presence of either base or acid, shows a significant increase in the total amount of cis isomer (un-ionized + ionized).[15]

The procedure used here provides an extraordinarily simple way to determine the rates of proton exchange and cis-trans equilibrium ratios of amides, which should have special utility for peptides. ^{1}H NMR is at best difficultly applicable to simultaneous measurement of exchange rates in systems of this kind because of the broadness of ^{14}N-H proton resonances.

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(7) The natural-abundance ^{15}N NMR spectra were obtained at 18.25 MHz with a Bruker WH-180 pulse spectrometer. A 25-mm-o.d. spinning sample tube containing ~25 mL of sample was used. A 5-mm concentric tube containing a 1.0 M solution of 98% ^{15}N-enriched nitric acid in D_2O provided both the external reference standard and the field-frequency lock. The ^{15}N spectra were obtained with a 45° pulse angle, 2K data points, 1200-Hz spectrum width, and a pulse interval of 3 s.

(8) The 1-aza-2-cyclononanone was obtained from Aldrich and recrystallized from benzene–hexane mixture.

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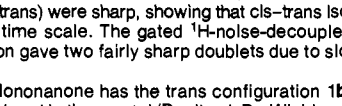
(13) When 2 mL of 4.0 M aqueous sodium hydroxide is added to a 2.5 M solution of 1 in dimethyl sulfoxide, the ^{1}H-noise-decoupled ^{15}N NMR spectrum showed two sharp and equally intense resonances at δ 250.0 and 253.8 ppm for the cis and trans isomers, respectively. The ^{15}N spectrum of the same sample after 10 h at room temperature showed an increase in the cis–trans intensity ratio to ~1.3. Similarly, addition of 2 mL of 20% hydrochloric acid to a 2.5 M dimethyl sulfoxide solution of 1 resulted in an increase in the proportions of the cis isomer, the cis–trans intensity ratio becoming ~1.5. For this solution at 25 °C, both ^{15}N resonances (δ 240.4, cis; δ 247.9, trans) were sharp, showing that cis–trans isomerization is slow on the NMR time scale. The gated ^{1}H-noise-decoupled spectrum of the acidic solution gave two fairly sharp doublets due to slow N–H proton exchange.

(14) 1-Aza-2-cyclononanone has the trans configuration **1b** with a rather distorted amide bond in the crystal (Dunitz, J. D.; Winkler, F. K. *Acta Crystallogr., Sect. B*, **1975**, 31, 251–263; Winkler, F. K.; Dunitz, J. D. *Ibid.*, **1975**, 31, 276–278), but when protonated, accepts the proton on oxygen and changes to the cis configuration with a nearly planar amide bond (Winkler, F. K.; Dunitz, J. D. *Ibid.*, **1975**, 31, 278–281). The ^{15}N spectra reported here show that the cis form of protonated 1 is the dominant configuration *in solution* at 25 °C.[13]

(15) Substantial enhancement of the double-bond character of the N–C(O) bond of 1 by removal of the amide proton is expected because delocalization



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of an unshared pair on nitrogen to the oxygen does not involve charge separation.

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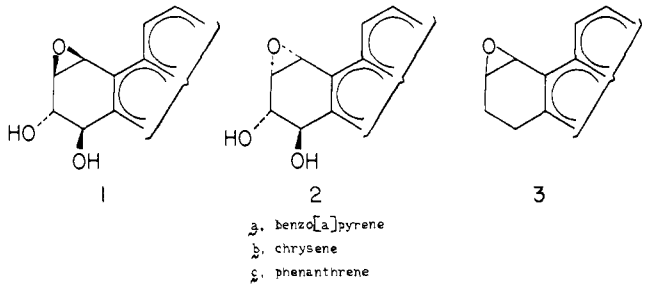
Stereoelectronic Factors in the Solvolysis of Bay Region Diol Epoxides of Polycyclic Aromatic Hydrocarbons

Sir:

Tumor studies have identified (±)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene[1a] and (±)-3α,4β-dihydroxy-1α,2α-epoxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene[1b] as ultimate carcinogenic metabolites of their respective hydrocarbons, in accord with the "bay-region" theory[1c-f] and preliminary studies on the binding of benzo[*a*]pyrene (BP) to nucleic acid.[1g,h] Thus, detailed knowledge of the chemistry of diol epoxides on saturated, angular, benzo rings in which the epoxide group forms part of a bay region of the hydrocarbon acquires special significance. Studies of the diastereomeric 7,8-diol 9,10-epoxides of BP have established that (1) they alkylate the exocyclic amino group of guanine[2a,b] and the phosphate backbone[2b,c] of nucleic acid, (2) they hydrolyze in water to form mixtures of tetraols[3] resulting from cis and trans opening of the oxirane ring at C-10 accompanied by a minor amount of 9-keto-7,8-diol,[3e] (3) the isomer in which the benzylic 7-hydroxyl group and the oxirane ring are cis is much more reactive toward nitrothiophenolate, presumably owing to anchimeric assistance,[4] and (4) this same isomer is 30-fold more reactive toward water at neutral to alkaline pH.[3e] The exact role of the hydroxyl groups in determining reaction rates and products remains unknown. To this end, we have prepared the diastereomeric bay-region diol epoxides (**1** and **2**) of phenanthrene and chrysene in order to compare the rates and products of their hydrolysis with those observed for the corresponding derivatives of BP. To help elucidate the role of the hydroxyl groups in the reactions of **1** and **2**, we have also studied the hydrolysis of tetrahydro epoxides (**3**). Rates and



1 2 3

a. benzo[a]pyrene
b. chrysene
c. phenanthrene

product distributions of acid-catalyzed hydrolysis of bay-region epoxides **1–3** in general were found to correlate with the predicted ease of carbonium-ion formation at the benzylic position, and stereoelectronic factors are proposed to account in part for a greater reactivity of the tetrahydro epoxides compared with the diol epoxides for a given hydrocarbon toward acid-catalyzed hydrolysis.

Hydrolyses of the diastereomeric diol epoxides **1** and **2** and the tetrahydro epoxides **3** in water or 25% dioxane–water were fit to the equation

$$k_{obsd} = k_{H^+}a_{H^+} + k_0$$

Values of the rate constants for acid-catalyzed hydrolysis (k_{H^+}) and spontaneous hydrolysis (k_0) pathways are summarized in Table I. In general k_{H^+} for isomer **2** is 2 to 3 times greater than that for isomer **1**, whereas k_0 for isomer **1** is 4 to 30 times greater than that for isomer **2**. Intramolecular hydrogen bonding between the oxirane oxygen and the benzylic hydroxyl group in diol epoxide **1** has been suggested to account for the decreased rate of **1** in acid[3b] and the increased rate of **1** in the k_0 region.[3e] The products of these pathways (Table II) consist of cis and trans hydration of the epoxides at the benzylic position, along with some isomerization to ketones in the k_0 region as illustrated.

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Table I. Rate Constants for Hydrolysis of **1-3 (a-c)** in Water or 25% Dioxane-Water at 25 °C[a,b]

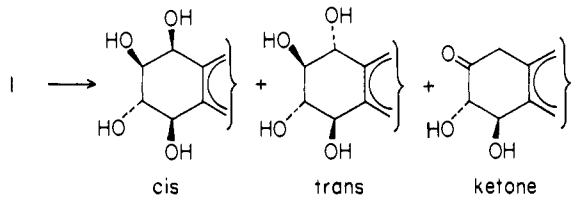
compd	solvent	k_{H^+}, M^{-1} s^{-1}	k_0, s^{-1}
benzo[*a*]pyrene[c]			
1a	water	$5.8 \pm 0.9 \times 10^2$	$1.8 \pm 0.1 \times 10^{-2}$
2a		$1.4 \pm 0.2 \times 10^3$	$5.4 \pm 0.8 \times 10^{-4}$
chrysene[d]			
1b[e]	water	$3.6 \pm 0.1 \times 10^1$	
2b		$1.27 \pm 0.04 \times 10^2$	$2.0 \pm 0.08 \times 10^{-5}$
phenanthrene[f]			
1c	water	$6.6 \pm 0.02 \times 10^1$	$1.27 \pm 0.04 \times 10^{-4}$
2c		$1.6 \pm 0.1 \times 10^2$	$3.4 \pm 0.3 \times 10^{-5}$
3c		$6.9 \pm 0.3 \times 10^3$	$3.1 \pm 0.2 \times 10^{-4}$
benzo[*a*]pyrene			
1a[c]	25% dioxane-water[g]	$4.1 \pm 0.1 \times 10^2$	$7.2 \pm 0.3 \times 10^{-4}$
2a[c,h]		$7.9 \pm 0.2 \times 10^2$	
3a[h]		$1.2 \pm 0.1 \times 10^4$	
chrysene[d]			
1b[h]	25% dioxane-water[g]	$2.1 \pm 0.2 \times 10^1$	
2b[h]		$5.7 \pm 0.2 \times 10^1$	
3b[h]		$1.6 \pm 0.1 \times 10^3$	

[a] Ionic strength = 0.1 ($NaClO_4$). Rates were monitored by observing the absorbance change of the reaction solution in the thermostated cell compartment (25.0 ± 0.2 °C) of a Gilford 2400 spectrophotometer. Rate constants were calculated from weighted least-squares plots of k_{obsd} vs. a_{H^+} in those cases where k_0 are listed, and by taking the average of k_{obsd}/a_{H^+} for a series of solutions with different pH values in those cases where k_0 was negligible compared with $k_{H^+}a_{H^+}$. The activity of hydronium ion was taken to be that measured by the glass electrode. [b] Solutions generally contained 0.01 M (total buffer concentration) of either acetic acid or Tris to maintain constant pH. Rates in these buffer solutions were found to be generally within experimental error of the rate in the absence of buffer. [c] Reference 3e. [d] Kinetics were monitored at 260 nm. [e] The k_0 term for **1b** in water could not be readily measured because of product instability. [f] Rates were monitored at 300 nm. [g] v/v. [h] Rates were determined only in the pH range of ~4-5, where the k_0 term was negligible compared with $k_{H^+}a_{H^+}$.

Table II. Relative Product Distributions Resulting on Acid-Catalyzed (k_{H^+}) or Spontaneous (k_0) Hydrolysis of Epoxides **1**, **2**, and **3**[a]

	acid catalyzed		spontaneous		
compd	cis	trans	cis	trans	ketone[b]
benzo[*a*]pyrene[c]					
1a	87	13	76	8	~16
2a	5	95	60	40	
3a	80	20	47	14	~27
chrysene[c]					
1b	57	43			
2b		~99			
3b	14	86			
phenanthrene[d]					
1c	50	50	21	14	59(5)
2c		~99	2	98	
3c	18	82	12	60	17 (11)

[a] The entries cis and trans refer to the stereochemistry of hydrolysis of the epoxide ring at the benzylic position by water while ketone indicates isomerization. Products were analyzed by HPLC as described in the supplemental material. [b] Analysis for ketones **3** was complicated by their instability above pH 8. This may account for the additional unknown products given in the parenthesis. [c] Determined by 25% dioxane-water which was 0.1 M in $NaClO_4$. [d] Determined in water which was 0.1 M in $NaClO_4$.



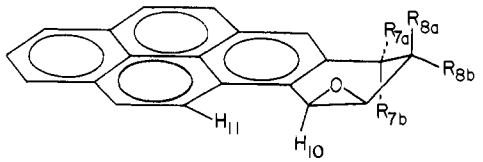
Both the ratio of cis to trans hydrolysis and k_{H^+} (Table I, 25% dioxane-water, μ = 0.1, $NaClO_4$, 25 °C) were found to increase in parallel with the predicted ease of carbonium-ion formation[1e,9] at the benzylic position for the series of tetrahydro epoxides **3b** (14:86), **3c** (18:82, $k_{H^+} = 3.7 \pm 0.1 \times 10^3$ M^{-1} s^{-1}), 1,2,3,4-tetrahydrobenzo[*a*]anthracene 1,2-epoxide (50:50, $k_{H^+} = 7.3 \pm 0.3 \times 10^3$ M^{-1} s^{-1}), and **3a** (80:20). Aryl substituents that favor carbonium-ion formation are known to markedly enhance the ratio of cis to trans hydrolysis products from 1-arylcyclohexene oxides.[10] The increase in trans hydration as the ability of the substituent to stabilize positive charge at the benzylic position decreased was attributed to the incursion of a "borderline A-1" hydrolysis mechanism, which would favor trans addition of solvent. This explanation could also account for the increased trans hydration (Table II) of the tetrahydro epoxides **3** as the ability of the aryl ring to stabilize positive charge at the benzylic position decreases.

Cis hydrolysis of **1a** and **3a** predominates over trans hydrolysis via the k_{H^+} pathway and thus parallels the predominant cis hydrolysis of 1-arylcyclohexene oxides with substituents that stabilize positive charge. The favored cis addition of solvent to the arylcyclohexene oxides has been attributed to the directing influence of the newly generated hydroxyl group. However, the fact that **2a** is even more reactive than **1a** and leads to >90% trans addition of solvent suggests that steric factors in the approach of water to the fully developed carbonium ion from **2a** may be more important than directing effects of hydroxyl groups. Thus, in either conformation, the carbonium ion from **2a** would prefer to undergo trans attack relative to the oxirane oxygen while attack on the carbonium ion from **1a** should only occur on the conformation in which all of the hydroxyl groups are equatorial and from the face of the molecule which bears the oxirane oxygen. In passing through the series of hydrocarbons from **a** to **b** and **c**, the incursion of a

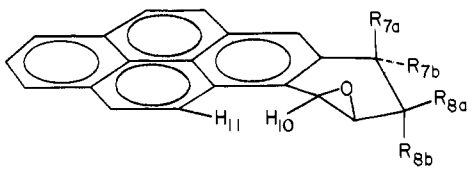
"borderline A-1" mechanism would explain the increased trans hydrolysis.

For each hydrocarbon studied, the tetrahydro epoxide was considerably more reactive toward acid-catalyzed hydrolysis (k_{H^+}) than either of the diastereomeric diol epoxides. For instance, the tetrahydro epoxide **3c** of phenanthrene was 43 times more reactive than **2c** and 105 times more reactive than **1c** (k_{H^+} in water from Table I and Figure 1). These differences in reactivities appear too large to be attributed solely to rate-retarding inductive effects of the hydroxyl groups.[11] Such differences in rates between the tetrahydro epoxides and diol epoxides are nicely accounted for, however, by a combination of stereoelectronic factors and polar substituent effects.

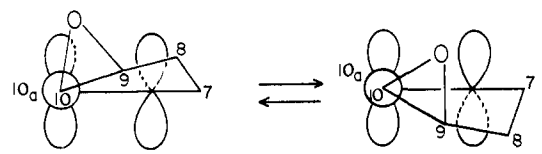
The tetrahydro epoxide **3a,** for example, can exist in two conformations, **4a** and **5a**. Molecular models indicate that a



4a, R = H
b, $R_{7a} = R_{8b}$ = OH
c, $R_{7b} = R_{8a}$ = OH



5a, R = H
b, $R_{7a} = R_{8b}$ = OH
c, $R_{7b} = R_{8a}$ = OH



6 7

severe nonbonding interaction exists between H_{10} and H_{11} in conformation **5a** which is relieved substantially in conformation **4a**. The benzylic C-O bond of the protonated epoxide that breaks in the hydrolysis reaction of **4a** is aligned such that it is nearly colinear with the p orbital of the adjacent aromatic nucleus (as indicated in **6**), an arrangement that allows maximum stabilization of developing positive charge at the transition state.

In contrast, NMR data indicate[12] that the more stable conformations of the diol epoxides of BP (**1a** and **2a**) correspond to structures **5b** and **5c,** respectively, in which the dihedral angle between the benzylic C-O bond and the p orbital of the aromatic nucleus is ~60° (depicted in **7**). This geometry does not allow for maximum stabilization of developing positive charge at the benzylic position in the hydrolysis reaction. Hydrolysis of **1a** and **2a,** therefore, must take place from the conformation less favored for formation of a benzylic cation (i.e., from **7**), or the diol epoxides must first undergo change to the less stable conformation (structure **6**) before hydrolysis occurs. As a result, a reduced reactivity of the diol epoxides

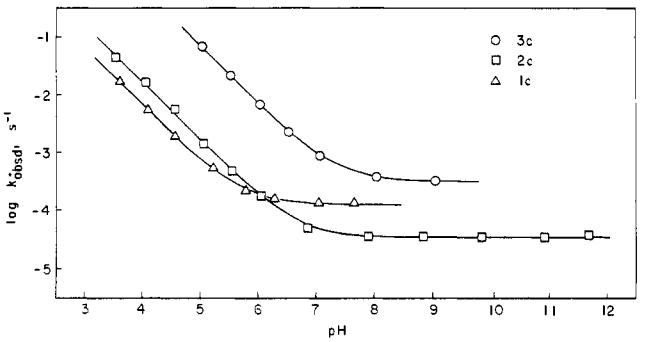


Figure 1. Plots of log k_{obsd} vs. pH for the hydrolysis of **1c-3c** in water (ionic strength = 0.1, $NaClO_4$) at 25 °C. The kinetic solutions contained either dilute acetate or Tris buffers (total buffer concentration 0.004 M) for maintenance of pH.

(relative to their tetrahydro epoxide) toward acid-catalyzed hydrolysis would be expected. The same trend is true in the **b** and **c** series. This interpretation also provides an explanation for much of the enhanced reactivity (~500) of cyclohexadiene oxide ($k_{H^+} = 1.6 \times 10^4\ M^{-1}\ s^{-1}$ at 25 °C)[13] which can exist in conformation **6,** compared with that of benzene oxide ($k_{H^+} = 32\ M^{-1}\ s^{-1}$ at 30 °C)[14] in spite of the fact that the intermediate carbonium ion from benzene oxide is more highly stabilized.[15]

Acknowledgment. This investigation was supported in part by Public Health Service Grant No. CA-17278 from the National Cancer Institute (D.L.W.).

Supplementary Material Available: Listing of the NMR spectra of the diol epoxides and their acetylated hydrolysis products as well as details of the HPLC analysis of the hydrolysis products (6 pages). Ordering information is given on any current masthead page.

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(5) Peroxy acids and *N*-bromoacetamide selectively attack the double bond of benzo ring, trans dihydrodiols from the face of the molecule which bears the allylic hydroxyl group[4] provided that the hydroxyl groups reside mainly in a quasi-diequatorial conformation.[6a] Such is the case for the trans 1,2-dihydrodiols of phenanthrene[6b] and chrysene.[6c,7] Thus, diol epoxides **2b** and **2c** were obtained in 90% yield by direct epoxidation while diol epoxides **1b** and **1c** were formed in 82-93% overall yield by cyclization of the intermediate bromotriols with the OH form of Amberlite resin. The tetrahydroepoxides (**3**) were prepared via cyclization of bromohydrins. Spectral properties of these compounds and their solvolysis products closely parallel those of related derivatives of benzo[*a*]pyrene and benzo[*a*]anthracene[3c,4,6] and are available as supplementary material to this paper.

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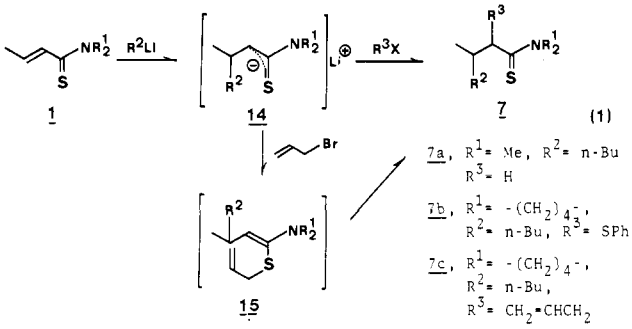
1,4-Addition Reaction of Organolithium and -magnesium Compounds to α,β-Unsaturated Thioamides

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



(1)

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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