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GENERATION OF sec-THIOAMIDE DIANIONS AND THEIR REGIOSELECTIVE REACTION WITH ELECTROPHILES.

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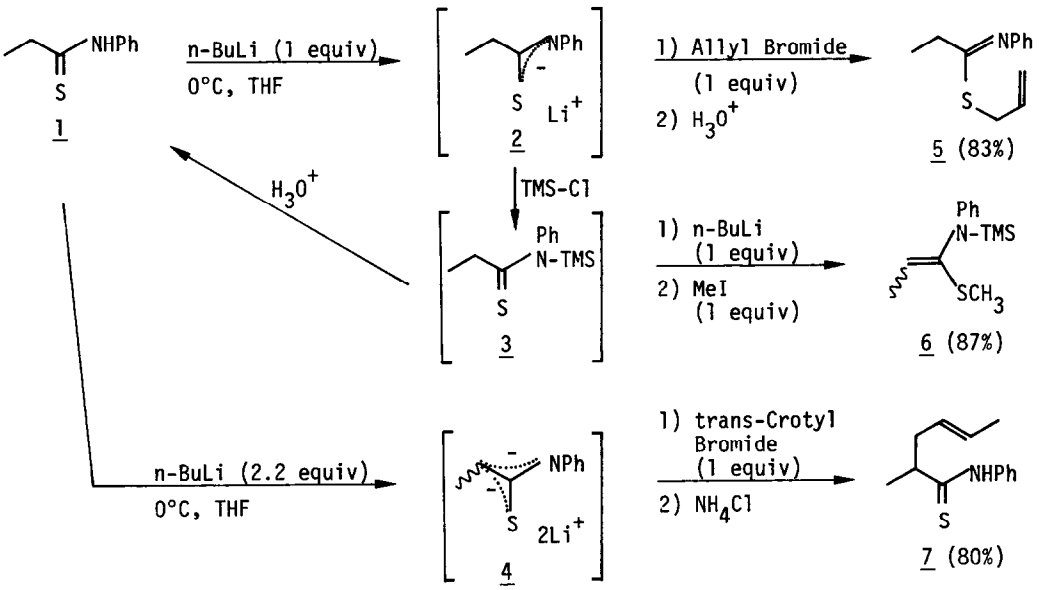
Summary. The enolates of sec-thioamides 8, which are generated by three different methods (scheme II and equation 1), are alkylated selectively at the α-carbon to the thiocarbonyl group. The unusual β'-lithiation to provide an intermediate 11 is observed for N-methyl-α,β-dimetylthioacrylamide and N-methyl-thiocyclohexenecarboxamide.

Although it has been believed that the alkylation of sec-thioamide and its monoanion takes place selectively at a sulfur atom to provide S-alkylthioimidate (e.g., 5),[1] we have found that the regioselectivity of alkylation depends on the nature of alkylation agent. Alkylation of monoanion with trimethylsilyl chloride (TMS-Cl) takes place on a nitrogen atom selectively as indicated by the isolation of ketene S,N-acetal (e.g., 6) and also by the complete recovery of the starting thioamide after aqueous work-up (Scheme I). The present selective N-alkylation was successfully applied to the activation of α,β-unsaturated sec-thioamide as a Michael acceptor.[2] These results suggest that the sulfur atom might not always be the center, which undergoes the alkylation even toward the soft nucleophiles.[3]

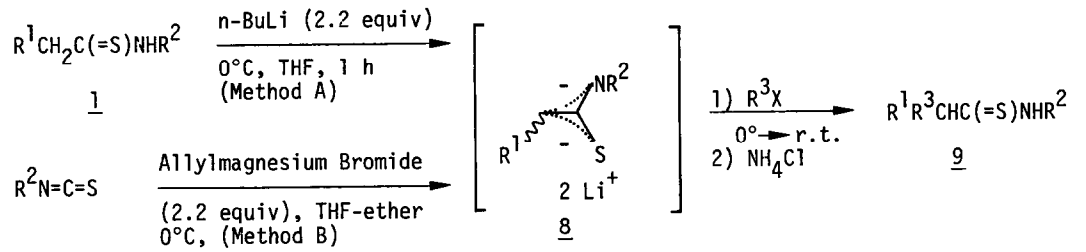
Taking this idea in mind, we examined the alkylation of sec-thioamide dianion (4) in expectation of alkylation of the carbon atom α to thiocarbonyl, because this carbon atom shares the allylic termini both of iminoenolate and thioenolate and might be the center with the highest nucleophilicity among the three allylic termini. Indeed this proved to be the ease and alkylation took place selectively on this carbon. Results are summarized in Table I. The dianion 8 (scheme II), which can be generated according to procedures A or B, is confined

Scheme I



to the thioamides 1 with the combination of either R^1= aryl(or vinyl) and R^2= alkyl or R^1= alkyl and R^2= aryl. For the sec-thioamide with R^1= aryl(or vinyl) and R^2= alkyl, the dianion can be generated either by treatment with 2.2

Scheme II.



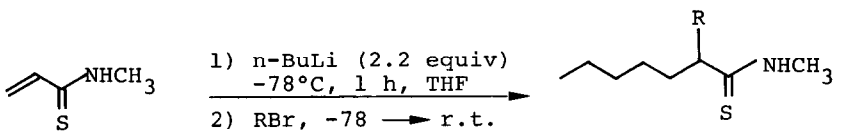
equiv. of n-BuLi or by treatment with 2.5 equiv. of i-PrMgBr. In the case of R^1= alkyl and R^2= aryl, use of 2.2 equiv. of n-BuLi or lithium diisopropylamide is necessary. Interestingly, dilithio N-methylthioacetamide (8, R^1= H, R^2= CH_3) is generated cleanly by treatment with 2.2 equiv. of n-BuLi (THF, 0°C), which makes a contrast to an unsuccessful dianion generation from the corresponding amide (entry 6, Table I).[4,5]

Table I. Alkylation of sec-Thioamide Dianions 8[a)]

Entry	Thioamide 1		Method	Electrophile	% Yield of 9
	R^1	R^2			
1	C_6H_5	CH_3	A	CH_3I	71
2	CH_3	C_6H_5	A	CH_3I	83
3	CH_3	C_6H_5	A	trans-$CH_3CH{=}CHCH_2Br$	80
4	CH_3	C_6H_5	A	$CH_2{=}CClCH_2Cl$	67
5	C_5H_{11}	C_6H_5	A	CH_3I	57
6	H	CH_3	A	$C_6H_5CH_2Br$	92
7	$CH_2{=}CH$	CH_3	B	C_2H_5Br	89
8	$CH_2{=}CH$	CH_3	B	$CH_2{=}CHCH_2Br$	84
9	$CH_2{=}CH$	CH_3	B	trans-$CH_3CH{=}CHCH_2Cl$	73[b)]
10	$CH_2{=}CH$	CH_3	B	$CH_2{=}CHCH(CH_3)Cl$	56[b)]

a) Refer to scheme II for the structures of 1 and 9 and for the methods A and B.
b) A mixture of R^3= trans-crotyl and R^3= α-methallyl (94:6 for entry 9 and 22:78 for entry 10).

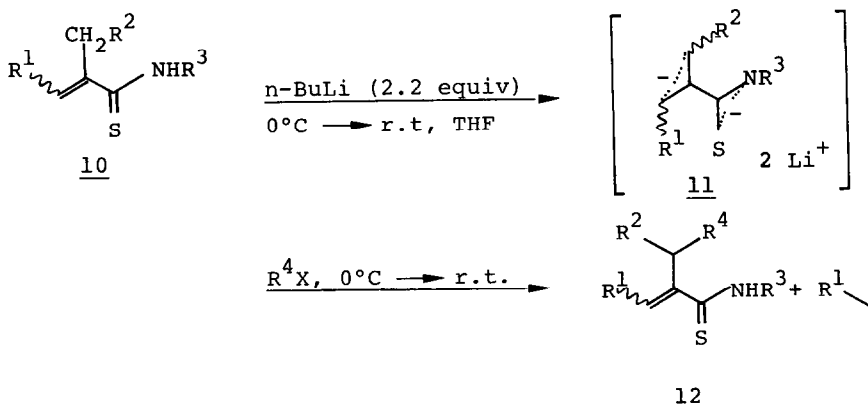
By the 1,4-addition technique, we can also generate the dianion,[2] which undergoes the selective C-alkylation nicely as shown in equation 1.



(1)

R = $C_6H_5CH_2$ (74%)

R = $CH_2{=}CBrCH_2$ (62%)



(2)

Table II. Reaction of sec-Thioamide Dianions 11 with Electrophiles[a)]

Entry	Thioamide 10			R^4-X	% Yield of 12 and 13 (12:13)
	R^1	R^2	R^3		
1	$-(CH_2)_3-$		CH_3	D_2O	77
2	$-(CH_2)_3-$		CH_3	C_2H_5Br	43
3	$-(CH_2)_3-$		CH_3	$CH_2=CHCH_2Br$	44
4	$-(CH_2)_3-$		CH_3	C_6H_5CHO	77[b)]
5	CH_3	H	CH_3	$(CH_3)_2CHCHO$	73 (7.3:1)[b)]

a) Refer to equation 2 for the structures of 10, 12, and 13.
b) Aldol addition products, whose diastereomeric ratios are not determined.

Next, we examined the alkylation of sec-thioamide dianion of a type 11 (equation 2), which possesses a unique structure of the deconjugated two allylic anion units.[2] Though the dianion 11 seems to be prepared in good yield as judged by the results of deuteration and aldol addition (entries 1, 4, and 5, Table II), the yield of alkylation with alkyl halide is pretty low. We are now under investigation of any side products, which might stem from a wrong regioselectivity.

References and Notes

1. W. Walter and J. Voss, "The Chemistry of Thioamides", in "The Chemistry of Amide", ed. by J. Zabicky, Interscience Publishers, 1970.
2. See the preceding paper.
3. Tse-Lok Ho, "Hard and Soft Acids and Bases Principle in Organic Chemistry", Academic Press, 1977.
4. T. Morwick, Tetrahedron Lett., 21, 3227(1980).
5. All new compounds reported in this and preceding papers showed satisfactory analytical (within 0.3% for C, H, N, and/or O) and spectral(^{1}H NMR, IR, mass) data. The spectral data of the typical compounds are as follows: 6; Bp. 95°C/10 mmHg. ^{1}H NMR(CCl_4, δ) 0.3 (s, 9 H), 1.80(d. J = 7 Hz, 3 H), 1.98(s, 3 H), 5.47(q, J = 7 Hz, 1 H), and 6.1∿7.4(m, 5 H) IR(neat film, cm^{-1}) 1625(w), 1598(s), 1495(s), 1248(s), 1158(m), 945(m), 935(m), 840(s), 750(m), and 690(m). Mass (m/e, relative int.) 251(M^+, 5), 204(78), 132(35), 131(64), 130 (50), 105(52), 77(53), and 73(100). 7; Mp. 75.5∿76.5(hexane-benzene). ^{1}H NMR (CCl_4, δ) 1.37(d, J = 7 Hz, 3 H), 1.72(d, J = 5 Hz, 3 H), 2.3∿3.1(m, 3 H), 5.4∿6.1(m, 2 H), 7.4∿7.95 (m, 5 H), and 9.0(br. s, 1 H) . IR (KBr disc, cm^{-1}) 3170(s) 3020(m), 1595(m), 1530(s), 1495(m), 1420(s), 1320(m), 985(m), 970(m), 760(m), and 695(s). Mass (m/e, relative int.) 219(M^+, 40), 204(30), 149(53), 136(40), 104(49), 93(41), and 77(100).

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