CHEMISTRY LETTERS, pp. 1411-1414, 1985.

N-PROTONATED AZOMETHINE YLIDES WITH A LEAVING GROUP AS SYNTHETIC EQUIVALENTS FOR NONSTABILIZED NITRILE YLIDES

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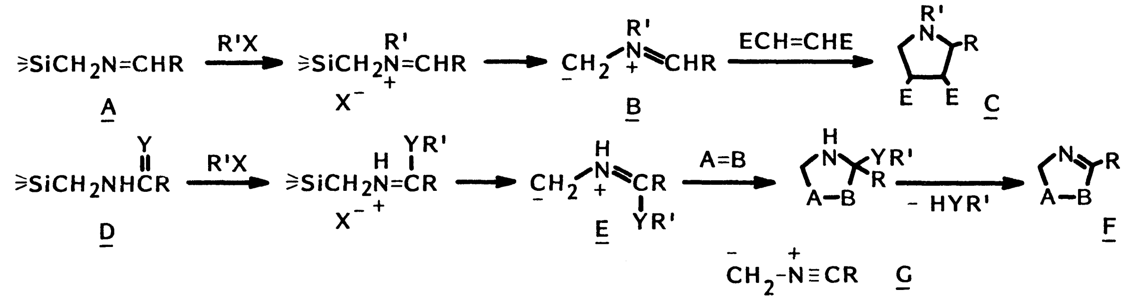
Through alkylation or silylation and then desilylation steps, N-(silylmethyl)amidines generate N-protonated azomethine ylides which cycloadd to olefins, acetylenes, and aldehydes giving 1- or 2-pyrrolines, pyrroles, and 2-oxazolines, respectively, after the elimination of N-substituted anilines. With this sequence, the amidines are useful synthetic equivalents of nonstabilized nitrile ylides.

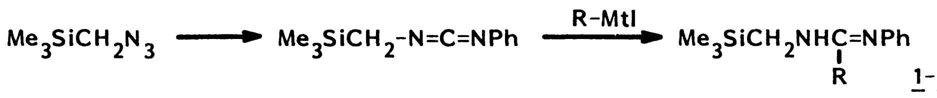
The talent of N-(silylmethyl)imines in the field of heterocyclic synthesis has been recently demonstrated as precursors of azomethine ylide 1,3-dipoles of nonstabilized type. The ylide generation is generally achieved in the following two steps: The initial quaternarization at the imine nitrogen with silyl triflates,[1] alkyl halides,[2] and acyl halides[3] and the subsequent desilylation step (A → B). Cycloaddition of the azomethine ylides thus generated to olefins leads to N-substituted pyrrolidines (B → C) as shown below.



If such an N-protonated azomethine ylide as E with a leaving group (YR') at the imine carbon is available, its cycloadditions would produce five-membered nitrogen heterocycles with an additional unsaturation after the elimination of the leaving group (E → F). Therefore, this azomethine ylide E should work as a synthetic equivalent of nonstabilized nitrile ylide G. One possible access to the protonated ylide E is an alkylation of N-(silylmethyl)amide-related compounds D (Y: heteroatom) and a successive desilylation.

N-(Silylmethyl)amidines were used, in the present work, as the precursors for

N-protonated azomethine ylides because of their easy accessibility. The amidines 1-5 were prepared in high yields in the reactions of 1-phenyl-3-(trimethylsilylmethyl)carbodiimide, easily available from trimethylsilylmethyl azide and phenyl isothiocyanate,4) with organometallic reagents at room temperature (Scheme 1, 1: 91%; 2: 95%; 3: 90%; 4: 95%; 5: 92% as 7:3 mixture of two tautomers).5) This method is quite useful for the introduction of a variety of substituents at the imine carbon of azomethine ylides.



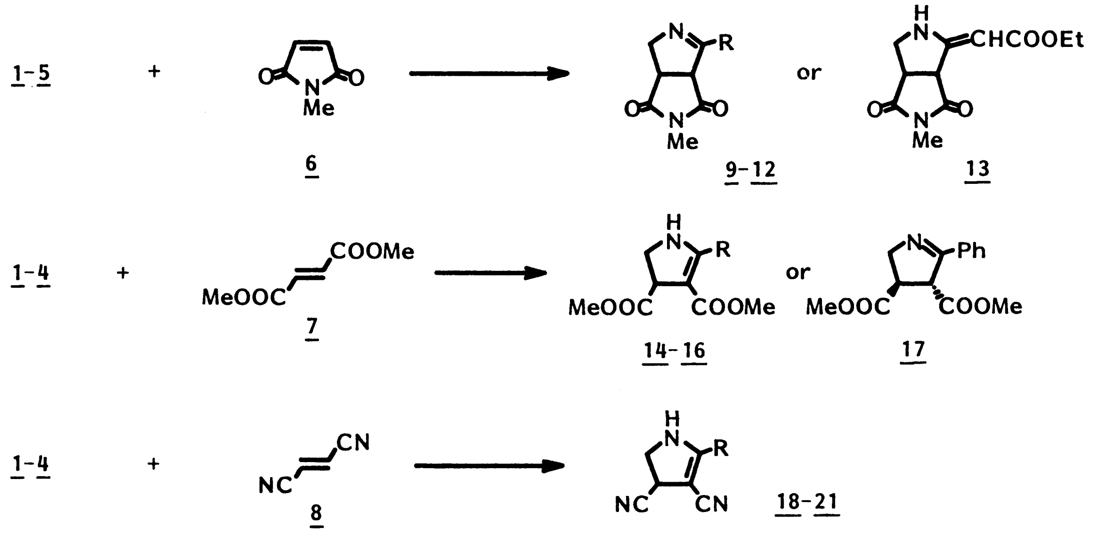
$$Me_3SiCH_2N_3 \longrightarrow Me_3SiCH_2\text{-}N{=}C{=}NPh \xrightarrow{R\text{-}Mtl} Me_3SiCH_2NH\underset{R}{\underset{|}{C}}{=}NPh$$

1-5

1: R=Me, 2: R=Et, 3: R=n-Bu,
4: R=Ph, 5: R=CH_2COOEt

Scheme 1.

The general procedure for the ylide generation and cycloaddition has been carried out as follows: The first step is the amidinium salt formation by treatment of the amidines 1-5 with methyl (MeOTf) or trimethylsilyl triflate (TMSOTf) in acetonitrile. This takes only a few minutes at room temperature. After dipolarophiles and then cesium fluoride (CsF) as a desilylating agent are added, the mixture is stirred at room temperature under nitrogen.6)



Scheme 2.

As anticipated, the N-protonated azomethine ylides E were generated and they cycloadded to some olefinic dipolarophiles 6-8 providing the cycloadducts 9-21 with one unsaturation (Scheme 2 and Table 1). The position of double bond in the isolated products depends upon the steric and electronic nature of substituents around the double bond and also the ring strains. Noteworthy is that even the azomethine

Table 1. Cycloaddition of 1-5 to Olefinic Dipolarophiles 6-8 [a]

Amidine	Olefin	Method[b]	Product	R	Yield/%[c]
1	6	A	9	Me	82
2	6	A	10	Et	77
3	6	A	11	n-Bu	70
4	6	A	12	Ph	74
5	6	A	13		36
1	7	A	14	Me	73
2	7	A	15	Et	63
3	7	A	16	n-Bu	53
4	7	B	17		67
1	8	A	18	Me	51
2	8	A	19	Et	51
3	8	A	20	n-Bu	58
4	8	B	21	Ph	69

a) All the reactions were performed in MeCN at room temperature for 12-15 h. b) A: MeOTf and then CsF (each 1 equiv.) were used; B: TMSOTf (1 equiv.) and then CsF (2 equiv.) were used. c) Isolated yields.

ylides carrying an alkyl substituent (R is alkyl in E), which shows poor ylide-stabilizing ability, afforded the satisfactory yields of cycloadducts. With these results, the generality of synthesis of the starting amidines 1-5 is sensible in a field of organic synthesis using the nonstabilized nitrile ylide synthons E.[7]

Scheme 3.

Similarly, the N-protonated azomethine ylides E were successfully captured with some acetylenic dipolarophiles 22-23 and aromatic aldehydes 26-29 producing the pyrroles 24-25 with no substituent at the nitrogen and 2,5-disubstituted 2-oxazolines 30-37, respectively (Scheme 3 and Table 2). High regioselection in the cycloaddition to aldehydes is particularly interesting, since this selectivity is opposite to that observed in the similar cycloadditions of nitrile ylides generated by the photolysis of azirines[8] or by the dehydrochlorination of imidoyl chlorides with base.[9]

Table 2. Cycloaddition of 1-4 to Acetylenes and Aldehydes[a]

Amidine	Acetylene or aldehyde	Method[b]	Product			Yield/%[c]
				E		
1	22 (E = COOMe)	A	24	COOMe		64
1	23 (E = COOPh)	A	25	COOPh		44
				Ar	R	
1	26 (Ar = Ph)	B	30	Ph	Me	65
1	27 (Ar = 2-thienyl)	B	31	2-thienyl	Me	20
2	26	B	32	Ph	Et	50
3	26	B	33	Ph	n-Bu	54
3	28 (Ar = 2-furyl)	B	34	2-furyl	n-Bu	46
3	29 (Ar = 2-pyridyl)	B	35	2-pyridyl	n-Bu	64
4	26	A	36	Ph	Ph	52
4	29	A	37	2-pyridyl	Ph	62

a) Conditions: At room temperature for 12-13 h in MeCN. b) A: TMSOTf and then CsF were used; B: MeOTf and then CsF were used. c) All isolated yields.

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5) All new compounds reported herein gave satisfactory elemental and spectral data.
6) Tetrabutylammonium fluoride (TBAF) could be used instead of CsF, but with poorer yields of cycloadducts.
7) The cycloadditions of N-(silylmethyl)thioimidates in the presence of water have an advantage that a wide variety of olefinic dipolarophiles can be successfully employed, but at the same time a disadvantage that the ylide carrying an alkyl substituent shows very poor reactivity toward olefinic dipolarophiles (O. Tsuge, S. Kanemasa, T. Yamada, and K. Matsuda, Heterocycles, 23, in press).
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(Received July 2, 1985)