WATER-INDUCED AZOMETHINE YLIDE GENERATION FROM N-(SILYLMETHYL)THIOIMIDATES, SYNTHETIC EQUIVALENTS OF NONSTABILIZED NITRILE YLIDES

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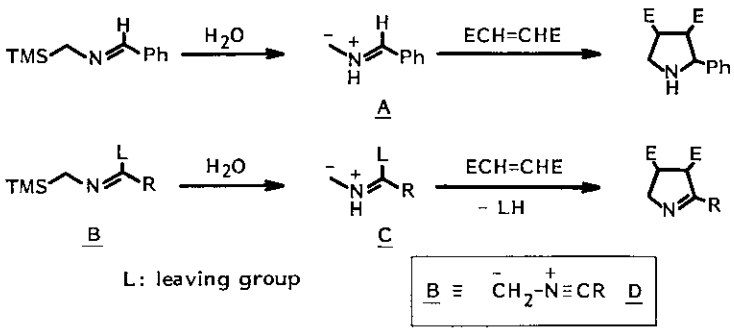
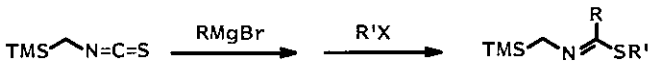
Abstract —— N-(Silylmethyl)thioimidates undergo a water-induced desilylation generating azomethine ylide 1,3-dipoles which cycloadd to a variety of electron-deficient olefins providing 1- or 2-pyrrolines after the elimination of thiol, indicating that the thioimidates are synthetic equivalents of nonstabilized nitrile ylides.

N-(Silylmethyl)imines owe their importance in heterocyclic synthesis much to the applications toward the generation of azomethine ylide 1,3-dipoles under mild conditions. The general route into the ylides consists of the initial quaternarization on the nitrogen and the subsequent desilylation with a fluoride ion[1]. A variety of azomethine ylides have been prepared according to this method and found wide applications in organic synthesis[2]. A rather exceptional generating method discovered in our laboratory involves the action of water to N-(silylmethyl)imines in polar solvents such as HMPA or DMF[3]. Cycloadditions of the ylide A thus formed to olefins provide pyrrolidines as shown below.



The present research is aiming at an extension of our method to an N-(silylmethyl)-imine B bearing a leaving group at the imine carbon. The cycloadditions of ylide C to olefinic dipolarophiles, followed by elimination of the leaving group, would lead to 1-pyrroline derivatives. By this sequence, the imine B will become the

synthetic equivalent of a nonstabilized nitrile ylide D. We have chosen some N-(silylmethyl)thioimidates as candidates for B.



1: R= Ph, R'=Me
2: R= Ph, R'=COPh
3: R= i-Pr, R'=Me
4: R= Et, R'=Me

Scheme 1.

The thioimidates 1-4 were readily available in one-pot reactions of trimethylsilylmethyl isothiocyanate[4] with Grignard reagents and then with methyl iodide or benzoyl chloride as shown in Scheme 1 (1: 83%; 2: 71%; 3: 71%; 4: 76%). This route might allow the introduction of a variety of substituents at the imine carbon of thioimidates[5].

The reaction of 1 with N-methylmaleimide 5 in the presence of an equivalent amount of water in HMPA at room temperature (method A) gave an excellent yield of the 1-pyrroline 10 (Scheme 2 and Table 1)[6]. Although some initial cycloadduct E was detected in the crude reaction mixture, it suffered from the ready and complete

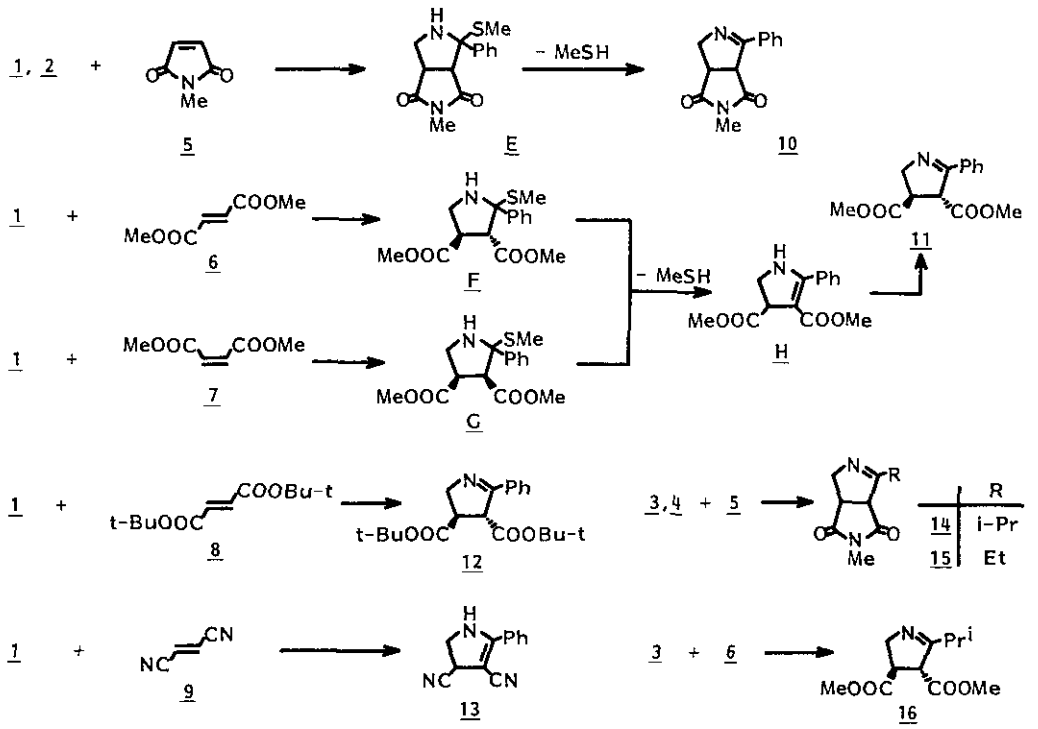
Table 1. Cycloadditions of 1-4 to Symmetrically Substituted Olefins.

N-Silylmethyl thioimidate	Olefin	Reaction conditions[a] Method[b]	Time/h	Product	Yield/%[c]
1	5	A	24	10	98
		B	16	10	25
		C	16	10	44
2	5	D	36	10	70
1	6	A	24	11	80
		B	24	11	38
1	7	A	24	11	62
1	8	A	24	12	70
1	9	A	24	13	77
3	5	A	24	14	15
4	5	A	24	15	10
3	6	E	24	16	23

a) Each equivalent amounts of the thioimidates and olefins were used. b) A: H_2O (equiv) in HMPA at rt; B: TMSOTf-CsF (each equiv) in HMPA at 60 °C; C: PhCOF (equiv) in MeCN at 60 °C; D: AcOH (equiv) in HMPA at 60 °C; E: AcOH (equiv) in HMPA at rt. c) All isolated yields.

elimination of methanethiol during the chromatographic procedure over silica gel providing 10. The conventional generating method using TMSOTf-CsF (method B) or PhCOF (method C) resulted in poorer yield of 10. The thioimidate 2 bearing benzoylthio moiety as a leaving group showed no advantage over the methylthio-substituted thioimidate 1.

It is surprising that the same *trans*-1-pyrroline 11 was the only product either in the reaction of 1 with dimethyl fumarate 6 or with dimethyl maleate 7, because the cycloaddition of nonstabilized azomethine ylide to olefins is known to be highly stereospecific[3]. The initial cycloadducts F and G must have been trans and cis, respectively. The thiol elimination at the 2-3 bond leads to the same 2-pyrroline H. The sterically hindered enamine of H undergoes a hydrogen migration forming the sterically more favored *trans*-1-pyrroline 11.



Scheme 2.

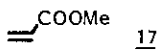
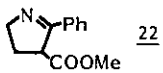
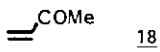
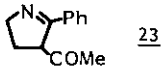
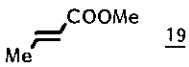
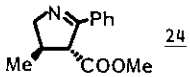
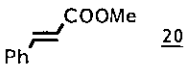
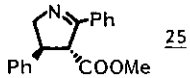
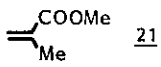
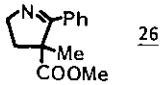
Similar reactions of 1 with di(t-butyl) fumarate 8 and fumaronitrile 9 gave the 1-pyrroline 12 and 2-pyrroline 13, respectively (Scheme 2 and Table 1). The cyano moiety at the 3-position of 13 is small in size so that it tolerates the fixation of double bond at the 2-position.

Although the thioimidates 3 and 4 carrying an alkyl substituent at the imine carbon underwent similar cycloadditions to 5 and 6, the yields of 14-16 were unfortunately

quite poor. This low yield might be partly due to the lack of ylide-stabilizing ability of the alkyl substituent. In these cases, the major reaction path was the polymerization of olefins employed.

The reactions of 1 with a variety of unsymmetrically substituted olefins 17-21 produced the regioselective 1-pyrrolines 22-26 in good yields (Table 2).

Table 2. Cycloadditions of 1 to Unsymmetrically Substituted Olefins.[a)]

Olefin		Product		Yield/%[b)]
	17		22	62
	18		23	75
	19		24	68
	20		25	75
	21		26	71

a) Conditions: H_2O (equiv) in HMPA at rt for 24 h. b) All isolated yields.

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5. Other substituents such as alkyl, aryl and vinyl moieties can be successfully introduced (unpublished results).
6. All new compounds reported herein gave satisfactory spectral and analytical results.

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