CHEMISTRY LETTERS, pp. 231-232, 1982.

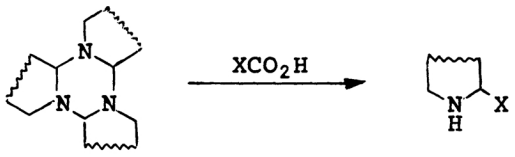
INTRODUCTION OF CARBON UNIT AT THE α-POSITION OF ALICYCLIC AMINES UTILIZING A DECARBOXYLATION REACTION WITH MALONIC ACID DERIVATIVES

Hidemichi FUKAWA, Yoshiyasu TERAO, Kazuo ACHIWA, and Minoru SEKIYA*
Shizuoka College of Pharmacy, 2-2-1 Oshika, Shizuoka 422

A new method for introducing carbon unit at the α-position of alicyclic amines has been exploited. The method involves a reaction of trimers of alicyclic imines with malonic acid derivatives, of which decarboxylation leads to a formation of carbon-carbon bond at the α-position of alicyclic amines.

Introduction of carbon unit at the α-position of alicyclic amines is of importance in synthesis of physiologically active alicyclic amines. The activation of α-position of alicyclic amines in advance by converting to imines,[1] N-chlorinated[2] or N-nitrosoated[3] amines or α-methoxylated amines[4] is necessary for this purpose. However, in the previous papers, the formation of these intermediates is not necessarily easy or the successive introduction of carbon unit has limited selectivity.

An alternative efficient method has been provided by a finding that tetracyclic hexahydro-1,3,5-triazines, trimers of alicyclic imines, available synthetically by dehydration of alicyclic amines by treatment with NaOCl,[5] $Na_2S_2O_8$[6] or N-chlorosuccinimide (NCS),[7] react with malonic acid derivatives, of which decarboxylated residues are introduced at the α-position of alicyclic amines.



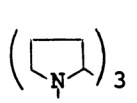
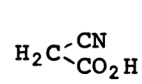
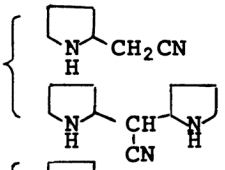
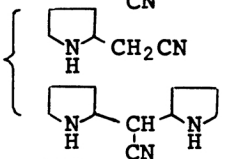
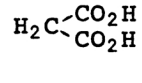
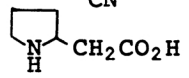
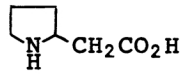
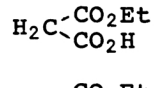
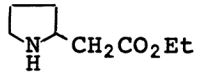
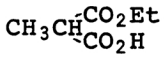
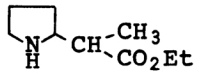
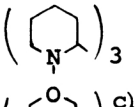
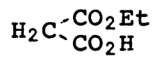
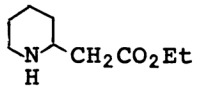
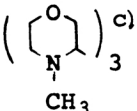
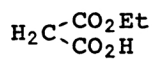
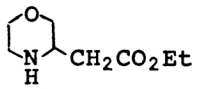
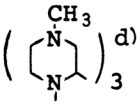
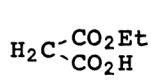
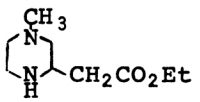
X : CH_2CN, CH_2CO_2Et, $CH(CH_3)CO_2Et$

Using 1-pyrroline trimer as a substrate, results of experiments with malonic acid derivatives, i.e., cyanoacetic acid, monoethyl malonate, and monoethyl methylmalonate, are summarized in Table 1. As can be seen, addition of triethylamine improved the yields of the products. The reaction with monoethyl malonate was extended to the use of other trimers as also shown in Table 1.

A typical experiment is as follow. A solution of 1-pyrroline trimer (0.02 mol), monoethyl malonate (0.12 mol), and triethylamine (0.12 mol) in 50 ml of acetonitrile was heated with stirring at 35-40°C until evolution of carbon dioxide ceased. After removal of the solvent, the residue was submitted to distillation to give ethyl 2-pyrrolidylacetate, bp 58-60°C (0.4 Torr), 5.9 g (63 %).

All the products, which are derivatives of alicyclic β-aminoacids, are expected to be transferred, by the known methods, into a variety of bicyclic β-lactams, one of the most biologically important groups.

Table 1.

Trimer	RCO_2H	Method[a]	Reaction (°C)	Condition (hr)	Product[b]	Yield (%)
		A	34-40	3.5		7 41
		B	50-55	3		47 35
		A	45-55	2		14
		B	55-60	2.5		57
		B	35-40	2		63
		B	65-70	2		59
		B	30-35	3		61
 c)		B	55-60	5.5		51
 d)		B	50-55	1.5		45

a) A : Trimer/RCO_2H = 1/6 (molar proportion), B : Trimer/RCO_2H/NEt_3 = 1/6/6 (molar proportion), Solv. : CH_3CN. b) All products gave satisfactory elemental analyses and their spectral data were consistent with the indicated structure. c) Newly prepared from morpholine by treatment with NaOCl according to the previous method,[5] bp 110-113°C(23 Torr). d) Newly prepared from N-methylpiperazine by treatment with NCS according to the previous method,[7] bp 86-88°C(0.5 Torr).

References

1) J. M. Grisar, G. P. Claxton, K. T. Stewart, R. D. Mackenzie, and T. Kariya, J. Med. Chem., 19, 1195 (1976); F. E. Scully, Jr., J. Org. Chem., 45, 1515 (1980).

2) G. Stork, R. M. Jacobson, and L. Levitz, Tetrahedron Lett., 1979, 771.

3) D. Seebach, D. Senders, and B. Renger, Chem. Ber., 110, 1852 (1977); B. Renger, H-O. Kalinowski, and D. Seebach, ibid., 110, 1866 (1977).

4) T. Shono, Y. Matsumura, and K. Tsubata, J. Am. Chem. Soc., 103, 1172 (1981).

5) C. Schöpf, A. Komzak, F. Brawn, and E. Jacobi, Liebigs Ann. Chem., 559, 1 (1948).

6) Y. Nomura, K. Ogawa, Y. Takeuchi, and S. Tomoda, Chemistry Lett., 1977, 693.

7) J. M. Grisar, G. P. Claxton, and K. T. Stewart, Synthesis, 1974, 284.

(Received November 30, 1981)