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NEW GENERATION OF 1,3-DIPOLES FROM ORGANOSILICON COMPOUNDS AND SYNTHESES OF HETEROCYCLES

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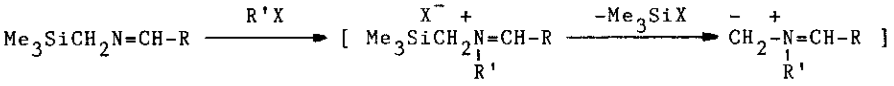
Abstract —— Recent development of the cycloaddition involving desilylation process has opened a new field in 1,3-dipolar cycloaddition chemistry. This review deals with the new methods for the generation of azomethine and thiocarbonyl ylides, and their cycloaddition reactions.

I. Introduction

The 1,3-dipolar cycloaddition chemistry has been developed during past 25 years and its synthetic utility has been proven in the preparation of a wide range of heterocycles[1]. Moreover, the recent finding of a convenient method for 1,3-dipole generation from organosilicon compounds promises the future development in this field. Although two reviews[2,3] on this chemistry have already appeared from a different point of view, we will describe the new methods including the latest informations for the generation of azomethine and thiocarbonyl ylides from organosilicon compounds, leading to facile syntheses of pyrrolidine and tetrahydrothiophene derivatives.

Heterolysis of a silicon-carbon bond is favored in such cases as the attack of fluoride ion[4] and the Peterson reactions[5]. Otherwise, it is not so easy by the attack of a usual nucleophile. The C-Si bond in α-trimethylsilyl onium salt is considered to be readily cleaved because of stabilization of the carbanion formed after the desilylation, owing to the ylide formation. Therefore, the strategy for new azomethine ylide generation was that the ylide (**3**) would be produced from N-[(trimethylsilyl)methyl]iminium salt (**2**), which is formed from N-[(trimethylsilyl)methyl]imines (**1**) and R'X, by the attack of the counter ion or a silylophile to the silicon atom (Scheme 1).



$$Me_3SiCH_2N{=}CH{-}R \xrightarrow{R'X} [\ \overset{X^-}{Me_3SiCH_2}\overset{+}{\underset{R'}{N}}{=}CH{-}R \xrightarrow{-Me_3SiX} \overset{-}{C}H_2{-}\overset{+}{\underset{R'}{N}}{=}CH{-}R\ ]$$

1 **2** **3**

Scheme 1

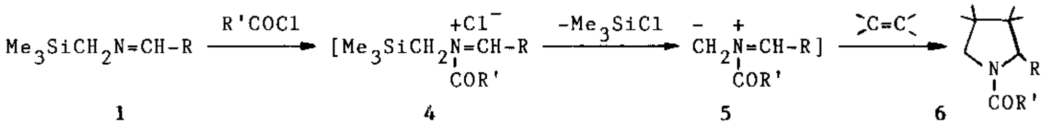
A variety of compounds containing a carbon-nitrogen double bond have been subjected to the azomethine ylide generation. In addition, thiocarbonyl ylides which are a relatively new type of 1,3-dipoles have been recently found to be generated from silylmethyl sulfide derivatives.

The individual method will hereinafter be described for each group of the starting materials generating 1,3-dipoles.

II. Azomethine Ylides

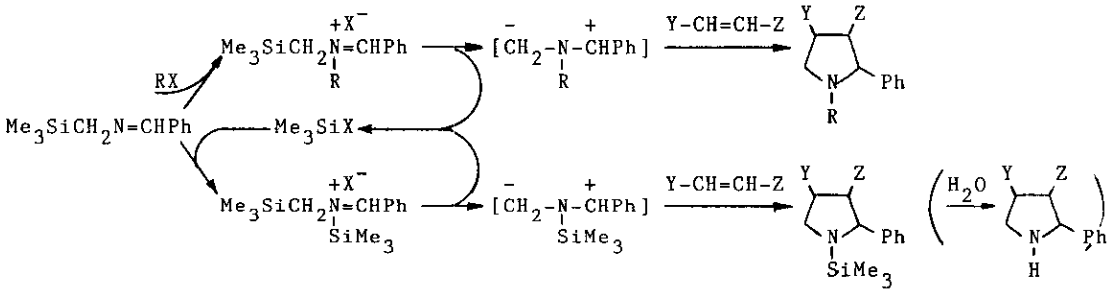
1. From N-(Silylmethyl)imines

N-(Silylmethyl)imines, which were readily prepared from N-(silylmethyl)amine and aldehyde by the usual method, have been found to undergo 1,3-cycloaddition to a conjugated olefin in the presence of an acid chloride[6]. The reaction proceeds via azomethine ylide intermediate (5) resulted from the N-acyliminium salt (**4**) initially formed (Scheme 2, Table 1). This desilylation technique provided a convenient method for syntheses of N-acyl pyrrolidine derivatives[7].



Scheme 2

The most remarkable feature of this reaction is that the desilylation of N-acyliminium salt (4) occurs by the attack of chloride ion in the absence of fluoride ion. This suggests that α-silyl group of onium salt is subjected to the attack of various nucleophiles toward the ylide generation. Actually, simple alkyl halides were also effective for the generation of azomethine ylide, the cycloaddition of which led to the syntheses of N-alkylpyrrolidines[8] (Table 2). In the cases of alkyl chlorides, N-unsubstituted pyrrolidines were produced predominantly, because the silyl chloride formed in the early stage competes with alkyl chloride for the production of iminium salt (Scheme 3).

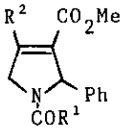
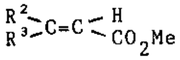
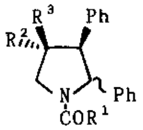


RX: alkyl halides or tosylate

Scheme 3

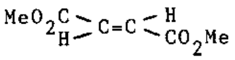
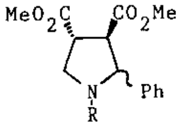
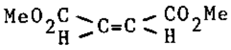
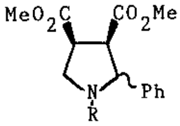
Besides, such two systems as silyl triflate/cesium fluoride (cat.)[9] and water/hexamethylphosphoramide (HMPA)[10] were used for synthesizing N-unsubstituted pyrrolidine derivatives. N-(Silylmethyl)iminium salts were also formed by alkylation of the N-(silylmethyl)imine with alkyl fluorosulfate or alkyl triflate, and the fluoride-induced desilylation afforded the azomethine ylides[3]. Regiospecific 1,3-cycloaddition reaction was realized by using N-[α-(piperidinocarbonyl)benzylidene]trimethylsilylmethylamine (7) which was designed as a model compound for erythrinane alkaloid synthesis[11]. The reaction of 7 with olefinic and

Table 1 Synthesis of N-Acyl-2,5-dihydropyrroles and N-Acylpyrrolidines[a)]

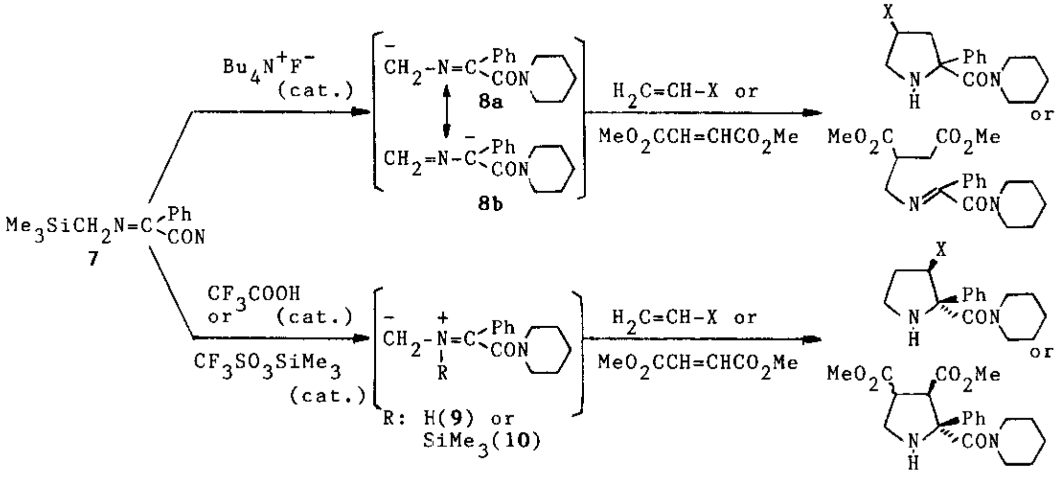
Dipolarophile	R^1COCl	Product	Yield (%)	2-Ph & 3-CO_2Me (*cis/trans*)
$R^2C{\equiv}CCO_2Me$				
	PhCOCl	R^1= Ph, R^2= CO_2Me	85	-
	$PhCH_2OCOCl$	R^1= OCH_2Ph, R^2= CO_2Me	78	-
	MeCOCl	R^1= Me, R^2= CO_2Me	79	-
	PhCOCl	R^1= Ph, R^2= H	26	-
 $\begin{matrix}R^2\\R^3\end{matrix}\!>C{=}C<\!\begin{matrix}H\\CO_2Me\end{matrix}$				
	PhCOCl	R^1= Ph, R^2= CO_2Me, R^3= H	81	1.5
	$PhCH_2OCOCl$	R^1= OCH_2Ph, R^2= CO_2Me, R^3= H	79	1.4
	PhCOCl	R^1= Ph, R^2= H, R^3= CO_2Me	68	2.0
	PhCOCl	R^1= Ph, R^2= R^3= H	80	1.2

a) All reactions were carried out with $PhCH{=}NCH_2SiMe_3$(**1a**) (5 mmol), R^1COCl (5 mmol), and dipolarophile (5.5 mmol) in THF (60 ml) at 40-45° for 2h.

Table 2 Synthesis of N-Alkylpyrrolidines and N-Unsubstituted Pyrrolidines[a)]

Dipolarophile	RX	Product	Yield (%)	2-Ph & 3-CO_2Me (*cis/trans*)
 $\begin{matrix}MeO_2C\\H\end{matrix}\!>C{=}C<\!\begin{matrix}H\\CO_2Me\end{matrix}$				
	BuI	R = Bu	61	1.5
	BuCl	R = H	76	0.83
	$PhCH_2Br$	R = CH_2Ph	79	1.2
	EtO_2CCH_2Br	R = CH_2CO_2Et	74	1.1
 $\begin{matrix}MeO_2C\\H\end{matrix}\!>C{=}C<\!\begin{matrix}CO_2Me\\H\end{matrix}$				
	BuI	R = Bu	61	0.50
	BuCl	R = H	76	0.43

a) Reaction conditions: molar ratio, **1a**/RX/dipolarophile= 1/1/1.2; solvent, HMPA; temp. 80-85°C; time, 2h acetylenic dipolarophiles in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF) was found to give the product derived from the intermediary carbanions (**8a** and **8b**), the regioselectivity of which depended on the structure of used dipolarophiles. Moreover, the reaction catalyzed by trifluoroacetic acid or trimethylsilyl triflate was found to yield regioselectively the corresponding products derived from the intermediary azomethine ylide (**9** or **10**) as shown in Scheme 4.

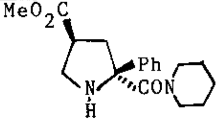
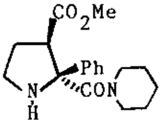
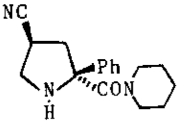
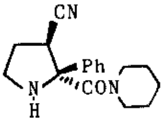
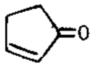
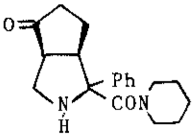
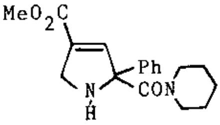
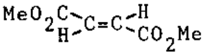
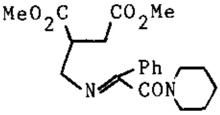
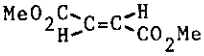
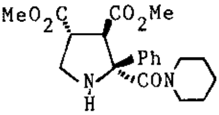
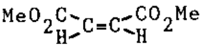
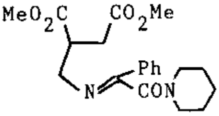
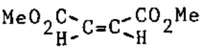
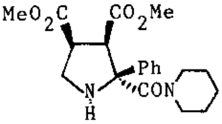


Scheme 4

It is noteworthy that the reaction with methyl acrylate or acrylonitrile afforded regioselectively 2,2,3-trisubstituted pyrrolidines by CF_3CO_2H or Me_3SiOTf-catalyzed method and 2,2,4-trisubstituted ones by TBAF-method (Table 3). In the TBAF promoted reaction, dimethyl fumarate and maleate yielded regoselectively the uncyclized products <u>via</u> the carbanion **8a** along with 4% and 14% cyclized products, respectively. These facts indicate that the carbanion **8b** plays an important role in the formation of cyclized products, whereas **8a** gives the uncyclized products. This distinct selectivity may be rationalized from the steric hindrance in formation of the C_2-C_3 bond and the relative stability of both carbanions, **8a** and **8b**.

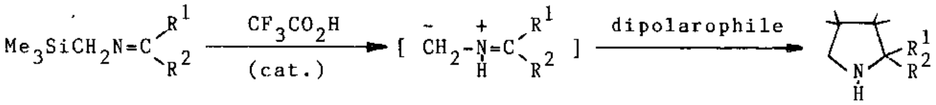
As the other example of trifluoroacetic acid-catalized cycloaddition, a convenient method for synthesis of proline derivatives was reported, where methyl N-(trimethylsilylmethyl)iminoacetate was used as the precursor of azomethine ylide[12]. The regio- and stereoselectivities in the typical three reactions (Table 4) were explained on the basis of frontier molecular orbital theory (FMO theory)[13].

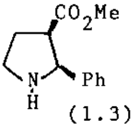
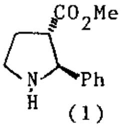
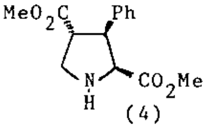
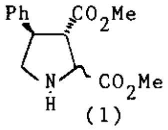
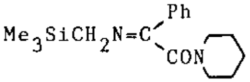
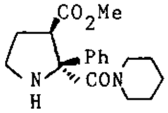
Table 3 Synthesis of Pyrrolidines and 2,5-Dihydropyrroles by Desilylation of N-[α-(Piperidinocarbonyl)benzylidene]trimethylsilylmethylamine (**7**)

Dipolarophile	Catalyst	Product	Yield (%)	Regioselectivity (%) Stereoselectivity (%)
$H_2C{=}CHCO_2Me$	$Bu_4N^+F^-$		56	97 100
$H_2C{=}CHCO_2Me$	CF_3CO_2H $[CF_3SO_3SiMe_3]$		88[94]	100[94] 96[97]
$H_2C{=}CHCN$	$Bu_4N^+F^-$		55	95 56
$H_2C{=}CHCN$	CF_3CO_2H		86	100 74
	$Bu_4N^+F^-$		58	100 100
$HC{\equiv}CCO_2Me$	$Bu_4N^+F^-$		43	100 –
 $MeO_2C(H)C{=}C(H)CO_2Me$	$Bu_4N^+F^-$		57	96 –
 $MeO_2C(H)C{=}C(H)CO_2Me$	$CF_3SO_3SiMe_3$		94	– 90
 $MeO_2C(H)C{=}C(H)CO_2Me$	$Bu_4N^+F^-$		77	86 –
 $MeO_2C(H)C{=}C(H)CO_2Me$	$CF_3SO_3SiMe_3$		69	– 90

a) Reaction conditions: molar ratio, **7**/dipolarophile/catalyst = 1/1.5/0.15; solvent, DMF or HMPA; temp, r.t.-50°C; time, 3-7h.

Table. 4. Regio- and Stereoselectivity in 1,3-Dipolar Cycloaddition



Reagent	Dipolarophile	Product[a)]	Regioselectivity(%) Stereoselectivity(%)
$Me_3SiCH_2N{=}CHPh$ **11**	$H_2C{=}CHCO_2Me$ **14**	 (1.3)  (1)	≈100 57
$Me_3SiCH_2N{=}CHCO_2Me$ **12**	$PhCH{=}CHCO_2Me$ **15**	 (4)  (1)	80 ≈100
 **13**	$H_2C{=}CHCO_2Me$ **14**		≈100 ≈100

a) Ratio of the isomers is described in parentheses.

Figures 1 and 2 show the results obtained by the ab initio molecular orbital calculation[14] at the STO-3G level on the fully optimized geometries of azomethine ylides and dipolarophiles. All these reactions are controlled by the ylides' HOMO according to Sustmann's classification[15] (Fig. 1). The frontier molecular orbital interactions between the dipoles and the dipolarophiles are indicated in Fig. 2 from the viewpoint of the FMO theory, in which the most developed lobe in HOMO of electron donors (dipoles) interacts the most developed lobe in LUMO of electron acceptors (dipolarophiles). These calculated results agree with the experimental regioselectivities. And the stereoselectivities are explained by the secondary molecular orbital interaction between the ester orbitals and the phenyl ones of dipoles or dipolarophiles as indicated in Fig. 2. It should be noted that the low stereoselectivity in the reaction of **11** with **14** was caused from the weakened secondary orbital interaction due to the less coplanarity between the azomethine group and the phenyl nuclei, that the low regioselectivity of **12** with **15** resulted from the similar LCAO coefficient values of the olefinic part in **15**, and that the stereospecificity in the reaction of **13** with **14** was enhanced by the steric hindrance between the rotated amide group of **13** and the ester of **14** in the stereoisomer-forming transition state.

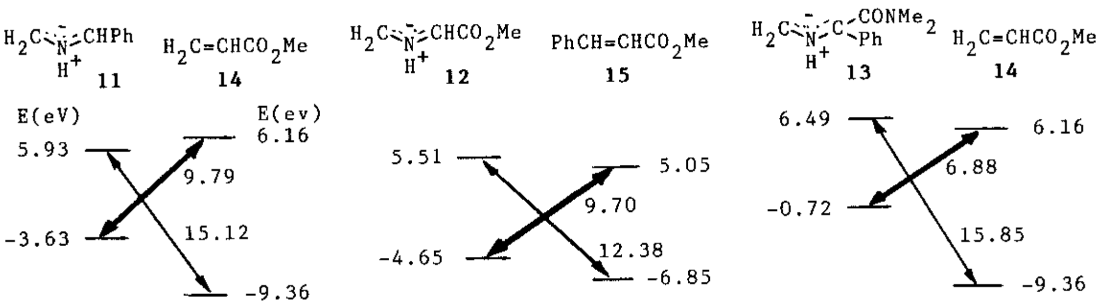


Fig. 1 HOMO-LUMO Correlation Diagram in 1,3-Dipolar Cycloaddition

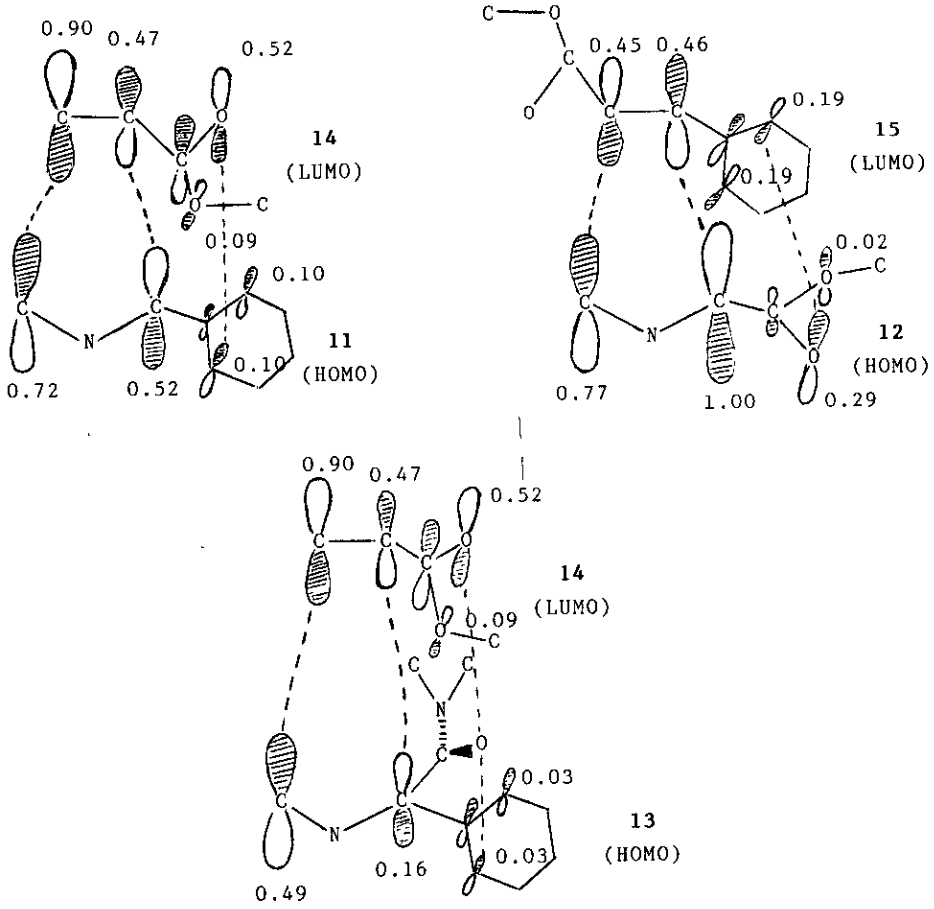
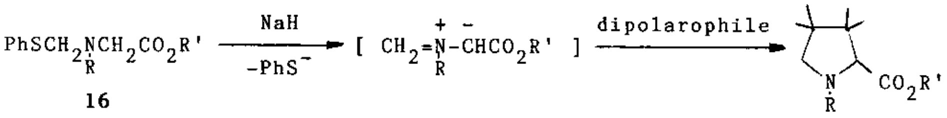


Fig. 2 The Frontier Molecular Orbital Interaction between Dipoles and Dipolarophiles in 1,3-Dipolar Cycloaddition The numerals beside the lobes indicate the frontier electron densities.

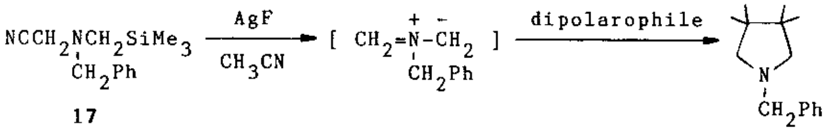
2. From N-(Silylmethyl)amines

The authors reported that N-(phenylthiomethyl)amino acid esters (**16**) underwent the 1,3-dipolar cycloaddition reaction in the presence of base, where the phenylthio group play a role in the iminium cation production[16] (Scheme 5). This suggested that N-(silylmethyl)aminal derivatives could serve as a precursor of azomethine ylides.



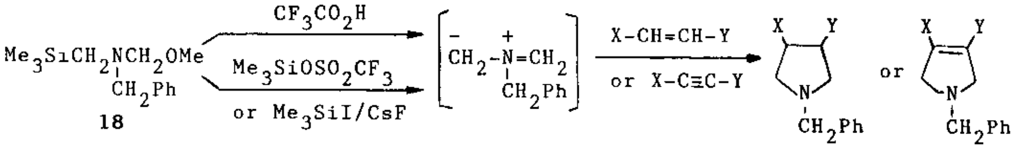
Scheme 5

N-(Silylmethyl)aminoacetonitriles (**17**) have been initially used as an azomethine ylide precursor by Padwa and co-workers[17]. The reaction is promoted with an equivalent of silver fluoride; silver causes the decyanation and fluoride does the desilylation simultaneously (Scheme 6).



Scheme 6

Hosomi and Sakurai have reported that N-(silylmethyl)aminomethyl ethers (**18**) underwent the ylide generation reaction in the presence of trimethylsilyl iodide or silyl triflate and cesium fluoride[18], while the authors have found independently a more convenient method catalyzed by a small amount of trifluoroacetic acid[19] (Scheme 7, Table 5).

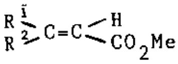
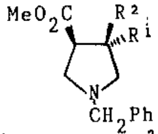
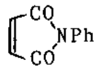
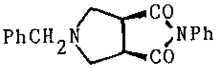
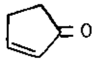
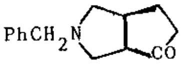
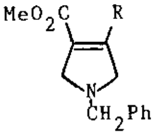


Scheme 7

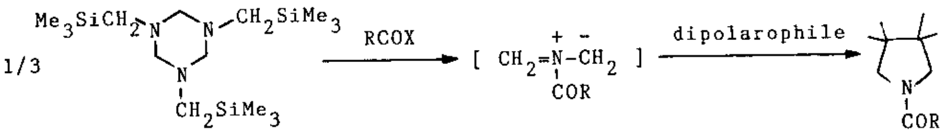
1,3,5-Tris(trimethylsilylmethyl)hexahydro-1,3,5-triazine (**19**) was also shown to behave as a useful synthon for the simplest N-acylazomethine ylide in the presence of acyl fluoride[20] (Scheme 8).

These methodologies provided new routes for generation of 1,3-unsubstituted azo-

Table 5 Synthesis of 3- or 3,4-Substituted Pyrrolidines and 2,5-Dihydropyrroles from N-(Trimethylsilylmethyl)benzylaminomethyl Methyl Ether(**18**)[a)]

Dipolarophile	Product	Yield(%)
		
	$R^1 = CO_2Me$, $R^2 = H$	97
	$R^1 = H$, $R^2 = CO_2Me$	94
	$R^1 = Ph$, $R^2 = H$	87
	$R^1 = R^2 = H$	89
		86
		65
RC≡CCO$_2$Me		
	R = CO$_2$Me	66
	R = H	58

a) Reaction conditions: molar ratio, **18**/dipolarophile/CF_3CO_2H = 1.2/1/0.1; solvent, CH_2Cl_2; temp., r.t.; time, 3h.



19

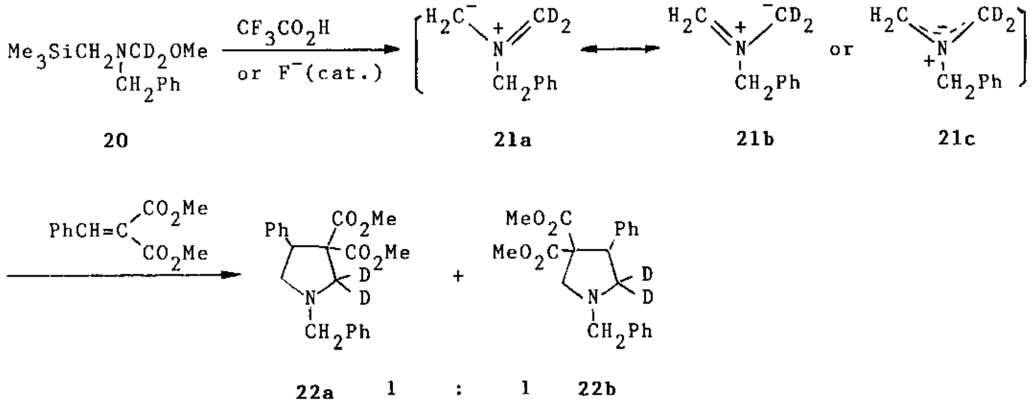
yield 49-82%

dipolarophile: $H_2C{=}CHCO_2Me$, $H_2C{=}CHCN$, $MeO_2CCH{=}CHCO_2Me$, $PhCH{=}CHCO_2Me$, N-methylmaleinide

Scheme 8

methine ylides, the cycloaddition of which gave 2,5-unsubstituted pyrrolidine derivatives, and prompted further mechanistic investigation described below.

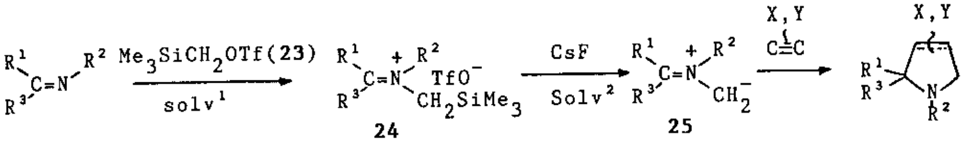
In the course of the investigation on the 1,3-cycloaddition reaction by desilylation technique, a question has been raised whether an azomethine ylide serves truly as an intermediate in such reactions. 1,3-Diole species have been known to have an ambivalent property, and this is one of the lines of evidence in support of the 1,3-dipole intermediate itself[1]. Therefore, the experimental evidence for clarification of net ambivalence was required to answer the above question. Because the electronic or steric interaction between substituents of a 1,3-dipole and those of a dipolarophile is considered to affect the regioselectivity, 1,3-unsubstituted azomethine ylide is well suited for this purpose. Thus, the deuterated N-(silylmethyl)-N-benzylaminomethyl methyl ether (**20**) was prepared and its 1,3-cycloaddition to the unsymmetrical dipolarophile, dimethyl benzylidenemalonate, was carried out in the presence of a small amount of trifluoroacetic acid to afford a 1 : 1 mixture of the cycloadduct **22a** and **22b**[21] (Scheme 9). This result shows that the negative charge of azomethine ylide (**21**) is delocalized between two carbons adjacent to nitrogen. The same sort of experimental result was presented by Padwa and co-workers[22].



Scheme 9

3. From Imines with Silylmethyl Triflate and Fluoride

Since in 1979 Vedejs and Martnez found that trimethylsilylmethyl triflate (**23**) was very useful for silylmethylation of amines, sulfides, and imines, and etc., and the resulted onium salts could be led to the generation of ylides by desilylation with fluoride ion[23], their pioneering work has made important contributions to the recent development in this field. Treatment of an imine with **23** gave N-(trimethylsilylmethyl)iminium triflate (**24**), the desilylation of which was successfully made with cesium fluoride leading to 1,3-cycloaddition of the azomethine ylide (**25**) (Scheme 10, Table 6).

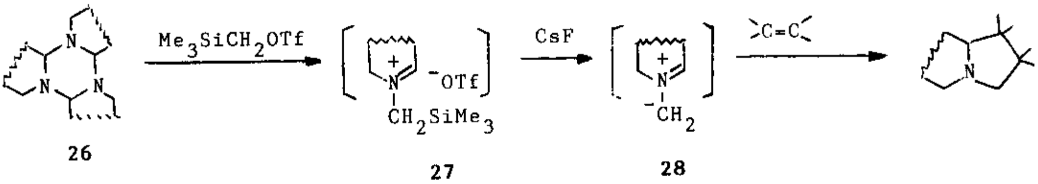


Scheme 10

Table 6

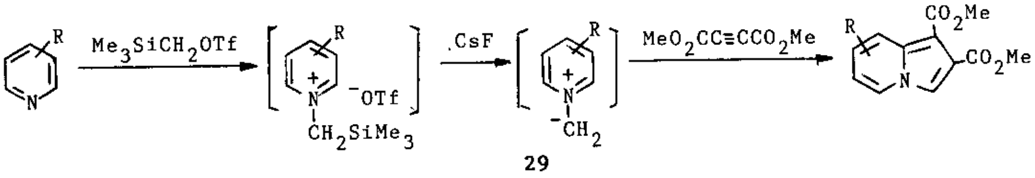
R^1	R^2	R^3	Dipolarophile	solv^1	solv^2	Yield(%)
Ph	Me	H	$MeO_2CC{\equiv}CCO_2Me$	CH_3CN	CH_3CN	70
$Ph(CH_2)_2$	t-Bu	H	$MeO_2CC{\equiv}CCO_2Me$	CH_3CN	CH_3CN	45
$Ph(CH_2)_2$	t-Bu	H	$H_2C{=}CClCN$	CH_3CN	CH_3CN	55
$PhCH_2$	Me	$PhCH_2$	$MeO_2CC{\equiv}CCO_2Me$	CH_2Cl_2	DME	48

The trimer of alicyclic imine (**26**) reacted with a dipolarophile in the presence of **23** and CsF to give pyrrolizidine or indolizidine derivatives[24]. This reaction also proceed via the azomethine ylide (**28**) generated from N-(silylmethyl)-iminium triflate (**27**) (Scheme 11, Table 7).



Scheme 11

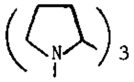
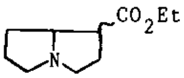
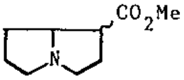
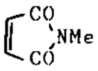
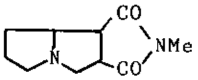
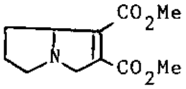
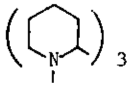
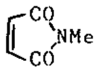
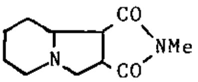
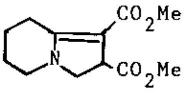
It is of interest that such procedure was employed in the formation of pyridinium N-methylide (**29**), leading to aromatic bicyclic amines synthesis by its cycloaddition to acetylenic dipolarophiles[25] (Scheme 12).



Scheme 12

The convenient technique involving silylation with Me_3SiCH_2OTf/desilylation with CsF has been used in generation of a azomethine ylide not only from simple amines but also from imidates.

Table 7 Synthesis of Pyrrolizidine and Indolizidine Derivatives from Alicyclic Imine Trimers [a)]

Substrate	Dipolarophile	Product	Yield(%)
	$H_2C{=}CHCO_2Et$		28
	$H_2C{=}CHCO_2Me$		30
			31
	$MeO_2CC{\equiv}CCO_2Me$		20
			15
	$MeO_2CC{\equiv}CCO_2Me$		20

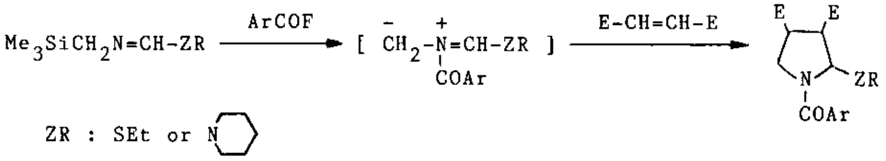
a) Molar ratio, substrate/$Me_3SiCH_2OSO_2CF_3$/dipolarophile = 1/3/3; solvent, DME

4. From Imidates, Thioimidates, and Amidines

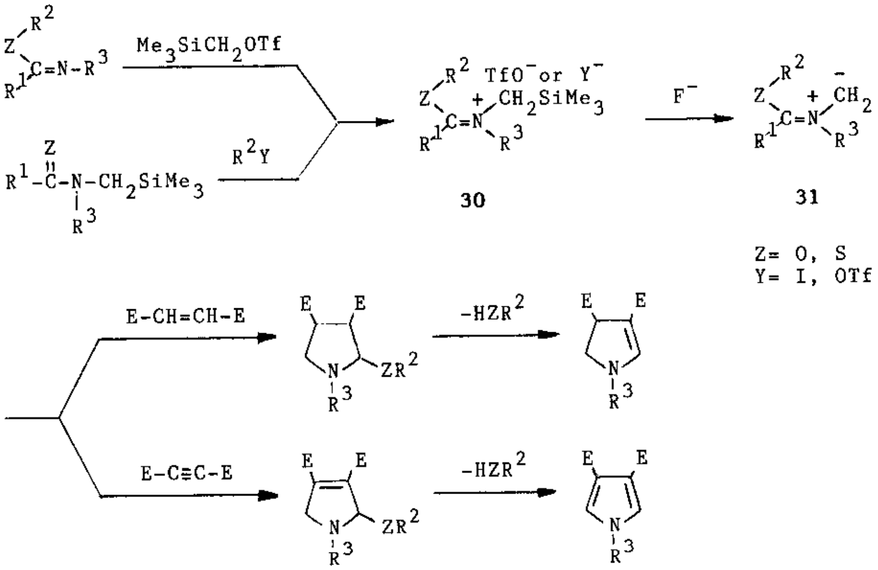
The imidate-type ylide (**31**) can be generated by fluoride-induced desilylation of the iminium salt (**30**) which is prepared by N-silylmethylation of amide or thioamide with silylmethyl triflate[26] or by O- or S-alkylation of N-(silylmethyl)amide or -thioamide[27,28b]. In its cycloaddition reaction, elimination of alcohol or mercaptan from the cycloadduct occurred usually to afford unsaturated pyrrolidines or pyrroles (Scheme 13).

Several experimental results extracted from the literatures are summerized in Table 8.

Livinghouse and Smith reported that the reaction of N-(silylmethyl)-formamidines and thioformimidates with acyl fluoride gave N-acyl imidate methylides and their cycloadducts were obtained in good yields[28] (Scheme 14).

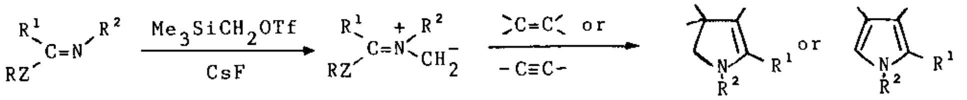
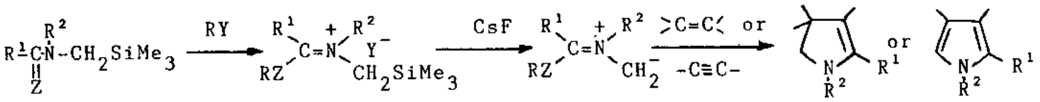


Scheme 14

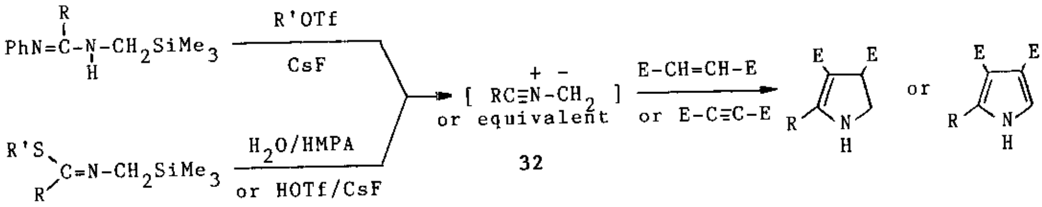


Scheme 13

Table 8 Synthesis of Dihydropyrroles and Pyrroles from Imidates or Thioimidates

R^1	R^2	RZ	Dipolarophile	Yield(%)	ref.
					
$-CH_2CH_2CH_2-$		MeO	$MeO_2CCH=CHCO_2Me$	44	3
$-CH_2CH_2CH_2-$		MeO	$H_2C=CHCO_2Me$	31	3
Ph	Me	EtO	$MeO_2CCH=CHCO_2Me$	45	26ab
Ph	Me	EtO	$MeO_2CC{\equiv}CCO_2Me$	48	26ab
Ph	Me	MeS	$MeO_2CC{\equiv}CCO_2Me$	74	26ab
H	Me	PhS	$MeO_2CH=CHCO_2Me$	62	28b
					
Me	$PhCH_2$	MeO	$H_2C=CHCO_2Me$	34	27b
Me	$PhCH_2$	MeS	$H_2C=CHCO_2Me$	53	27b
Me	$PhCH_2$	MeS	$HC{\equiv}CCO_2Me$	69	27b
$-CH_2CH_2CH_2-$		MeO	$H_2C=CHCO_2Me$	37	27b
$-CH_2CH_2CH_2-$		MeS	$H_2C=CHCO_2Me$	66	27b
$-CH_2CH_2CH_2CH_2-$		MeS	$H_2C=CHCO_2Me$	61	27b
$-CH_2CH_2CH_2CH_2-$		MeS	$HC{\equiv}CCO_2Me$	56	27b
$-CH_2CH_2CH_2CH_2-$		MeS	$MeO_2CC{\equiv}CCO_2Me$	66	27b
Ph	Me	MeO	$MeO_2CC{\equiv}CCO_2Me$	58	26b
Ph	Me	MeO	$MeO_2CC{\equiv}CCO_2Me$	74	26b

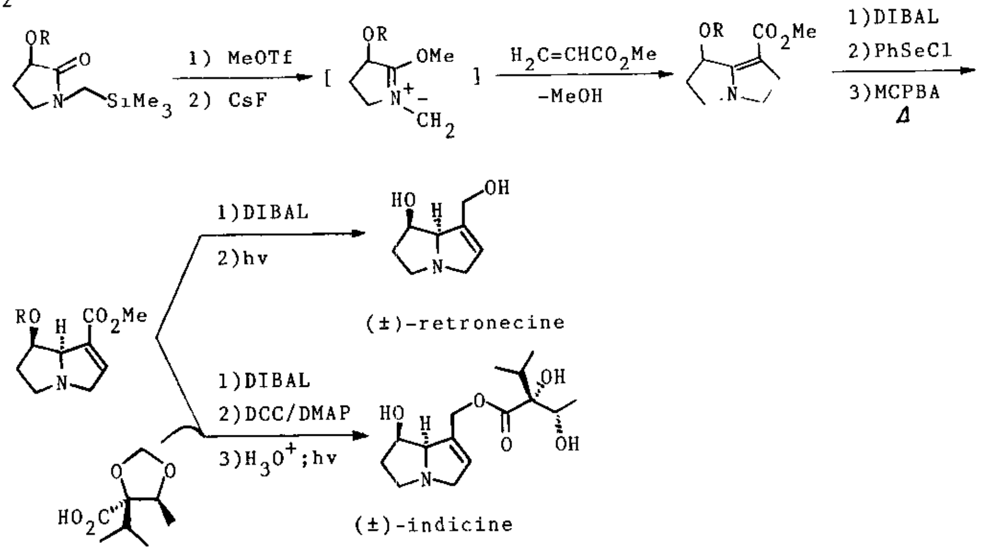
Tsuge and his co-workers suggested that N-protonated azomethine ylides (32) generated from N-(silylmethyl)-amidines and thioamidates are useful synthetic equivalents of nitrile ylides[29] (Scheme 15).



Scheme 15

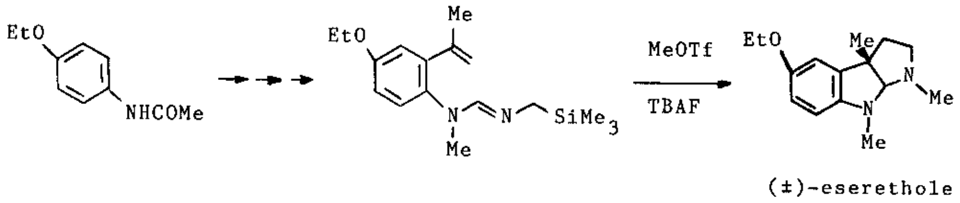
5. Application to Syntheses of Natural Prducts

Vedejs and his co-workers have successfully applied the cycloaddition of imidate-type ylide to the total syntheses of (±)-retronecine and (±)-indicine[27] (Scheme 16). Livinghouse and his co-workers reported the syntheses of (±)-eserethole[28b] (Scheme 17) and erythrinane skeleton[30] (Scheme 18) by the intramolecular cycloaddition of corresponding azomethine ylides. Padwa and Parker sythesized the Reniera isoindoles by using N-(silylmethyl)aminoacetonitrile[31] (Scheme 19). The new method for pyrrolizidine ring formation from the trimer of 1-pyrroline with Me_3SiCH_2OTf and CsF was applied to the syntheses of some pyrrolizidine alkaloids[24]

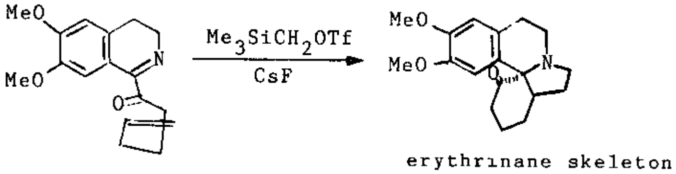


Scheme 16

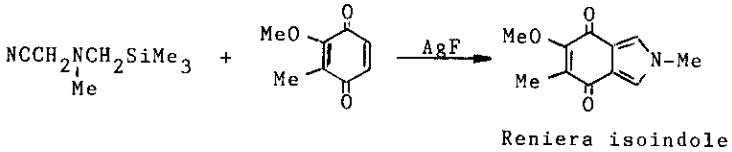
(Scheme 20). Asymmetric synthesis of (-)-cucurbitine has been achieved by the 1,3-dipolar cycloaddition of N-(silylmethyl)aminomethyl ether followed by asymmetric hydrolysis of the cycloadduct with esterase[32] (Scheme 21).



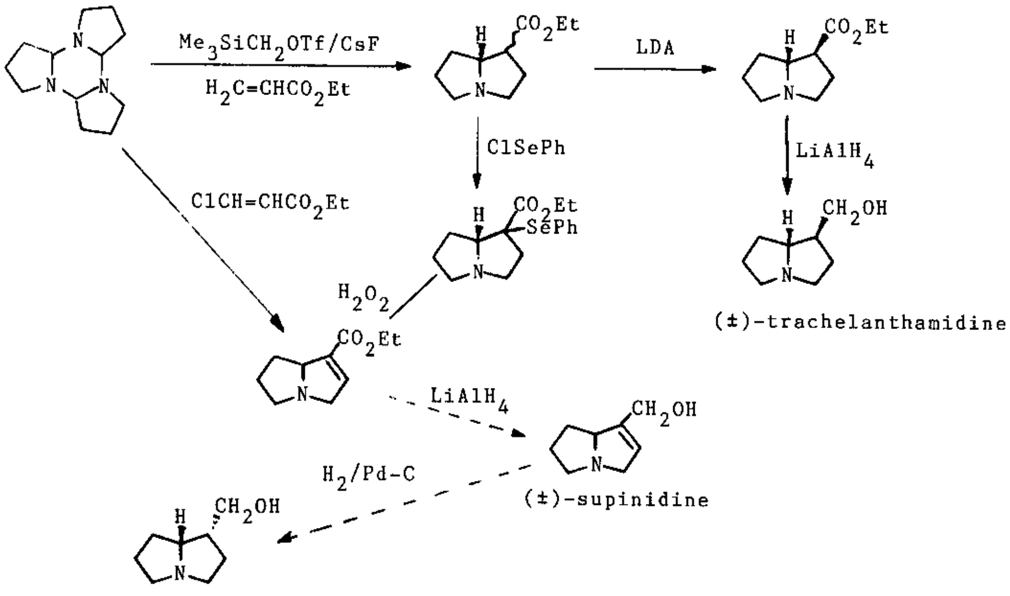
Scheme 17



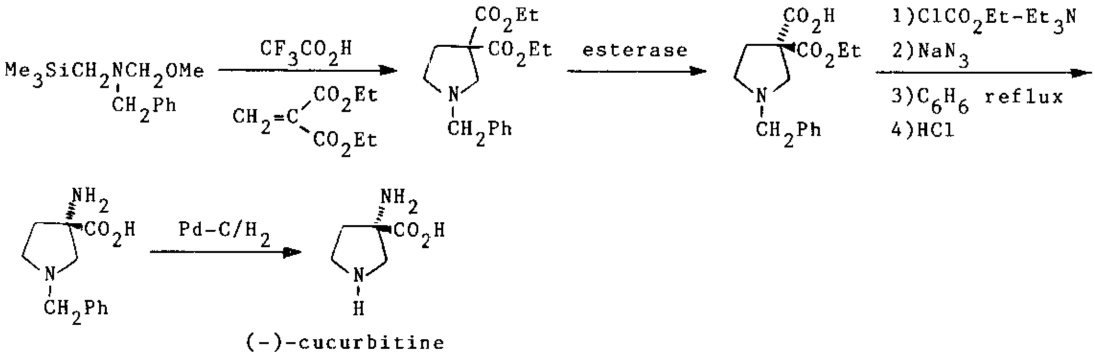
Scheme 18



Scheme 19



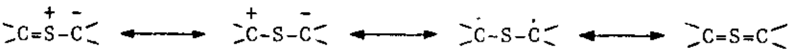
Scheme 20



Scheme 21

III. Thiocarbonyl Ylides

Thiocarbonyl ylide is conveniently represented by the structure (**33**), which includes 1,3-dipolar structure (**34**) as a resonance form (Scheme 22).



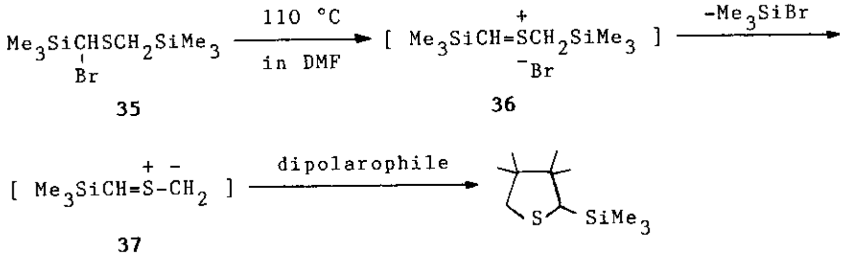
33 **34**

Scheme 22

The chemistry of thiocarbonyl ylides has been developed since Kelloge and his co-workers presented clean-cut evidence for the intermediary of the ylide in thermolysis of thiadiazolidines[33]. Generation of thiocarbonyl ylides from thiadiazolidines and their cycloaddition reaction have investigated in detail by Huisgen and his co-workers[34]. However, these methods seem not to be convenient due to the difficulty in synthesizing the starting materials and lack of generality of these reactions. Such problems have recently dissolved by introduction of the desilylation method. New routes to thiocarbonyl ylides will be described in this section.

1. From α-Halo(silylmethyl) Sulfides

The new method for the generation of thiocarbonyl ylides has been found on the basis of information on the azomethine ylides described in the preceding section. Bromo(trimethylsilyl)methyl (trimethylsilyl)methyl sulfide (**35**) was designed as a convenient agent for thiocarbonyl ylide generation. Sulfide **35** was easily prepared by bromination of bis(trimethylsilylmethyl) sulfide produced from trimethylsilylmethyl chloride and sodium sulfide. It has shown that thermolysis of **35** causes elimination of the trimethylsilyl bromide to give the ylide intermediate, trimethylsilylthioformaldehyde S-methylide (**37**), which is trapped with dipolarophiles leading to production of tetrahydrothiophene derivatives[35] (Scheme 23, Table 9).



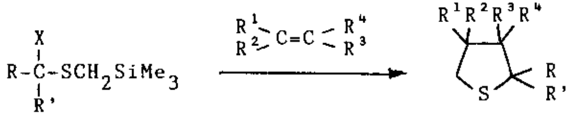
Scheme 23

From the mechanistic point of view, the stabilization of the β-cation by silicon[4] seems to promote the formation of the sulfonium cation in the initial step, and the stabilization of the carbanion due to the formation of thiocarbonyl ylide aids the C-Si bond cleavage by nucleophilic attack of the bromide anion on the silicon atom in the second step.

Hosomi and Sakurai prepared also chloromethyl (trimethylsilyl)methyl sulfide, which underwent 1,3-dipolar cycloaddition in the presence of cesium fluoride in acetonitrile at room temperature to give the corresponding tetrahydrothiophenes in good yield[36] (Table 9).

The dipole species **37** with a trimethylsilyl group at the terminus was used to reveal the effect of a silyl group on the selectivities in cycloaddition reaction. The results of the cycloadditions of **37** to several unsymmetrical dipolarophiles are summerized in Table 10[35b,37]. Entry 1 shows the obvious regioselection due to the substitution of a trimethylsilyl group. The regioselectivity observed in entry 3 is not negligible in view of the fact that the 2,2,3-trisubstituted cycloadduct was produced in a slight excess in spite of the large steric hindrance of the two trimethylsilyl groups. The high regioselectivity in entries 4 and 5 seems to be mostly owing to the effect of the phenyl group, because the phenyl group at the dipole terminus affected the regioselectivity in the 1,3-dipolar cycloaddition of azomethine ylides[9,11]. The origin of these regioselectivities was discussed on the basis of the FMO theory[38].

Table 9 Synthesis of Tetrahydrothiophenes from Halomethyl Trimethylsilylmethyl Sulfides



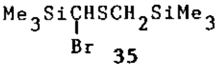
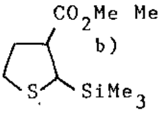
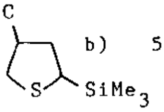
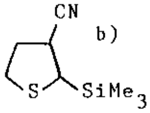
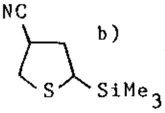
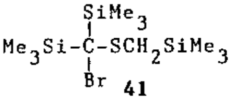
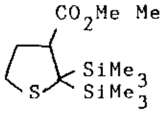
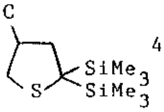
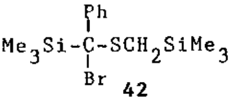
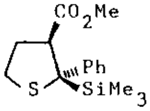
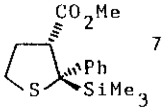
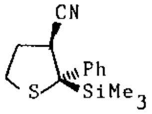
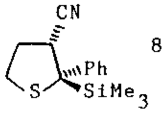
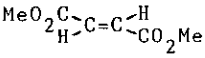
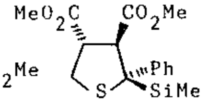
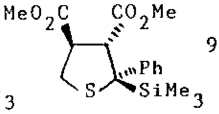
Sulfide	Method[a)]	R^1	R^2	R^3	R^4	Yield(%)	Ref
$Me_3Si\overset{Br}{C}HSCH_2SiMe_3$	A	H	CO-N(Ph)-CO		H	95	35
	A	H	CO-N(Me)-CO		H	96	35
	A	H	CO-O-CO		H	91	35
	A	CO_2Me	H	CO_2Me	H	90	35
	A	CO_2Me	H	H	CO_2Me	94	35
	A	CN	H	CN	H	98	35
$Me_3Si\overset{Br}{\underset{Ph}{C}}SCH_2SiMe_3$	A	CO_2Me	H	CO_2Me	H	95	35
$ClCH_2SCH_2SiMe_3$	B	CO_2Me	H	CO_2Me	H	86	36
	B	$CO_2SiMe_2CMe_3$	H	H	H	78	36
	B	CO_2menth-3-yl	H	H	H	78	36
	B	CO_2born-2-yl	H	H	H	65	36
	B	COMe	H	H	H	82	36
	B	CO_2Me	H	CO_2Me	H	83	36
	B	CO_2Me	H	H	CO_2Me	84	36
	B	CO_2Me	H	Ph	H	81	36
	B	COMe	H	Ph	H	58	36
	B	CO_2Me	——		CO_2Me	56[b)]	36

a) Method A : molar ratio, sulfides/dipolarophile = 1.5; solvent, DMF; temp., 110°C; time, 2h. Method B : molar ratio, sulfides/dipolarophile/CsF = 1.2/1/1; solvent, MeCN; temp., r.t.; time, 15-48h.

b) Dimethyl 2,5-dihydrothiophene-3,4-dicarboxylate.

Figures 3 and 4 show the results obtained by the molecular orbital calculation on thiocarbonyl ylides (**38**, **39**, **40**) and methyl acrylate (**14**) by means of ab initio procedures at the STO-3G level[14]. (The simple trihydrosilyl groups of **38**, **39**, and **40** were used for calculation instead of the trimethylsilyl groups formed from **35**, **41**, and **42**, respectively[39].) All three reactions are controlled by HOMO of the dipoles because of the slight instabilization of the dipoles' HOMO energy by the

Table 10 Effect of the Silyl Group on Regio- and Stereoselectivities in 1,3-Dipolar Cycloaddition[a)]

Entry	Sulfide	Dipolarophile	Product (Ratio of isomers)	Total yield (%)
1	 $Me_3Si\underset{Br}{CH}SCH_2SiMe_3$ **35**	$H_2C=CHCO_2Me$	 b)  b) **43a** (3 : 1) **43b**	52
2		$H_2C=CHCN$	 b)  b) (3 : 2)	56
3	 $Me_3Si-\overset{SiMe_3}{\underset{Br}{C}}-SCH_2SiMe_3$ **41**	$H_2C=CHCO_2Me$	  **44a** (7 : 6) **44b**	46
4	 $Me_3Si-\overset{Ph}{\underset{Br}{C}}-SCH_2SiMe_3$ **42**	$H_2C=CHCO_2Me$	  **45a** (5 : 2) **45b**	72
5		$H_2C=CHCN$	  (3 : 1)	87
6			  (4 : 3)	95

a) Reaction conditions: molar ratio, sulfide/dipolarophile = 1.5; solvent, DMF; temp., 110°C; time, 2h. b) A mixture of two possible stereoisomers.

electron donating silyl group and the lowering of the dipolarophiles' LUMO energy by the electron withdrawing ester group (Fig. 3). Figure 4 shows the interactions between the dipoles **38-40** and the dipolarophile **14**, and proves successfully the fact that the main product in the 1,3-dipolar cycloaddition of **35** with **14** was 2,3-disubstituted tetrahydrothiophene. And then production of 2,4-disubstituted ones as a minor product can be explained by the calculated results that the frontier electron density of the dipole carbon atom (C-2) in the silyl-substituted terminus is nearly equal to that of the dipole carbon atom (C-1) in the other ter-

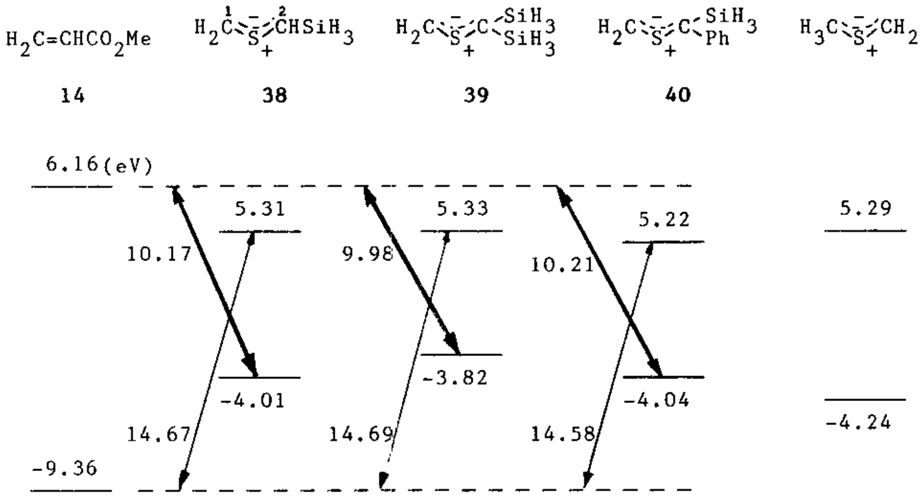


Fig. 3. The Frontier Orbital Energies of Thiocarbonyl Ylides and Methyl Acrylate. The thick arrows indicate the more favorable interactions between HOMO and LUMO.

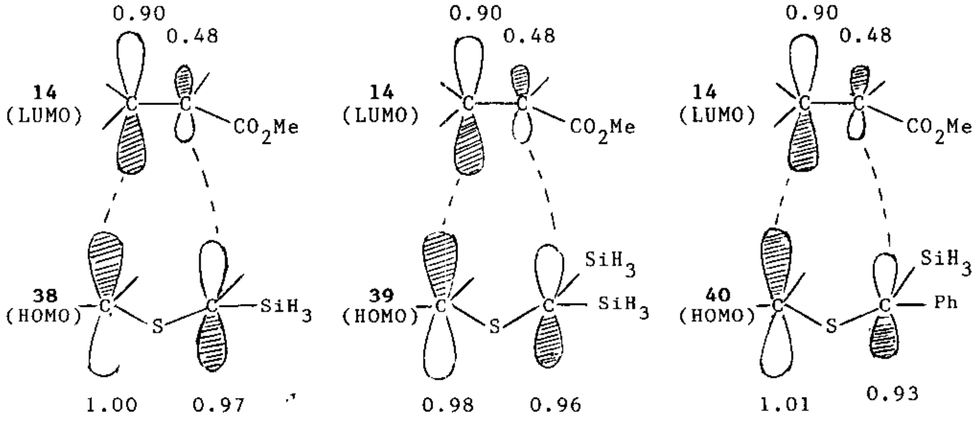
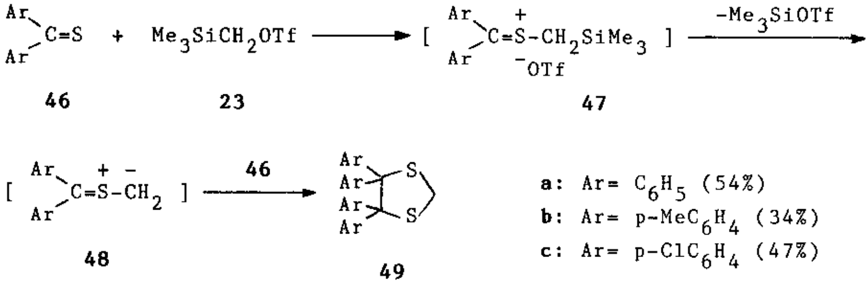


Fig. 4. The Frontier Molecular Orbital Interaction between Thiocarbonyl Ylides and Methyl Acrylate. The numerals beside the lobes indicate the frontier electron densities.

minus. The interactions of **39** with **14** and **40** with **14** are the same as that of **38** with **14**, which also proves that 2,3-di- or 2,2,3-trisubstituted tetrahydrothiophenes (**44a**, **45a**, and **45b**) were mainly obtained in the reactions of **41** with **14** and **42** with **14** (see Fig. 4). The regioselectivity in the reaction of **41** with **14** is lower than one in the reaction of **35** with **14** because the difference of the frontier electron densities on the two dipole termini of **39** is smaller than one of **38**. The reaction of **42** with **14** proceeds regioselectively because the difference of the frontier electron densities on the two dipole termini of **40** is enough large in comparison with that of **38** and **39**.

The stereoselectivities in entries 4 and 5 may be attributed to the steric effect of silyl group on the conformation of neighboring phenyl group (decrease of the secondary molecular orbital interaction described already).

The above methods involve the formation of silylmethyl sulfonium salts and the subsequent cleavage of the Si-C bond by attacking of the counter anion. This result prompted us to search for more convenient preparation of thiocarbonyl ylide via an intermediate sulfonium salt **36** by direct reaction of a thiocarbonyl compound and silylmethyl triflate. Treatment of 2 equiv. of thioketone (**46**) and trimethylsilylmethyl triflate (**23**) in dimethoxyethane (DME) at room temperature gave only 4,4,5,5-tetrasubstituted 1,3-dithiolane (**49**) in moderate yield[40] (Scheme 24).



a: Ar= C_6H_5 (54%)
b: Ar= p-MeC_6H_4 (34%)
c: Ar= p-ClC_6H_4 (47%)

Scheme 24

Generation of ylides **48** proceeds via the silylmethyl sulfonium salts (**47**) from one equiv. of **46** and **23**, and the successive reaction of **48** with dipolarophiles **46** gave the corresponding cycloadducts **49**. Figure 5 shows the results obtained by the frontier molecular orbital calculation of the dipole **48a** and the dipolarophile **46a** by means of the MNDO method[41]. These calculated results prove successfully the experimental fact that the product in 1,3-dipolar cycloaddition of **48a** with **46a** was 4,4,5,5-tetrasubstituted 1,3-dithiolane.

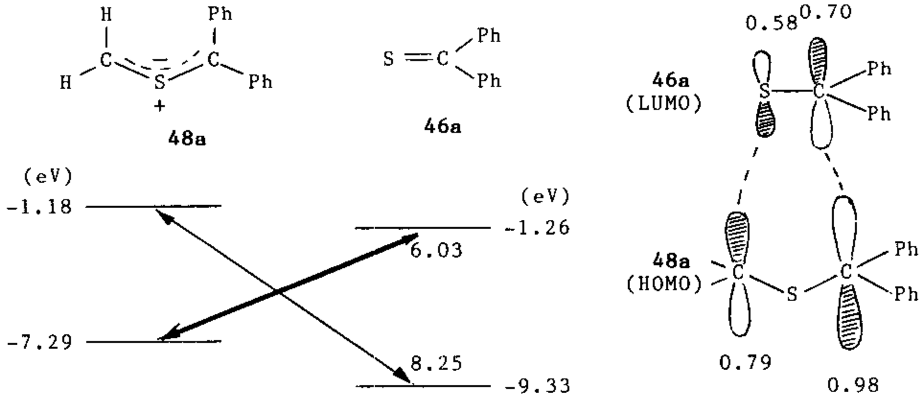
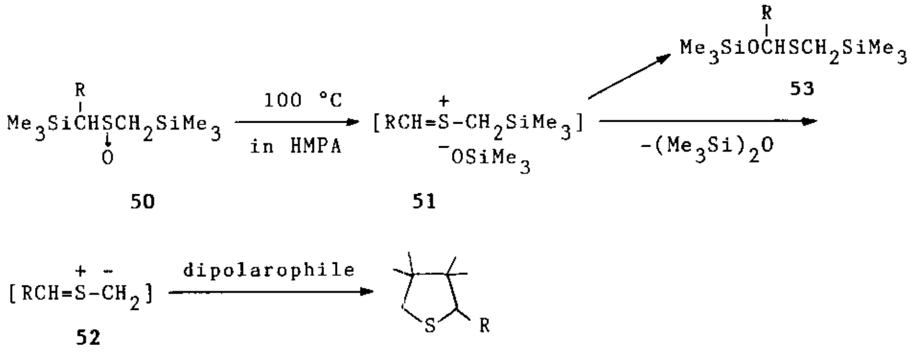


Fig. 5. HOMO-LUMO Correlation Diagram and the Frontier Orbital Interaction between Dipole and Dipolarophile in 1,3-Dipolar Cycloaddition. The thick arrows indicate the more favorable interactions between HOMO and LUMO. The numerals beside the lobes indicate the frontier electron densities.

2. From Bis(silylmethyl) Sulfoxides

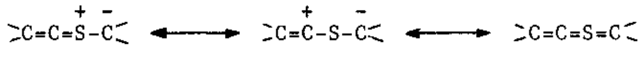
On the basis of the strategy involving the release of disiloxane through a pathway related to the sila-Pummerer rearrangement shown in Scheme 25, bis(trimethylsilylmethyl) sulfoxide (**50**) have been found to undergo 1,3-cycloadditions to conjugated dipolarophiles under the neutual and mild conditions[42].



Scheme 25

Treatment of the rearrangement product (**53**) with a dipolarophile under similar conditions did not give any cycloadduct. This fact suggests that intermediate **51** partitions between the desired ylide **52** and the sila-Pummerer rearrangement product **53**.

This method was utilized for generation of various thiocarbonyl ylides such as thioformaldehyde S-methylide, and aromatic and aliphatic thioaldehyde S-methylides. Reaction of their ylides with dipolarophiles gave the corresponding cycloadducts in good to moderate yields (Table 11). In paticular, thioketene S-methylide (**54**) constitutes a new class of thiocarbonyl ylides, the resonance structures of which include a 1,3-dipole species (**55**) and an interesting heterocumulene skeleton (**56**) containing a tetravalent sulfur (Scheme 26).

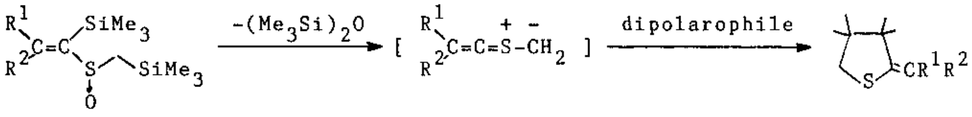


$$>C{=}C{=}\overset{+}{S}{-}\overset{-}{C}< \longleftrightarrow >C{=}\overset{+}{C}{-}S{-}\overset{-}{C}< \longleftrightarrow >C{=}C{=}S{=}C<$$

54 **55** **56**

Scheme 26

α-(Trimethylsilyl)vinyl (trimethylsilyl)methyl sulfoxides (**57**) have been found to undergo 1,3-cycloadditions to dipolarophiles, leading to synthesis of 2-alkylidenetetrahydrothiophene derivatives[43] (Scheme 27, entries 9-15 in Table 11).



57

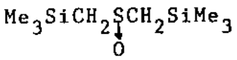
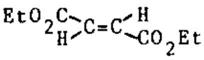
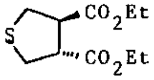
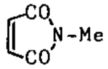
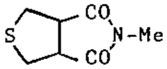
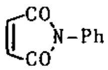
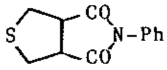
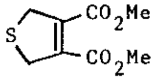
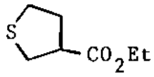
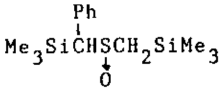
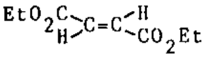
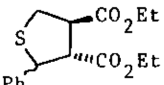
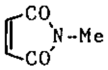
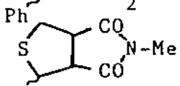
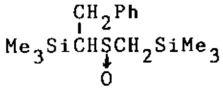
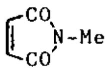
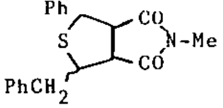
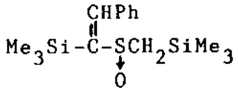
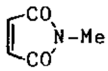
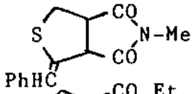
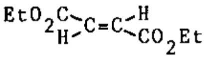
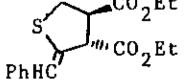
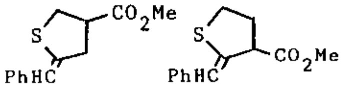
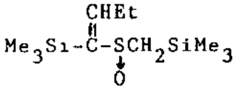
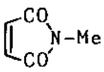
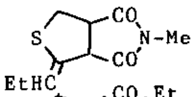
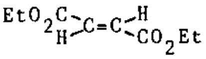
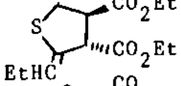
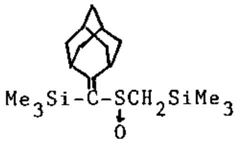
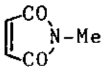
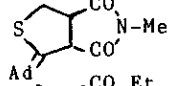
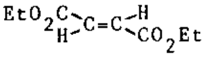
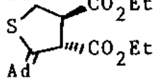
Scheme 27

It seems difficult that thioketene S-methylides are synthesized by the other methods using a thioketene as a starting material, such as thermolysis of thiadiazolines[33,34], because the thioketene is well known to be very unstable[44]. The methods by employing organosilicon compounds described in this section may promise a new development in the chemistry of thiocarbony ylides.

IV. Conclusion

The methodology involving the desilylation of (trimethylsilylmethyl)onium salt has provided a new route to generation of 1,3-dipole species and a new method for synthesizing heterocycles. The most remarkable feature of such method is that the reactions proceed under mild and neutral conditions. Therefore, the procedure can be applicable to the syntheses of a wide range of complex molecules.

Tabe 11 Synthesis of Tetrahydrothiophens from Bis(silylmethyl) Sulfoxides

Entry	Sulfoxide	Dipolarophile	Product	Yield(%)
1	 $Me_3SiCH_2\underset{\overset{\downarrow}{O}}{S}CH_2SiMe_3$			80
2				81
3				70
4		$MeO_2CC\equiv CCO_2Me$		61
5		$H_2C=CHCO_2Et$		55
6	 $Me_3Si\overset{Ph}{C}H\underset{\overset{\downarrow}{O}}{S}CH_2SiMe_3$			50
7				65
8	 $Me_3Si\overset{CH_2Ph}{C}H\underset{\overset{\downarrow}{O}}{S}CH_2SiMe_3$			65
9	 $Me_3Si-\overset{CHPh}{\overset{\|}{C}}-\underset{\overset{\downarrow}{O}}{S}CH_2SiMe_3$			78
10				60
11		$H_2C=CHCO_2Me$	 (2 : 1)	45
12	 $Me_3Si-\overset{CHEt}{\overset{\|}{C}}-\underset{\overset{\downarrow}{O}}{S}CH_2SiMe_3$			36
13				50
14				65
15				50

a) Reaction conditions: molar ratio, sulfoxide/dipolarophile = 1.5; solvent, HMPA; temp, 100°C; time, 10 min.

The Pd-mediated [3+2] cycloaddition of trimethylenemethanes discovered by Trost and his co-workers[45], and the [4+2] cycloaddition of o-quinodimethane by Ito and his co-workers[46] were also the attractive subjects for authors because of involving the desilylation process. However, they are beyond the scope of this review.

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