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AN ECONOMICAL AND CONVENIENT PREPARATION OF 2-(PHENYLTHIO)CYCLOBUTANONE, A SYNTHETIC EQUIVALENT OF CYCLOBUTANONE [1]

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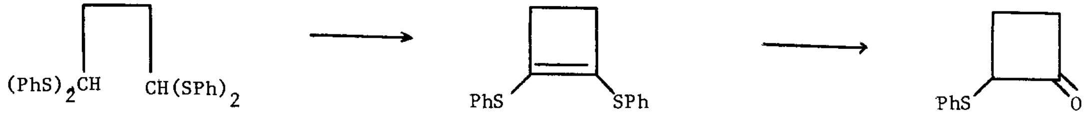
Abstract: A practical procedure is given for the preparation of 2-(phenylthio)cyclobutanone (3) and the use of the latter as a convenient substitute for cyclobutanone is demonstrated.

We recently reported a new ring-forming reaction resulting in the production of 1,2-bis-(phenylthio)cyclobutene (2) and a corresponding cyclopentene by an unconventional methyllithium-induced 1,4- and 1,5-elimination, respectively, of two thiophenol molecules from appropriate bis-dithioacetals.[2] For example, treatment of the bis-dithioacetal 1, available in quantitative yield from a rather inexpensive commercial reagent, gave 1,2-bis(phenylthio)cyclobutene (2) upon treatment with methyllithium in tetrahydrofuran (THF) in the presence of tetramethylethylenediamine (TMEDA). The product (2) can be chlorinated in the allylic position and it can be hydrolyzed to 2-(phenylthio)cyclobutanone (3). Further study of these reactions has resulted in substantial improvements in the yields of 2 and 3 and in a preparation of 3 which does not require purification of 2; as a result, this procedure represents one of the most economical and convenient syntheses of a simple, usefully functionalized[3] cyclobutanone.

Our investigation revealed that the requirement of an excess of alkyllithium in the ring closure step[2] was a result of the destruction of alkyllithium by deprotonation of 2 to a somewhat unstable anion. Treatment of 2 with sec-butyllithium and TMEDA (1 equivalent each) at -45° for one hour, conditions which approximate those now used for production of 2, followed by quenching with D_2O, yielded only 65% of 2; the recovered material was mainly monodeuterated although some undeuterated and dideuterated material was also present. When the reaction mixture was quenched with diphenyl disulfide the major product was 1,2,3-tris(phenylthio)cyclobutene.



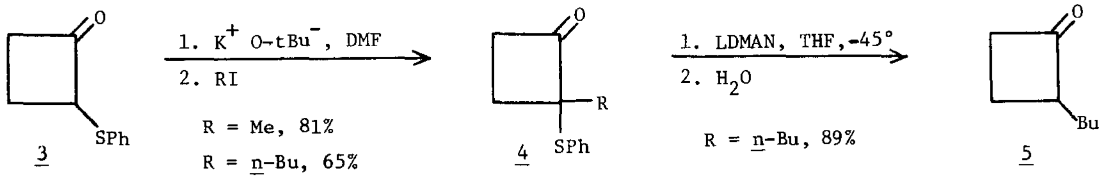
1 2 3

The improvement in the yield of 2 was achieved by replacing methyllithium with the stronger base sec-butyllithium; this allowed the use of lower reaction temperatures and shorter times which minimized destruction of the anion of 2. It was found that during the hydrolysis step, released thiophenol was apparently reacting with either 2 or 3 to produce 1,1,3-tris(phenylthio)-cyclobutane, which could be independently prepared in 93% yield by treatment of a solution of 2 in thiophenol with HCl; since thioketals are hydrolyzed by aqueous cupric chloride,[4] the latter was added to the aqueous titanium tetrachloride during the hydyrolysis step and the yield of 3 increased from 70 to 85%.

The procedure for the production of 3 follows. Quantitative production of reasonably pure 1 as a white solid, mp 89-91° (lit.[5] mp. 93-94°) after one recrystallization from ethanol, was achieved by passing HCl in to a solution of 2,5-dimethoxytetrahydrofuran in excess thiophenol for 7.5 h at 25°. *Sec*-butyllithium (3.05 mmol) in cyclohexane was added to a solution of 1.01 mmol of 1 and 3.1 mmol of TMEDA in 14 mL of THF at -78° under argon. After 10 min of stirring at that temperature, the mixture was warmed to 0° and stirred for 20 min. The usual work-up provided 350 mg of crude product which could be purified by preparative TLC (1% ether/hexanes, 5X) to give 192 mg (70%) of 2 as a pale yellow oil; ^{1}H NMR (CCl_4) δ 2.55 (s, 4H) 7.1 - 7.5 (m, 10H); ms 270.0530 ($C_{16}H_{14}S_2$ requires 270.0537). This material (1.31 mmol) was stirred for 15 min. in a solution containing 1.54 mmol of $CuCl_2 \cdot 2H_2O$, 4.1 mmol of $TiCl_4$, and 1.5 mL of water in 13 mL of acetic acid at 25° to produce crude ketone which was purified by silica chromatography to yield 85% of 3; ^{1}H NMR (CCl_4) δ 1.5 - 3.1 (m, 4H), 4.1 - 4.5 (m, 1H), 7.0 - 7.4 (m, 5H); IR 1780 cm^{-1}; ms 178.0446 ($C_{10}H_{10}OS$ requires 178.0452).

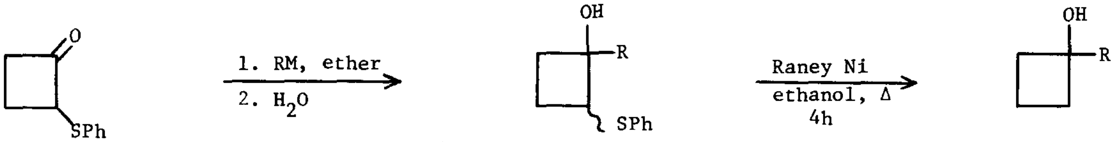
A 50 g sample of 1 could be similarly treated. Hydrolysis of *crude* 2 yielded crude 3 which could be partially purified on a wash column containing 250 g of silica (hexanes, then 5% ethyl acetate/hexanes). Distillation produced 49% of pure 3, bp 130° (0.5 mm).

Trost has used 3 to prepare 2-methoxy-3-(phenylthio)butadiene which is useful in Diels-Alder reactions; the procedure involves monobromination of cyclobutanone and displacement of bromide by thiophenoxide ion.[6] Since the removal of sulfur from organic compounds is a simple matter,[3] we envision 3 as an easily prepared and handled substitute for cyclobutanone, recent syntheses[7] of which require extensive extractions, because of its solubility in water, and/or double distillations, the final one of which must be done with great care through a packed column or more usually a spinning band column necessitated by its high volatility; 3 is neither volatile nor water soluble. Indeed, for one type of use, 3 is much superior to cyclobutanone which can not be satisfactorily monoalkylated.[8] The well known[9] increase in acidity of the thiophenyl-bearing carbon atom allows monoalkylation of 3; treatment of 3 with 1.05 equivalents of potassium *t*-butoxide in DMF at -40° followed by addition of 1.05 equivalents of methyl or *n*-butyl iodide and warming to 25° yielded the monoalkylated products 4 in satisfactory yield. Desulfurization of 4 (R=Bu) via reductive lithiation with lithium 1-dimethylaminonaphthalenide[10] (LDMAN) yielded the monosubstituted cyclobutanone.



Unfortunately, attempts to monoalkylate 4 at the α'-position using a similar procedure led to a mixture of monoalkylated and dialkylated products.

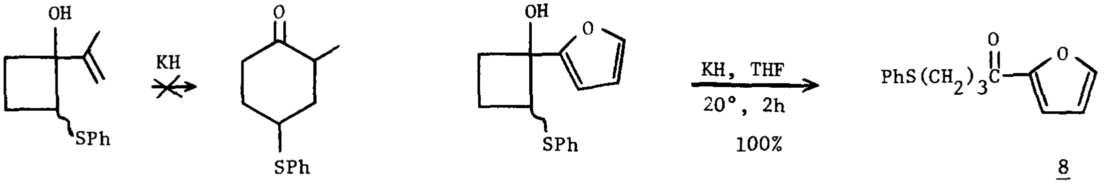
Addition of Grignard reagents or organolithium compounds in ether to the carbonyl group of 3 occurs in acceptable yield. Attempts to add organolithium compounds in THF failed due to extensive enolization.[11] The adduct (6; R = cyclohexyl) with cyclohexylmagnesium bromide was desulfurized with Raney nickel to produce 1-cyclohexylcyclobutanol (7; R = cyclohexyl) which we have also prepared by similar Grignard addition to cyclobutanone.[1]



3 6 7

RM = $\underline{c}$-$C_6H_{11}MgBr$, 56%
RM = $\underline{n}$-BuMgBr, 68%
RM = 2-lithiofuran,[12] 63%
RM = isopropenyllithium,[13] 73%
RM = CH_2 = CHMgBr, 82%

R = cyclohexyl, 87%



6; R = isopropenyl

6; R = 2-furyl

8

In an attempt to cause an alkoxide induced[14] vinylcyclobutane (1,3-sigmatropic[15]) rearrangement of 6 (R = isopropenyl), as shown, the latter was treated with potassium hydride; only tars were formed. The same treatment of alcohol 6 (R = 2-furyl) led to a quantitative ring opening to 8. Presumably, both potassium alkoxides open to yield a sulfur-stabilized anion which, by prototropic rearrangement, produces an enolate anion. Destruction of the enolate anion of the conjugated enone may occur during quenching which allows the nucleophilic anion to react with its very electrophilic protonation product. Trost has noted a far slower ring opening of a cyclobutanol bearing a pair of geminal sulfur atoms at the 2-position and induced by sodium methoxide.[16,17] The use of the potassium salt in a non-hydrogen bonding solvent and the presence of an unsaturated group on the carbinol carbon atom (a methyl group was present instead in Trost's case) must be responsible for the great rate acceleration in the present case despite the presence of only one sulfur atom to stabilize the first formed carbanion. The importance of this unsaturated group is demonstrated by the finding that 6 (R = $\underline{n}$-butyl) was stable to potassium hydride; the relative stabilities of the potassium salts of 6 (R = isopropenyl and 2-furyl) on the one hand and 6 (R = $\underline{n}$-butyl) on the other is parallelled by those of the adducts of a benzocyclobutanone with phenylmagnesium bromide (ring opening occurred) and benzylmagnesium bromide (simple addition was observed).[18]

Unlike cyclopentanone and cyclohexanone, cyclobutanone is rarely used as a reagent in synthesis probably because of the difficulties mentioned above. 2-(Phenylthio)cyclobutanone is now a readily available and conveniently handled surrogate for cyclobutanone and a reagent which for some purposes is far superior to cyclobutanone. Successful ring expansions of various addition products of 3 will be communicated in due course.[19]

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References and Notes

1. Taken in part from the M.S. thesis of Daniel Ouellette, University of Pittsburgh, 1980.
2. T. Cohen, D. Ouellette, and W. M. Daniewski, Tetrahedron Lett., 5063 (1978).
3. For discussions of the remarkable versatility of α-(phenylthio)ketones, see: D. Seebach and M. Teschner, Chem. Ber., 109, 1601 (1976); B. M. Trost, Chem. Rev., 78, 363 (1978); B. M. Trost, Acct. Chem. Res., 11, 453 (1978).
4. K. Narasaka, T. Sakashita, and T. Mukaiyama, Bull. Chem. Soc. Japn., 45, 3724 (1972).
5. A. J. Mura, Jr., Ph.D. thesis, University of Pittsburgh, 1976.
6. B. M. Trost, J. Ippen, and W. C. Vladuchick, J. Am. Chem. Soc., 99, 8116 (1977); B. M. Trost and A. J. Bridges, ibid., 98, 5017 (1976).
7. B. M. Trost and W. C. Vladuchick, Synthesis, 821 (1978); J. R. Salaun, J. Champion, and J. M. Conia, Org. Syn., 57, 36 (1977); M. Hanack, T. Dehesch, K. Hummel, and A. Nierth, ibid., 54, 84 (1974); D. Seebach and A. K. Beck, ibid., 51, 76 (1971); K. Ogura, M. Yamashita, M. Suzuki, and G. Tsuchihashi, Tetrahedron Lett., 3653 (1974); G. Stork, J. C. Depezay, and J. d'Angelo, ibid., 389 (1975).
8. J.-M. Conia and J.-P. Sandre, Bull. Soc. Chim. Fr., 752 (1963).
9. R. M. Coates, H. D. Pigott and J. Ollinger, Tetrahedron Lett., 3955 (1974).
10. T. Cohen and J. R. Matz, Synth. Commun., 311 (1980). Treatment of 4 with lithium in liquid ammonia[9] led to an amide via ring cleavage; Raney nickel caused not only desulfurization of 4 but also reduction to a cyclobutanol.
11. Similar behavior has recently been reported: H. J. Reich, J. J. Rusek, and R. E. Olson, J. Am. Chem. Soc. 101, 2225 (1979).
12. V. Ramanathan and R. Levine, J. Org. Chem., 27, 1216 (1962).
13. Prepared by treatment of 2-bromopropene with two equivalents of t-butyllithium; H. Neumann and D. Seebach, Tetrahedron Lett., 4839 (1976).
14. D. A. Evans and A. M. Golob, J. Am. Chem. Soc., 97, 4765 (1975).
15. S. R. Wilson and R. N. Misra, J. Org. Chem., 43, 4903 (1978).
16. B. M. Trost, M. Preckel, and L. M. Leichter, J. Am. Chem. Soc., 97, 2224 (1975).
17. (a) B. M. Trost, M. J. Bogdanowicz, W. J. Frazee, and T. N. Salzmann, J. Am. Chem. Soc., 100, 5512 (1978). (b) For extensive references to nucleophilically induced ring openings of cyclobutanones, see footnotes 1 and 2 of ref. 17a.
18. J. K. Landquist and A. Stanier, Tetrahedron Lett., 1611 (1975).
19. All products were characterized by ^{1}H NMR, IR, and mass spectroscopy. Elemental compositions were determined for new compounds by combustion analysis or exact mass determination

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