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A Convenient Laboratory Synthesis of Cyclobutanone

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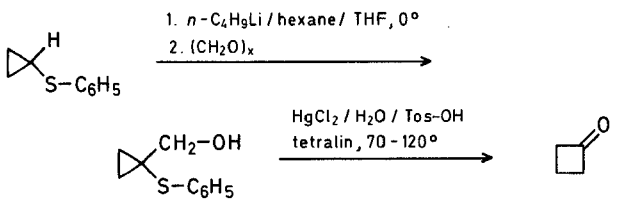
Cyclobutanone is a potentially very valuable basic building block. More extensive use of such a versatile compound is hampered by its relatively high cost and its low availability[1]. Renewed interest in the potential of this compound has led to several recently reported syntheses[2]. We wish to report a convenient laboratory-scale preparation of this compound that has made it readily available.

The method is based upon our general 2- and 2,2-disubstituted cyclobutanone synthesis[3]. Condensation of 1-lithio-1-phenylthiocyclopropane with paraformaldehyde leads to 1-hydroxymethyl-1-phenylthiocyclopropane in 80% yield. Heating this compound in the presence of an acid and a thiol trap ($HgCl_2$) in a high-boiling solvent allows direct distillation of cyclobutanone with some water.



Drying and redistillation gives a 70% yield of pure cyclobutanone in 56% overall yield. Since cyclopropyl phenyl sulfide is available in two steps in about 90% yield from commercially available compounds (thiophenol and 1-bromo-3-chloropropane), cyclobutanone is available in ~ 50% overall yield on relatively large scale.

1-Hydroxymethyl-1-phenylthiocyclopropane:
A 3-l, three-necked, round-bottomed flask, equipped with an internal thermometer, a nitrogen inlet, a mechanical stirrer, and a 1-l pressure-equalizing additional funnel, is charged with cyclopropyl phenyl sulfide (168 g, 1.12 mol) and anhydrous tetrahydrofuran (1200 ml). The solution is cooled to ~0° in an ice-bath. To the stirred solution is added over 1 h a 1.4 molar solution of butyllithium in hexane (930 ml, 1.3 mol). The resulting solution is stirred at 0° for 2 h and then allowed to warm to room temperature over 2 h. To the rapidly stirred solution, paraformaldehyde (39 g, 1.3 mol) is added slowly at room temperature via goose-neck tubing. As the addition occurs an exothermic reaction takes place which requires periodic application of an ice-bath to maintain the internal temperature below 30°. When the addition is complete (20–35 min), the solution is stirred for an additional hour. The reaction is quenched by the dropwise addition of saturated aqueous ammonium chloride. The phases are separated and the aqueous portion is back-extracted with ethyl acetate (2 × 350 ml). The combined organic portions are washed with saturated aqueous sodium chloride and dried with sodium sulfate. The solvents are removed on a rotary evaporator to yield 222.5 g of crude product. The residual oil is distilled through a 50-cm Vigreux column at reduced pressure; yield: 35 g (21% recovery) of cyclopropylphenyl sulfide, b.p. 58–60°/0.2 torr; 127 g (80% based on recovered starting material) of 1-hydroxymethyl-1-phenylthiocyclopropane, b.p. 98–102°/0.2 torr.

$C_{10}H_{12}OS$ (180.2)	calc.	C 66.65	H 6.71
	found	66.71	6.65

M.S.: *m/e* (relative intensity) = 180 (66), 162 (18), 161 (10), 150 (10), 149 (79), 147 (34), 135 (13), 134 (23), 129 (42), 117 (13), 116 (21), 115 (24), 111 (12), 110 (100), 109 (29), 107 (17), 105 (26), 91 (40), 78 (17), 77 (28), 73 (12), 71 (35), 69 (19), 66 (19), 65 (23), 53 (13), 51 (27); high resolution: 180.06074 (calc. 180.06089).

I.R. (CCl_4): ν_{max} = 3600–3250 (broad); 3060; 3000; 2915; 2860; 1590; 1490; 1400; 1045; 685 cm^{-1}.

^{1}H-N.M.R. (100 MHz, CCl_4): δ = 1.0 (s, 4H); 2.2 (bs, 1H); 3.5 (s, 2H); 7.1–7.6 ppm (m, 5H).

Cyclobutanone:
A 500-ml, three-necked, round-bottomed flask, equipped with a mechanical stirrer, a nitrogen inlet, and a variable take-off head (10-cm Vigreux), is charged with 1-hydroxymethyl-1-phenylthiocyclopropane (108 g, 0.6 mol), tetralin (150 ml), mercury(II) chloride (95 g, 0.35 mol), water (12.6 ml, 0.7 mol), and *p*-toluenesulfonic acid (11.4 g, 0.06 mol). The slurry is heated to 70° and maintained at this temperature for 90 min. The pot temperature is increased to 120° and the distillate collected for 90 min. The two-phase distillate is separated. The aqueous portion is saturated with sodium chloride and back-extracted with dichloromethane (2 × 20 ml). The combined organic portions are dried with sodium sulfate and then distilled at atmospheric pressure through a 15-cm column packed with glass helices; yield: 28.9 g (70%); b.p. 97–99° (Ref. [2], b.p. 98–99°).

We wish to thank the National Science Foundation for their generous support of our programs.

Received: June 20, 1978

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0039–7881/78/1132–0821 $ 03.00