (1H, q), 2.47 (3H, s), 7.22

(5H, s). Irradiation of a solution of 1-methyl-2-phenylaziridine in acrylonitrile or methyl acrylate for 40~50 hr with a 100 W high pressure mercury lamp gave four isomers (acrylonitrile: 39.5%, 5: 4.5: 4: 1; methyl acrylate: 28%, 4: 4: 2: 1). Repetition of the above reactions with a 100 W low pressure mercury lamp gave no adducts. The thermal reactions were also examined according to the method of Hiene and Peavy⁴⁾ but no adducts were obtained below 140°C. The reaction in an autoclave (350°C)⁵⁾ gave poor yields of the four isomers with dominant formation of polymers (acrylonitrile: 8%, 2: 2: 1: 1; methyl acrylate: 6%, 2: 2: 1: 1). These products were separated from each other by preparative vaporphase chromatography, and their structures were assigned on the basis of physical data.

In the case of acrylonitrile, besides the four isomers (I, II, III, IV), bis (β -cyanoethyl)amine was obtained: mp 150.5°C (HCl salt), MS *m/e* 83, 54, 40; NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.61 (1H, s), 2.55 (4H, t), 3.00 (4H, t); IR: 2250 cm⁻¹ (ν_{CN}).

The position of the substituent, CN, was determined by the coupling pattern of Ha proton. While the Ha signals of I and II in NMR spectra were of doublet, those of III and IV were of triplet. According to the reported spectra of nicotine and its derivatives,⁶⁾ this

FIG. 2. Mass Spectra of the Isomers.

means that I and II have a substituent at 3-carbon, and hence III and IV have a substituent at 4-carbon. Stereochemical assignments of I and II could be made on the basis of the magnitude of the coupling constant for the C-2 methine proton.⁶⁾ The value of $J_{\text{H}_a-\text{H}_b}$ for the *cis* isomer was 9.0 Hz and that for the *trans* isomer was 1.8 Hz. The configurations of III and IV could not be assigned because of the complex coupling patterns of He and Hf protons. These assignments are also supported by the mass spectra. Each of the four isomers was a 1:1 adduct of acrylonitrile and 1-methyl-2-phenylaziridine. The spectrum of I is very similar to that of II. On the other hand, those of III and IV resemble to each other. This suggests that the positions of the substituent in I and II are same, and so are in III and IV. Peaks at m/e 109, 132, 185 ($\text{M}-1^+$), 186 (M^+) were postulated from the studies of nicotine and its derivatives.⁷⁾

In the case of methyl acrylate and 1-methyl-2-phenylaziridine, each of the 1:1 adducts, V, VI, VII, VIII, gave the mass spectra with a small parent peak at m/e 219 and intense peaks at 142 and 111 which correspond, respectively, to the loss of phenyl group, and phenyl and $-\text{OCH}_3$ groups from the parent ion. These peaks of pyrrolidine ring moieties were also postulated from the studies on nicotine and its derivatives.⁷⁾ The positions of the substituents couldn't be determined, but the spectra of V and VI resemble to each other and the similarity suggests that the

positions of the substituent, $-\text{COOCH}_3$, are same. Similarly, it is expected that positions of the substituent in VII and VIII are same.

Of the four methods examined, either of the reactions with high pressure mercury lamp, and in an autoclave seems to be effective for the synthesis of 1:1 adducts which were expected to be based on the mechanism of 1,3-dipolar cycloaddition. Unreacted 1-methyl-2-phenylaziridine is relatively stable and was easily recovered unchanged from the reaction system. The application of these procedures for the synthesis of nicotine and its derivatives is now under progress.

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