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1,4-ADDITION REACTION OF ORGANOMETALLICS TO α,β-UNSATURATED sec-THIOAMIDES

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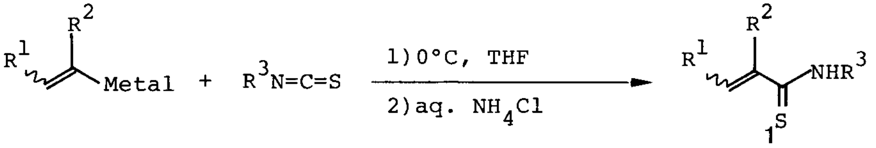
Summary: Preparation of α,β-unsaturated thioamides and their reactions (1,4-addition and β'-lithiation) with organometallics are described.

In this and accompanying communications we disclose some interesting reactivities of saturated and α,β-unsaturated secondary thioamides toward organometallics: generation of dianion and its reaction with electrophiles. While saturated sec-thioamides can be prepared in good yields by treatment of the corresponding amides with phosphorous pentasulfide in dimethoxyethane (r.t ∿70°C), α,β-unsaturated sec-thioamides can be hardly prepared by the similar procedure, probably owing to polymerization of product under the reaction conditions.[1] Then, α,β-unsaturated thioamides with structural variety were prepared in quantity (20∿40 mmol) by the reaction of N-methyl- or N-phenyl isothiocyanate either with olefinic organometallics (0°C, THF, equation 1, procedure A) or with allylmagnesium bromide[2] followed by a base catalyzed conjugation (cat. DBU, THF reflux, equation 2, procedure B). Results are summarized in Table I. N-Methylthioamides, except for N-methylthioacrylamide (**1a**), can be purified by distillation without significant loss.



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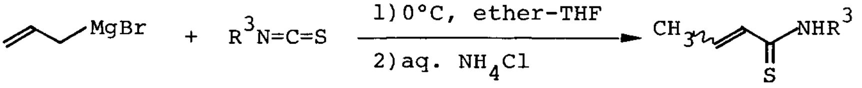
(1)



1d, **1e**

(2)

For the purification of N-phenylthioamides and **1a**, a column chromatography (silica gel) is recommended. N-Methylthioacrylamide (**1a**) is rather unstable even in the presence of hydroquinone and should be prepared prior to use. Other thioamides in Table I are thermally stable and can be stored in a refregerator without noticeable decomposition for a long period of time.

1,4-Conjugate addition has been recognized as one of the most useful C-C

Table I. Preparation of α,β-Unsaturated sec-Thioamides

	Thioamide[a)]			Method[b)]	Yield (%)[c)]	Bp (°C/mmHg)
	R^1	R^2	R^3			
1a	H	H	CH_3	A	75	110/0.5[d)]
1b	H	CH_3	CH_3	A	62	150/6
1c	H	CH_3	C_6H_5	A	87	----[d)]
1d	CH_3	H	CH_3	B	82	130/0.5
1e	CH_3	H	C_6H_5	B	87	----[d)]
1f	CH_3	CH_3	CH_3	A	94	150/5
1g	CH_3	CH_3	C_6H_5	A	77	150/0.1
1h	CH_3	C_2H_5	CH_3	B[e)]	89	153/3
1i	$-(CH_2)_4-$		CH_3	A	98	150/1.5
1j	$-(CH_2)_4-$		C_6H_5	A	98	85°C[f)]
1k	CH_3	$CH_2=CHCH_2$	CH_3	B[e)]	84	152/5

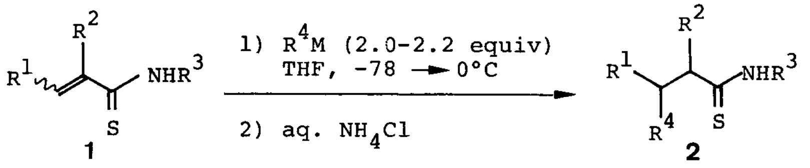
a) Grignard reagents were used for the preparation of 1a-1h and 1k. For the preparation of 1i and 1j, cyclohexenyllithium was applied. b) Methods A and B are meant to refer to the equations 1 and 2, respectively. c) Isolated yields. d) Decomposition during distillation. e) For the preparation of these thioamides, see the accompanying paper. f) Recrystallized from benzene-hexane.

Table II. 1,4-Addition of Organometallics to α,β-Unsaturated sec-Thioamides[a)]

Entry	Thioamide 1			Organometallics	% yield of 2
	R^1	R^2	R^3	R^4M	
1	H	H	CH_3	n-BuLi	87
2	H	H	CH_3	sec-BuLi	70
3	H	H	CH_3	$CH_2=CHCH_2Li$	47
4	CH_3	H	C_6H_5	n-BuLi	82
5	CH_3	H	C_6H_5	sec-BuLi	75
6	CH_3	H	C_6H_5	C_6H_5Li	85
7	H	CH_3	C_6H_5	n-BuLi	80
8	H	C_2H_5	C_6H_5	n-BuLi	69[b)]
9	CH_3	CH_3	C_6H_5	n-BuLi	74[c)]
10	$-(CH_2)_4-$		C_6H_5	n-BuLi	71

a) Refer to equation 3. b) α-Monodeuteration by quenching with d_1-acetic acid. c) Based on 74% conversion.

bond forming reactions and used for natural and unnatural product syntheses.[3] In connection with wide flexibility of α,β-unsaturated tertiary thioamides toward the 1,4-addition of organometallics,[4] we examined the ability of α,β-unsaturated sec-thioamides as a Michael acceptor. α,β-Unsaturated sec-thioamides **1** were treated with 2∿2.2 equiv. of organolithium and -magnesium compounds in the expectation of the second equivalent of organometallics to undergo the 1,4-addition to the monometalo sec-thioamides (equation 3).[5] As apparent from Table II, the organometallics, which undergo the 1,4-addition, are limited only to lithium reagents with hard anion character. Grignard reagents were unreactive and **1** was recovered. Interestingly, N-methylthiocrotonamide (**1d**) and N-methylthio-α-methacrylamide (**1b**) decomposed by treatment with 2.2 equiv. of n-BuLi, but substitution of N-methyl for N-phenyl effected the Michael addition (entries 4∿8, Table II). On treatment with 2.2 equiv. of n-BuLi, N-phenylthiocyclohexenecarboxamide (**1j**) provided the addition product (entry 10, Table II), while N-methyl derivative (**1i**) is apparently unreactive and recovered in ca. 80% yield. However, quenching the reaction mixture with d_1-acetic acid provided the β'-deuterated product, reflecting the unusual β'-lithiation of **1i**.[6] The similar dependence of reaction on the substituents on a nitrogen atom is also observed for 2,3-dimethylthioacrylamide (**1f** and **1g**).[7]



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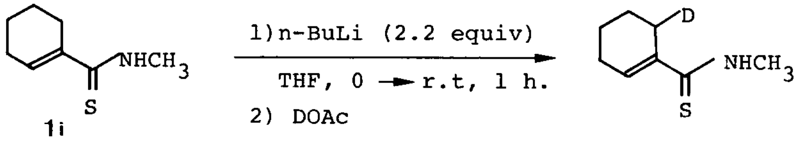

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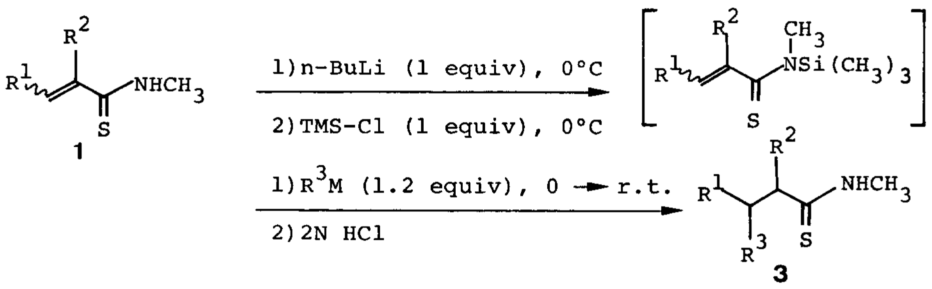
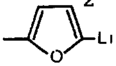


(5)

Although the above evidences indicate the limited use of **1** as a Michael acceptor, we could overcome this undesirable feature by making use of the selective N-silylation of monoanion of **1**,[8] recently discovered in our laboratories. Thus, N-methyl, N-trimethylsilyl substituted tert-thioamide, prepared in situ by a sequencial addition of 1 equiv. of n-BuLi and 1 equiv. of trimethylsilyl chloride into a THF solution of **1**, was treated with organometallics. Usual extractive work up (2N HCl, Et_2O) caused a hydrolytic cleavage of N-Si bond and provided the expected addition products (equation 5). Efficiency of this procedure, not optimized yet, is apparent from the results summarized in Table III, which tolerates the reactions with lithio derivatives of alkyl, aryl and enolate and Grignard reagents. Full scope of the present reaction and the optimization of conditions are under extensive study.

Table III. 1,4-Addition of Organometallics to N-Methyl,N-Trimethylsilyl-α,β-Unsaturated Thioamides Generated in situ.a)

Entry	Thioamide 1		Organometallics	% Yield of 3b)
	R^1	R^2	R^3M	
1	CH_3	H	n-BuLi	80
2	CH_3	H	CH_2=CHMgBr	91 (79)
3	CH_3	H	i-PrMgBr	93 (87)
4	CH_3	H	$t\text{-}BuO_2CCH_2Li$	88
5	CH_3	H		94 (77)
6	H	CH_3	C_6H_5Li	70
7	H	CH_3	i-PrMgBr	79
8	CH_3	CH_3	n-BuLi	32

a) Refer to equation 5. b) Isolated yields based on conversion, shown in parentheses.

References and Notes

1) α,β-Unsaturated tert-thioamides are prepared in reasonable yields according to this procedure, see Y. Tamaru, T. Harada, and Z. Yoshida, J. Am. Chem. Soc., 102, 2392 (1980).
2) P. Gosselin, S. Masson, and A. Thuillier, Tetrahedron Lett., 21, 2421 (1980).
3) G. H. Posner, Org. React., 19, 44 (1972).
4) (a) Y. Tamaru, T. Harada, H. Iwamoto, and Z. Yoshida, J. Am. Chem. Soc., 100, 5221 (1978); (b) Y. Tamaru, T. Harada, and Z. Yoshida, ibid., 101, 1316 (1979).
5) For the Michael addition reaction to α,β-unsaturated sec-amides, see (a) J. E. Baldwin and W. A. Dupont, Tetrahedron Lett., 21, 1881 (1980); (b) G. B. Mpango, K. K. Mahalanabis, Z. Mahdvi-Damghani, and V. Snieckus, ibid., 21, 4823 (1980).
6) P. Beak and D. J. Kempf, J. Am. Chem. Soc., 102, 4550 (1980).
7) See the accompanying paper.
8) The alkylation of monoanion of sec-thioamide with alkyl halide usually proceeds selectively at a sulfur atom to provide thioimidate.[7]

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