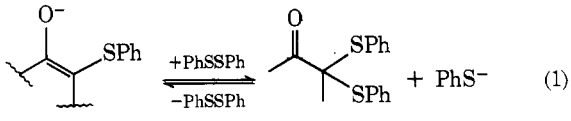
Secosulfenylation of Cyclobutanones

Summary: Treatment of cyclobutanones with sodium methoxide and diphenyl disulfide in refluxing methanol leads to in situ bissulfenylation and ring cleavage.

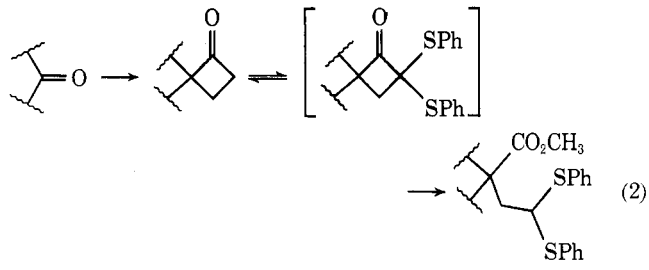
Sir: The increasing number of methods that make cyclobutanones readily available from olefins[1] and carbonyl[2,3] partners enhances the utility of these compounds as synthetic intermediates in the creation of carbon skeletons.[4] Our interest in the replacement of the C–O bonds of a carbonyl group with C–C bonds via cyclobutanone annelation depends critically on the facility of the ring cleavage. While a number of methods exist to achieve a geminal alkylation, all of these are multistep.[5] We wish to report a new single-step chemospecific process that has the added advantage of introducing the acetaldehyde unit masked as a thioacetal.

The procedure evolved from our study of the sulfenylation of ketones[6] in which we found that the enolate of a β-keto sulfide is sulfenylated by diphenyl disulfide but that the byproduct, phenylthiolate, reverses the reaction and the equilibrium represented by eq 1, lies to the left. If, however, the



(1)

product is irreversibly removed, the reaction can be driven to the right. The use of diphenyl disulfide rather than a more reactive sulfenylating agent is necessary to avoid decomposition of the sulfenylating agent under the reaction conditions and to maintain the equilibrium represented by eq 1. Since we had shown that an α,α-bissulfenylated cyclobutanone is readily cleaved by methoxide ion[5b,7] we suspected that we could drive the above equilibrium to the right by ring cleavage in such cases. Equation 2 summarizes the overall sequence and Table I summarizes the specific examples.

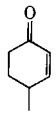
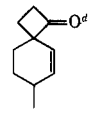
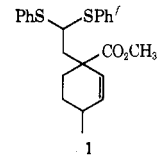
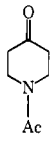
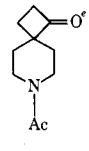
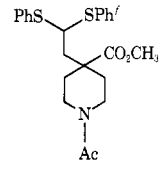
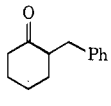
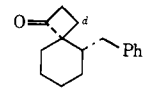
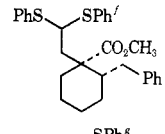
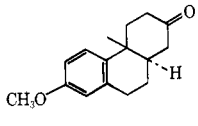
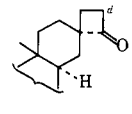
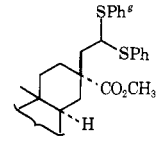


(2)

Typically, the reaction is performed by treating 1 equiv of cyclobutanone with ~3–4 equiv of diphenyl disulfide in methanol containing 3–4 equiv of sodium methoxide at reflux.[8] While the reactions are normally slow (~5 days for completion) at the concentrations utilized (0.1 M in cyclobutanone), they are free of side reactions and generate the product in high purity. The products are characterized by ir bands at ~1730, 1260, 1230, and 1020 cm^{-1} for the ester and NMR absorptions at δ ~3.6 (s) for CO_2CH_3 and 4.2 (t, $J \sim 6$ Hz) for $-CH(SPh)_2$. In the case of compound **1**, it was further characterized by transacetalization (iodine, methanol, reflux) to the methyl acetal which had been previously prepared by an independent route.

The chemospecificity of this net oxidative cleavage is underscored by entries 1, 2, and 4. Particularly noteworthy is the inapplicability of the bromination–ring cleavage approach in the case of entries 1 and 4. The advantage of this approach stems from the versatility that phenyl thioacetals have in synthesis which includes their alkylation,[9] elimination to enol thioethers,[10] and desulfurization. The further advantages of this approach are highlighted by entries 3 and 4 which point out the stereocontrol of this geminal alkylation. Since the spiroannelation is virtually completely stereoselective, so is the overall process.[2] Thus, the combination of spiroannelation and secosulfenylation constitutes a highly efficient two-stage approach to geminal alkylation. The requirement for relatively high ring strain for success for this procedure is illustrated by

Table I. Geminal Alkylation via Secosulfenylation

Entry	Ketone	Spiroannelation method[a]	Cyclobutanone	Product[b]	% yield[c]
1		A			80
2		B			61
3		B			74
4		B			70

[a] Method A utilizes 1-lithiocyclopropyl phenyl sulfide.[2a,b] Method B utilizes diphenylsulfonium cyclopropylide.[2c] [b] All new compounds have been characterized spectrally and by elemental compositions. [c] All yields are for isolated pure compounds and have not been optimized. [d] J. Rigby, unpublished results. [e] See ref 5a. [f] Reaction time 5 days. [g] Reaction time 10 days.

the failure to isolate a ring cleavage product from norbornanone under similar conditions.[11]

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References and Notes

(1) (a) M. Braun, R. Dammann, and D. Seebach, *Chem. Ber.*, **108**, 2368 (1975); (b) A. Sidani, J. Marchand-Brynaert, and L. Ghosez, *Angew. Chem., Int. Ed. Engl.*, **13**, 267 (1974); (c) W. T. Brady and G. A. Scherubel, *J. Am. Chem. Soc.*, **95**, 7447 (1973); (d) L. Ghosez, R. Montaigne, A. Roussel, H. Vanlierde, and P. Mollet, *Tetrahedron*, **27**, 615 (1971); (e) M. Rey, S. Roberts, A. Dieffenbacher, and A. S. Dreiding, *Helv. Chim. Acta*, **53**, 417 (1970).
(2) (a) B. M. Trost, D. E. Keeley, and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **95**, 3068 (1973); (b) B. M. Trost and D. E. Keeley, *ibid.*, **96**, 1252 (1974); (c) B. M. Trost and M. J. Bogdanowicz, *ibid.*, **95**, 5321 (1973).
(3) (a) J. E. Baldwin, G. A. Höfle, and D. W. Lever, Jr., *J. Am. Chem. Soc.*, **96**, 7125 (1974); (b) J. R. Wiseman and H. F. Chan, *ibid.*, **92**, 4749 (1970); (c) J. K. Crandall and D. R. Paulson, *J. Org. Chem.*, **33**, 991, 3291 (1968).
(4) For reviews see B. M. Trost, *Acc. Chem. Res.*, **7**, 85 (1974); B. M. Trost, *Fortschr. Chem. Forsch.*, **41**, 1 (1973); D. Seebach in "Methodender Organischen Chemie (Houben-Weyl-Müller)", Band 1v/4, Georg Thieme, Stuttgart, 1971.
(5) (a) B. M. Trost, M. J. Bogdanowicz and J. Kern, *J. Am. Chem. Soc.*, **97**, 2218 (1975); (b) B. M. Trost, M. Preckel, and L. M. Leichter, *ibid.*, **97**, 2224 (1975).
(6) B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.*, **95**, 6840 (1973); B. M. Trost, T. N. Salzmann, and K. Hiroi, *ibid.*, in press.
(7) Also see E. Cossement, R. Biname, and L. Ghosez, *Tetrahedron Lett.*, 997 (1974).
(8) To a solution of 10.0 g (66.7 mmol) of 7-methylspiro[3.5]non-5-en-1-one in 500 ml of methanol was added 40 g (183 mmol) of diphenyl disulfide and 10 g (183 mmol) of sodium methoxide. Reflux continued until TLC analysis utilizing benzene as eluting solvent indicated the absence of starting material (R_f ~0.6) and the presence of product (R_f ~0.7). The time was normally about 5 days. The reaction was cooled and washed with three portions of aqueous sodium chloride solution. The ether layer was dried and evaporated in vacuo to give the crude product. Chromatography on silica gel eluting with benzene purified the ring cleaved product. In one run, beginning with 150 mg (1.0 mmol) of this cyclobutanone, 870 mg (4.0 mmol) of diphenyl disulfide, and 160 mg (3.0 mmol) of sodium methoxide in 10 ml of methanol gave 320 mg (80%) of pure 3-carbomethoxy-3-[2',2'-bis(phenylthioethyl)]-6-methylcyclohex-1-ene. In the large-scale reaction, the crude thioacetal was dissolved in 400 ml of methanol containing 20 g of iodine and refluxed for 1.5 h. The solution was diluted with ether and washed with two portions of saturated aqueous sodium thiosulfate solution, two portions of saturated aqueous sodium bicarbonate solution, and one portion of saturated aqueous sodium chloride solution. After drying and evaporation in vacuo, the oil was distilled at 110–112 °C (0.3 mm) to give 10 g (62%) of pure 3-carbomethoxy-3-[2',2'-bis(methoxyethyl)]-6-methylcyclohex-1-ene.
(9) T. Cohen, D. Kuhn, and J. R. Falck, *J. Am. Chem. Soc.*, **97**, 4749 (1975); S. Yamamoto, M. Shiono, and T. Mukaiyama, *Chem. Lett.*, 961 (1973); T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Am. Chem. Soc.*, **94**, 8641 (1972); E. J. Corey and D. Seebach, *J. Org. Chem.*, **31**, 4097 (1966).
(10) T. Cohen, G. Herman, J. R. Falck, and A. J. Mura, Jr., *J. Org. Chem.*, **40**, 812 (1975).
(11) For cleavage of α-bissulfenylated cycloalkanones of ring sizes larger than four, see J. A. Marshall and D. E. Seitz, *J. Org. Chem.*, **40**, 534 (1975).

Barry M. Trost,* James H. Rigby
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706
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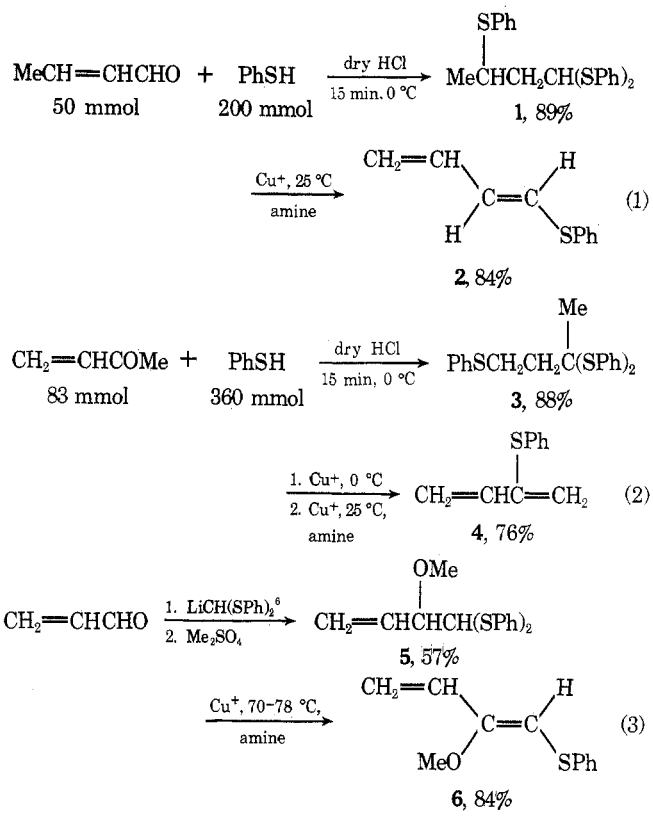
Removal of Sulfur Groups from Molecules by Copper(I). Preparation of Sulfur-Substituted 1,3-Dienes for the Diels–Alder Reaction[1]

Summary: The elimination of thiophenol by copper(I) from readily prepared precursors leads in good yield to several useful phenylthio-subtituted Diels–Alder dienes including (*Z*)-1-phenylthio-2-methoxy-1,3-butadiene which yields a *m*-methoxy adduct with methyl vinyl ketone.

Sir: We wish to report a simple procedure for the preparation of 1,3-dienes which are substituted by phenylthio groups. Because of the great versatility of sulfur in organic compounds, the Diels–Alder adducts of these dienes should be of considerable value in synthesis.

Our procedure consists of the copper(I)-induced removal[2] of one or two thiophenol molecules from readily available diene precursors; eq 1–3 are given as examples.[3,4]



A typical procedure for performing the elimination step follows. A solution of 2.87 mmol of 1,1,3-tris(phenylthio)butane (**1**) in 2 ml of tetrahydrofuran was added at 0 °C to a solution of 15.5 mmol of the benzene complex of cuprous trifluoromethanesulfonate [Cu_2-$C_6H_6(CF_3SO_3)_2$][7] and 17.6 mmol of diisopropylethylamine dissolved in 120 ml of benzene and the solution was allowed to stir at 25 °C for 14 h. The mixture was passed rapidly through a short silica column, and the light yellow oil which was eluted with ether was submitted to molecular distillation (45–50 °C/0.02 mmHg) in the presence of a small quantity of hydroquinone to give 84% diene as a colorless oil. More concentrated solutions resulted in some polymerization and reduced yields.

As indicated previously,[2] the temperature required for the elimination depends upon the stability of the carbonium ion left after the removal of a thiophenoxide ion. In the case of **1**, the reaction cannot be stopped after the loss of one thiophenol molecule. In the case of **3**, however, the product of loss of one thiophenol molecule, 1,3-bis(phenylthio)-2-butene,[5,8] must be warmed to 25 °C in the presence of cuprous ion in order to convert it to the diene **4**.

The dienes **2** and **6** are stereochemically homogeneous[9] and are assumed to be *E* and *Z*, respectively, on the basis of their ready reactions with dienophiles. Dienes **2**, **4**, and **6** gave well-characterized Diels–Alder adducts (eq 4–6)[12] in the