

2,5-Unsubstituted Pyrrolidines from Formaldehyde and Amino Acids through *in situ* Azomethine-ylide 1,3-Dipolar Cycloaddition to Alkenes

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Formaldehyde and α -amino acids such as sarcosine and glycine react with alkenes to give *N*-Me and *N*-H pyrrolidines *via in situ* generated azomethine-ylides.

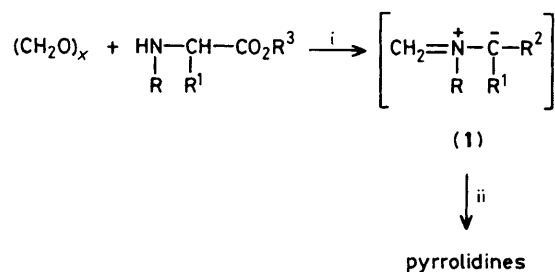
Non-stabilized azomethine-ylides are valuable synthons in pyrrolidine synthesis. In the past years several original synthetic methods have appeared, mainly desilylation reactions from iminium precursors¹ and base-induced elimination from amino derivatives.²

The direct condensation of α -amino acids and α -amino acid derivatives with aldehydes and ketones has received some recent applications³ but, to our knowledge, no reaction involving the parent compound formaldehyde and α -amino acids has been reported.

Table 1. *N*-Methyl-2,5-unsubstituted pyrrolidines.

Alkene	Product (yield) ^{a,b}		¹³ C N.m.r. ^c		
			C-2 or C-5	C-3 or C-4	Me(N)
Methyl acrylate	 (2)	(88)	58.48 (t) 55.74 (t)	42.33 (d) 28.20 (t)	41.66 (q)
Methyl maleate	 (3)	(92)	58.05 (t)	45.68 (d)	41.79 (q)
Methyl fumarate	 (4)	(75)	58.72 (t)	45.75 (d)	41.48 (q)
Methyl (<i>E</i>) cinnamate	 (5)	(68)	59.51 (t) 63.96 (t)	47.51 (d) 51.90 (d)	41.85 (q)
Dimethyl benzylidene-malonate	 (6)	(90)	61.94 (t) 62.80 (t)	65.72 (s) 49.77 (d)	41.73 (q)

^a Yields refer to isolated products from bulb to bulb distillation. ^b All compounds gave spectroscopic data in good agreement with the proposed structures. 500 MHz ¹H n.m.r. [WM 500 Bruker (D. Davoust, Centre de Spectroscopie, Université, P. et M. Curie, Paris)], 300 MHz ¹H n.m.r. (AM 300 WB Bruker), mass spectrometry (Varian MAT 311), ¹³C n.m.r. (Jeol FX 100, WP 80 DS Bruker) were recorded by MM. S. Sinbandhit, J. Y. Le Gall, and P. Guénot, Centre de Mesures Physiques de l'Ouest.



Scheme 1. i, Refluxing benzene or toluene; $-\text{H}_2\text{O}$, Dean–Stark trap; ii, alkene.

The reaction of paraformaldehyde with α -amino acid derivatives leads to the reactive methylene azomethine-ylides (1) which undergo 1,3-dipolar cycloaddition reactions with alkenes to give pyrrolidines in a one-pot three component reaction, Scheme 1.

Depending on the nature of R^3 , two different azomethine-ylides (1) can result: with $\text{R}^3 = \text{H}$, decarboxylative dehydration occurs leading to non-stabilized azomethine-ylides (1), $\text{R}^2 = \text{H}$, and with $\text{R}^3 \neq \text{H}$, stabilized azomethine-ylides (1), $\text{R}^2 = \text{CO}_2\text{R}^3$, are formed.^{3h,4}

We report here our first results with sarcosine[†] and glycine. Thus paraformaldehyde, sarcosine, and alkenes [such as methyl acrylate, maleate, fumarate, cinnamate (*E*), and benzylidene malonate] in refluxing benzene for several hours give 2,5-unsubstituted pyrrolidines (2)–(6) in good yields (Table 1).

In the same way paraformaldehyde, glycine, and methyl fumarate in refluxing toluene with a Dean–Stark trap for seven hours leads to pyrrolidine (7) (85% based on n.m.r. spectroscopy). With methyl maleate a mixture of pyrrolidines (8) + (7)[‡] is recovered (80:20 based on n.m.r. spectroscopy).§

If 1,3-dipolar cycloaddition reactions are involved in this three component pyrrolidine synthesis³ we assume that the parent azomethine-ylide (9) is generated in these conditions.

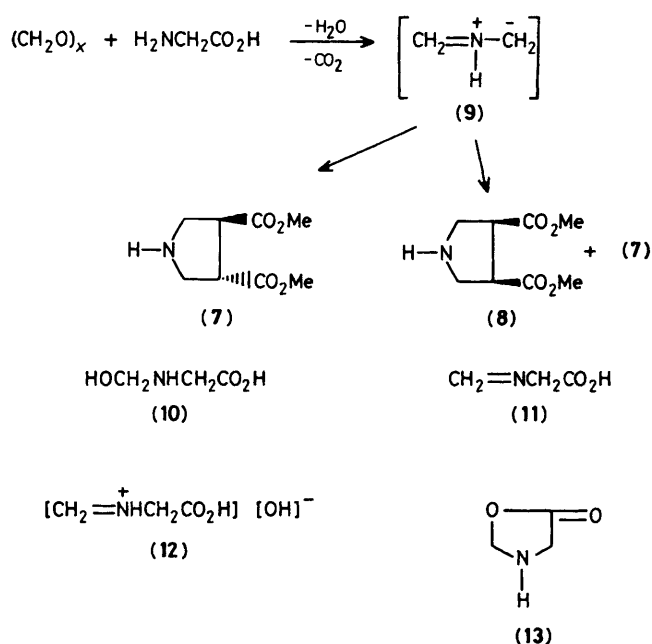
Azomethine-ylides in this reaction could arise from several intermediates. For instance (9) could be generated through the initial hydroxymethylglycine intermediate (10) which could equilibrate with (11), (12), and (13). All four intermediates could give rise to the parent azomethine-ylide (9).

The fact that an oxazolidinone^{3b} reacts with tetramethoxycarbonyl ethylene to give pyrrolidine is not significant enough to determine which intermediates are involved.

[†] Sarcosine gives a quantitative intramolecular cycloaddition adduct with *o*-allylsalicylaldehyde by direct condensation without use of the silylated sarcosine as was previously reported (ref. 3e).

[‡] (7) m/z 187, M^+ , $\text{C}_6\text{H}_{13}\text{NO}_4$; calc. 187.08445, found 187.0844; 300 MHz ^1H n.m.r.: 3.76 (s, 6H), 3.44 (m, 2H), 3.20 (d, 1H, NH), 3.00 (m, 2H), 2.85 (m, 2H); ^{13}C n.m.r.: C-2, C-5: 55.10 (t), C-3, C-4: 45.29 (d), MeO: 52.19 (q); C=O: 173.95 (s); i.r. (film) $\nu_{\text{N-H}}$: 3445 (w), $\nu_{\text{C=O}}$: 1730 cm^{-1} (s). (8) m/z 187, M^+ , $\text{C}_6\text{H}_{13}\text{NO}_4$; calc. 187.08445, found 187.0844; 300 MHz ^1H n.m.r.: 3.66 (s, 6H), 3.35 (s, 1H, NH), 3.28 (m, 2H), 3.17 (m, 2H), 2.84 (m, 2H); ^{13}C n.m.r.: C-2, C-5: 54.42 (t), C-3, C-4: 45.25 (d), MeO: 51.85 (q), C=O: 173.03 (s); i.r. (film) $\nu_{\text{N-H}}$: 3445 (w); $\nu_{\text{C=O}}$: 1730 cm^{-1} (s).

§ Depending on the reaction conditions variable amounts of pyrrolidines (3) and (4) have been obtained together with (7) and (8); (7) could arise from the isomerisation of methyl maleate by the base catalysis from pyrrolidine (8) in these reaction conditions; for similar results see ref. 3h.



The scope of this reaction, using other aldehydes and/or other α -amino acids and derivatives,[¶] is under active investigation.

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¶ For instance proline and methyl acrylate gave four compounds both regio- and stereo-isomers in equivalent amounts. This is in agreement with the general behaviour of methyl acrylate in 1,3-dipolar cycloaddition reactions with other 1,3-dipoles, ref. 5.