salt. Alternatively, rapid diffusion of $SO_2^{-}\cdot$ from the cage may occur followed by similar steps. The interaction of sulfur dioxide with 1-benzyl-1,4-dihydronicotinamide thus may proceed as shown in Scheme I.

These apparent one-electron transfers from a model for NADH are in accord with suggestions of Kosower[7c,14] and Bruice[15] for NAD-catalyzed enzymic reactions, which provide an alternative to the widely held view that reductions by NADH are hydride ion transfers.[16]

Registry No. 1, 16183-83-8; 1·Cl, 5096-13-9; 2, 33976-40-8; SO_2, 7446-09-5; $CH_2{=}CHSO_2CH_3$, 3680-02-2; $(CH_2{=}CH)_2SO_2$, 77-77-0; $(CH_3SO_2CH_2CH_2)_2SO_2$, 13063-95-1; $(H_2NCOCH_2CH_2)_2SO_2$, 13063-92-8; $CH_2{=}CHCONH_2$, 79-06-1; 1-benzyl-1,4-dihydronicotinamide, 952-92-1.

Supplementary Material Available: Full experimental details (6 pages). Ordering information is given on any current masthead page.

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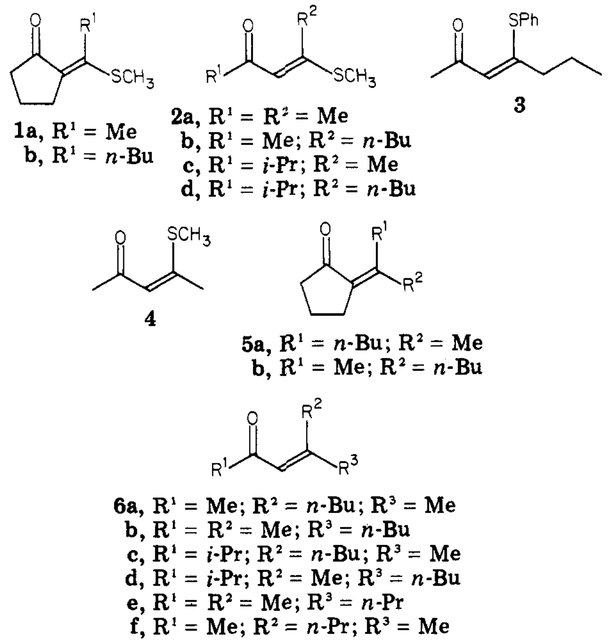
Stereoselectivity in the Addition of Organocuprates to β-Alkylthio α,β-Enones

Summary: Factors affecting the direction and degree of stereoselectivity in the conjugate addition–elimination reaction of organocuprates with β-alkylthio α,β-enones are described.

Sir: We report that the reaction of *E* β-methylthio α,β-enones with organocuprates[1] exhibits an extraordinary solvent effect and can be induced to proceed stereoselectively with either inversion or retention of configuration. While α,β-unsaturated carbonyl compounds containing good leaving groups at the β-carbon atom (e.g., halide,[2] acetate,[3] phosphate,[4] alkoxy,[5,6g] and alkylthio[6] substituents) readily undergo alkyl substitution upon reaction with organocuprates, the substitution has frequently occurred with predominant retention of configuration for the extensively studied ester derivatives.[2a,g,3,4,6c,6e–g] Significantly, only two reports[2a,c] have appeared that describe stereoselective substitutions for the more reactive ketone analogues that sometimes undergo nonchemoselective bis conjugate addition reactions.[6h] Our study indicates that stereoselectivity is far more difficult to obtain for ketone substrates but can be achieved by careful control of reaction conditions. These results provide an efficient and versatile synthetic route to regio- and stereospecifically substituted α,β-unsaturated ketones.[7]

Chart I



1a, R^1 = Me
b, R^1 = *n*-Bu

2a, R^1 = R^2 = Me
b, R^1 = Me; R^2 = *n*-Bu
c, R^1 = *i*-Pr; R^2 = Me
d, R^1 = *i*-Pr; R^2 = *n*-Bu

3

4

5a, R^1 = *n*-Bu; R^2 = Me
b, R^1 = Me; R^2 = *n*-Bu

6a, R^1 = Me; R^2 = *n*-Bu; R^3 = Me
b, R^1 = R^2 = Me; R^3 = *n*-Bu
c, R^1 = *i*-Pr; R^2 = *n*-Bu; R^3 = Me
d, R^1 = *i*-Pr; R^2 = Me; R^3 = *n*-Bu
e, R^1 = R^2 = Me; R^3 = *n*-Pr
f, R^1 = Me; R^2 = *n*-Pr; R^3 = Me

β-Alkylthio α,β-enones **1** (**a**,**b**) and **2** (**a**–**d**) (Chart I) were readily prepared from the corresponding α-oxoketene dithioacetals by an established procedure.[6a,8] The phenylthio derivative **3** was obtained from 3-heptyn-2-one[9] by

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(8) Reaction of 4,4-bis(methylthio)-3-buten-2-one (i) with lithium methyl- or *n*-butylphenylthiocuprate in THF afforded **2a** (87%) and **2b** (80%), respectively, along with minor quantitites of the corresponding *Z* isomers (e.g., **4** was obtained from **i** in <5% yield). The *E* isomers (**2a** and **2b**) were readily purified by MPLC (silica gel, petroleum ether/10% ethyl acetate, v/v). Ketones **2c** and **2d** were prepared in a similar fashion from 1,1-bis(methylthio)-4-methyl-1-penten-3-one.

Table I. Organocuprate Additions to β-Alkylthio α,β-Enones

entry	substrate	cuprate[a] ligand R	reaction conditions solvent, temp, °C	products[b]	E/Z[c]	yield,[d] %	ref[e]
1	1a	*n*-Bu	ether, −78	5b/5a	12/88	84	
2		*n*-Bu[f]	ether, −78		30/70	63	
3			THF, −78		90.2/9.8	78	
4			THF, −60		88/12	90	
5	1b	Me	ether, Me_2S, −78		93/7	83	
6	2a	*n*-Bu	ether, −65	6b/6a	4.9/95.1	97	7f
7			THF, −65		70/30	87	
8			THF, Me_2S, −78		97.4/2.6	93	
9	2b	Me	ether, −65		96.3/3.7	95	
10			THF, ether,[g] −35		30/70	77	
11			THF, −65		46/54	76	
12	2c	*n*-Bu	ether, −78	6d/6c	4/96	98	
13			THF, Me_2S, −18		60/40	79	
14	2d	Me	ether, −78		91/9	99	
15			THF–ether,[g] −18		33/67	89	
16	3	Me	ether, −78	6e/6f	97/3	91	7k
17			THF–ether,[g] −78		93/7	69	
18	4	*n*-Bu	ether, −78	6b/6a	4/96	64	
19			THF, −78		8/92	61	

[a] Unless otherwise noted, lithium dialkylcuprates were employed. [b] The assigned structures were in accord with infrared, proton, and carbon NMR spectral data. New compounds gave satisfactory C and H combustion analysis. [c] Ratios were determined by GC peak areas. [d] All yields are based upon isolated products (existing as E/Z mixtures) purified by column chromatography. [e] For previous preparation of these products, see the indicated reference. [f] $(MeOCMe_2C{\equiv}CCuMe)Li$ was employed. [g] See ref 13.

Michael addition of thiophenol.[10] The E and Z β-alkylthio α,β-enones were configurationally[11,12] unstable over long periods of time (e.g., several days to weeks) and were purified by MPLC (medium-pressure liquid chromatography) immediately before use. *The E β-alkylthio α,β-enones 1 (**a**,**b**) and 2 (**a**–**d**) undergo stereoselective substitution by organocuprates with predominant inversion of configuration in predominant ether and with predominant retention of configuration in THF.* Reaction of **2a**, for example, with lithium di-*n*-butylcuprate in ether afforded a 4.9:95.1 mixture of **6b** [NMR ($CDCl_3$, 60 MHz) δ 2.11 vinyl methyl][12] and **6a** (δ 1.86 vinyl methyl)[12] in 97% yield while reaction in THF afforded a 97.4:2.6 mixture of **6b** and **6a** in 93% yield (Table I, entries 6 and 8, respectively). The phenomenon is a general one and has been observed for both cyclic and acyclic substrates. Several observations are noteworthy. First, the degree of stereoselectivity is critically dependent upon reaction temperature (entries 3 and 8 vs. 4 and 7, respectively). When the reaction mixtures were allowed to warm to 0 °C or the enone was added at a relatively moderate temperature (entries 13 and 15), little or no stereoselectivity was achieved. Maximum stereoselectivity was generally obtained by addition of a precooled (−78 °C) enone solution to cold (−78 °C) organocuprate solutions. Utilization of low reaction temperatures, however, occasionally resulted in reduced chemical yields (compare entries 3 and 4) with resultant recovery of unreacted enones. Second, chemical yields were generally higher in diethyl ether than in THF (entries 6, 9, 12, 14 vs. 7, 10, 13, 15, respectively). Similarly, in THF the *n*-butylcuprates generally afforded higher chemical yields than the methylcuprates (entries 7 and 8 vs. 10 and 11). These observations form a pattern consistent with the known effect of substitution (n-$Bu_2CuLi > Me_2CuLi$) and solvent ($Et_2O >$ THF) on organocuprate reactivity in conjugate addition reactions[14] and suggest that maximum stereoselectivity may be achieved by using highly reactive cuprates in accelerating solvents. These conditions permit the use of very low reaction temperatures, which appears to be the most critical factor affecting the degree of stereoselectivity. Reaction of **1a** with *n*-butylcuprates in diethyl ether afforded side products, indicating that cuprate reactivity and substrate structure[15] may conspire to provide alternative reaction pathways. Third, the configurational specificity of the reaction is substrate dependent with only the E β-alkylthio α,β-enones displaying a solvent effect. The Z phenylthio analogue **3** and Z β-methylthio α,β-enone **4** underwent organocopper substitution with retention of configuration in either diethyl ether or THF (entries 16–19). These latter observations are in contrast with the nonstereoselective reaction of several Z substituted ester[2a,3c] and ketone[2a] derivatives with organocopper reagents.

These observations are consistent with an addition–elimination mechanism involving the intermediacy of an enolate anion. The carbon–sulfur bond of the alkylthio leaving group must achieve an antiperplanar relationship to the enolate π-cloud for facile expulsion. A 60° rotation

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[9] 3-Heptyn-2-one was prepared by reaction of 1-lithiobutyne with acetyl chloride in THF at −76 °C. For an alternative preparation, see: Castro, C. E.; Havlin, R.; Honwad, V. K.; Malte, A.; Moje, S. *J. Am. Chem. Soc.* **1969**, *91*, 6464.

[10] Reaction of 3-heptyn-2-one with thiophenol and triethylamine in THF afforded **3** as an E:Z mixture in 67–71% yield. The isomers were separated by column chromatography and the configurations determined by NMR spectroscopy: olefinic proton [δ 5.6 (E), δ 6.30 (Z)], C5-methylene protons [δ 2.70 (E), δ 2.08 (Z)]. These chemical shift trends were consistent with those reported for E and Z isomers of ethyl 3-(phenylthio)-2-butenoate (see ref 6g). For an alternative synthetic procedure, see ref 6e.

[11] The E β-alkylthio α,β-enones consistently exhibited a more intense UV absorption at shorter wavelengths than the corresponding Z isomer. See: Furuhawa, N.; Fukumura, M.; Nishio, T.; Oae, S. *Phosphorus Sulfur* **1978**, *5*, 191. Owen, L. M.; Sultanbawa, M. U. S. *J. Chem. Soc.* **1949**, 3109.

[12] A methyl substituent cis to the carbonyl functionality in β-methyl α,β unsaturated carbonyl compounds resonates downfield in the NMR spectrum relative to the trans methyl substituent. See: (a) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: London, 1969; pp 222–224. (b) Tori, K.; Horibe, I.; Shigemoto, H. *Tetrahedron Lett.* **1975**, *2199*. (c) Conia, J.-M.; Amice, P. *Bull. Soc. Chim. Fr.* **1968**, 3327.

[13] The use of ether solutions of methyllithium to generate lithium dimethylcuprate in THF resulted in a 4:1 to 10:1 THF–ether solvent mixture.

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[15] *GLC* analysis indicated an unidentified compound in addition to **5a** and **5b**. In a recent study, acyclic α,β-unsaturated ketones displayed a significantly larger rate constant for reaction with lithium dimethylcuprate than endo- or exocyclic enones. See: Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141.

about the β-carbon atom will lead to retention of configuration whereas a 120° rotation will result in inversion of configuration. The use of coordinating solvents (e.g., THF) that can effectively complex with the enolate counterion[16] will accelerate the elimination process and favor minimum motion (60° rotation) in the transition state, leading to retention of configuration.[17] Reaction of β-alkylthio α,β-enones with organocuprates in diethyl ether involves a solvent of low coordinating ability. Here, the E and Z β-methylthio α,β- enones undergo a stereospecific substitution with inversion and retention of configuration, respectively. In these reactions, the sulfur substituent tends to rotate away from the enolate oxygen atom and the stereospecificity may result from dipolar interactions involving proximate oxygen and sulfur heteroatoms.

Sequential organocopper conjugate additions to α-oxoketene dithioacetals may be exploited in a stereocontrolled synthesis of tri- and tetrasubstituted α,β-unsaturated ketones. Since stereoselectivity can be controlled by the sequence of operations as well as by choice of solvent, the method is extremely flexible and allows for experimentally determined combinations that will afford high stereoselectivities and chemical yields. *Synthetically, it is important to note that a mixture of E and Z β-methylthio α,β-enones will afford, in diethyl ether, the same stereoisomer in a highly stereoselective process.* This methodology constitutes a high-yield stereoselective synthesis of α-alkylidene ketones and provides an entry into the rich chemistry of regio- and stereospecificially substituted allylic alcohols.[18] The method should provide ample opportunity for synthetic variations employing organocopper reagents containing functionalized alkyl ligands.

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Registry No. **1a**, 84308-03-2; **1b**, 84308-04-3; **2a**, 86310-01-2; **2b**, 86310-02-3; **2c**, 86310-03-4; **2d**, 86310-04-5; **3**, 86310-05-6; **4**, 62453-10-5; **5a**, 86310-06-7; **5b**, 86310-07-8; **6a**, 36219-17-7; **6b**, 23732-25-4; **6c**, 86310-08-9; **6d**, 86310-09-0; **6e**, 23732-22-1; **6f**, 23732-23-2; lithium dimethylcuprate, 15681-48-8; lithium di-*n*-butylcuprate, 24406-16-4.

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