(6) (a) D. M. Jerina, H. Selander, H. Yagi, M. C. Wells, J. F. Davey, V. Mahadevan, and D. T. Gibson, *J. Am. Chem. Soc.*, **98**, 5988 (1976); (b) R. E. Lehr, M. Schaefer-Ridder, and D. M. Jerina, *J. Org. Chem.*, **42**, 736 (1977); (c) J. M. Karle, H. D. Mah, D. M. Jerina, and H. Yagi, *Tetrahedron Lett.*, 4021 (1977).
(7) (a) D. R. Thakker, H. Yagi, R. E. Lehr, W. Levin, A. Y. H. Lu, R. L. Chang, A. W. Wood, A. H. Conney, and D. M. Jerina, *Mol. Pharmacol.*, **14**, 502 (1978); (b) A. W. Wood, R. L. Chang, W. Levin, R. E. Lehr, M. Schaefer-Ridder, J. M. Karle, D. M. Jerina, and A. H. Conney, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 2746 (1977).
(8) R. E. Lehr, M. Schaefer-Ridder, and D. M. Jerina, *Tetrahedron Lett.*, 539 (1977).
(9) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry", McGraw-Hill, New York, N.Y., 1969, pp 304–306.
(10) C. Battistine, A. Balsarme, G. Berti, P. Crotti, B. Macchia, and F. Macchia, *J. Chem. Soc., Chem. Commun.*, 712 (1974).
(11) For example, the rate of acid-catalyzed hydrolysis (25 °C, water, 0.1 M $NaClO_4$) of *trans*-2-phenyl-3-(hydroxymethyl)oxirane (k_{H^+} = 4.0 M^{-1} s^{-1}) is only three times slower than that of *trans*-2-phenyl-3-methyloxirane (k_{H^+} = 12.1 M^{-1} s^{-1}).
(12) Comparison of the magnitude of J_{diol} for the diastereomeric pairs of diol epoxides (**1** and **2**) from naphthalene,[4] phenanthrene and chrysene (this study), benzo[*a*]anthracene,[8] and benzo[*a*]pyrene[4] indicates that all of the isomer **2** diol epoxides have J_{diol} ~ 9 Hz, while the isomer 1 diol epoxides generally have J_{diol} ~ 3–6 Hz. Also, the benzylic hydroxyl group in the isomer **1** series shows a downfield shift of usually ~0.5 ppm from its expected position, possibly due to shielding by the oxirane ring.
(13) D. L. Whalen, *J. Am. Chem. Soc.*, **95**, 3432 (1973).
(14) G. J. Kasperek and T. C. Bruice, *J. Am. Chem. Soc.*, **94**, 198 (1972).
(15) *Note Added in Proof.* Since submission A. W. Wood et al. have noted high mutagenic activity of the tetrahydro epoxides **3b** and **3c** derived from chrysene and phenanthrene: 30–40 and 10–15%, respectively, of the activity of 7,8,9,10-tetrahydrobenzo[*a*]pyrene 9,10-epoxide in *S. typhimurium* strain TA 100.

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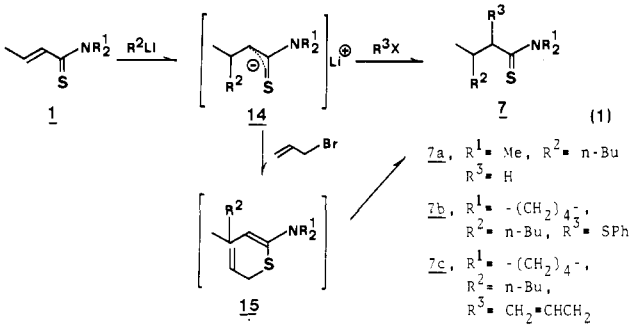
1,4-Addition Reaction of Organolithium and -magnesium Compounds to α,β-Unsaturated Thioamides

Sir:

Thioamides have already been shown to be easily convertible to a variety of types of compounds (e.g., amines,[1] enamines,[2] ketene *S,N*-acetals,[3] amides,[4] etc.) and fully proved to be synthetically potential by the total syntheses of vitamin B_{12}[5] and indole alkaloids.[6] During the course of our study to explore further versatility of thioamides,[1b] we have found that α,β-unsaturated thioamides react with organolithium and -magnesium compounds selectively at carbon in marked contrast to other thiocarbonyl compounds (e.g., thioketones,[7] α,β-unsaturated thioketones,[8] thioketenes,[9] dithioesters,[10,7b] trithiocarbonates,[11] etc.), which generally react at sulfur to give thioethers and their derivatives.[12] In this communication we wish to report the first example of the selective 1,4-addition reaction of organolithium and -magnesium compounds to α,β-unsaturated thioamides, which covers the deficit of the 1,4-addition reaction of organolithium or -copper reagents to α,β-unsaturated amides.[13]

Crotonoylpyrrolidine reacted with *n*-BuLi to give a 1:1 mixture of 1,2- and 1,4-addition products (*n*-butyl propenyl ketone and 3-methylheptanoylpyrrolidine) in 20 and 22% yields, respectively.[14] However, under similar conditions, *N,N*-dimethylthiocrotonamide (**1**, R^1 = CH_3) reacted with *n*-BuLi to give selectively a 1,4-addition product (*N,N*-dimethylthioheptanamide, **7a**, after aqueous workup) in 94% isolated yield (eq 1). The formation of thioenolate anion **14** is evident[15] from the following observations; i.e., treatment of



the resultant reaction mixture with electrophiles (e.g., diphenyl disulfide and allylic bromides) furnished α-phenylsulfenylthioamide (**7b**) and α-allylthioamide (**7c**). The formation of **7c** probably involves a thio-Claisen rearrangement[16] of vinyl allyl sulfide (**15**).

The efficiency of this one-flask addition–alkylation method is augmented by the ease with which it is performed as typified in the following example. (a) To a solution of **1** (R^1 = CH_3, 2 mmol) in 3 mL of anhydrous THF was added *n*-BuLi (15% hexane solution, 2.2 mmol) at 0 °C under argon. After 30 min, the reaction was quenched with methanol and the reaction mixture was extracted with EtOAc. After the mixture was dried over Na_2SO_4 and the solvent was evaporated the colorless residue was subjected to column purification (silica gel, PhH–EtOAc gradient) to give **7a** in 94% yield, pure enough for analysis. (b) To a solution prepared from **1** (R_2^1 = $-(CH_2)_4-$, 2 mmol) and *n*-BuLi (2.2 mmol) at 0 °C for 30 min was added allyl bromide (2.4 mmol) at 0 °C. the resulting mixture was allowed to warm to ambient temperature and stirred for 1 h. After extraction with EtOAc, drying over Na_2SO_4, and evaporation of the solvent, the residue was purified by column chromatography (silica gel, PhH–EtOAc gradient) to give **7c** in 83% yield. (c) A solution of diphenyl disulfide (2.4 mmol) in 2 mL of dry THF was added to the prepared solution of **14** (R_2^1 = $-(CH_2)_4-$, 2 mmol) at ambient temperature and the reaction mixture was stirred for 75 min. By similar workup and column purification (silica gel, PhH–EtOAc gradient) **7b** was isolated in 77% yield: $\delta_{CCl_4}^{Me_4Si}$ 0.7–1.5 (m, 12 H), 1.6–2.0 (m, 5 H), 3.1–3.8 (m, 5 H), 7.2–7.6 (m, 5 H); ν_{neat}^{max} 1440 (s), 1260 (m), 790 (s), 695 cm^{-1} (s); *m/e* (rel intensity) 321 (M^+, 1.4), 210 (100).

The generality of this reaction is apparent from the results summarized in Table I which covers various kinds of thioamides and organomagnesium and -lithium reagents. Thioamides other than those of tiglic acid (**4**) and 3,3-dimethylacrylic acid (**3**) reacted with 1.1–1.2 equiv of *n*-BuLi completely within 90 min at between 0 °C and ambient temperature. With **4**, the reaction was very slow and yielded a 1,4-addition product **11** in low yield (28% isolated yield in 48% conversion with 1.2 equiv of *n*-BuLi in THF, 0 °C, 30 min). The reaction was improved remarkably by the treatment with 2.2 equiv of *n*-BuLi in diethyl ether (61% isolated yield, room temperature, 2 h, entry 17). Both thioamide **3** and **3'** (*N,N*-dimethylamide) were unreactive to 1.1 equiv of *n*-BuLi and were recovered completely. Addition of 1 equiv of hexamethylphosphoric triamide (HMPT) caused proton elimination to give deconjugated thioamide **10'** in 71% yield (room temperature, 15 h, entry 16). Treatment of **3** with 2.2 equiv of *n*-BuLi in diethyl ether gave a mixture of 3,3-dimethylthioheptanoylpyrrolidine (**9**) and **10** in 22 and 20% isolated yields, respectively.[17]

Interestingly, *n*-BuLi reacted with *N,N*-dimethylthiosorbamide (**6**) in a 1,4-addition manner selectively to give *N,N*-dimethyl-3-propenylthioheptamide (**13**, R^1 = *n*-Bu) in 71% yield: $\delta_{CCl_4}^{Me_4Si}$ 0.9, 1.3 (br m, 10 H), 1.65 (d, *J* 5 Hz, 3 H), 2.76 (br s, 2H, $CH_2C(=S)N$), 3.33, 3.46 (s, 6 H), 5.3–5.7 (m, 2 H); ν_{neat}^{max} 1505 (s), 1400 (s), 965 cm^{-1} (s); *m/e* (rel intensity)

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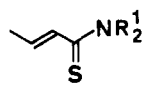
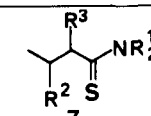
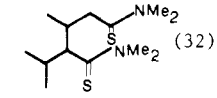
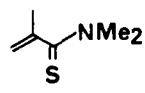
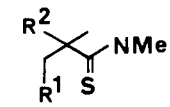
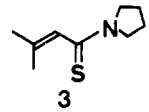
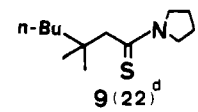
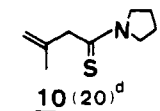
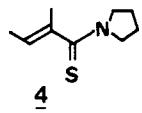
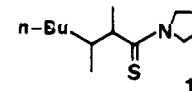
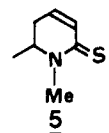
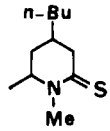
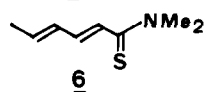
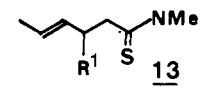
Table I. 1,4-Addition Reaction of Organolithium and Magnesium Compounds to α,β-Unsaturated Thioamides[a]

Entry	α,β-Unsaturated Thioamides	R-M[b]	Solvent	Electrophile	Product(% yield)[c]
	 **1**				 **7**
1		n-BuLi	THF	H^+	R^1= Me, R^2= n-Bu, R^3= H (94)[d]
2		n-BuLi	THF	H^+	R^1= $-(CH_2)_4-$, R^2= n-Bu, R^3= H (84)
3		n-BuLi	THF	PhSSPh	R^1= $-(CH_2)_4-$, R^2= n-Bu, R^3= PhS (77)
4		n-BuLi	THF	CH_2=$CHCH_2Br$	R^1= $-(CH_2)_4-$, R^2= n-Bu, R^3= CH_2=$CHCH_2$ (83)
5		n-BuLi	THF	CH_2=$CBrCH_2Br$	R^1= Me, R^2= n-Bu, R^3= CH_2=$CBrCH_2$ (68)
6		MeMgI	Et_2O	H^+	R^1= Me, R^2= Me, R^3= H (57)[d] +  (32)[d]
7		$MeSOCH_2Li$	THF	H^+	R^1= Me, R^2= $MeSOCH_2$, R^3= H (62)
	 **2**				 **8**
8		n-BuLi	THF	H^+	R^1= n-Bu, R^2= H (97)[d]
9		sec-BuLi	THF	H^+	R^1= sec-Bu, R^2= H (92)[d]
10		EtMgBr	Et_2O	H^+	R^1= Et, R^2= H (61)[d]
11			THF	H^+	R^1=  , R^2= H (50)
12		n-BuLi	THF	CH_2=$CHCH_2Br$	R^1= n-Bu, R^2= CH_2=$CHCH_2$ (81)[d]
13		PhMgBr	Et_2O	H^+	R^1= Ph, R^2= H (85)[d]
14		CH_2=CHMgBr	THF	H^+	R^1= CH_2=CH, R^2= H (68)[d]
15	 **3**	n-BuLi (2.2 eq)	Et_2O	H^+	 **9** (22)[d]  **10** (20)[d]
16	**3**'(NMe_2)	n-BuLi	THF-HMPA	H^+	**10**'(NMe_2) (71)[d]
17	 **4**	n-BuLi (2.2 eq)	Et_2O	H^+	 (61)[d] **11**
18	 **5**	n-BuLi	Et_2O	H^+	 (77)[d] **12**
	 **6**				 **13**
19		n-BuLi	THF	H^+	R^1= n-Bu (71)[d]
20		EtMgBr	Et_2O	H^+	R^1= Et (80)[d]

[a] Except for entries 15, 16, and 17, the reaction was undertaken at between 0 °C and ambient temperature for 30-90 min. For entries 15, 16, and 17, see text. [b] Unless otherwise mentioned, 1.1-1.2 equiv of organolithium or -magnesium compounds (prepared from 1.5 equiv of alkyl halides, not titrated) were used. [c] Isolated yield. In any case, the conditions are not optimized. All products showed satisfactory spectral data (IR, ^1H NMR, mass). [d] Satisfactory analytical results (within ±0.3% for C, H, N) were obtained for these compounds.

213 (M^+, 19), 184 (63), 156 (100). This forms a striking contrast to the selective 1,6 addition of organocopper reagents to the conjugated dienoates.[18]

Although sodium dimethyl malonate was either unreactive (with **1**, $R_2^1 = -(CH_2)_4-$) or gave many products (with **2**, at least 7 spots except for the starting spot on a silica gel plate, 8:1 PhH–EtOAc), a variety of organolithium and -magnesium compounds,[19] possessing harder carbanion character, reacted with α,β-unsaturated thioamides with similar ease and selectivity. The present reaction with phenylmagnesium bromide, vinylmagnesium bromide, lithiodithiane, and dimsyllithium, coupled with the quenching with a variety of electrophiles, provides an extremely desirable feature since these functionalities may be employed in further structural transformations. Work is in progress to investigate the full scope of the present reaction and to apply our method to the synthesis of naturally occuring compounds.

References and Notes

(1) (a) For the desulfurization with Raney nickel, see G. R. Pettit and E. E. van Tamelen, *Org. React.*, **12**, 385 (1962), and references cited therein. (b) Thioamides have also been desulfurized in high yields with excess $LiAlH_4$: Y. Tamaru, T. Harada, and Z. Yoshida, *J. Am. Chem. Soc.*, **100**, 1923 (1978).

(2) (a) M. Roth, P. Dubs, E. Götshi, and A. Eschenmoser, *Helv. Chim. Acta*, **54**, 710 (1971); (b) G. C. Gerrans, A. S. Howard, and B. S. Orlek, *Tetrahedron Lett.*, 4171 (1975); (c) A. Gossauer, R.-P. Hinze, and H. Zilch, *Angew. Chem.*, **89**, 429 (1977).

(3) R. Gompper and W. Elser, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 780.

(4) Amides and thioamides are easily convertible to each other generally in high yields by the treatment of amides with P_2S_5[3] (from amides to thioamides) and by a basic hydrolysis of *S*-alkyl onium salts (from thioamides to amides).[1b] For the transformations of amides to ketones, aldehydes and carboxylic acid, see (a) J. Zabicky, "The Chemistry of Amides", Wiley, New York, N.Y., 1970, pp 800, 847; (b) P. G. Gassman, P. K. G. Hodgson, and R. J. Balchunis, *J. Am. Chem. Soc.*, **98**, 1276 (1976).

(5) (a) R. B. Woodward, *Pure Appl. Chem.*, **17**, 519 (1968); **25**, 283 (1971); **33**, 145 (1973). (b) A. Eschenmoser, *Q. Rev.*, **24**, 366 (1970).

(6) S. Takano, M. Hirama, T. Araki, and K. Ogasawara, *J. Am. Chem. Soc.*, **98**, 7087 (1976).

(7) (a) M. Dagonneau and J. Vialle, *Bull. Soc. Chim. Fr.*, 2067, (1972). (b) P. Beak and J. W. Worley, *J. Am. Chem. Soc.*, **92**, 4142 (1970); **94**, 597 (1972). (c) D. Paquer and R. Pou, *Bull. Soc. Chim. Fr.*, 3887 (1972).

(8) P. Metzner and J. Vialle, *Bull. Soc. Chim. Fr.*, 1703 (1973).

(9) E. Schaumann and W. Walter, *Chem. Ber.*, **107**, 3562 (1974).

(10) J.-L. Burgot, J. Masson, and J. Vialle, *Tetrahedron Lett.*, 4775 (1976).

(11) D. Seebach, *Chem. Ber.*, **105**, 487 (1972).

(12) In some and special cases thioketones reacted with organolithium and -magnesium reagents selectively at the C=S carbon atoms: (a) D. Paquer and J. Vialle, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **275**, 589 (1972); (b) M. Dagonneau, ibid., **276**, 1683 (1973).

(13) G. H. Posner, *Org. React.*, **19**, 44 (1972).

(14) With Grignard reagents crotonamides (*N,N*-dialkyl-, *N*-alkyl-, *N*-aryl-, and *N,N*-diaryl-) react to give the 1,4-addition products in quantitative to ~40% yields mainly depending on the nature of N substituents: M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, New York, N.Y., 1954, p 875 and pp 885, 886.

(15) Considerable controversy surrounds the mechanism of the addition reaction of organometallics to thiocarbonyl compounds: (a) D. Paquer, *Bull. Soc. Chim. Fr.*, 1439 (1975); (b) P. Beak, J. Yamamoto, and C. J. Upton, *J. Org. Chem.*, **40**, 3052 (1975); (c) A. Ohno, K.Nakamura, Y. Shizume, and S. Oka, *Bull. Chem. Soc. Jpn.*, **50**, 1003 (1977).

(16) (a) P. J. W. Schuijl and L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, **87**, 929 (1968); (b) S. Takano, E.Yoshida, M. Hirama, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 776 (1976).

(17) To 2 equiv of lithium di-*n*-butylcuprate, **3** was also unreactive and was recovered completely.

(18) (a) J. M.-Petersen, C. Bretting, P. M. Jorgensen, S. Refn, and V. K. Andersen, *Acta Chem. Scand.*, **15**, 277 (1961); (b) T. Cohen, G. Herman, J. R. Falck, and A. J. Mura, Jr., *J. Org. Chem.*, **40**, 812 (1975); (c) T. Cohen, D. Kuhn, and J. R. Falck, *J. Am. Chem. Soc.*, **97**, 4749 (1975).

(19) Allylmagnesium bromide (3 equiv in diethyl ether) reacted with **2** at the C=S carbon atom to give *N,N*-dimethyl-1,1-diallyl-2-methyl-2-propenylamine in 47% isolated yield. Details of the reaction with allylmagnesium halides will be reported elsewhere. For the reaction of thioketones with allylmagnesium halides, which provide *tert*-thiols, see M. Dagonneau and J. Vialle, *Tetrahedron*, **30**, 415 (1974).

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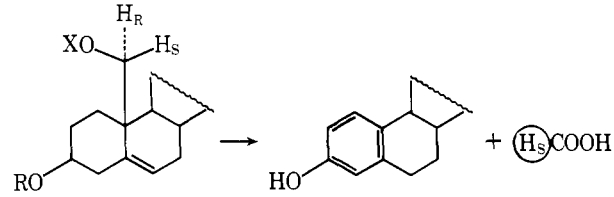
Biosynthesis of Estrogens. Assignment of the Chemical Shift of the 19-*pro*-Chiral Hydrogen Atoms of a 19-Hydroxy Precursor

Sir:

Akhtar and Skinner[1] have shown that the conversion of **1a** to an estrogen (**2**) by placental enzymes is a stereospecific process involving the removal of a specific 19-*pro*-chiral hydrogen atom, as water. The second 19-*pro*-chiral hydrogen atom is retained by the formic acid released in the aromatization reaction. It was then accepted that, in the biosynthetic transformation of androgens to estrogens, a 19-*pro*-chiral hydrogen atom is eliminated during the NADPH-oxygen-dependent oxidation of **1a** to **3** and **4**.[1]

To determine which of the 19-hydrogen atoms is lost as water and which is retained by the formic acid, it was necessary to differentiate the *pro* chiralities of the C-19 hydrogen atoms of **1**. These *pro* chiralities were inferred from an NMR investigation of the chiral 19-$^2H_1$ alcohol(s) and from the product(s) of the rearrangements of the corresponding 19-tosyl ester(s) (**1b**) to a 5(10)-cyclopropyl-6β-hydroxy derivative(s)[2] (**5**). Based on these considerations, the 19-hydrogen atoms of the 19-acetates **1c** and **1d** were assigned the following chemical shifts:[2] δ 4.44 (H_R) and 3.95 (H_S).

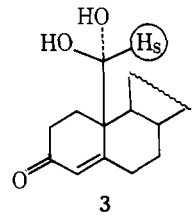
The chemical shifts of the 19-hydrogen atoms of (19*R*)- and (19*S*)-19-methylandrost-5-ene-3β,17β,19-triols, whose configurations were established by x-ray crystallography were in accord with these assignments.[3] The x-ray studies revealed that



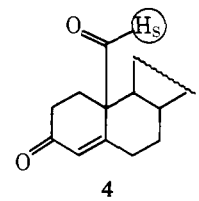
1a, R = H; X = H
b, R = CH_3; X = Ts
c, R = CH_3; X = Ac
d, R = H; X = Ac

2

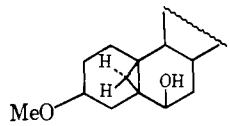
The H_S designation of the encircled hydrogen atoms refers to their prochirality in the parent compound 1



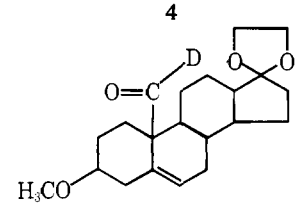
3



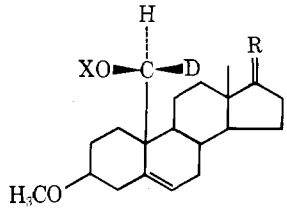
4



5



6



7a, R = $(CH_2O)_2$; X = H
b, R = O; X = Ac

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