

PREPARATION AND SYNTHETIC UTILITY OF CYCLOPROPYL PHENYL SULFIDES

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Abstract. Primary alkyl halides and epoxides react with 1-lithiocyclopropyl phenyl sulfide to give derivatives suitable for transformation to carbonyl compounds or for desulfurization.

There is much current interest in developing methodology which utilizes cyclopropanes for polarity inversion operations.¹ In particular, the adducts of 1-lithiocyclopropyl phenyl sulfide and carbonyl compounds^{2a} have been employed in a variety of synthetic routes which lead to cyclobutanones,^{2b} cyclobutenyl sulfides,^{2b} γ -ketosulfides,^{2c} and β -bromoethyl vinyl sulfides^{2d} via Wagner-Meerwein rearrangements. We now report that 1-lithiocyclopropyl phenyl sulfide, 1, reacts smoothly with alkylating agents and that the derivatives thus formed give carbonyl compounds after electrophilic cleavage of the cyclopropane ring and hydrolysis.

As shown in Table I, treatment of 1 with primary alkyl iodides or bromides generally gives the substitution product, 2, in high yields.³ With benzyl bromide, however, halogen-metal exchange occurs leading to bibenzyl and 1-bromocyclopropyl phenyl sulfide. The basicity of the reagent presents a problem in systems prone to elimination such as phenethyl bromide where styrene is the predominant product.⁴ Further, we find that 1 adds to epoxides providing access

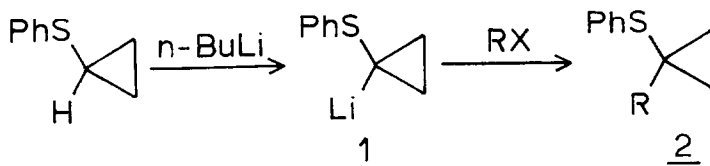
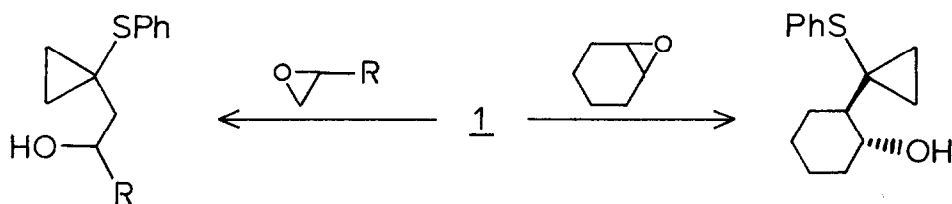


Table I. Alkylation of 1-Lithiocyclopropyl Phenyl Sulfide (1)

RX	YIELD of <u>2</u> %	b.p. of <u>2</u>
Ph(CH ₂) ₃ I	83	152-6 ⁰ (0.075 mm)
CH ₃ (CH ₂) ₃ Br	79	102-4 ⁰ (1.5 mm)
CH ₃ (CH ₂) ₇ Br	62	104-7 ⁰ (0.075 mm)

to 1-(β -hydroxy)cyclopropyl phenyl sulfides. Excellent regioselectivity of attack at the less hindered primary carbon of 1,2-epoxybutane is observed and even with cyclohexene oxide, a

high yield of adduct was obtained.^{3a}



R = H; 53%; b.p. 85-90° (0.02 mm)

R = Et; 86%; oil

64%, oil

Having established the general reactivity of 1-lithiocyclopropyl phenyl sulfide toward these alkylating agents we investigated methods by which these alkylated cyclopropyl phenyl sulfides could be transformed into carbonyl compounds.⁵ Several substituted cyclopropyl phenyl sulfides were heated with a mixture of 46% HBr/HOAc (1:1) for 3-8 hours. Work-up, followed by preparative TLC, afforded the ethyl ketones, 3, identical with authentic samples, as well as diphenyl disulfide.⁶ We also explored a milder Lewis acid-promoted ring opening with mercuric chloride.⁶ Interestingly, we observed conversion of the cyclopropyl phenyl sulfides into γ -ketosulfides, 4, compounds which can serve as precursors to enones and ethyl ketones.^{2c} The mechanistic course of this process is under investigation.

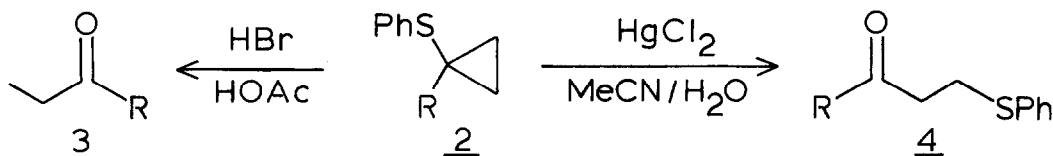
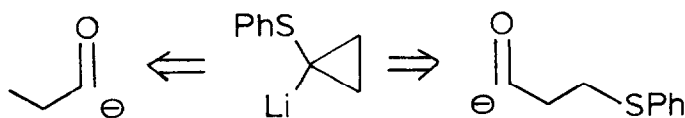


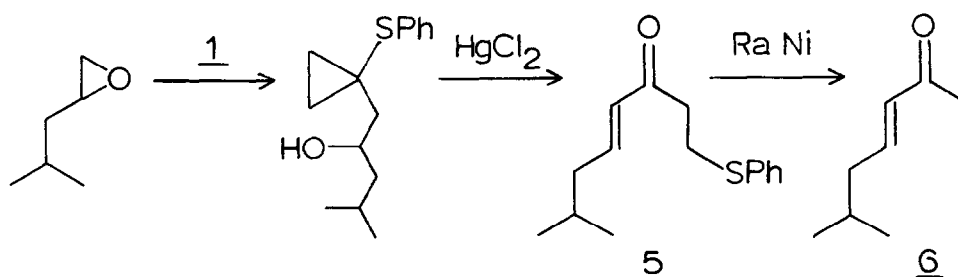
Table II. Transformations of cyclopropyl phenyl sulfides into carbonyl compounds

YIELD OF <u>3</u> %	R	YIELD OF <u>4</u> %
40	Ph(CH ₂) ₃	52
51	CH ₃ (CH ₂) ₃	77
59	CH ₃ (CH ₂) ₇	60

These transformations demonstrate the equivalency of 1-lithiocyclopropyl phenyl sulfide to either the β -phenylthiopropionyl carbanion or to the propionyl carbanion depending upon the conditions employed for unmasking.



Products obtained from the opening of epoxides by organometallic 1 also appeared to be candidates for conversion to carbonyl compounds. To test this application the fragrant (*E*)-7-methyl-4-octen-3-one (6), recently isolated as the major metabolite of the marine sponge, *Plakortis zygompha*, was chosen as a target.⁷ Addition of 1 to 4-methyl-1,2-epoxypentane⁸ occurred regioselectively in 87% yield. Cleavage, hydrolysis and dehydration with mercuric chloride in refluxing $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (3:1) afforded β -phenylthio enone 5 in 42% isolated yield. Reduction with Raney nickel in DMSO⁹ gave rise to 6 (13% yield) which exhibits spectral characteristics (250 MHz NMR, IR) identical to those reported for the natural material.⁷ No effort was made to optimize the yield since selective desulfurizations of this type are not a trivial matter.⁹ Presently, we are attempting to expand this methodology and utilize the fact that



compounds like 5 are equivalent to a cross-conjugated dienone where one double bond is "protected" and may be unmasked via oxidation-sulfoxide elimination. In addition cyclopropyl phenyl sulfides may be desulfurized in high yield (>80%) by Ra Ni in hot ethanol or acetone. Synthetically useful yields of alkyl cyclopropanes thus may be obtained by alkylation of 1-lithiocyclopropyl phenyl sulfide followed by desulfurization, a procedure which provides a route to substituted cyclopropanes which are not available by direct alkylation of cyclopropyl lithium.¹⁰

As a variety of cyclopropyl phenyl sulfides have been made available by 1,3-elimination reactions¹¹ and by the addition of sulfur stabilized carbenes to olefins¹² the carbonyl forming reactions and desulfurizations reported herein should enhance the synthetic utility of this class of compounds.

Typical Procedure: To a cold (-78°) solution of 1-lithiocyclopropyl phenyl sulfide (20.0 mMol), prepared by the method of Trost and coworkers^{2a}, in THF (75 ml) was added dropwise under argon a solution of *n*-butyl bromide (3.00 g, 22.0 mMol) in THF (5 ml). After 3 h the orange solution was allowed to warm to 20° and stirred overnight. The reaction was quenched with aqueous NH_4Cl (20%) and worked up in the usual manner. Careful fractional distillation afforded 1-butylcyclopropyl phenyl sulfide, (3.26 g, 79%) as a colorless oil (b.p. $102\text{--}104^\circ$, 1.5 mm). Refluxing the sulfide (0.31 g, 1.5 mMol) with a mixture of 48% HBr/HOAc (1:1) (6 ml) for 3 h gave, after work-up and chromatography on silica, 3-heptanone (0.087 g, 51%). Alternatively, treatment of the sulfide (0.206 g, 1.00 mMol) with HgCl_2 (0.314 g, 3.00 mMol) in refluxing $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (3:1; 8 ml) for 48 h afforded, after work-up and chromatography on silica, the γ -ketosulfide as an oil

(0.170 g, 77%). NMR (CDCl_3) δ 0.85 (t, 3H), 1.35 (m, 4H), 2.35 (t, J=8 Hz; 2H), 2.70 (t, J=7 Hz; 2H) 3.15 (t, J=8 Hz; 2H) 7.25 (m, 5H). IR, $\text{C}=\text{O}$, 1710 cm^{-1} . It is convenient to visualize the ketones by spraying analytical TLC plates with 2,4-DNPH reagent.

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