A New and General Route to *N*-Unsubstituted Azomethine Ylides from *N*-(Silylmethyl)thioureas: Cycloaddition of Synthetic Equivalents of Nonstabilized Aminonitrile Ylides

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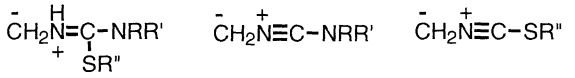
The *S*-methylation of *N*-(silylmethyl)thioureas followed by the desilylation generates *N*-unsubstituted azomethine ylides having both methylthio and amino groups at the ylide carbon. These azomethine ylides react with electron-deficient olefins to give formal aminonitrile ylide cycloadducts, novel 2-aminopyrrolines. Thus, the azomethine ylides can be synthetic equivalents of nonstabilized aminonitrile ylides which are otherwise relatively inaccessible.

The importance of 1,3-dipoles such as azomethine ylides in organic synthesis has been considerably enhanced 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, of *N*-(silylmethyl)iminium salts.[2] The resultant azomethine ylides can be trapped with electron-deficient olefins and acetylenes to give a variety of pyrrolidines, pyrrolines, and pyrroles.

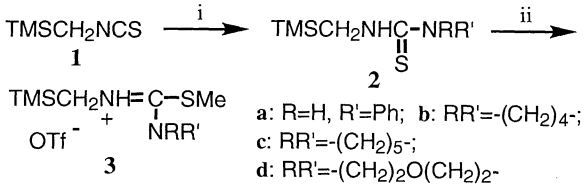
Water-induced desilylation of *N*-(silylmethyl) imines,[3] or thioimidates,[4] and fluoride-mediated desilylation after the S- or *N*'-alkylation of *N*-(silylmethyl) thioimides[5] or amidines,[5,6] are synthetically valuable since they can lead to novel 1,3-dipoles, *N*-unsubstituted azomethine ylides. It should be emphasized that the *N*-unsubstituted azomethine ylides carrying a leaving group such as alkylthio[4,5] or amino moiety[5,6] at the ylide carbon can be synthetic equivalents of nonstabilized nitrile ylides.

The present research is to aim at the development of a new and general route to *N*-unsubstituted azomethine ylides carrying alkylthio and amino moieties, both of which serve as a leaving group, at the ylide carbon. Our approach to the *N*-unsubstituted azomethine ylides (**A**) carrying both alkylthio and amino moieties



A **B** **C**

consists of initial S-alkylation of *N*-(silylmethyl)thioureas leading to *N*-(silylmethyl)iminium salts, and subsequent desilylation with fluoride. Elimination of the leaving alkylthio group or amino group from the cycloadducts gives formal cycloadducts of nonstabilized aminonitrile ylides (**B**) or alkylthionitrile ones (**C**), whose generation is little known heretofore,[7] respectively.



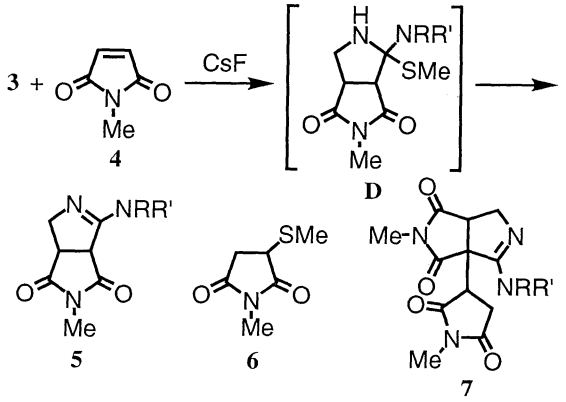
a: R=H, R'=Ph; **b**: RR'=-$(CH_2)_4$-; **c**: RR'=-$(CH_2)_5$-; **d**: RR'=-$(CH_2)_2O(CH_2)_2$-

Reagents and conditions: i, RR'NH, reflux, benzene, 1h, 93-100%. ii, MeOTf, reflux, CH_2Cl_2, 1.5h, 95-100%.

Scheme 1.

[2-Methyl-3-(trimethylsilyl)methyl]thiouronium triflates (**3**) as precursors of azomethine ylides (**A**) were prepared by *S*-methylation of *N*-[(trimethylsilyl)methyl]thioureas (**2**) obtained from (trimethylsilyl)methyl isothiocyanate (**1**)[8] (Scheme 1).[9]

The reaction of **3** with *N*-methylmaleimide (**4**) in the presence of CsF was first investigated under a variety of conditions (Scheme 2, Table 1). In all cases, the initial cycloadducts (**D**) could not be isolated. Instead, methanethiol was eliminated from **D** and formal aminonitrile ylide cycloadducts (**5**) were obtained.



Scheme 2.

Table 1. Cycloaddition with *N*-methylmaleimide (**4**)[a]

Entry	3	Solvent[b]	Molar ratio[c]	Product: yield/%
1	**3a**	DME	1/1/1	**5a** (83)
2	**3a**	AN	1/1/1.2	**5a** (75)
3	**3a**	DME	1/2/1.2	**5a** (90)
4	**3b**	DME	1/1/1	**5b** (24), **6** (2)
5	**3b**	DME	1/2/1.2	**5b** (41), **6** (60), **7b** (14)
6	**3b**	DME	1/2.5/1.2	**6** (52), **7b** (48)
7	**3c**	DME	1/1/1	**5c** (51), **6** (26)
8	**3c**	AN	1/1/1	**5c** (39), **6** (41)
9	**3c**	THF	1/1/1	**5c** (45), **6** (27)
10	**3c**	DME	1/2/1.2	**5c** (45), **6** (65),**7c** (17)
11	**3c**	DME	1/2.5/1.2	**6** (30), **7c** (60)
12	**3d**	DME	1/1/1	**5d** (49), **6** (7)
13	**3d**	DME	1/2/1.2	**5d** (32), **6** (49), **7d** (17)
14	**3d**	DME	1/2.5/1.2	**6** (43), **7d** (51)

[a]The reactions were carried out in dry solvent at room temperature (entries 1-3) or at reflux (entries 4-14) for 10 h under nitrogen. [b]DME: 1,2-dimethoxyethane; AN: acetonitrile; THF: tetrahydrofuran. [c]Molar ratio of **3**/**4**/CsF.

Thiouronium salt (**3a**) gave the cycloadduct (**5a**) as the sole isolated product in a high yield, but the reaction of less reactive reagents **3b**-**3d** with an equivalent amount of **4** afforded the

corresponding cycloadduct (**5b-5d**) in low to moderate yield, together with *N*-methyl-2-methylthiosuccinimide (**6**) whose structure correponds to the Michael adduct of eliminated methanethiol to **4**. In contrast to the reaction of **3a** giving a high yield of **5** (entry 3), interestingly, **3b-3d** reacted with excess **4** to form novel 1:2 adduct (**7b-7d**) as major product (entries 6,11, 14).[10] The structure of **7** corresponded to the adduct of **4** to the most crowded position 6a in **5**, and was determined as 6-amino-2-methyl-6a-[3-(1-methyl-2,5-dioxopyrrolidinyl)]-1,2,3,3a,4,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1,3-dione on the basis of spectral data and X-ray crystallographic analysis of **7d**. The ORTEP drawing of **7d** is shown in Figure 1.[11]

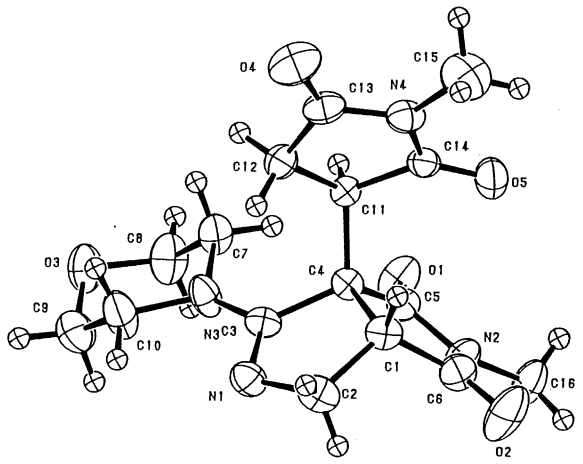
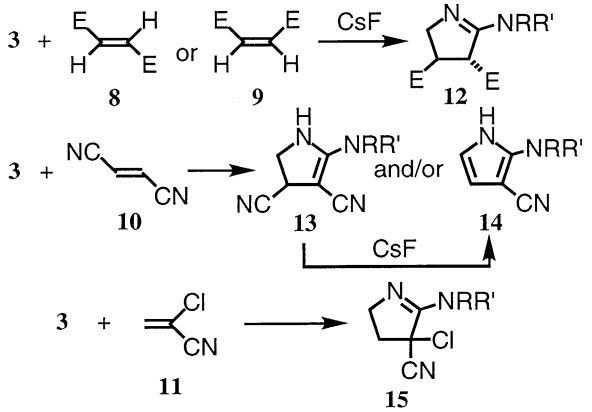


Figure 1. ORTEP drawing of 1:2 adduct **7d**.

Next, the reaction of **3** with electron-deficient acyclic olefins such as dimethyl fumalate (**8**), maleate (**9**), fumaronitrile (**10**), and 2-chloroacrylonitrile (**11**) in the presence of CsF in dry DME (Scheme 3, Table 2). Although these acyclic dipolarophiles were somewhat less reactive than **4**, the corresponding aminonitrile ylide cycloadducts were obtained in all cases.



Scheme 3.

The reaction of *cis*-olefin (**9**) gave the thermodynamically stable *trans*-bis(methoxycarbonyl)-1-pyrroline (**12**), which was identical with the cycloadduct from trans-olefin (**8**).[5] On the other hand, **3** reacted with **10** to give a mixture of 2-pyrroline (**13**)[12] and/or 3-cyanopyrrole (**14**) whose relative yields depended upon reaction conditions: Heating **13a** or **13c** with CsF in DME for 24 h afforded **14a** or **14c** in 85 or 79% yield, respectively. In the reaction of **3** with 1,1-disubstituted olefin (**11**) regioselective 3-chloro-3-cyanao-1-pyrroline (**15**) was obtained as the sole isolated product, though its yield was low.

Table 2. Cycloaddition with acyclic olefins **8**, **9**, **10**, and **11**

Entry	3	Olefin	Molar ratio[a]	Temp	Time/h	Product Yield/%
1	**3a**	**8**	1/1/1	r.t.	20	**12a** (71)
2	**3c**	**8**	1/1/1	r.t.	20	**12c** (38)
3	**3c**	**8**	1/1/1	reflux	10	**12c** (52)
4	**3a**	**9**	1/1/1	r.t.	20	**12a** (52)
5	**3c**	**9**	1/1/1	reflux	10	**12c** (35)
6	**3d**	**9**	1/1/1	reflux	10	**12d** (30)
7	**3a**	**10**	1/1/1	r.t.	10	**13a** (61)
8	**3b**	**10**	1/1/1	r.t.	10	**13b** (48)
9	**3c**	**10**	1/1/1	r.t.	10	**13c** (46)
10	**3d**	**10**	1/1/1	r.t.	10	**13d** (48)
11	**3a**	**10**	1/1/2	reflux	10	**13a** (35), **14a** (23)
12	**3c**	**10**	1/1/2	reflux	10	**13c** (24), **14c** (25)
13	**3d**	**10**	1/1/2	reflux	10	**14d**(46)
14	**3a**	**11**	1/1/1.2	reflux	5	**15a** (31)
15	**3d**	**11**	1/1/1.2	reflux	10	**15d** (18)

[a]Molar ratio of **3**/olefin/CsF.

In conclusion, azomethine ylides readily generated by the desilylation of thiouronium triflates (**3**) react with electron-deficient olefins to give formal nonstabilized aminonitrile ylides cycloadducts, novel 2-aminopyrrolines which are otherwise relatively inaccesible.

References and Notes

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2 The desilylative route to azomethine ylides has been reviewed: a) E. Vedejs and F. G. West, *Chem. Rev.*, **86**, 941 (1986). b) Y. Terao, M. Aono, and K. Achiwa, *Heterocycles*, **27**. 981 (1988).

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6 O. Tsuge, S. Kanemasa, and K. Matsuda, *Chem. Lett.*, **1985**, 1411.

7 It has been reported that the reaction of 1-methyl-2-[(methylthio(trimethylsilylimino)methylimino]-1,2-dihydropyridine with carbonyl compounds in the presence of fluoride ion afforded the formal [3+2] cycloadducts of the aminonitrile ylide (S. Kohra, K. Ueda, and Y. Tominaga, *Chem. Pharm. Bull.*, **43**, 204 (1995).

8 O. Tsuge, S. Kanemasa, and K. Matsuda, *J. Org. Chem.*, **49**, 2688 (1984).

9 The structures of all the new compounds in this paper were fully characterized by the spectroscopic and elementary analysis.

10 No 1:2 adducts (**7b-7d**) were obtained from the reaction of the corresponding 1:1 adduct (**5**) with **4** in the presence or absence of CsF in refluxing DME. The reaction pathway for the formation of **7** is not clear.

11 X-Ray crystallographic analysis was carried out on a Rigaku AFC5S diffractometer. The diffraction data were collected with the use of MoKα radiation and 2121 independent reflcctions were used for solving the structure by the TEXSAN program. Crystal data for **7d**: $C_{16}H_{20}N_4O_5$, F.W.=348.36, monoclinic, space group $P2_1$ (#4), a=10.375(1) Å, b=6.482 (1) Å, c=12.292 (1) Å, ß=102.304(8)°, V=807.6(2) Å^3, Z=2, Dcal=1.432 g/cm^3, R=0.045, Rw=0.051.

12 Position of double bond in each cycloadduct has been found to depend upon the electronic nature and the steric size of the substituents (lit. 5). The double bond in pyrrolines presumably migrate to the thermodynamically most stable location.