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CYCLOADDITION OF NEW *N*-UNSUBSTITUTED AZOMETHINE YLIDES GENERATED FROM *N*-[(TRIMETHYLSILYL)METHYL]-THIOCARBAMATES, SYNTHETIC EQUIVALENTS OF NON-STABILIZED ALKOXY- OR ALKYLTHIONITRILE YLIDES

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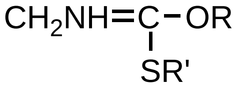
Abstract - The reaction of (trimethylsilyl)methyl isothiocyanate with alcohol in the presence of *aluminum alkoxide* provides a useful route for the preparation of *N*-[(trimethylsilyl)methyl]thiocarbamates. The *S*-methylation of thiocarbamates followed by desilylation generates nonstabilized azomethine ylides having both methylthio and alkoxy groups at the ylide carbon. These azomethine ylides react with electron-deficient carbon-carbon multiples bonds to give formal alkoxynitrile ylide- and/or methylthionitrile ylide-cycloadducts. Thus, the azomethine ylides can be synthetic equivalents of nonstabilized alkoxy- or methylthionitrile ylides that are otherwise relatively inaccessible.

The importance of 1,3-dipoles such as azomethine ylides in heterocyclic chemistry has grown rapidly by the development of mild and versatile methods for the generation.[1] A particularly mild method for the generation of nonstabilized azomethine ylides involves the desilylation, usually under the influence of fluoride ion, of *N*-(silylmethyl)iminium salts.[2] The resultant azomethine ylides reacted with electron-deficient multiple bonds to give the corresponding nitrogen-containing five-membered heterocycles.


$\overset{-}{C}H_2\overset{+}{N}H=\underset{SR'}{\underset{|}{C}}-OR$

A


$\overset{-}{C}H_2\overset{+}{N}\equiv C-OR$

B

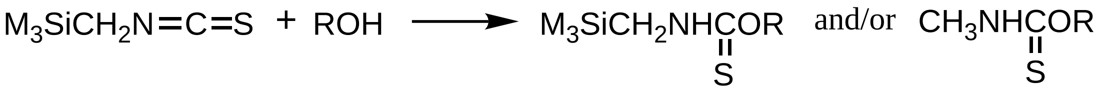

$\overset{-}{C}H_2\overset{+}{N}\equiv C-SR'$

C

We have previously reported that *N*-unsubstituted azomethine ylides carrying a leaving group such as alkylthio,[3,4] amino[4,5] or the both moieties[6] at the ylide carbon can be synthetic equivalents of nonstabilized nitrile ylides. In an effort to expand the scope of this method, we initiated investigation aimed at the generation of nonstabilized *N*-unsubstituted azomethine ylides such as **A** having alkoxy and alkylthio moieties, both of which serve as a leaving group, at the ylide carbon. Our approach to the azomethine ylides (**A**) consists of preparation of *N*-[(trimethylsilyl)methyl]thiocarbamates from (trimethylsilyl)methyl isothiocyanate, their *S*-alkylation to *N*-[(trimethylsilyl)methyl]iminium salts, and subsequent desilylation with fluoride ion. Elimination of the alkylthio or alkoxy group from the cycloadducts gives formal cycloadducts of nonstabilized alkoxynitrile ylides (**B**)[7a] or alkylthionitrile ones (**C**),[7a,7b] whose generation is little known heretofore, respectively.

Since *O*-ethyl-*N*-(silylmethyl)thiocarbamate was only prepared by the addition of ethanol to (trimethylsilyl)-methyl isothiocyanate (**1**)[8] in the presence of *hazardous* bis(tributyltin) oxide,[7a] the preparation of *N*-[(trimethylsilyl)methyl]thiocarbamates by the addition of alcohols to isothiocyanate (**1**) was first investigated under various conditions, some of which are listed in Table 1. It is well known that the reactions of isothiocyanates with alcohols are accelerated by catalytic amounts of *tert*-amines.[9] Thus, the reactions of isothiocyanate (**1**) with ethanol and 2-propanol were investigated in the presence of *tert*-amine. Under these conditions the expected *N*-(silylmethyl)thiocarbamate (**2**) was only formed in low yield, together with the desilylated thiocarbamate (**3**) and/or recovery of **1** (Entries 1-3).

Table 1. Reaction of Silylmethyl Isothiocyanate (**1**) with Alcohols



$$\mathrm{M_3SiCH_2N{=}C{=}S} + \mathrm{ROH} \longrightarrow \mathrm{M_3SiCH_2NH}\underset{\overset{\|}{\mathrm{S}}}{\mathrm{C}}\mathrm{OR} \quad \text{and/or} \quad \mathrm{CH_3NH}\underset{\overset{\|}{\mathrm{S}}}{\mathrm{C}}\mathrm{OR}$$

1 **2** **3**

a: R = Et; **b**: R = *i*-Pr

Entry	ROH	Catalyst	Molar ratio[a]	Temp.	Time/h	Products (Yield, %[b])		Recovery of **1**/%
						2	**3**	
1	EtOH	Et_3N	1/1/10	reflux	8	**2a** (9)	**3a** (20)	61
2	EtOH	DBU[c]	1/0.5/10	rt	2	**2a** (2)	**3a** (83)	0
3	*i*-PrOH	Et_3N	1/1/10	reflux	8	**2b** (+)[d]	**3b** (+)[d]	86
4	EtOH	ZnI_2	1/1/28	reflux	4	**2a** (15)	**3a** (0)	75
5	*i*-PrOH	ZnI_2	1/1/15	reflux	8	**2b** (6)	**3b** (0)	82
6	EtOH	AE[e]	1/1/30	reflux	12	**2a** (11)	**3a** (0)	81
7	EtOH	AE[e]	1/1/5	reflux	48	**2a** (56)	**3a** (0)	35
8	*i*-PrOH	AP[f]	1/1/5	reflux	24	**2b** (61)	**3b** (0)	32
9	*i*-PrOH	AP[f]	1/1/5	reflux	48	**2b** (95)	**3b** (0)	+[d]
10	*i*-PrOH	AP[f]	1/0.5/5	reflux	48	**2b** (64)	**3b** (0)	30

[a]Molar ratio of **1**/catalyst/ROH. [b]Isolated yield based on **1**. [c]DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene. [d]+ Sign means trace amounts. [e]AE: Aluminum ethoxide. [f]AP: Aluminum isopropoxide.

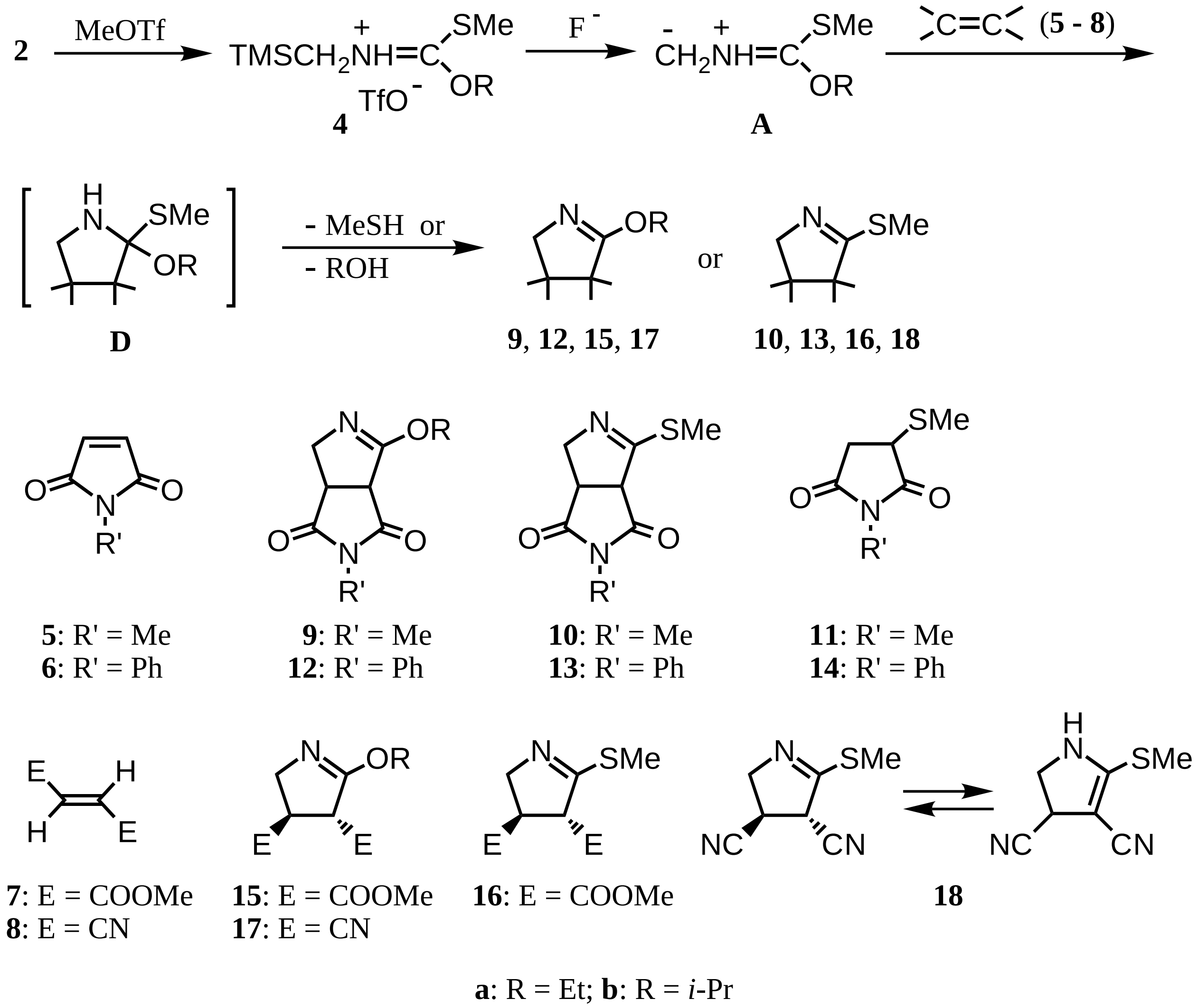
Next, the Lewis acid-catalyzed reactions were investigated: in the presence of zinc iodide desilylated thiocarbamate (**3**) was not formed at all, but the expected silylated thiocarbamate (**2**) was only obtained in low yield along with a large amount of unreacted **1** (Entries 4, 5). However, we have eventually found an effective method for the preparation of **2** under the influence of aluminum alkoxide (Entries 6-10).[10]

In analogy with *N*-(silylmethyl)thioamides[4] and *N*-(silylmethyl)thioureas,[6] the selective *S*-methylation of thiocarbamates (**2**) with methyl triflate proceeded smoothly to give the corresponding *N*-(silylmethyl)-

iminium triflates (**4**) in an almost quantitative yield.[11] Thus, generation of azomethine ylides by desilylation of **4** and subsequent cycloaddition with a variety of dipolarophiles were investigated. A one-pot *S*-methylation-desilylation-cycloaddition procedure was used: methyl triflate was added to the solution of **2** in a dry solvent, and the resultant solution was stirred at room temperature for 1 h under argon in order to complete the methylation. A dipolarophile and then cesium fluoride (CsF) were added, and the mixture was allowed to stir at room temperature until no further reaction was observed by TLC.

Electron-deficient olefins such as *N*-methyl- (**5**), *N*-phenylmaleimide (**6**), dimethyl fumarate (**7**), and fumaronitrile (**8**) were first employed as dipolarophiles. In all cases, the initial cycloadducts (**D**) could not be isolated, but instead the leaving group was eliminated to furnish the corresponding 2-alkoxy- (**9**, **12**, **15**, **17**) and 2-methylthiopyrrolines (**10**, **13**, **16**, **18**). In the reaction with **5** or **6**, the corresponding 2-methylthiosuccinimide (**11**) or (**14**) were also formed. The results are summarized in Table 2.

The above results clearly show that the azomethine ylides (**A**) generated from **4** serve as synthetic equivalents of nonstabilized alkoxynitrile (**B**) or methylthionitrile ylides (**C**) through a cycloaddition and elimination sequence.



Scheme 1

As shown in Table 2, the 2-alkoxypyrroline (**9**, **12**, **15**, **17**) was formed in preference to the corresponding 2-methylthiopyrroline (**10**, **13**, **16**, **18**) in all cases: taking into account the reactivity of methylthio and alkoxy group as the leaving group these results are reasonable. However, it is interesting that the ratio OR/SMe of the reaction in DME becomes much smaller than that in acetonitrile (compare Entry 3 with 4, 6 with 7, and 10 with 11, respectively).

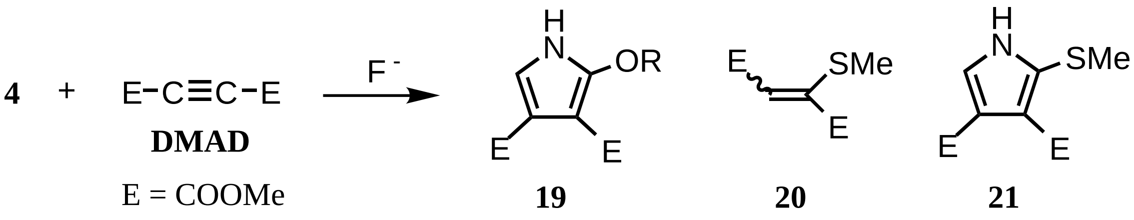
Table 2. Cycloaddition to Carbon-Carbon Multiple Bonds[a]

Entry	Precursor	Dipolarophile	Solvent	Molar ratio[b]	Products (Yield, %[c])	OR/SMe[d]
1	**2a**	**5**	MeCN	1/1/1	**9a** (36), **10** (17), **11** (35)	100/47
2	**2a**	**5**	MeCN	1/2/1	**9a** (57), **10** (28), **11** (42)	100/49
3	**2b**	**5**	DME	1/1/1	**9b** (31), **10** (23), **11** (16)	100/74
4	**2b**	**5**	MeCN	1/1/1	**9b** (38), **10** (9), **11** (20)	100/24
5	**2a**	**6**	MeCN	1/1/1	**12a** (45), **13** (2), **14** (37)	100/4
6	**2b**	**6**	DME	1/1/1	**12b** (27), **13** (23), **14** (23)	100/85
7	**2b**	**6**	MeCN	1/1/1	**12b** (45), **13** (6), **14** (41)	100/13
8	**2a**	**7**	MeCN	1/1/1	**15a** (35), **16** (16)	100/46
9	**2b**	**7**	MeCN	1/1/1	**15b** (38), **16** (14)	100/37
10	**2a**	**8**	DME	1/1/1	**17a** (47), **18** (21)	100/45
11	**2a**	**8**	MeCN	1/1/1	**17a** (68), **18** (11)	100/16
12	**2b**	**8**	MeCN	1/1/1	**17b** (72), **18** (5)	100/7
13	**2a**	DMAD	MeCN	1/1/1	**19a** (49), **20** (46)[e]	100/0
14	**2b**	DMAD	MeCN	1/1/1	**19b** (53), **20** (40)[e]	100/0
15	**2b**	DMAD	MeCN	1/2/1	**19b** (61), **20** (32)[e]	100/0

[a] All the reactions were performed at room temperature for 24 h under argon. [b] Molar ratio of **2**/dipolarophile/CsF. [c] Yield estimated by ^{1}H NMR. [d] Ratio of 2-alkoxypyrroline/2-methylthiopyrroline. [e] Isolated yield.

Bis(methoxycarbonyl)pyrrolines (**15**, **16**) and 2-alkoxydicyanopyrrolines (**17**) exist only as the corresponding 1-pyrroline,[12] but 2-methylthiodicyanopyrroline (**18**) exists as a mixture of 1- and 2-pyrrolines.[13]

Cycloaddition of these azomethine ylides to acetylenic dipolarophiles is, therefore, expected to be a convenient route to *N*-unsubstituted 2-alkoxy- or 2-methylthiopyrroles. Unfortunately, the reactivity of diaroyl- and aroylarylacetylenes toward **A** was low and the reaction under more forced conditions resulted in the formation of intractable materials. The reaction of **4** with dimethyl acetylenedicarboxylate (DMAD) under the influence of CsF, however, furnished the corresponding 2-alkoxypyrrole (**19**) together with 1,2-bis(methoxycarbonyl)-1-methylthioethylene (**20**) whose structure corresponds to a Michael adduct of the eliminated methanethiol to DMAD, but no 2-methylthiopyrrole (**21**) was formed (Table 2 and Scheme 2).



a: R = Et; **b**: R = *i*-Pr

Scheme 2

In conclusion, azomethine ylides readily generated by the desilylation of iminium salts react with electron-deficient olefinic and acetylenic dipolarophiles to give formal nonstabilized alkoxynitrile ylide- and/or methylthionitrile ylide-cycloadducts that are otherwise relatively inaccessible.

REFERENCES AND NOTES

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6. O. Tsuge, T. Hatta, Y. Kakura, H. Tashiro, H. Maeda, and A. Kakehi, *Chemistry Lett.*, **1997**, 945; *Tetrahedron*, 2000, **56**, 7723. O. Tsuge, T. Hatta, H. Tashiro, and H. Maeda, submitted in *Heterocycles.*
7. (a) Recently, it has been reported that 2-azaallyl anions generated *N*-silylmethylated iminothiocarbonate and iminodithiocarbonate reacted with carbonyl compounds to give the formal [3 + 2] cycloadducts of the alkoxy- and alkylthionitrile ylides such as **B** and **C**, respectively: M. Oba, M. Yoshihara, J. Nagatsuka, and K. Nishiyama, *Heterocycles*, 1997, **45**, 1913. (b) We have reported[3] that 2-azaallyl anion generated from *N*-silylmethyliminodithiocarbonate reacted with dimethyl fumarate to give a Michael adduct, but afforded the formal [3 + 2] cycloadduct of alkylthionitrile ylide (**C**) in the reaction of mono- or 1,1-disubstituted electron-deficient olefins.
8. O. Tsuge, S. Kanemasa, and K. Matsuda, *J. Org. Chem.*, 1984, **49**, 2688.
9. C. N. Rao and R. Venkataraghavan, *Tetrahedron*, 1962, **18**, 531; E. Cherbuliez, J. Marzalek, and J. Rabinowitz, *Helv. Chim. Acta*, 1965, **48**, 643; W. Walter and K. D. Bode, *Angew. Chem.*, 1967, **79**, 285.
10. The structures of all new compounds in this paper were fully characterized by the spectroscopic and elementary analysis. It has been reported that thiocarbamates exist as a mixture of *cis* and *trans* isomers in solution (R. A. Bauman, *J. Org. Chem.*, 1967, **32**, 4129; R. A. Bauman, *Tetrahedron Lett.*, **1971**,

419). It has been found that *N*-(silylmethyl)thiocarbamates (**2**) exist as an approximately equal mixture of *cis* and *trans* isomer in $CDCl_3$. For example, ^1H NMR spectral data of **2a** (mp 38-39 ˚C, bp 73-75 ˚C/1.2 mmHg) in $CDCl_3$: δ 0.09, 0.11 (each s, 4.5H), 1.32, 1.37 (each t, J = 7.2 Hz, 1.5H), 2.82 (d, J = 6.3 Hz, 1H), 3.09 (d, J = 5.9 Hz, 1H), 4.48, 4.55 (each q, J = 7.2 Hz, 1H), 6.11, 6.68 (each br s, 0.5H).

11. *N*-(Silylmethyl)iminium triflates (**4**) exist also as a mixture of *cis* and *trans* isomers. For example, ^1H NMR spectral data of **4b** (colorless oil) in $CDCl_3$: δ 0.15 (s, 5.4H), 0.21 (s, 3.6H), 1.51 (d, J = 6.1 Hz, 3.6H), 1.52 (d, J = 6.1 Hz, 2.4 Hz), 2.55 (s, 1.8H), 2.86 (s, 1.2H), 3.14 (s, 0.8H), 3.28 (s, 1.2H), 5.0-5.65 (m, 1H), 10.15 (br s, 1H).
12. Formation of 3,4-*trans*-1-pyrrolines (**15-17**) is due to a ready imine/enamine tautomerism (or a 1-pyrroline/2-pyrroline isomerisation such as **18** shown in Scheme 1).[5,6]
13. Position of double bond in each cycloadduct has been found to depend on the electronic nature and the steric size of the substituents. The double bond in pyrrolines presumably migrates to the thermodynamically most stable location.[5,6] 2-Methylthio-3,4-dicyanaopyrroline (**18**) (colorless plates, mp 108-110 ˚C) exists as a mixture of 1- and 2-isomer (ratio 3/1) in $CDCl_3$: ^1H NMR δ 2.49 (s, 2.25H, SMe in 1-isomer), 2.50 (s, 0.75H, SMe in 2-isomer), 3.68-3.90 (m, 1.25H), 4.13 (dd, J = 10.1, 6.3 Hz, 0.75H, 5-H in 1-isomer), 4.21 (dd, J = 6.3, 1.3 Hz, 0.75H, 5-H in 1-isomer), 4.32-4.44 (m, 0.5 H, 5-H in 2-isomer), 5.51 (br s, 1H).