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PYRROLIDINES FROM α-AMINO-ACIDS DERIVATIVES

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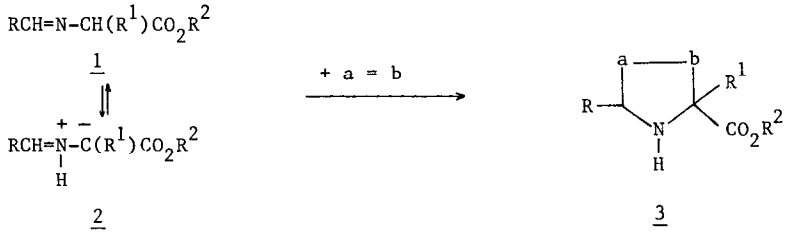
ABSTRACT : On heating with benzaldehyde and alkenes, N-alkylamino acids derivatives lead to pyrrolidines.

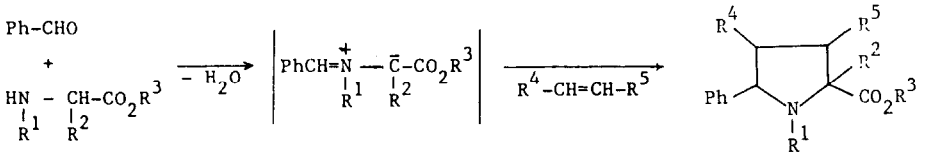
Imines 1, potential azomethine ylides 2 were reacted with dipolarophiles to give NH-pyrrolidines 3[1,2].



In the same way, α-*aminoacids* and carbonyl compounds gave rise to in situ azomethine-ylide formation which lead to pyrrolidines by addition to dipolarophiles probably via an intra[3] and an intermolecular[4,5,6] 1,3-dipolar cycloaddition.

The recent publication of two papers dealing with *intramolecular cycloaddition* starting from α-*aminocarboxylates* and carboxyl derivatives[7,8] prompted us to disclose our own results related to the analogous intermolecular reaction.

The general scheme for this reaction is as follow :



4

5 - 8

9 - 19

4a : $R^1 = CH_2Ph$; $R^2 = H$; $R^3 = Me$

4b : R^1, $R^2 = (CH_2)_4$; $R^3 = Et$

4c : R^1, $R^2 = (CH_2)_3$; $R^3 = Me$

5 : (E) ; $R^4 = R^5 = CO_2Me$

6 : (Z) ; $R^4 = R^5 = CO_2Me$

7 : R^4, R^5 = -CO-N(Me)-CO-

8 : $R^4 = CO_2Me$; $R^5 = Ph$

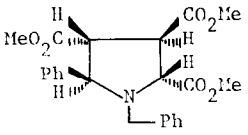
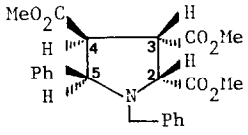
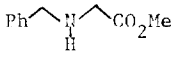
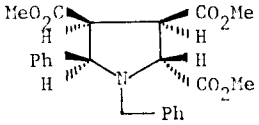
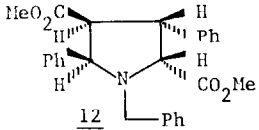
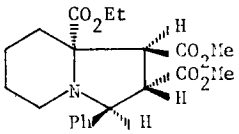
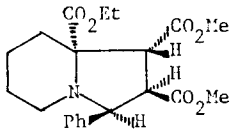
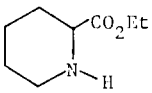
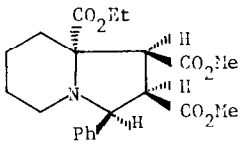
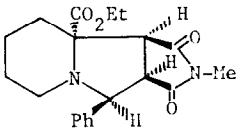
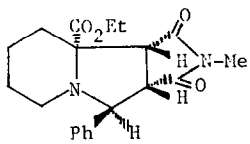
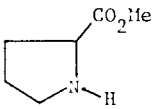
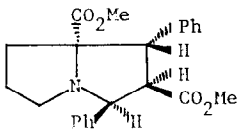
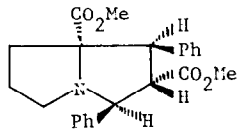
In practice the reaction was carried out by reacting benzaldehyde, α-aminoester 4 and alkenes 5-8 in refluxing toluene for several hours and driving out the water by means of a Dean-Stark trap. After removal of the solvent under vacuum, the crude pyrrolidines 9-19 were obtained in nearly quantitative yields (table). Spectroscopic data were in agreement with the proposed structures[9].

The assigned stereochemistry for carbons 4 and 5 was established on the basis of the upfield chemical shift of a methyl group when ester and phenyl groups are in a cis position[10]. This occurs for pyrrolidines 10 and 11.

The relatives configurations at C_2 and C_5 and at C_3 and C_4 for pyrrolidines 9-12 were deduced from the X-ray analysis of 11[9] (Scheme 1a) ; phenyl and carboxyl group were in a trans relationship and substituents at C_3 and C_4 were assumed to keep the same stereochemistry from the alkene[11].

The change of stereochemistry at C_3 and C_4 for indolizidines 13 and 14 issued from the reaction of 4b and 6 could arise from the initial base induced isomerisation of 6 to 5 -mixing 4b and 6 in the same reaction condition gave 4b and 5 on 4 hours- but we could not exclude the possible isomerization at the pyrrolidine ring itself ; at the end of the normal reaction of 4b, benzaldehyde with a slight excess of 6, some of this last compound was recovered unchanged.

X-ray crystal analysis for 13[9] (Scheme 1b) issued from the former reaction confirmed the stereochemistry and clearly indicated the relative configuration at C_2 and C_5 which was extended by analogy to the other indolizidines and pyrrolizidines 13-19.

α-Aminoesters	Alkenes	Cycloadducts	Yield
	5	 9  10	95 %
 4a	6	 11 (F = 106°)	75 %
	8	 12	10 %
	5	 13 (F = 76-77° ; 50 %)  14 (50 %)	95 %
 4b	6	 15 (10 %) + 13 (45 %) + 14 (45 %)	95 %
	7	 16 (F = 129° ; 75 %)  17 (25 %)	95 %
 4c	8	 18 (50 %)  19 (F = 149° ; 50 %)	90 %

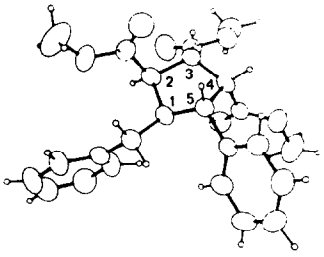


Schéma 1a

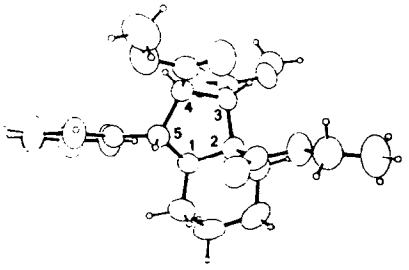


Schéma 1b

We are investigating other applications of this pyrrolidine ring formation.

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