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AMINO ACID APPROACH AS A GENERAL ROUTE TO NONSTABILIZED AZOMETHINE YLIDES. FACILE GENERATION OF PARENT METHANIMINIUM METHYLIDE AND ITS 1-MONO- AND 1,1-DISUBSTITUTED DERIVATIVES

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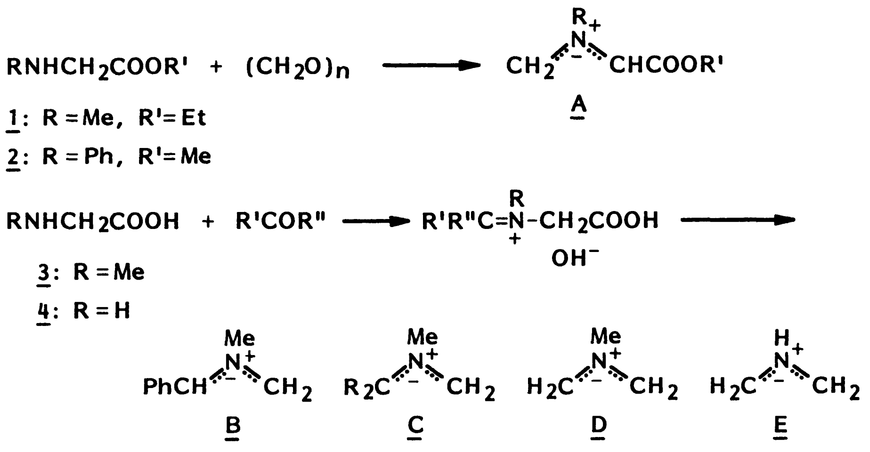
Decarboxylative condensation of glycine or N-substituted glycines with a variety of carbonyl compounds such as formaldehyde, aromatic aldehyde, or ketones is a convenient and general route to parent methaniminium methylide and its 1-mono- and 1,1-disubstituted derivatives with or without an N-substituent.

Rapidly growing interest in heterocyclic synthesis using 1,3-dipolar cycloaddition reactions arises from the recent discovery of new generation methods for nonstabilized ylides.[1,2] Although desilylation of N-(silylmethyl)iminium salts or 1,3-elimination of N-alkoxymethyl and N-cyanomethyl silylmethylamines is useful as an access to nonstabilized azomethine ylides, variation of substituents on the ylide carbon is quite limited.[3,4]

Conceptually, azomethine ylides can be available by elimination of a cationic leaving group at the α-position of iminium salts, and the most direct approach to iminium salts is condensation between secondary amines and carbonyl compounds. As it is known that thermal decarboxylation of 2-imino acids can generate azomethine ylides,[5] a condensation of N-substituted 2-amino acids with carbonyl compounds and decarboxylation sequence looks promising as a general route to nonstabilized azomethine ylides.[6] However, no such reaction has been reported so far,[7] and synthetic versatility of this and related sequence is ambiguous.

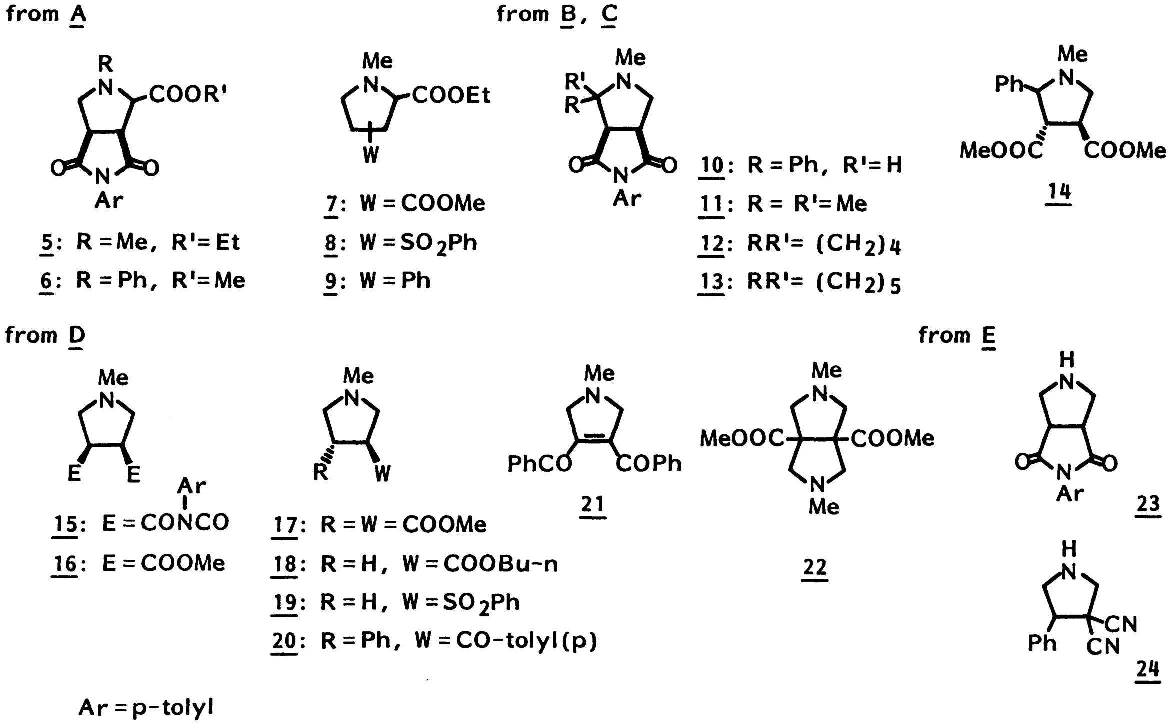
The present communication describes the first use of formaldehyde as a carbonyl compound in the condensation with N-substituted 2-amino esters. This reaction leads to ester-stabilized azomethine ylides carrying no additional substituent at the carbon. The decarboxylative condensation of N-substituted 2-amino acids with carbonyl compounds is next shown as a general and effective way to nonstabilized azomethine ylides with a variety of substituents. As an extension of this method, the decarboxylative condensation of glycine with formaldehyde is tested, and the first generation of parent methaniminium methylide is described.[8]

We first investigated the reaction of ethyl 2-(methylamino)acetate $\underline{1}$ or methyl 2-anilinoacetate $\underline{2}$ with paraformaldehyde, because direct generation of azomethine ylides by the condensation of formaldehyde with 2-amino acids or esters has not been reported.[9] A mixture of $\underline{1}$ or $\underline{2}$ and excess of paraformaldehyde (5 equiv.) was



Scheme 1.

heated under reflux in toluene in the presence of N-(p-tolyl)maleimide as a ylide trapper. The water formed during the condensation was removed by the aid of Dean-Stark trap. High yield formation of cycloadducts 5, 6 indicates that the condensation between N-substituted 2-amino esters and formaldehyde works well as a new generation method for simple ester-stabilized azomethine ylides A (Scheme 1). In many respects, the present method looks more useful than the previous method which involves thermal ring opening of 1-substituted aziridine-2-carboxylates.[10,11] Although ylide A is reactive not only to electron-deficient olefins but also to such a nonactivated olefin as styrene,[12] stereo- and regioselectivity of this reaction is very poor (cycloadducts 5-9 in Scheme 2 and Table 1).



Scheme 2.

Heating a mixture of sarcosine 3 and carbonyl compounds under reflux in toluene resulted in smooth generation of nonstabilized azomethine ylides (Scheme 1). This procedure can offer a convenient and general approach to the ylides with a variety of substituents such as ylide D with no substituent at the ylide carbon or its 1-mono- B and 1,1-disubstituted derivatives C. The ylides thus generated were trapped with olefinic dipolarophiles giving high yields of cycloadducts 10-20 (Scheme 2 and Table 1). With acetylenes, 3-pyrroline 21 or perhydropyrrolo[3,4-c]pyrrole-3a,6a-dicarboxylate 22 was obtained.

Finally, the decarboxylative condensation of glycine itself with formaldehyde was examined in order to open an effective route to parent methaniminium methylide E. Under similar conditions, ylide E was successfully generated and underwent

Table 1. Cycloadditions of Azomethine Ylides A-E with Olefins and Acetylenesa)

Amine	Carbonyl compound	Dipolarophile	Conditionsb)	Product	Yield/%c)	Isomer ratio
1	$(CH_2O)_n$	N-(p-tolyl)maleimide	A 1 h	5	93	62:38d)
2	"	"	B 1 h	6	78	50:50d)
1	"	CH_2=CHCOOMe	A 1 h	7	100	6:5e)
1	"	CH_2=$CHSO_2Ph$	A 1 h	8	82	4:1e)
1	"	CH_2=CHPh	C 12 h	9	61	1:1e)
3	PhCHO	N-(p-tolyl)maleimide	D 1 h	10	86	71:29f)
3	MeCOMe	"	D 9 h	11	85	
3	$\underline{\lceil(CH_2)_4\rceil}CO$	"	D 5 h	12	79	
3	$\underline{\lceil(CH_2)_5\rceil}CO$	"	D 3 h	13	91	
3	PhCHO	MeOOCCH=CHCOOMe (t)	D 1 h	14	86	1:1f)
3	$(CH_2O)_n$	N-(p-tolyl)maleimide	A 15 min	15	89	
3	"	MeOOCCH=CHCOOMe (c)	A 15 min	16	84	
3	"	MeOOCCH=CHCOOMe (t)	A 15 min	17	80	
3	"	CH_2=CHCOOBu-n	A 15 min	18	79	
3	"	CH_2=$CHSO_2Ph$	A 15 min	19	84	
3	"	PhCH=CHCO-tolyl(p) (t)	A 15 min	20	93	
3g)	"	PhCOC≡CCOPh	A 30 min	21	23	
3g)	"	MeOOCC≡CCOOMe	A 15 min	22	68	
4	"	N-(p-tolyl)maleimide	E 1 h	23	76	
4	"	PhCH=C$(CN)_2$	F 12 h	24	73	

a) Amino acids 3, 4 (2 equiv.) and paraformaldehyde (5 equiv.) were used in excess. b) A: under reflux in toluene; B: at 150 °C in toluene with K_2CO_3 in a selaed tube; C: at 180 °C in toluene with K_2CO_3 in a selaed tube; D: under reflux in toluene with diisopropylethylamine (1.5 equiv.); E: under reflux in DMF; F: under reflux in toluene with K_2CO_3. Dean-Stark trap was used to remove water in the cases of A, D, E, and F. c) Isolated yield based on the dipolarophile used. d) The ratio of 3a,4-trans:3a,4-cis. e) The ratio of two stero- or regio isomers. f) The ratio of two stereoisomers. g) Four equivalents of 3 were employed.

cycloadditions with olefins to afford 1,2,5-unsubstituted pyrrolidines 23, 24 in good yields (Schemes 1, 2 and Table 1).

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11) Our method can be performed under mild conditions using readily available 2-amino esters and paraformaldehyde affording better yields of cycloadducts.

12) Cycloaddition of stabilized azomethine ylides with styrene is unknown so far.

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