Thioaldehyde Diels-Alder Reactions

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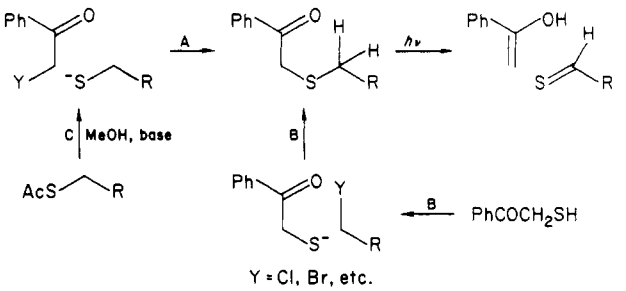
Thioaldehydes containing virtually any α-substitutent can be generated by photofragmentation of phenacyl sulfides. Donor-substituted derivatives are reactive toward electron-rich dienes and give 2 + 4 cycloadducts with regiochemistry corresponding to advanced C–C bonding in the transition state. Acceptor-substituted thioaldehydes react in the opposite regiochemical sense with C–S bonding advanced. A number of unusual thioaldehydes have been trapped, including the parent HCH=S, Me_3SiCHS, $Ph_2P(O)CH{=}S$, $PhSO_2CH{=}S$, and CNCH=S, as well as more conventional alkyl- or acyl-substituted derivatives.

Our interest in thioaldehydes began in connection with the effort in cytochalasin synthesis.[1] We required a means to connect a six-membered sulfur ring to a complex isoindolone fragment without disturbing sensitive functionality. After evaluating a longer approach using α-oxodithioester cycloaddition,[2] we examined the in situ Diels–Alder trapping of thioaldehydes. Marginal results were obtained by generating NCCH=S from dibromoacetonitrile + $C_2H_5OCS_2^-K^+$ in the presence of dienes.[2] However, photochemical thioaldehyde generation[3,4] from phenacyl sulfides proved far more efficient and gave good yields of 2 + 4 cycloadducts with a variety of electron-rich dienes. Applications of this procedure to cytochalasin synthesis are described elsewhere.[5] Here, we will focus on the Diels–Alder reactions of simple thioaldehydes to illustrate the versatility of the photochemical method.

Prior to our work,[2,4] there was one paper on intermolecular Diels–Alder trapping of a thermally generated thioaldehyde, but not under preparatively useful conditions.[6] There was a much larger body of literature dating back to the 1840's on generation of transient thioaldehydes,[7] but little in this mass of information suggested that synthetic applications might be feasible. We became aware of a recent study where a photochemically generated thioaldehyde had been trapped by 2 + 3 cycloaddition,[8] and this example encouraged us to try a similar procedure for Diels–Alder trapping experiments as summarized in Tables I and II. (For NMR data see Tables III and IV.) After our initial report in 1982,[4] several groups have described Diels–Alder reactions of thioaldehydes generated thermally or by a variety of elimination reactions.[9] Some of these techniques may prove advantageous for large scale work, but the photochemical method is the mildest, and so far, the most general.

Photolysis of phenacyl sulfides was first described by Hogeveen and Smit[3a] and was later shown to produce thiocarbonyl compounds by several other groups.[3] There is good reason to believe that a six-center Norrish type fragmentation is involved in the step leading to thioaldehyde.[3] For application to Diels–Alder trapping, the only limitations for this method are that the diene must be transparent to light in the ≥320-nm range, and that the diene must be sufficiently reactive to intercept the thioaldehyde near room temperature.

Phenacyl sulfide starting materials are easily prepared in excellent yield by alkylating appropriate mercaptans with alkyl halides. If the mercaptan corresponding to the desired thioaldehyde is available, S-alkylation with phenacyl halides is most convenient (method A). Alternatively,



phenacyl mercaptan,[10] prepared easily by a revision of the literature method (see experimental) can be alkylated by various halides (method B). Optimized yields are typically >90% for either method. To avoid handling mercaptans, we often use a variation of method A where the mercaptan is generated in situ from a thiol acetate and methanolic carbonate.

The photolytic procedure is trivial. An ordinary sun lamp is used to irradiate an ice-cooled solution of phenacyl sulfide in the presence of diene. Depending on the relative cost of the reactants, either the diene or the phenacyl sulfide may be used in excess to maximize conversion of the more expensive reactant. A 1.5–2 mole excess of diene is sufficient for trapping acceptor-substituted thioaldehydes XCH=S (X = acyl, ester, cyano, etc.) as shown in Table I. In the case of aliphatic thioaldehydes RCH=S

(1) Vedejs, E.; Reid, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 4617 and references therein.

(2) Vedejs, E.; Arnost, M. J.; Dolphin, J. M.; Eustache, J. *J. Org. Chem.* **1980**, *45*, 2601.

(3) (a) Hogeveen, H.; Smit, J. J. *Recl. Trav. Chim. Pays-Bas* **1966**, *87*, 489. (b) Trost, B. M. *J. Am. Chem. Soc.* **1967**, *87*, 138. (c) Fish, R. H.; Chow, L. C.; Caserio, M. C. *Tetrahedron Lett.* **1969**, 1259. (d) Caserio, M. C.; Cauer, W.; Novinson, T. *J. Am. Chem. Soc.* **1970**, *92*, 6082. (e) Padwa, A.; Pashayan, D. *J. Org. Chem.* **1971**, *36*, 3550. (f) Cheney, J.; More, C. J.; Raleigh, J. A.; Scott, A. I.; Young, D. W. *J. Chem. Soc., Chem. Commun.* **1974**, 47. (g) Brandt, A.; Bassignani, L.; Re, L. *Tetrahedron Lett.* **1976**, 3975.

(4) (a) Vedejs, E.; Eberlein, T. H.; Varie, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1445. (b) Vedejs, E.; Perry, D. A.; Houk, K. N.; Rondan, N. G. *Ibid.* **1983**, *105*, 6999. (c) Vedejs, E., Perry, D. A. *J. Org. Chem.* **1984**, *49*, 573. (d) Vedejs, E.; Reid, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 4617.

(5) See: ref 1; also, Rodgers, J. D. Ph.D. Dissertation, University of Wisconsin, 1985.

(6) Dice, D. R.; Steer, R. P. *Can J. Chem.* **1974**, *52*, 3518.

(7) Reviews: (a) Campaigne, E. *Chem. Rev.* **1946**, *39*, 1, (b) Wagner, A. In "Methoden der Organischen Chemie"; Muller, E., Ed.; Houben-Weyl: Berlin, 1944; Vol. IX, p 699. (c) Duus, F. In "Comprehensive Organic Chemistry"; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: New York, 1978; Vol. 3, p 373. (d) See also: "Organic Compounds of Sulphur, Selenium, and Tellurium"; The Chemical Society: London; Vols. 1 to current.

(8) Burri, K. F.; Paioni, R.; Woodward, R. B., unpublished results; we are grateful to Dr. Burri for informing us of these findings.

(9) (a) Baldwin, J. E.; Lopez, R. C. G. *Tetrahedron* **1983**, *39*, 1487. (b) Kirby, G. W.; Lochead, A. A. *J. Chem. Soc., Chem. Commun.* **1983**, 1325. (c) Bladon, C. M.; Kirby, G. W. *Ibid.* **1983**, 423. (d) Kirby, G. W.; Lochead, A. W.; Sheldrake, G. N. *Ibid.* **1984**, *922*, 1469. (e) Krafft, G. A.; Meinke, P. T. *Tetrahedron Lett.* **1985**, *26*, 1947. (f) Block, E.; Ahmad, S.; Jain, M. K.; Crecely, R. W.; Apitz-Castro, R.; Cruz, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 8295.

(10) Asinger, F.; Thiel, M.; Püchel, P.; Haaf, F.; Schäfer, W. *Liebigs Ann. Chem.* **1962**, *660*, 85.

0022-3263/86/1951-1556$01.50/0

Table I. Acceptor Thioaldehydes XCH=S + Dienes

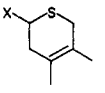
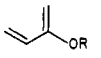
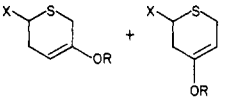
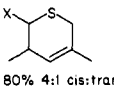
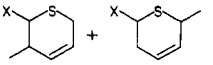
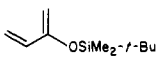
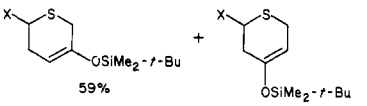
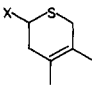
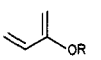
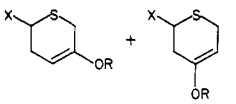
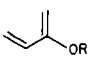
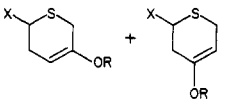
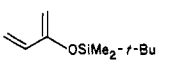
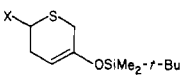
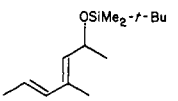
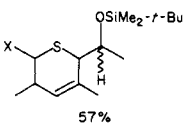
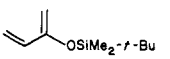
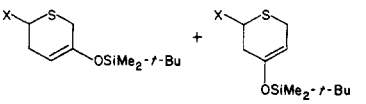
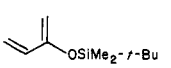
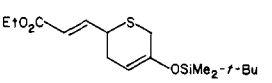
starting XCH_2SCH_2COPh (method; yield)	entry	diene	adduct(s)
X = CH_3CO (B; 84%)	1		 51%
			
	2	R = C_2H_5	33% 5%
	3	R = $OSiMe_2$-t-Bu	43% 12%
	4		 80% 4:1 cis:trans
	5		 36% 11% 3.7:1 cis:trans
	6		 59% 4:1 endo:exo
	7		 76% 20:1 endo:exo
X = PhCO (71% (ref 17))	8		 59% 5%
	9		 61%
X = CN (A; 86%)			
	10	R = C_2H_5	71% 5%
	11	R = $SiMe_2$-t-Bu	70% 4%
X = $R'O_2C$ (A; 90%)			
	12	R' = i-Pr, R = $SiMe_2$-t-Bu	53% 9%
	13	R' = CH_3, R = C_2H_5	58% (ratio not det.)
X = Ph_2PO (C; 90%)	14		 75%
	15		 57%
X = $PhSO_2$ (C; 80%) (ref 18)	16		 57% 6%
X = EtO_2CCHCH (B; 83%)	17		 10%

Table II. Donor Thioaldehydes RCH=S + Dienes

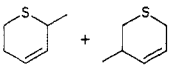
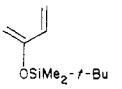
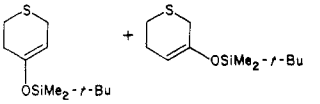
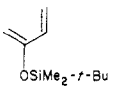
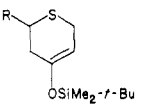
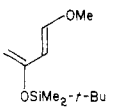
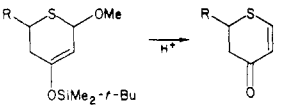
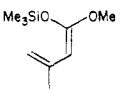
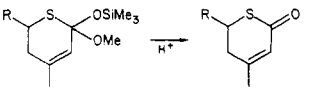
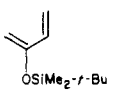
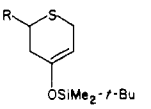
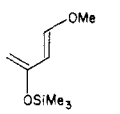
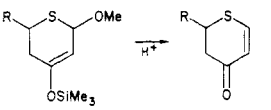
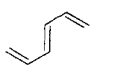
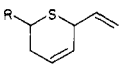
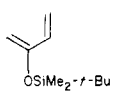
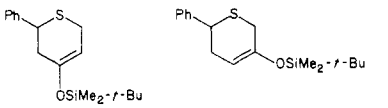
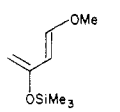
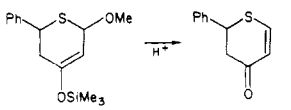
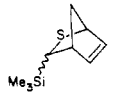
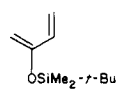
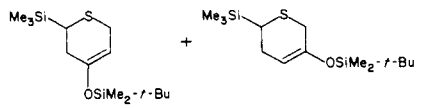
starting RCH_2SCH_2COPh (method; yield)	entry	diene	adduct(s)
R = H (B; 63%)	1		 55%
	2		 70% 21% (isolated as sulfones, MCPBA)
	3		 67% 7%
R = $PhCH_2CH_2$ (A; 97%)	4		 23%
	5		 84%
	6		 69% 3.6:1 ratio
	7		 78%
R = $AcOCH_2$ (A; 80%) (ref 19)	8		 74%
R = $PhSeCH_2CH_2$ (C; 98%)	9		 73%
R = $ClCH_2CH_2$ (C; 95%)	10		 51%
R = Ph (A; 85%) (ref 20)	11		 10% 5%
	12		 74%
	13		 84% 4:1 ratio
R = TMS (C; 96%)	14		 65% 5:1 ratio
	15		 30% 3%

Table III. NMR Data for Table I[a]

entry	phenacyl $PhCOCH_2$	sulfide SCH_2R	adducts Hα	Hβ	Hγ	Hα′	C-methyls
1	3.90	3.40	2.94, br s			3.54, t, J = 5.3	2.31, s, 1.69, s
3 major	3.90	3.40	2.93, br s		4.95, t, J = 5	3.5, t, J = 5	2.30, s
3 minor	3.90	3.40	3.2, m	5.03, m		3.65, t, J = 5	2.30, s
4 cis	3.90	3.40	3.02, 2.87, ABq, J = 16.5		5.43, br s	3.69, d, J = 4.4	2.25, s, 1.74, s, 1.03, d, J = 7
4 trans	3.90	3.40	2.89, 2.77, ABq, J = 16.5		5.43, br s	3.19, d, J = 4	2.33, s, 1.72, s, 1.1, d, J = 7
5 major[b]	3.90	3.40	3.1, br ABq, J = 17	5.8, m	5.8, m	3.78, d, J = 5	1.07, d, J = 7
6 major	3.90	3.40	4.1, br s	6.43, dd, J = 5.5, 2.9	5.86, dd, J = 5.5, 3.1	4.42, d, J = 4	2.13, s
6 minor	3.90	3.40	4.1, br s	6.39, dd, J = 5.5, 2.9	5.99, dd, J = 5.5, 3.3	3.41, s	2.30, s
7 major[b]	3.90	3.40	3.37–3.26, m	6.56, t, J = 7.5	6.23, t, J = 7.5	3.97, d, J = 2.9	2.10, s
8 major[b]	3.81	3.81	3.02, ABq, J = 16.6		5.06, t, J = 4.4	4.59, t, J = 5.2	
9	3.81	3.81	2.82, br s			4.2, t, J = 6	1.72 s
10 major[d]	4.10[c]	3.41	3.58, 2.97, ABq, J = 17.5		4.68, br s	3.7 obsc	1.29, t, J = 7
10 minor[e]	4.10[c]	3.41	3.80, dd, J = 16.9, 5.7, 3.21, dd, J = 16.9, 5.7	4.9, dt, J = 5.7, 2.9		3.84, t, J = 4	1.3, t, J = 7.3
11 major[b]	4.10[c]	3.41	3.24, ABq, J = 16.9		4.95, br t, J = 2.6	3.68, t, J = 4.4	
11 minor[b]	4.10[c]	3.41	obsc	5.15, m		3.86, t, J = 4.2	
12 major[b]	3.94	3.12	3.09, br s		4.94, t, J = 4.0	3.50, m	1.46, d, J = 7
12 minor[b]	3.94	3.12	3.21, m	obsc		3.64, m	obsc
13	3.94	3.12	3.08, br s		4.62, m	3.50, m	1.24, t, J = 7
14	4.04[f]	3.3, d J(P–CH) = 6	3.23, 2.89, ABq, J = 16.6		4.97, br s	3.50, ddd, J = 10.2, 6.4, 6.6	
15 major[g] diastereomer	4.04[f]	3.3, d J(P–CH) = 6	4.0, m		5.46, br d, J = 5	3.16, d, J = 9	1.29, s, 1.16, d, J = 6.5, 0.98, d, J = 6
16 major[b]	4.11[i]	3.92	3.42, d, J = 15, 2.8 obsc		4.9, m	3.92, dd, J = 3.6, 3.5	
16 minor[b]	4.11[i]	3.92	obsc		5.04, m	4.11, dd, J = 3.8, 3.6	
17	3.71	3.25, dd J = 7.5, 1.2	3.04, br d, J = 16.9, 2.97, br d J = 16.9		4.94, t, J = 4.3	3.48, m	

[a] $CDCl_3$, ppm; J, Hz. [b] Minor isomers not separated. [c] Phenacyl sulfide, mp 38–40 °C. [d] Adduct, mp 53–55 °C. [e] Adduct, mp 48–49 °C. [f] Phenacylsulfide, mp 67–69 °C. [g] Adduct, mp 168–170 °C. [h] Adduct, mp 121–122 °C. [i] Phenacyl sulfide, mp 63–64 °C.

(R = saturated alkyl), a larger excess of diene and carefully purified reagents are necessary to minimize catalyzed thial self-condensation. However, the XCH=S derivatives (X = acceptor) react well even without such precautions. Somewhat cleaner product mixtures are obtained by use of a copper sulfate bath to filter wavelengths below 320 nm. This precaution minimizes secondary photochemical reactions presumably sensitized by acetophenone, the other fragment obtained by Norrish cleavage of the phenacyl sulfides, but it does not always improve the yield of 2 + 4 cycloadducts.

In those experiments where the diene is not sufficiently reactive, secondary reactions produce a complex mixture resulting from photodecomposition of thioaldehyde-derived oligomers. Thus, irradiation of $PhCOCH_2SCH_2C(CH_3)_3$ in the presence of 2,3-dimethyl-1,3-butadiene affords a solid thioaldehyde polymer (ca. 50%) and some dineopentyl disulfide, but no Diels–Alder adduct.[11] Prolonged photolysis of the polymer in the presence of acetophenone results in more dineopentyl disulfide and other complex decomposition products. Similar experiments with $PhCOCH_2SCH_2CO_2CH_3$ do give 2 + 4 cycloadducts, but if dienes are omitted, then the disulfide $(CH_3O_2CCH_2S)_2$ is formed in ca. 30% yield together with complex nonvolatile products and acetophenone. Since no well-defined polymer is formed in this case, the formation of disulfide from thioaldehyde-derived oligomers by secondary photochemical reactions has not been confirmed. However, this product is not formed in significant amounts when a good thioaldehyde trapping agent is present.[12]

Diels–Alder Trapping

Acceptor-Substituted Thioaldehydes. It is convenient to distinguish those thioaldehydes XCH=S having electron-withdrawing substituents X from RCH=S systems (R = alkyl). Properties of the acceptor series, XCH=S, are closely analogous to those of conventional all-carbon dienophiles. Inspection of Table I shows that this family of thioaldehydes reacts with "typical" Diels–Alder regiochemistry where acceptor X prefers the ortho or para positions relative to diene donor substitutents in the final cycloadduct. Similar selectivity is known for acceptor-substituted dithioester dienophiles.[2,14] This se-

(11) Vedejs, E.; Perry, D. A.; Wilde, R. G. submitted for publication.

(12) We have not ruled out some competing, reversible dissociation of $PhCOCH_2SCH_2X$ into the radical pair $PhCOCH_2\cdot$ + $\cdot SCH_2X$.

(13) Review: Weinreb, S. *Heterocycles*, **1979**, *12*, 949.

Table IV. NMR Data for Table II[a]

entry	phenacyl $PhCOCH_2$	SCH_2R	adducts Hα	Hβ	Hγ	Hα′	C-methyls
2 major[c]	ref 6		3.6, m	5.8, dtd, J = 10.7, 3.9, 2.4, or 5.52, ddt, J = 10.7, 3.0, 1.5		3.1, m	1.47, d, J = 7.1
3 major	ref 6		3.15, dt, J = 4.5, 2.2	5.05, tt, J = 4.5, 1.5		2.75, t, J = 5.8	
3 minor	ref 6		3.00, m	4.95, tt, J = 4.5, 1.5		2.60, m	
4	3.8	2.7 or 2.6 t, J = 7	3.32, ddt, J = 16.5, 2.5, 2.5; 3.03 ddt, J = 16.5, 5.2, 1.5	5.04, m		2.86, m	
5 enone	3.8	2.7 or 2.6 t, J = 7	7.4, d, J = 10	6.15, d, J = 10		3.45, m	
6 major	3.8	2.7 or 2.6 t, J = 7	4.02, m	6.40, dd, J = 5.5, 2.9	5.76, dd, J = 5.5, 3.1	3.95, m	
6 minor	3.8	2.7 or 2.6 t, J = 7	3.95, m	6.28, dd, J = 5.5, 2.9	5.90, dd, J = 5.5, 3.1	4.02, m	
7 thiolactone	3.8	2.7 or 2.6 t, J = 7		5.97, m		3.47, m	1.94, br s
8	3.82	2.80	3.18, m	5.04, tt, J = 4.5, 1.5		3.18, m	2.07, s
9 enone	3.71	2.95 or 2.65 t, J = 7	7.37, d, J = 10.1	6.15, d, J = 10.1		3.66, m	
11 major	3.65	3.54	3.55, m	3.05, m	5.16, m	4.04, dd, J = 10, 4.5	
11 minor	3.65	3.54	3.46, m	2.89, m	5.09, m	3.95, dd, J = 9.5, 4.5	
12 enone	3.65	3.54	7.49, d, J = 10.1	6.27, dd, J = 10.1, 0.5		4.69, dd, J = 13.8, 3.5	
13 major[b]	3.65	3.54	4.16, m	6.54, dd, J = 5.5, 2.9	5.54, dd, J = 5.5, 3.1	4.94, d, 3.8	
13 minor[b]	3.65	3.54	4.24, m	6.43, dd, J = 5.5, 2.7	6.15, dd, J = 5.5, 3.1	4.94 obsc	
14 major	3.75	1.84	4.01, m	6.17, dd, J = 5.5, 3.0	5.65, dd, J = 5.5, 3.2	2.73, d, J = 3.2	
14 minor	3.75	1.84	4.10, m	6.10, dd, J = 5.5, 3.8	5.89, dd, 5.5, 3.2	2.73, d, J = 3.2	
15 major[b]	3.75	1.84	2.8, m	5.02, dt, J = 3, 1.5		2.7, t, J = 6	

[a] $CDCl_3$, ppm; J, Hz. [b] Minor isomers not separated. [c] Phenacyl sulfide, mp 63–64 °C.

lectivity is opposite to that seen with the acceptor-substituted carbonyl compounds.[13]

In all examples studied, the cycloadditions are also analogous to their all-carbon counterparts in regard to stereochemistry. The "endo" rule seems to be followed, perhaps due to secondary orbital interactions. Firm proof for the endo stereochemistry is available for the cyclopentadiene adduct of entry 6, Table I, based on europium shift reagent studies, and also on the conversion of the 4.3:1 kinetic endo:exo mixture into a thermodynamic mixture of 1:3 endo:exo using base catalysis. In other examples (entries 4,5) the stereochemistry is deduced from base-induced equilibration of the kinetically favored product (axial, equatorial) to the diequatorial isomer. Recent papers by Kirby et al. using different methods for generation of acceptor-substituted thioaldehydes report similar stereochemical results.[9b-d]

The acceptor-substituted thioaldehydes react efficiently with typical Diels–Alder dienes, especially with cisoid or donor-substituted derivatives. Using the more reactive dienes (cyclopentadiene, etc), we have never failed to trap an acceptor thioaldehyde, even in cases such as entries 14–16 where the oxygen analogs are inaccessible (formyl sulfones; formyl phosphine oxides). The last entry (17) demonstrates low yield trapping of an α,β-unsaturated thioaldehyde. We have not found any well-defined thioaldehyde self-condensation products in this case, but the parent thioacrolein undergoes Diels–Alder dimerization and cannot be trapped by simple dienes under similar conditions.[4a,16] Even the Danishefsky diene is only marginally effective in trapping thioacrolein.[4b]

Donor-Substituted Thioaldehydes, RCH=S. When the results of Table II are compared with those of Table I, it is evident that alkanethials differ from their analogues having π-acceptor groups directly attached to the thioformyl group. Diels–Alder trapping is still observed, but the yields depend more strongly on the choice of diene, the nature of thioaldehyde substituent R, and on reaction conditions. A large excess of diene is important, and so is the purity of both reactants. There is now a very pronounced advantage to trapping with "good" Diels–Alder dienes, and best results are obtained with cyclopentadiene or with the highly oxygenated Danishefsky diene. Finally, and most important, the regiochemistry of the reactions in Table II (RCH=S) is reversed compared to analogous reactions in Table I (XCH=S). All of these differences can be rationalized by frontier MO considerations.[4b]

The activation barrier for Diels–Alder trapping is related to the HOMO–LUMO energy gap between the reaction

(14) (a) Vyas, D. M.; Hay, G. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 180. Vyas, D. M.; Hay, G. W. *Can. J. Chem.* **1971**, *49*, 3755; (b) Ohno, A.; Ohnishi, Y.; Tsuchihashi, G. *Tetrahedron* **1969**, *25*, 871.

(15) Friedrich, K.; Zamkanei, M. *Tetrahedron Lett.* **1977**, 2139.

(16) Bock, H.; Mohmand, S.; Hirabayashi, T.; Semkow, A. *J. Am. Chem. Soc.* **1982**, *104*, 312.

(17) Tafel, J.; Mauritz, A. *Chem. Ber.* **1897**, *23*, 3474.

(18) Thiol acetate cleavage was performed using $LiEt_3BH$ in THF, −70 °C to room temperature. Standard Na_2CO_3 cleavage gave poor results.

(19) Phenacyl chloride + Et_3N + 2-mercaptoethanol in THF followed by Steglich acylation (Ac_2O/DMAP).

(20) Wahl, C. *Ber. Dtsch. Chem. Ges.* **1922**, *55B*, 1449.

π-systems. Since the most electron-rich dienes are the best trapping agents in all cases, especially in the RCH=S examples of Table II, it is clear that the thioaldehyde always participates in 2 + 4 cycloaddition as the LUMO component with the diene providing the HOMO. Donor groups in the diene raise the HOMO energy and therefore reduce the LUMO–HOMO gap, resulting in a lowering of the activation barrier and an increase in trapping efficiency.[4b] The presence of π-acceptors in the thioaldehyde (XCH=S, Table I) exerts a similar beneficial effect by lowering the LUMO energy. Consequently, the acceptor-substituted thioaldehydes are less sensitive to the choice of diene reactant. Apparently, even a simple α-acetoxy substitutent inductively lowers the LUMO energy level because $AcOCH_2CH$=S (Table II, entry 4 vs. entry 8) is trapped more efficiently than is $PhCH_2CH_2CH$=S. However, there may also be some effect due to differences in the rates of thioaldehyde self-condensation which this simple argument neglects.

The regiochemistry reversal between Tables I and II suggests a trend for reversal in the LUMO polarization of thioaldehyde π* depending on substituents. Calculations by Houk and Rondan indicate that in HCH=S, carbon has the larger LUMO coefficient and is therefore more electrophilic than sulfur in the cycloaddition with electron-rich dienes.[4b] This tendency is reinforced by alkyl groups in RCH=S which typically react in the same regiochemical sense and with higher selectivity than does HCH=S, but with somewhat lower efficiency due to higher LUMO energy.

Thiobenzaldehyde reacts with a significant reduction in regiochemistry (entry 11, Table I) and there is a corresponding decrease in LUMO polarization. Stronger π-acceptor substituents (Table II) have a larger effect and eventually cause a reversal in LUMO polarization. The experimental results show a more dramatic reversal in regiochemistry than implied by the calculations,[4b] but trends are clearly in the correct direction. Sulfur becomes the more electrophilic center in the cycloaddition process, and the regiochemistry follows the pattern where diene donor groups prefer ortho, para positions relative to the dienophile acceptor group. The regiochemical selectivity in Table I is usually not as good as for the donor-substituted thioaldehydes. In other words, strong π-acceptors exert an effect which is opposed to and stronger than the intrinsic orientational preference of the thiocarbonyl group. However, yields in Table I tend to be higher, as expected from a lowering of LUMO energy by π-acceptor groups. Similar, although less dramatic, trends are seen in 2 + 4 cycloadditions of thioketones and dithioesters.[14,15]

Conclusions

Thioaldehyde Diels–Alder additions can be used conveniently to prepare dihydrothiopyrans. Since regiochemistry can be reversed depending on whether the thioaldehyde contains a donor or a π-acceptor at the α-carbon, a wide range of dihydrothiopyrans becomes accessible. The variation using Danishefsky's diene is probably the best way currently available for synthesis of dihydrothiopyrones. Future papers will describe more complex synthetic applications which use the 2 + 4 cycloaddition to form precursors for various ring expansion sequences.

Experimental Section

2-(*tert*-Butyldimethylsiloxy)butadiene. A solution of lithiumdiisopropylamide (LDA) was prepared by dropwise addition of *n*-butyllithium (Foote Mineral, 1.3 M in hexane, 6.40 mL, 8.32 mmol) to a stirred solution of diisopropylamine (Aldrich, distilled from CaH_2, 0.866 g, 1.20 mL, 8.58 mmol) in 10 mL of THF at 5 °C under nitrogen. The syringe used to transfer the n-butyllithium was rinsed with THF (10 mL) and this was added to the stirred solution. The solution was cooled to −78 °C and methyl vinyl ketone (Aldrich, technical grade (97%), 0.560 g, 7.76 mmol) in 15 mL of THF was added dropwise via cannula over 40 min, and the resulting mixture stirred for an additional 10 min. Then HMPA (Aldrich, distilled from CaH_2, 6 mL) was added followed by *tert*-butyldimethylsilyl chloride (Petrach, 1.285 g, 8.54 mmol) in 5 mL of THF. The reaction mixture was warmed to 0 °C, stirred for 30 min, and then poured into a stirred mixture of pentane (150 mL) and 1 M acetic acid (50 mL). The layers were separated and the pentane was rinsed with 2 × 50 mL water. The combined aqueous layers were extracted with pentane (15 mL) and the combined organic layers were rinsed with brine and dried ($MgSO_4$). After filtration, removal of the solvent via distillation (Vigreaux column, 1 ft) left ca. 10 mL of a yellow oil which was transferred to a 25-mL round-bottom flask equipped with a 1 cm × 10 cm distillation column packed with glass helices. The residual solvent was removed by slowly lowering the pressure (Langdon pump) within the system (bath temperature = 40 °C) to ca. 40 mm. The glass helix packed column was removed and the product distilled through a short path distillation head (pb 70 °°C, 20 mm) to give the title compound (1.1 g, 6.0 mmol, 77%) as a colorless liquid. NMR ($CDCl_3$, δ): 6.17 (1 H, dd, J = 17, 10.5 Hz), 5.5 (1 H, dd, J = 17, 2 Hz), 5.07 (1 H, br d, J = 10.5 Hz), 4.3 (2 H, overlapping br s) 1.04 (9 H, s), 0.14 (6 H, s). On a larger scale (24.2 mmol), 1.75 g of methyl vinyl ketone gave 3.437 g (77%) of diene.

Representative Preparation of Phenacyl Sulfides. Method A. Mercaptan and Phenacyl Chloride. *S*-Phenacyl Isopropylthioglycolate. Phenacyl chloride (Aldrich, 6.00 g, 0.039 mmol) and isopropylthioglycolate (prepared by Fischer esterification of thioglycolic acid with isopropyl alcohol, 5.20 g, 0.039 mmol) were added to 50 mL of dry THF. Oven-dried potassium carbonate (27.0 g, 0.195 mmol) was added and the mixture stirred under nitrogen for 24 h. The solution was filtered from the carbonate, and the filter cake was washed with ethyl acetate (50 mL). After solvent removal, the product was obtained by Kugelrohr distillation 145 °C/0.15 mm) as a clear oil (8.44 g, 86%), R_f = 0.41, 25% ethyl acetate/hexane. NMR ($CDCl_3$, δ): 7.88 (2 H, m), 7.44 (3 H, m), 5.0 (1 H, septet, J = 7 Hz), 4.0 (2 H, s), 3.28 (2 H, s), 1.24 (6 H, d, J = 7 Hz): IR (neat, cm^{-1}): 1730 (s), 1685 (s), 1600 (m). Mass spectrum: calcd for $C_{13}H_{16}O_3S$ 252.0820, found 252.0820.

Method B. Phenacyl Mercaptan and Alkyl Halide. Phenacyl Mercaptan. An improved modification of the literature procedure[21] is used to make phenacyl mercaptan. Thus, a 10% solution of $PhCOCH_2SCOCH_3$ in ether is stirred vigorously with 10% $NaOH/H_2O$ (equal volumes) for 20 min at room temperature. The intensely yellow aqueous layer is separated and acidified with 10% H_2SO_4, and the mercaptan is extracted into CH_2Cl_2. After drying and solvent removal, the product is distilled, bp 90–100 °C (0.2 mmHg), 91%.

Phenacylthioacetone ($PhCOCH_2SCH_2COCH_3$). A solution of phenacyl mercaptan (2.24 g, 14.7 mmol) in dry THF (distilled from Na–benzophenone) was combined with triethylamine (2.05 mL, 14.7 mmol) at 0 °C under N_2 and stirred 0.5 h. Chloroacetone (freshly distilled) was then added, and the solution was allowed to warm slowly to room temperature and stirred 45 min more. The mixture was then filtered through a 15 × 2 cm plug of silica gel, the column was washed with THF (ca. 30 mL), and the eluant was concentrated to a yellow oil which solidified (aspirator). Recrystallization from hot ether gave 2.5 g (82%) of white product in two crops and another 6% could be obtained by repeated crystallization of the mother liquors, mp 53–55°: NMR ($CDCl_3$, δ) 7.4–7.9 (5 H), 3.90 (2 H, s), 3.40 (2 H, s), 2.29 (3 H, s).

Method C. In Situ Mercaptide Generation from Thiolacetate and Methanol/Methoxide Followed by Alkylation. Trimethylsilylmethyl Phenacyl Sulfide. A mixture of thiolacetic acid (5 mL, 0.7 mmol), anhydrous powdered Na_2CO_3 (7.42

(21) (a) Asinger, F.; Thiel, M.; Schafer, W. *Liebigs Ann. Chem.* **1960**, *637*, 146. (b) Asinger, F.; Thiel, M.; Puchel, P.; Haaf, F.; Schafer, W. *Ibid.* **1962**, *660*, 85.

g, 0.7 mmol), and (chloromethyl)trimethylsilane (Petrarch, 10.5 mL, 75 mmol) was stirred vigorously in 100 mL of dry THF overnight. After filtration through Celite, the solvents were removed (aspirator) and the residue was fractionally distilled at aspirator pressure. A fraction boiling at 61–7° (25 mm) was sufficiently pure by NMR for use in the next step.

The thiol ester (3.24 g, 20 mmol) in methanol (10 mL) was added slowly to a stirred solution of 1.49 g of NaOMe in methanol (50 mL) at room temperature under nitrogen. The yellow color of thiol ester faded quickly, but stirring was continued for 4 h to ensure complete conversion to mercaptide. A solution of phenacyl chloride (3.1 g) in methanol (15 mL) was added dropwise and the salt was precipitated at once. After overnight stirring, methanol was evaporated and the solution was partitioned between water and CH_2Cl_2. The organics were dried ($MgSO_4$), evaporated (aspirator), and purified by filtration chromatography over silica gel (150 g) using 10% ether–hexane to give 4.55 g of product as a yellow oil: NMR ($CDCl_3$, δ) 7.4–8 (5 H), 3.75 (2 H, s), 1.84 (2 H, s) 0.45 (9 H, s); *m/e*, 238.0847 ($C_{12}H_{18}OSSi$), 0 ppm error.

General Procedure for Photochemical Thioaldehyde Diels–Alder Reactions. A solution of thioaldehyde precursor in dry CH_2Cl_2 or dry THF/hexane (1/1) was prepared in a dry Pyrex round-bottom flask equipped with a sitrring bar. A septum was placed on the flask and dry nitrogen was bubbled through the solution for 15 min. Diene was then added via syringe. The flask was placed in a water cooling bath consisting of a Pyrex crystallizing dish (150 × 75 mm) containing a copper tubing cooling coil. This maintained the cooling bath at approximately 28 °C during photolysis. The stirred solution was photolyzed with a 275-W sun lamp (positioned 1 in. below the cooling bath) under static nitrogen pressure. Cleaner products were obtained using 5% $CuSO_4$ in the water bath.

Table I, Entry 11. Cyanothioformaldehyde + 2-(*tert*-Butyldimethylsiloxy)butadiene: Distilled 2-(*tert*-butyldimethylsiloxy)butadiene (0.276 g, 1.5 mmol) was added via syringe to a solution of *S*-phenacylthioacetonitrile (0.191 g, 1.0 mmol) in dry CH_2Cl_2 (10 mL). The solution was photolyzed for 4 h as described above. After solvent evaporation the residue was purified by PLC (10% ethyl acetate/hexane, 2 elutions). The band at R_f 0.72 gave a mixture of 2 + 4 adducts (0.189 g, 0.74 mmol, 74%) as a colorless oil (R_f 0.43, hexane/CH_2Cl_2/ether, 60/30/10). The 270-MHz NMR spectrum indicated an 18:1 mixture by integration of the vinyl proton signals (4.95 and 5.15 ppm, respectively). NMR (270 MHz, $CDCl_3$, δ): major isomer, 4.95 (1 H, pseudo triplet, J = 2.6 Hz), 3.68 (1 H, t, J = 4.4 Hz), 3.24 (2 H, AB quartet, J_{AB} = 16.9 Hz), 2.68, (2 H, m), 0.92, (9 H, s), 0.17 (6 H, s). MS: *m/e* 255.1123 ($C_{12}H_{21}OSSiN$), 4 ppm error.

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Registry No. $PhCOCH_2SCOCH_3$, 53392-49-7; $PhCOCH_2SCH_2COCH_3$, 6581-69-7; $ChCOCH_2SCH_2COPh$, 2461-80-5; $PhCOCH_2SCH_2CN$, 80737-85-5; $PhCOCH_2SCH_2CO_2Pr$-*i*, 80737-86-6; $PhCOCH_2SCH_2CO_2CH_3$, 36615-92-6; $PhCOCH_2SP(O)Ph_2$, 80738-04-1; $PhCOCH_2SCH_2SO_2Ph$, 100946-65-4; $PhCOCH_2SCH_2CH{=}CHCO_2Et$, 100946-66-5; $PhCOCH_2SCH_3$, 5398-93-6; $PhCOCH_2S(CH_2)_3Ph$, 87598-28-5; $PhCOCH_2S(CH_2)_2OAc$, 100946-67-6; $PhCOCH_2S(CH_2)_3SePh$, 100946-68-7; $PhCOCH_2S(CH_2)_3Cl$, 100946-69-8; $PhCOCH_2SCH_2Ph$, 2408-88-0; $PhCOCH_2SCH_2TMS$, 87598-27-4; 2,3-dimethyl-1,3-butadiene, 513-81-5; 2-ethoxy-1,3-butadiene, 4747-05-1; 2-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-1,3-butadiene, 80738-05-2; 2-methyl-1,3-pentadiene, 1118-58-7; 1,3-pentadiene, 504-60-9; 1,3-cyclopentadiene, 542-92-7; 1,3-cyclohexadiene, 592-57-4; 2-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4-methyl-3,5-heptadiene, 100946-70-1; 2-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-4-methoxy-1,3-butadiene, 71735-01-8; 1-[(trimethylsilyl)oxy]-1-methoxy-3-methyl-1,3-butadiene, 73311-51-0; 2-acetyl-4,5-dimethyl-3,6-dihydro-2*H*-thiopyran, 80738-11-0; 2-acetyl-3,6-dihydro-5-ethoxy-2*H*-tiopyran, 80737-93-5; 2-acetyl-3,6-dihydro-4-ethoxy-2*H*-thiopyran, 81134-65-8; 2-acetyl-3,6-dihydro-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2*H*-thiopyran, 80737-92-4; 2-acetyl-3,6-dihydro-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2*H*-thiopyran, 81134-64-7; *cis*-2-acetyl-3,6-dihydro-3,5-dimethyl-2*H*-thiopyran, 73496-56-7; *trans*-2-acetyl-3,6-dihydro-3,5-dimethyl-2*H*-thiopyran, 73496-57-8; *cis*-2-acetyl-3,6-dihydro-3-methyl-2*H*-thiopyran, 73496-58-9; *trans*-2-acetyl-3,6-dihydro-3-methyl-2*H*-thiopyran, 73496-59-0; 2-acetyl-3,6-dihydro-6-methyl-2*H*-thiopyran, 100946-71-2; *endo*-3-acetyl-2-tioabicyclo[2.2.1]hept-5-ene, 100946-72-3; *exo*-3-acetyl-2-thiabicyclo[2.2.1]hept-5-ene, 100946-73-4; 2-benzoyl-3,6-dihydro-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2*H*-thiopyran, 80737-89-9; 2-benzoyl-3,6-dihydro-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2*H*-thiopyran, 81134-61-4; *endo*-3-acetyl-2-thiabicyclo[2.2.2]oct-5-ene, 100946-74-5; *exo*-3-acetyl-2-thiabicyclo[2.2.2]oct-5-ene, 101052-98-6; 2-benzoyl-3,6-dihydro-4,5-dimethyl-2*H*-thiopyran, 80738-10-9; 2-cyano-3,6-dihydro-5-ethoxy-2*H*-thiopyran, 73496-60-3; 2-cyano-3,6-dihydro-4-ethoxy-2*H*-thiopyran, 81134-58-9; 2-cyano-3,6-dihydro-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2*H*-thiopyran, 80737-87-7; 2-cyano-3,6-dihydro-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2*H*-thiopyran, 81134-59-0; isopropyl 3,6-dihydro-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2*H*-thiopyran-2-carboxylate, 80737-90-2; isopropyl 3,6-dihydro-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2*H*-thiopyran-2-carboxylate, 81134-62-5; methyl 3,6-dihydro-5-ethoxy-2*H*-thiopyran-2-carboxylate, 100946-75-6; methyl 3,6-dihdyro-4-ethoxy-2*H*-thiopyran-2-carboxylate, 100946-76-7; 3,6-dihydro-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]2-(diphenylphosphinyl)-2*H*-thiopyran, 100993-52-0; 6-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]ethyl]-3,5-dimethyl-2-(diphenylphosphinyl)-2*H*-thiopyran, 100946-77-8; 3,6-dihydro-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]2-(phenylsulfonyl)-2*H*-thiopyran, 100946-78-9; 3,6-dihydro-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2-(phenylsulfonyl)-2*H*-thiopyran, 100946-79-0; ethyl 3,6-dihydro-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2*H*-thiopyran-2-propenoate, 100946-80-3; 2-thiabicyclo[2.2.1]hept-5-ene, 6841-59-4; 3,6-dihydro-6-methyl-2*H*-thiopyran, 100946-81-4; 3,6-dihydro-3-methyl-2*H*-thiopyran, 100946-82-5; 3,6-dihydro-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2*H*-thiopyran, 100946-83-6; 3,6-dihydro-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2*H*-thiopyran, 100946-84-7; 3,6-dihydro-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2-(2-phenylethyl)-2*H*-thiopyran, 100946-85-8; 3,6-dihydro-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-6-methoxy-2-(2-phenylethyl)-2*H*-thiopyran, 100946-86-9; 3,4-dihydro-2-(2-phenylethyl-2*H*-thiopyran-4-one, 100946-87-0; *endo*-3-(2-phenylethyl)-2-thiabicyclo[2.2.1]-hept-5-ene, 100946-88-1; *exo*-3-(2-phenylethyl-2-thiabicylco-[2.2.1]hept-5-ene, 100946-89-2; 3,6-dihydro-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2-acetoxymethyl-2*H*-thiopyran, 100946-90-5; 3,6-dihydro-6-methoxy-2-(2-(phenylselenyl)ethyl)-4-[(trimethylsilyl)oxy]-2*H*-thiopyran, 100946-91-6; 3,4-dihydro-2-(2-(phenylselenyl)ethyl)-2*H*-thiopyran-4-one, 100946-92-7; 2-(2-chloroethyl)-3,6-dihydro-6-ethenyl-2*H*-thiopyran, 100946-93-8; 3,6-dihydro-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2-phenyl-2*H*-thiopyran, 100946-94-9; 3,6-dihydro-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2-phenyl-2*H*-thiopyran, 100946-95-0; 3,6-dihydro-6-methoxy-2-phenyl-4-[(trimethylsilyl)oxy]2*H*-thiopyran, 100946-96-1; 3,4-dihydro-2-phenyl-2*H*-thiopyran-4-one, 78965-33-0; *endo*-3-phenyl-2-thiabicyclo[2.2.1]hept-5-ene, 95416-99-2; *exo*-3-phenyl-2-thiabicyclo[2.2.1]hept-5-ene, 95417-00-8; *endo*-3-(trimethylsilyl)-2-thiabicyclo[2.2.1]hept-5-ene, 100946-97-2; *exo*-3-(trimethylsilyl)-2-thiabicylco[2.2.1]hept-5-ene, 100946-98-3; 3,6-dihydro-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2-(trimethylsilyl)-2*H*-thiopyran, 100946-99-4; 3,6-dihydro-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-2-(trimethylsilyl)-2*H*-thiopyran, 100947-00-0; 3,6-dihydro-6-methoxy-4-methyl-2-(2-phenylethyl)-6-[(trimethylisilyl)oxy]-2*H*-thiopyran, 100947-01-1; 4-methyl-6-(2-phenylethyl)tetrahydro-2*H*-thiopyran-2-one, 100947-02-2; phenacyl mercaptan, 2462-02-4; mercaptoacetonitrile, 54524-31-1; isopropyl mercaptoacetate, 7383-61-1; methyl mercaptoacetate, 2365-48-2; 3-phenylpropanethiol, 24734-68-7; 2-acetoxyethanethiol, 5862-40-8; benzenemethanethiol, 100-53-8; 2-chloro-1-phenylethanone, 532-27-4; thiolacetic acid, 507-09-5; (chloromethyl)trimethylsilane, 2344-80-1; chloroacetone, 78-95-5; 1,3,5-hexatriene, 2235-12-3.