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REGIOCONTROLLED 1,2-, 1,4-, AND 1,6-ADDITIONS OF ORGANOMETALLICS TO UNSATURATED THIOAMIDES

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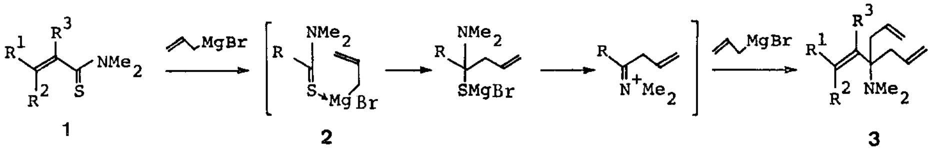
Summary: 1,4-Addition of allyllithiums to α,β-unsaturated thioamides and 1,4-(kinetic) and 1,6-(thermodynamic)regiocontrolled additions of lithium enolates to thiosorbamide are reported.

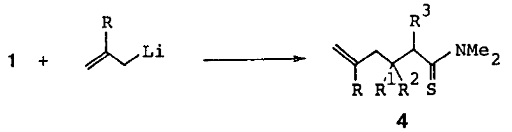
During the course of our study on the Michael addition reaction of organometallics to α,β-unsaturated thioamides,[1,2] two types of unusual reactions, which impose a limitation to the synthetic versatility of thioamide as a Michael acceptor, are observed: one is the 1,2-addition of 2 moles of allylmagnesium to α,β-unsaturated thioamides to provide amines 3 (equation 1).[1] Another is the selective 1,4-addition of organometallics to α,β,γ,δ-unsaturated thioamide to provide a type of compound 11 (equation 3).[1,2]

In this report, we disclose the successful 1,4-addition of allyllithiums to unsaturated thioamides (equation 2) and the regioselective 1,6-addition of lithium enolates to thiosorbamide to provide 12 (equation 3).

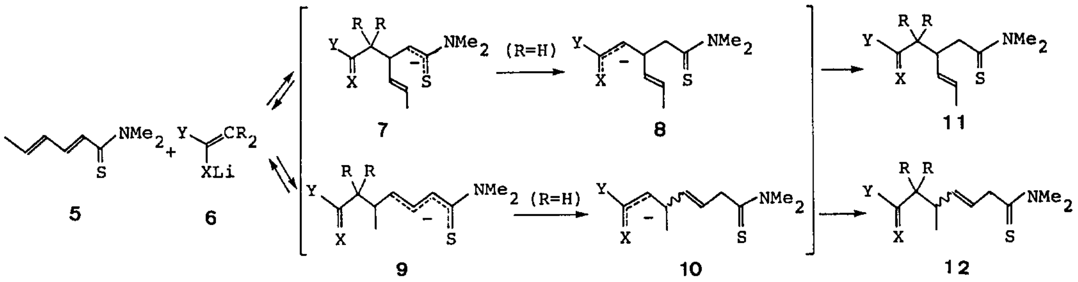
Taking into consideration that even the highly nucleophilic n-BuLi or MeMgI shows neither the carbo- nor the thiophilic reactivity[3] toward thioamides and serves either as a Michael donor (to unsaturated thioamides)[1] or as a base for a proton abstraction (toward saturated thioamides to generate thioenolates),[4] the 1,2-addition of allylmagnesium to 1b and 1c (entries 1 and 2, Table I) merits some mechanistic considerations. A similar, but exceptional, carbophilic reaction of allylmagnesium with thioketone is reported,[5] where is obtained *tert*-thiol. These results might be accounted for on the basis of a strong coordination of Mg(II) to the C=S sulfur atom, which might facilitates an attack of allylic moiety to the C=S carbon atom through a six-membered cyclic transition state 2 (equation 1). This idea in mind, we have undertaken experiments in the direction to prevent the sulfur-metal interaction and found that allyllithium in THF at -78°C was viable conditions. Allyllithium reacted with 1a under the above conditions to provide exclusively the 1,4-addition product 4a in 81% yield (entry 5, Table I).[6,7] Both the reaction media and temperature are crucial: the same reaction, when performed at 0°C in diethyl ether or THF, provided only a trace of 4a. In Table I are summarized the reaction consitions and products for the addition reaction of allyllithiums and magnesium to α,β-unsaturated thioamides.

The selective 1,4-addition of n-BuLi, EtMgBr,[1] lithium enolates of amide


(1)


(2)

a: $R^1 = R^2 = H$, $R^3 = CH_3$ b: $R^1 = CH_3$, $R^2 = R^3 = H$, c: $R^1 = R^2 = CH_3$, $R^3 = H$
d: $R^1 = CH{=}CHCH_3$, $R^2 = R^3 = H$


(3)

a: X = S, Y = NMe_2, R = H b: X = O, Y = NMe_2, R = H c: X = O, Y = NMe_2, R = Me
d: X = O, Y = O^tBu, R = H e: X = O, Y = O^tBu, R = Me

and ester,[2] and allyllithium (entry 7, Table I) to thiosorbamide is rather unique reactivity of thioamide, making sharp contrast to the selective 1,6-addition of organocopper reagents to conjugated dienoates.[8] This anomalous reactivity of thioamide may be also attributed to a strong coordination of the sulfur atom to a metal, which directs organometallics to react at the proximal position to the thiocarbonyl group. This idea is verified by using enolates as a probe. Addition of thiosorbamide **5** to a solution of lithium enolate in a given solvent system and quick quenching provided 1,4-addition product exclusively (entries 1 and 11, Table II) or predominantly (entries 4, 8, and 14). The population of 1,4- and 1,6-addition products changed dramatically in favor of the 1,6-adduct along with the reaction period of time and reached a stationary state after 20h at r.t. These results, together with the solvent effect [lower 1,4-selectivity in polar solvent (entry 3) and higher 1,4-selectivity in less polar solvent (entry 7)], indicate that the 1,4-addition is a kinetic process directed by the sulfur atom.

The thermodynamic stability of **9**, compared with **7**, is striking: the results in entries 1 and 2 indicate that the selectivities of kinetic (**7a**) and thermodynamic enolate (**9a**) are more than 99%.[9,10] The low thermodynamic selectivity, as observed for the enolates of amides and esters, may partly be as-

Table I. 1,2- and 1,4-Addition of Allyllithium and Magnesium Compounds to Unsaturated Thioamides[a]

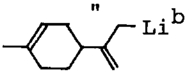
Entry	Thioamide	Allyl-metal(equiv)		Solv.	Temp (°C)	Time (min)	Product	(% Yield)[c]
1	1b	$CH_2=CHCH_2MgBr$	(3.0)	Et_2O	0	5	3b	(45)
2	1c	"	(3.0)	Et_2O	0	15	3c	(73)
3	1c	$CH_2=CHCH_2Li$	(2.0)	Et_2O	0	25	3c	(51)
4	1b	"	(2.0)	THF	-78	30	4b	(47)
5	1a	"	(1.5)	THF	-78	20	4a	(81)
6	1a	 [b]	(3.0)	THF	-78	30	4a	(69)
7	1d	$CH_2=CHCH_2Li$	(2.0)	THF	-78	20	4d	(89)

Table II. 1,4- and 1,6-Addition Selectivity of Enolates 6 to Thiosorbamide 5[a]

Entry	Enolate	Solv.	Temp(°C)	Time(h)	Products	[Ratio][d]	% Yield[c]
1	6a	THF	r.t	0.5	11a, 12a	[100:0]	91
2		THF	r.t	20		[0:100]	87
3		THF-HMPA[e]	r.t	0.03		[94:6]	
4	6b	THF	r.t	0.1	11b, 12b	[80:20]	86
5		THF	r.t	3.0		[65:35]	
6		THF	r.t	20		[64:36]	88
7		Et_2O	r.t	0.25		[88:12]	66
8	6c	THF	r.t	0.1	11c, 12c	[78:22]	67
9		THF	r.t	21		[9:91]	
10		THF-HMPA[e]	r.t	22		[8:92]	79
11	6d	THF	-10→r.t[f]	0.5	11d, 12d	[100:0]	78
12		THF-HMPA[e]	-10→r.t[f]	0.5		[82:18]	65
13		THF-HMPA[e]	-20→r.t[f]	20		[66:34]	28
14	6e	THF	-20→r.t[f]	2.0	11e, 12e	[74:26]	83
15		THF	r.t	20		[15:85]	85

(a) For the structure, see equations 1,2, and 3.

(b) Crawford, R. J.; Erman, W. F.; Broaddus, C. D. J. Am. Chem. Soc., 1972, 94, 4298.

(c) Isolated yield for the spectroscopically pure materials.

(d) See footnote 9.

(e) 2 equiv. of HMPA is used.

(f) After completion of addition of 5 to a solution of 6 at -10 or -20°C, the reaction temp. is raised to r.t.

cribed to an isomerization **7** and **9** to **8** and **10** (R=H), respectively, and/or intervention of some side reactions, as suggested by the low isolated yields of **11d** and **12d** in entry 13.

In conclusion, this communication has dealt with the successful 1,4-addition of allyllithiums to α,β-unsaturated thioamides and 1,6-addition of enolates to thiosorbamide, both of which expand the utility of thioamides as a Michael acceptor.[11]

References and Notes

1) Tamaru, Y., Harada, T.; Iwamoto, H.; Yoshida, Z. *J. Am. Chem. Soc., 1978*, **100**, 5221.
2) Tamaru, Y.; Harada, T.; Yoshida, Z. *Ibid., 1979*, **101**, 1316.
3) For the thiophilic reaction of organometallics to thiocarbonyl compounds, see the references cited in ref. 1.
4) Tamaru, Y.; Harada, T.; Nishi, S.; Mizutani, M.; Hioki, T.; Yoshida, Z. *J. Am. Chem. Soc., 1980*, **102**, 7806.
5) Dagonneau, M.; Vialle, J. *Tetrahedron, 1974*, **30**, 415.
6) All new products reported in this paper showed satisfactory spectral (IR, Mass, ^{1}H NMR) and analytical data.
7) A typical experimental procedure is as follows: To a solution of allyltriphenyltin (1.18 g, 3 mmol) in 9 ml of THF is added a THF solution of phenyllithium (3 mmol) at an ambient temp. under argon. After stirring for 30 min, the reaction mixture is cooled to -78°C and a solution of **1a** (285 mg, 2 mmol) in 2ml of THF was added over a few minutes. After allowed to react at the same temp. for 20 min, the reaction is quenched by addition of methanol. After usual extractive workup and purification by means of column chromatography (silica gel, benzene-EtOAc gradient), **4a** is isolated in 81% yield. **4a**: Bp 120°C/0.05 mmHg. IR (neat film) 1640, 1510, 1385, 1280, 995, and 915 cm^{-1}. ^{1}H NMR (CCl$_4$, TMS) δ 0.98 (br. d, J = 6 Hz, 3 H), 2.1 (m, 3 H), 2.7 (m, 2 H), 3.30 (s, 3 H), 3.43 (s, 3 H), 4.9-5.2 (m, 2 H), and 5.8 (m, 1 H). Mass (m/e, relative int.) 171 (M$^+$, 46), 138 (18), 88 (48), and 70 (100).
8) (a) M. -Petersen, J.; Bretting, C.; Jorgensen, P. M., Refn, S.; Andersen, V. K. *Acta. Chem. Scand., 1961*, **15**, 277. (b) Cohen, T.; Herman, G.; Falck, J. R.; Mura, A. J. Jr. *J. Org. Chem., 1975*, **40**, 812. (c) Cohen, T.; Kuhn, D.; Falck, J. R. *J. Am. Chem. Soc., 1975*, **97**, 4749.
9) Reactions are performed according to the similar procedure to that described in footnote 7 under the conditions given in Table II. The product ratio is determined as an avaraged value of at least two analytical methods [area intensities on ^{1}H NMR and VPC and isolated yield of individual product].
10) **11a**: Bp 180∿190°C/0.001 mmHg. IR (neat film) 1520, 1390, 1280, and 970 cm^{-1}. ^{1}H NMR (CCl$_4$, TMS) δ 1.67 (br. d, J = 4 Hz, 3 H), 2.6 (m, 1 H), 2.85 (m, 4 H), 3.40 (s, 12 H), and 5.5 (m, 2 H). Mass (m/e, relative int.) 258 (M$^+$, 9), 225 (21), and 156 (100). **12a**: Bp 160∿170°C/0.001 mmHg. IR (neat film) 1515, 1385, 1280, 1045, and 970 cm^{-1}. ^{1}H NMR (CCl$_4$, TMS) δ 1.14 (br. d, J = 7 Hz, 3 H), 2.4∿3.1 (m, 3 H), 3.36 (s, 3 H), 3.38 (s, 3 H), 3.54 (s, 6 H), 3.7 (m, 2 H), and 5.66 (m, 2 H). Mass (m/e, relative int.) 258 (M$^+$, 14), 225 (35), and 154 (100).
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