d, J = 6 Hz, CH_3[b]), 1.1. (6 H, d, J = 7.5 Hz, CH_3[a] and CH_3[c]), 3.4 (H, s, OCH_3), 4.5 (1 H, d, J = 6 Hz, -C=CH), 4.65 (2 H, s, OCH_2O). Ozonolysis of **15** in acetone (−78 °C), followed by oxidation of the ozonide (CrO_3), afforded, presumably via **3a**, (±) Djerassi-Prelog lactonic acid (**1**) which was crystallized from ethanol, mp 114–115 °C,[16] in 26% yield from **15**. The spectral data (IR, NMR) were completely identical with those of an authentic sample[5] of the (±) Djerassi-Prelog lactonic acid.[17]

Acknowledgment. We express our thanks to Professor Carl Djerassi for a sample of the (+)-lactonic acid derived from methymycin and to Professor S. Masamune for a sample of his synthetic (±) material and its spectra. We also thank the National Institutes of Health and the National Science Foundation for the support of this work.

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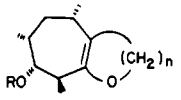

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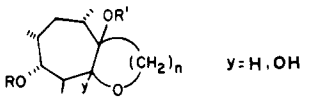

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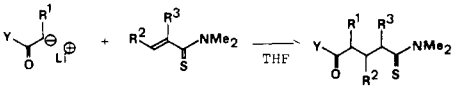
1,4-Addition Reactions of Lithium Enolates to α,β-Unsaturated Thioamides

Sir:

1,4-Addition reactions of organometallic compounds to α,β-unsaturated carbonyl compounds constitute one of the fundamental processes;[1] especially those with kinetically formed enolates are valuable to prepare the functionalized molecules desirable for the further transformations to natural and unnatural products. Therefore, owing to the unsuccessful 1,4 addition of lithium enolates or enolate copper reagents, studies have been focused on the modifications of Michael-type acceptors.[2]

In connection with the recently reported 1,4-addition reaction of organolithium, -magnesium, and -sodium compounds to α,β-unsaturated thioamides,[3] we have found that α,β-unsaturated thioamides serve as excellent Michael acceptors for various enolates. We report here the 1,4-addition reaction of lithium enolates of symmetrical and unsymmetrical ketones, ester, amides, and sodium ethyl acetoacetate to α,β-unsaturated thioamides (eq 1) and the very easy transformation of the thus obtained δ-carbonylthioamides to the corresponding δ-carbonyl esters (Table I).



(1)

1 2 3

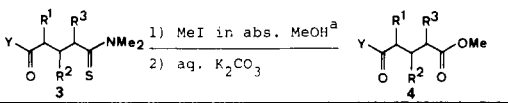
1a: R^1 = H, Y = NMe_2
1b: R^1 = Me, Y = NMe_2
1c: R^1 = H, Y = $OCMe_3$
1d: R^1 = H, Y = CMe_3
1e: R^1 = H, Y = Ph
1f: R^1 = H, Y = $CHMe_2$
1g: R^1-Y = $-(CH_2)_2CHMe-$
1h: R^1-Y = $-(CH_2)_3CHMe-$
1i: R^1-Y = $-(CH_2)_4-$
1j: R^1 = H, Y = $NaCHCO_2C_2H_5$

2a: R^2 = Me, R^3 = H
2b: R^2 = Ph, R^3 = H
2c: R^2 = H, R^3 = Me
2d:

2e: R^2 = MeCH=CH-, R^3 = H

The efficiency of the present 1,4-addition reaction is augmented by the ease with which it is performed, as typified in the following example (Table II, entry 7). To a THF (3 mL) solution of *tert*-butyl α-lithioacetate (**1c**), prepared from *tert*-butyl acetate (1.5 mmol) and lithium diisopropylamide (LDA, 1.5 mmol), was added a THF (1 mL) solution of *N,N*-dimethylthiocrotonamide (**2a**, 1 mmol) at −20 °C under argon. After the mixture was allowed to warm gradually to ambient temperature over a 30-min period, the reaction was quenched with CH_3OH and extracted with EtOAc. After this was dried over Na_2SO_4 and the solvent was evaporated, the faintly yellow residue was subjected to column purification (silica gel, benzene–ethyl acetate gradient) to give *N,N*-dimethyl-3-methyl-4-carbo-*tert*-butoxythiobutanamide (**3h**) in 93% yield: bp 135~140 °C (0.001 mmHg) (Kugelrohr); NMR (CCl_4) δ 1.05 (d, J = 5 Hz, 3 H), 1.25 (s, 9 H), 2.0~3.0 (m,

Table I. Conversion of Thioamides to Esters



3 4

Reactant[b]	Product[c] (% yield)[d]				
3	4	Y	R^1	R^2	R^3
3a	4a (91)	NMe_2	H	Me	H
3b	4b (83)	NMe_2	H	Ph	H
3h	4h (100)	O^tBu	H	Me	H
3i	4i (86)	O^tBu	H	Ph	H
3k	4k (92)	^tBu	H	Me	H
3r	4r (71)	$-(CH_2)_4-$		Me	H

[a] 4–16 equiv of MeI was used. [b] For the structures of *3a–r*, see Table II. [c] All new compounds showed satisfactory spectral (IR, NMR, mass) and analytical results (within ±0.3% for C and H (and N for **4a** and **4b**)). [d] Isolated yields.

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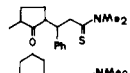
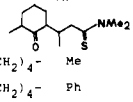
Table II. 1,4-Addition Reaction of Lithium Enolates to α,β-Unsaturated Thioamides[a]

Entry	Enolate 1 (equiv)	Thioamide 2	Temp (°C),[b] Time (h)	Product[c] 3	Y	R^1	R^2	R^3	Yield[e] (%)
1	1a (1.5)	2a	0, 0.5	3a[d]	NMe_2	H	Me	H	90
2	1a (1.5)	2b	0, 0.5	3b	NMe_2	H	Ph	H	94
3	1a (1.5)	2c	0, 0.3	3c[d]	NMe_2	H	H	Me	69 (89)
4	1a (1.5)	2d	r.t, 1.3	3d[f]					54
5	1a (1.5)	2e	r.t, 0.1	3e[d] + 3f	NMe_2	H	$MeCH{=}CHCH_2$-	H	69 + 17
6	1b (1.5)	2a	0, 0.3	3g[d,f]	NMe_2	Me	Me	H	91
7	1c (1.5)	2a	-20, 0.5	3h[d]	^tBuO	H	Me	H	93
8	1c (1.5)	2b	-20, 1.8	3i[d]	^tBuO	H	Ph	H	76
9	1c (1.5)	2e	-20, 0.5	3j	^tBuO	H	$MeCH{=}CHCH_2$-	H	78
10	1d (1.8)	2a	r.t, 4	3k[d]	^tBu	H	Me	H	95
11	1d (1.2)	2b	r.t, 3[g]	3l	^tBu	H	Ph	H	69
12	1d (1.5)	2c	65, 2.8[g]	3m	^tBu	H	H	Me	50 (74)
13	1e (1.5)	2a	r.t, 4[g]	3n	Ph	H	Me	H	65
14	1f (3.0)	2a	r.t, 3	3o[d]	$CHMe_2$	H	Me	H	73 (75)
15	1g (3.0)	2b	r.t, 15[g]	3p[d,f]					76
16	1h (3.0)	2a	r.t, 3.5[g]	3q[f]					71
17	1i (3.0)	2a	r.t, 4[g]	3r[d,f]	$-(CH_2)_4-$	Me		H	99
18	1i (3.0)	2b	r.t, 3[g]	3s[f]	$-(CH_2)_4-$	Ph		H	99
19	1j (1.5)	2a	r.t, 1	3t[d]	CH_2CO_2Et	H	Me	H	86
20	1j (2.0)	2b	r.t, 1.5	3u	CH_2CO_2Et	H	Ph	H	82

[a] For the notation of **1a-j, 2a-e,** Y, R^1, R^2, and R^3, refer to eq 1. [b] After completion of addition of reagents, the reaction temperatures (0 or −20 °C) were allowed to increase gradually to ambient temperatures over the periods of indicated times. [c] All products showed satisfactory spectral data (IR, ^1H NMR, mass). [d] Satisfactory analytical results were obtained for these compounds (within ±0.3% for C, H, N, and S). [e] Yields refer to isolated yields. Values accompanied with values in parentheses refer to the isolated yields based on conversions (in parentheses). [f] Mixtures of stereoisomers. [g] HMPT (1-2 equiv) was added.

5 H), 3.40 (s, 3 H), 3.45 (s, 3 H); IR (neat film) 1720 (s), 1515 (m), 1150 (s) cm^{-1}; mass spectrum *m/e* (rel intensity) 245 (P^+, 13), 189 (42), 172 (24), 103 (100). Results of some typical experiments are summarized in Table II, which shows that the present reaction is tolerant of considerable variation in the structures of donors and acceptors. The enolates of amides and ester seem to be much more reactive than those of ketones; *N,N*-dimethyl-α-lithioacetamide (**1a**) reacted rapidly with **2a** (complete reaction within a few minutes at 0 °C, entry 1), while α-lithiopinacolone required 4 h at ambient temperature for completion of reaction (entry 10). *N,N*-Dimethylthio-α-methacrylamide (**2c**) was somewhat unreactive compared with **2a,** and **2c** was recovered from the reaction with **1d** even under forcing conditions (THF, reflux). The difficulty encountered with soft nucleophiles[4] could partly be overcome by using 1∼2 equiv of hexamethylphosphoric triamide (HMPT) and/or using excess enolate (entries 14-18); under THF-HMPT reflux conditions, **1d** reacted with **2c** to give *N,N*-dimethyl-5-oxo-2,6,6-trimethylthioheptanamide (**3m**) in 50% yield (based on 74% conversion). Although the more substituted enolates showed higher reactivity than the less substituted ones, as exemplified by the competitive reaction of enolates of diisopropyl ketone and pinacolone with **2a,**[5] the 1,4-addition reactions of the enolates of unsymmetrical ketones took place selectively at the less substituted sites. This indicates the selective addition of kinetically generated enolates. That is, 2-methylcyclopentanone and 2-methylcyclohexanone reacted with **2a** selectively[6] at the 5 and 6 positions, respectively, and 3-methylbutan-2-one at the 1 position exclusively (entries 14, 15, and 16). Sodium ethyl acetoacetate[4] reacted slowly with **2a** to give *N,N*-dimethyl-3-methyl-4-carbethoxy-5-oxothiohexanamide (76% yield based on 25% conversion at ambient temperature for 43 h), whereas the dianion of ethyl acetoacetate reacted rapidly with **2a** and **2b** at the methyl carbon of acetyl group to provide highly functionalized thioamides **3t** and **3u,** respectively, in high yields (entries 19 and 20).

It is worthwhile to note that *tert*-butyl α-lithioacetate, similarly to *n*-BuLi and EtMgBr,[3] reacted with *N,N*-dimethylthiosorbamide to provide a 1,4-addition product (**3j**) exclusively in 78% yield, in marked contrast to the selective 1,6-addition reaction of organocopper reagents to conjugated dienoates.[7] As an exception, *N,N*-dimethyl-α-lithioacetamide (**1a**) provided a mixture of 1,4- (69%) and 1,6-addition products (17%), the proportion of the latter increasing with increase of the polarity of reaction media.[8]

Transformation of the thus-obtained thioamides into the corresponding esters could be performed very easily and efficiently[9] (Table I); **3h** was exposed to 12 equiv[10] of MeI in absolute methanol at ambient temperature for 10 h. After addition of aqueous K_2CO_3 and extractive workup, *tert*-butyl methyl 3-methylglutarate (**4h**) was isolated by distillation in 100% yield: bp 120 °C (2∼7 mmHg) (Kugelrohr); NMR (CCl_4) δ 0.98 (d, J = 6 Hz, 3 H), 1.45 (s, 9 H), 2.2 (m, 5 H), 3.60 (s, 3 H); IR (neat film) 1720 (s), 1260 (m), 1210 (m), 1150 (s) cm^{-1}; mass spectrum *m/e* (rel intensity) 160 ($P^+ - C_4H_8$, 25), 143 (100). As shown in Table I, this transformation of thioamides to esters is general for δ-keto-, δ-carboalkoxy-, and δ-amidothioamides. Taking into consideration that, under the above reaction conditions, ζ-amidothioamide (**3f**) or more generally *N,N*-dialkyl aliphatic thioamides are converted to the corresponding amides,[11] the intramolecular participation of δ-carbonyl groups seems to play an important role to determine the course of the reaction. The methodology for the transformation of thioamides to esters, ketones, and aldehydes,[12] established recently in this laboratory, increases the versatility of the presently reported 1,4-addition reaction. Work is in progress to investigate the full scope of the present reaction and to apply our method to the synthesis of alkaloid natural products.

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(3) Y. Tamaru, T. Harada, H. Iwamoto, and Z. Yoshida, *J. Am. Chem. Soc.*, **100,** 5221 (1978).

(4) Sodium dimethylmalonate was either unreactive (with **1c**) or gave many untractable products (with **1a**).[3]

(5) The mixture of the independently prepared enolates of diisopropyl ketone (3 mmol) and pinacolone (3 mmol) was reacted with **2a** (1 mmol) at ambient temperature. The reaction was almost complete within 3 h. The reactivity ratio of the enolate of diisopropyl ketone to that of pinacolone was roughly estimated to be 3 on the basis of product ratio.

(6) Although the accurate selectivity could not be determined, the high regioselectivity of these reactions (entries 15 and 16) was concluded on the bases of the thorough decoupling experiments of the NMR spectra of the product mixtures (**3p** and **3q**): for example, except for the four doublets due to methyl groups at the 2 position of cyclopentanone of four possible diastereoisomers (**3p**), no singlets due to methyl groups of other two possible diastereoisomers, which might be produced by the reaction at the 2 position of 2-methylcyclopentanone, were detectable.

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(8) In ether 1,4- and 1,6-addition products were isolated in 58 and 8% yields, respectively, while in THF containing 2 equiv of HMPT the ratio of the isolated yields changed to 46:28.
(9) Freshly dried and distilled solvent (methanol or ethanol) should be used; otherwise amides are produced as byproducts.
(10) The similar results were obtained with 4 equiv of MeI.
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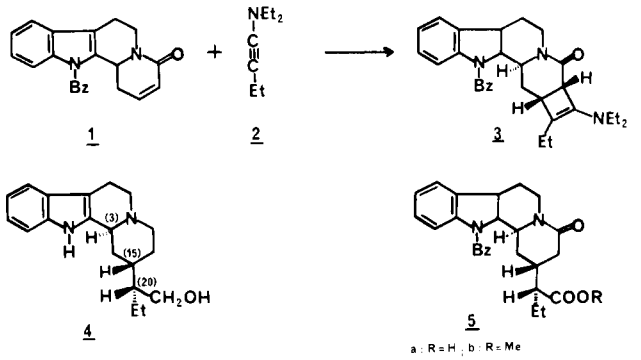
Stereoselective Synthesis of (±)-Dihydroantirhine

Sir:

We describe here a new route to indole alkaloids which leads specifically to the less stable anti relationship of the centers at C_3 and C_{15}.[1] The first stereoselective synthesis of (±)-dihydroantirhine (**4**)[2,3] will serve to illustrate our synthetic approach. It is noteworthy not only because of its complete stereoselectivity (all three asymmetric centers of dihydroantirhine are rigorously controlled) but also by its efficiency: the overall yield of (±)-dihydroantirhine is 40% starting from lactam **1** (20% based on tryptamine).

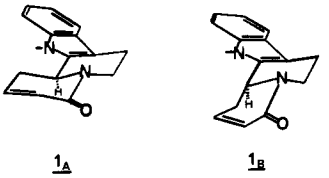


1 2 3 4 5

The two key steps on which this new approach is based are the cycloaddition of the ynamine **2**[4] with the unsaturated lactam **1**[5] (**1** + **2** → **3**) and the hydrolysis of the enamine system of the resulting cycloadduct **3** (**3** → **5a**).

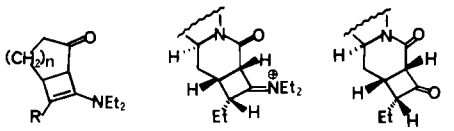
The initial cycloaddition of ynamines with α,β-unsaturated lactams was made possible, as we described in the case of unsaturated nitriles,[6] by the addition of magnesium bromide.

The first stereochemical problem was that of establishing the correct anti relationship of C_3 and C_{15} which is characteristic of the antirhine alkaloids. The cycloaddition[7] of ynamine **2** with **1** offers a solution to this problem because perpendicular attack[8] of **2** at C_{15} would be expected to involve a transition state in which the lactam is in a half-chair conformation (cf. $\mathbf{1}_A$) leading to **3** rather than in a half-boat conformation (cf. $\mathbf{1}_B$) which would have led to a syn relationship of the relevant centers.



$\mathbf{1}_A$ $\mathbf{1}_B$

The second problem involves the control of the relative configuration of the centers at C_{15} and at C_{20} in dihydroantirhine. This control of a center in a flexible chain adjacent to a ring can be achieved during the hydrolysis of the cycloadduct (**3** → **5a**). Treatment of **3** with 10% hydrochloric acid for 1 h at 20 °C gave the acid **5a**, mp 186–187 °C (acetonitrile–ethanol).[9] The methyl ester **5b** (diazomethane, 50% overall yield from **1**; IR ($CDCl_3$) 1650–1730 cm^{-1}; ^1H NMR δ 0.9 (t, 3 H), 3.5 (s, 3 H)), was clearly a single isomer as shown by its ^{13}C NMR spectrum.[10] This result shows that the same very high stereoselectivity is observed in the hydrolysis of the cyclobutane enamine **3** which is fused to a lactam, as is observed when the fusion is to a cyclanone as in the previously studied case of **6**.[11]



6 7 8

Under the kinetic control involved in the conditions described above, the β-ketolactam **8** is formed via the immonium ion **7** by addition of the proton on the more accessible exo face. Irreversible cleavage of the β-ketolactam **8** is more rapid under these conditions than equilibration of **7** or **8**, and thus leads directly to the acid **5a** in which the crucial center at C_{20} in the side chain is maintained in the correct configuration.

Reduction of the ester **5b** with an excess (3 equiv) of lithium aluminium hydride (THF, reflux, 2 h), followed by debenzylation of the indole nitrogen (Na, NH_3),[12] then gave (±)-dihydroantirhine (**4**) in 80% yield. The synthetic substance and its acetate proved identical (IR, mass, ^1H NMR, ^{13}C NMR)[13] with samples prepared starting from natural antirhine.[14]

References and Notes

(1) For the biogenetic nomenclature of indole alkaloids, see J. Le Men and W. I. Taylor, *Experientia*, **21**, 508 (1965). This nomenclature is used here in the case of the intermediates which are nonalkaloidal.
(2) For the structure of dihydroantirhine, see S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Aust. J. Chem.*, **20**, 1463 (1967); Y. K. Sawa and H. Matsumura, *Tetrahedron*, **25**, 5319 (1969).
(3) For previous syntheses, see (a) E. Wenkert, P. W. Sprague, and R. L. Webb, *J. Org. Chem.*, **38**, 4305 (1973); (b) L. Chevolot, H. P. Husson, and P. Potier, *Tetrahedron*, **31**, 2491 (1975).
(4) Prepared according to J. Ficini and C. Barbara, *Bull. Soc. Chim. Fr.*, 2787 (1965).
(5) Lactam **1** (^1H NMR ($CDCl_3$) 6.09 (d, d, 1 H), 6.55 (m, 1 H); mp 162 °C after chromatography on silica gel (1/1 CH_2Cl_2—ether)) was prepared according to the method of H. J. Reich, I. L. Reich, and J. M. Renga (*J. Am. Chem. Soc.*, **95**, 5813 (1973)) and K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi (*ibid.*, **95**, 6137 (1973)), with an overall yield of 65% (3 equiv of lithium diisopropylamine, THF, 2 h, −78 °C, then 3 equiv of C_6H_5SeCl, 15 min, −78 °C, and then $NaIO_4$, 4 equiv in aqueous methanol, 30 min, 25 °C) from the corresponding saturated lactam (mp 189 °C) which is obtained after benzylation of the indole nitrogen (HNa, Me_2SO, benzyl chloride, 60 °C, 2 h, 95% yield) of the known saturated lactam (mp 250 °C): S. Corsano and S. Algieri, *Ann. Chim. Rome*, **50**, 75 (1960).
(6) J. Ficini and A. M. Touzin, *Bull. Soc. Chim. Fr.*, 2385, 2388 (1972); J. Ficini, A. Eman, J. d'Angelo, and A. M. Touzin, *Tetrahedron Lett.*, 683 (1976); J. Ficini and J. d'Angelo, *ibid.*, 687 (1976); J. O. Madsen and S. O. Lawesson, *Tetrahedron*, **30**, 3481 (1974).
(7) Ynamine **2** (8.2×10^{-3} mol) was added, under nitrogen, at room temperature to a THF solution of lactam **1** (2.74×10^{-3} mol) containing $MgBr_2$ prepared from 4.1×10^{-3} mol of Mg and 4.1×10^{-3} mol of dibromoethane in THF. After refluxing for 1.5 h, the reaction mixture was cooled and poured onto a saturated solution of ammonium chloride and ammonia. The crude cycloadduct **3** (IR (neat) 1665, 1635, 1585 cm^{-1}) obtained after distillation of the solvents was used without purification.
(8) E. Toromanoff, *C.R. Acad. Sci.*, **286**, 385 (1978); *Top. Stereochem.*, **2**, 162 (1967).
(9) The crude acid **5a** was used without purification in the esterification with diazomethane to give **5b**.
(10) The ^{13}C NMR spectrum of **5b** was taken on a Bruker WP 80 apparatus for which we thank J. P. Genêt (Université P. et M. Curie, Paris) ($CDCl_3$): δ 174.3, 170.0, 138.2, 137.6, 134.4, 128.8, 127.4, 126.8, 125.8, 122.3, 119.9, 118.5, 110.8, 109.9, 51.4, 50.7, 47.5, 40.3, 35.8, 33.4, 31.8, 23.2, 21.3, 11.8 ppm.

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