



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record\\_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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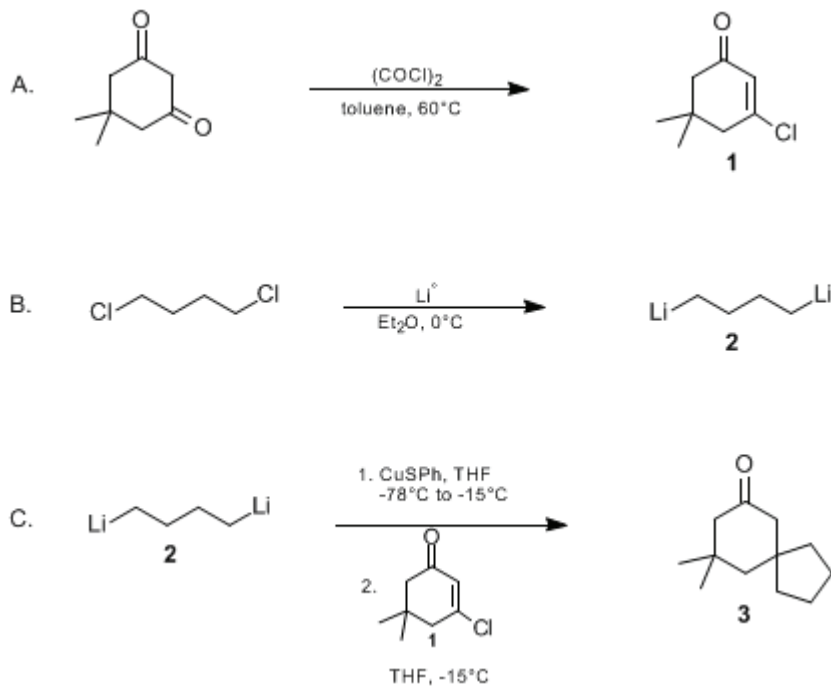
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 9, p.350 (1998); Vol. 70, p.204 (1992).*

## SPIROANNEULATION VIA ORGANOBIS(CUPRATES): 9,9-DIMETHYLSPIRO[4.5]DECAN-7-ONE

### [Spiro[4.5]decan-7-one, 9,9-dimethyl-]



Submitted by Paul A. Wender<sup>1,2</sup>, Alan W. White<sup>1</sup>, and Frank E. McDonald<sup>2</sup>.  
Checked by Naoki Hirayama and Hisashi Yamamoto.

### 1. Procedure

*Note: All reactions should be conducted in an efficient fume hood.*

A. *3-Chloro-5,5-dimethylcyclohex-2-en-1-one* (**1**)<sup>3,4</sup> (Note 1). An oven-dried, 250-mL, one-necked, round-bottomed flask is equipped with a magnetic stirring bar and graduated addition funnel topped with a nitrogen inlet. The flask is charged with **dimedone** (28.1 g, 200 mmol) and **toluene** (100 mL) (Note 2). The suspension is stirred while **oxalyl chloride** (35 mL, 400 mmol) is slowly added via the addition funnel over a 10-min period (Note 3). After the addition is complete and gas evolution has subsided, the addition funnel is quickly exchanged for a reflux condenser topped with a nitrogen inlet. The mixture is then heated at 60–70°C for 30 min, or until no more suspended **dimedone** remains and gas evolution has ceased. (Additional **oxalyl chloride** may be added until **dimedone** has completely reacted.) The reaction is allowed to cool and concentrated by rotary evaporation at reduced pressure. The crude red oil is distilled through a short path apparatus to give **3-chloro-5,5-dimethylcyclohex-2-en-1-one** (**1**) (29.3 g, 93% yield) as a colorless oil, bp 68–71°C (6.0 mm) (Note 4).

B. *1,4-Dithiolithobutane* (**2**)<sup>5,6,7</sup> (All transfers are conducted under dry **nitrogen**; reagents are introduced into reaction vessels through rubber septa using a cannula or syringe.) An oven-dried, 1-L, three-necked, round-bottomed flask is equipped with a large magnetic stirring bar and glass beads (ca. 3-mm diameter), graduated addition funnel, stopper, and large diameter **nitrogen** inlet (at least 2 mm in diameter). The flask is purged with **nitrogen**, charged with anhydrous **diethyl ether** (250 mL) (Note 2), and cooled to 0°C. The stopper is removed from the flask and replaced with a conical funnel while a rapid flow of dry **nitrogen** is passed through the flask. **Lithium** wire, 1% Na (9.48 g, 1.36 mol, 4.5 eq.)

(Note 5), prewashed with hexanes, is held with forceps over the funnel and cut with clean scissors into pieces no larger than 2 mm in length (Note 6) so that the freshly cut lithium pieces drop directly into the anhydrous ether. 1,4-Dichlorobutane (33.5 mL, 300 mmol) (Note 2) is then dissolved in anhydrous diethyl ether (85 mL) and introduced into the addition funnel; approximately 10% of this solution is introduced into the lithium/ether suspension, and the reaction is initiated by vigorous stirring. A white precipitate (LiCl) signaling initiation of the reaction should be apparent within 5 to 15 min, at which time the remainder of the solution is added dropwise over a 1 to 2-hr period (Note 7). The white suspension is rapidly stirred for 20 hr at 0°C.

The mixture is most conveniently filtered by gravity filtration through an oven-dried coarse (15 µm) sintered glass frit (Note 8), (Note 9). The concentration of 1,4-dilithiobutane (2) in ether is determined by titration with *sec*-butyl alcohol using 1,10-phenanthroline as indicator. The molarity of the solution obtained under these optimized conditions is approximately 1.7 M in "RLi", i.e., 0.9 M in 1,4-dilithiobutane (2) (Note 10). This solution is stable for several months when stored at -10°C under nitrogen.

C. *9,9-Dimethylspiro[4.5]decan-7-one* (3).<sup>6,7</sup> (All transfers are conducted under dry nitrogen; reagents are introduced into reaction vessels through rubber septa using a cannula or syringe.) An oven-dried, 2-L, three-necked, round-bottomed flask is equipped with a graduated addition funnel, overhead mechanical stirrer, and a nitrogen inlet. The flask is purged with nitrogen and charged with copper(I) thiophenoxide (36.7 g, 212 mmol) and anhydrous tetrahydrofuran (400 mL) (Note 2), and the heterogeneous suspension is mechanically stirred while cooling in a -78°C cold bath (dry ice-acetone). 1,4-Dilithiobutane (2), 0.87 (± 0.02) M in diethyl ether (122 mL, 106 mmol) is added via the addition funnel over 5 min, and then the reaction mixture is allowed to slowly warm to -15°C (Note 11) over a 20 to 45-min period, during which time the initial yellow color changes to brown-red with concomitant dissolution of copper thiophenoxide. The addition funnel is washed with a few milliliters of anhydrous tetrahydrofuran, and a solution of 3-chloro-5,5-dimethylcyclohex-2-en-1-one (1) (15.85 g, 100 mmol) in anhydrous tetrahydrofuran (250 mL) is added dropwise over a 1 to 2-hr period, while the temperature of the cold bath is maintained at -15°C to -20°C. The reaction turns olive-green and then black as the chloroenone is added. After the addition is complete, the cold bath is removed and the reaction flask is allowed to warm to room temperature.

After 30 to 45 min, the reaction mixture is opened to the air and poured into approximately 500 mL of saturated aqueous ammonium chloride solution, diluted with approximately 500 mL of diethyl ether washings, and allowed to stir for 10 to 15 min. The resulting mixture is filtered through a Büchner funnel, washing with small portions of diethyl ether (Note 12). The layers are separated in a separatory funnel, the aqueous layer is extracted with diethyl ether, and the combined organic layers are washed with water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried over approximately 100 g of sodium sulfate, filtered through a Büchner funnel, and concentrated by rotary evaporation. The concentrated product may still contain solid diphenyl disulfide that can now be efficiently removed by chromatography of the neat crude product mixture through a 5-cm diameter × 10-cm height silica gel column and elution with hexane-diethyl ether (7:1) (Note 13). Evaporation of solvent by rotary evaporation at reduced pressure gives 13.28 g (74% yield) of *9,9-dimethylspiro[4.5]decan-7-one* (3) as a pale yellow to colorless oil (Note 14).

## 2. Notes

1. This procedure is identical to that originally published by Heathcock and Clark,<sup>3,4</sup> except that toluene has been substituted for benzene and chloroform as the solvent, because of the relative health hazards associated with the latter two solvents.

2. Dimedone, oxalyl chloride, 1,4-dichlorobutane, and copper thiophenoxide were purchased from Fluka Chemical Corporation, and were used without further purification. The checkers purchased dimedone, oxalyl chloride and 1,4-dichlorobutane from Nacalai Tesque, Inc., Kyoto, Japan and Tokyo Kasei Kogyo Co., LTD, Japan, and prepared copper thiophenoxide from thiophenol and copper(I) oxide. Toluene, diethyl ether and tetrahydrofuran were distilled from sodium-benzophenone ketyl immediately prior to use.

3. The addition of oxalyl chloride was accompanied by much gas evolution, but no apparent exothermic

reaction. Two equivalents of oxalyl chloride were required in order to consume completely the dimedone.<sup>3,4</sup>

4. The spectral properties of **1** were as follows: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 1.10 (s, 6 H), 2.26 (s, 2 H), 2.57 (d, 2 H, J = 1.4), 6.23 (t, 1 H, J = 1.4); IR (film) cm<sup>-1</sup>: 2980 (m), 1680 (s), 1616 (m), 1346 (m), 1300 (m), 1276 (m), 1008 (m). The submitters obtained 30.1 g (95% yield) of **1**, bp 79–80°C (7.5 mm).

5. Lithium wire was obtained from Aldrich Chemical Company, Inc. The use of 4.5 equiv of lithium represented a 12.5% excess. The use of only 4 equiv of lithium gave a lower titer of 1,4-dilithiobutane (**2**), and a small amount of unreacted lithium always remained even after prolonged reaction times.

6. The lithium wire must be freshly cut and in pieces not exceeding 2 mm in length. The yield dropped sharply when the average length of lithium wire was increased to 5 mm. The preparation of 1,4-dilithiobutane (**2**) from 1,4-dichlorobutane failed with the use of lithium shot<sup>5</sup> or low-sodium (<0.8% Na) lithium wire.

7. We have not yet observed an exothermic reaction in the initiation of this reaction, although maintaining the temperature at 0°C might help to control safely the lithiation reaction as well as to maximize the yield of 1,4-dilithiobutane (**2**).

8. Gravity filtration was preferred over vacuum filtration, since the latter method tended to pull LiCl through the frit. Small amounts of LiCl did not interfere with the formation or reaction of the biscuprate generated in Section C. The checkers used this solution without filtration.

9. In order to quench the small amount of unreacted lithium wire remaining in the reaction flask, the stopper was replaced by a reflux condenser open to the atmosphere at the top. Approximately 100 mL of diethyl ether was added to the reaction flask containing the lithium and the flask was cooled to 0°C under a stream of nitrogen. A 4:1 mixture of t-butyl alcohol : water was then added dropwise via the addition funnel until all of the lithium wire was consumed. *Caution: The quench is exothermic and is accompanied by the evolution of large amounts of hydrogen gas.* The mixture was then transferred to a separatory funnel for separation of the organic and aqueous layers followed by disposal.

10. Significant amounts of ether solvent are lost presumably by evaporation during the nitrogen flush and/or filtration steps. Thus, the molarity of the 1,4-dilithiobutane (**2**) solution is not an accurate indication of yield. The submitters titrated with menthol instead of with sec-butyl alcohol

11. Temperature control of the cold bath at –15°C was accomplished by addition of small amounts of dry ice to acetone and monitoring with a low-temperature thermometer. A slurry of dry ice in ethylene glycol was occasionally used as a –15°C cold bath.

12. The omnipresent solid contaminant was diphenyl disulfide, which was sparingly soluble in diethyl ether. Each filtration noted in the text was necessary for a successful workup on this large scale. The submitters used a medium (90 μm) sintered glass frit for these filtrations. The attempted removal of product **3** by distillation from diphenyl disulfide was largely unsuccessful because of efficient entrainment of **3** in diphenyl disulfide.

13. Pure **3** is best obtained by chromatography. Product **3** could also be purified by vacuum distillation through a 10-cm Vigreux column, bp 100–103°C (2.2 mm). However, distillation did not efficiently separate **3** from diphenyl disulfide, and bumping was often a serious problem.

14. The spectral properties of **3** were as follows: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 1.02 (s, 6 H), 1.42–1.68 (m, 8 H), 1.70 (s, 2 H), 2.18 (s, 2 H); IR (film) cm<sup>-1</sup>: 2950 (s), 1710 (s), 1450 (m), 1370 (m), 1280 (m), 1230 (m). The submitters obtained 13.01 g (72% yield) of **3**.

### Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

### 3. Discussion

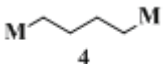
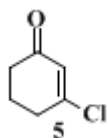
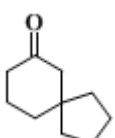
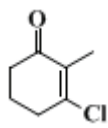
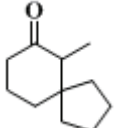
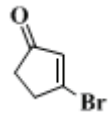
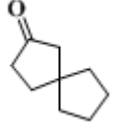
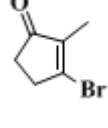
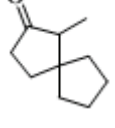
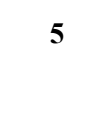
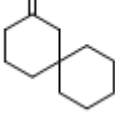

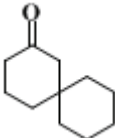
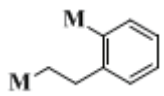
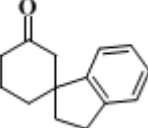
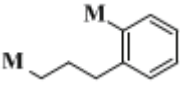
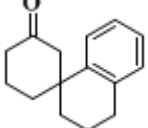
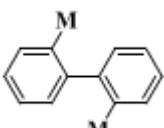
The procedure in Section C is representative of the synthesis of spirobicyclic systems featuring the reaction of bis(nucleophile) reagents with geminal bis(electrophile) acceptors. This strategy provides for formation of both carbon-carbon bonds of the new ring in a single step.

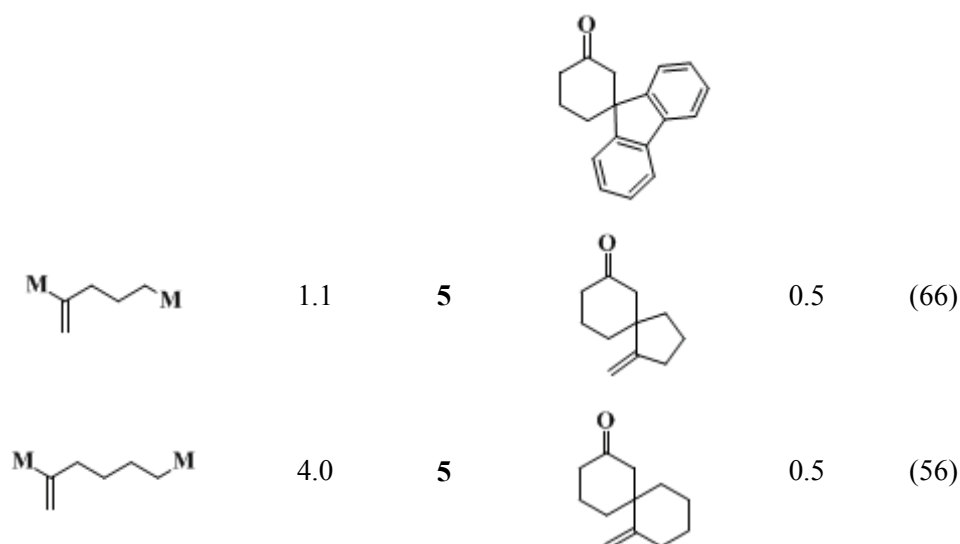
The starting material 3-chloro-5,5-dimethylcyclohex-2-en-1-one (**1**) is easily synthesized from dimedone by the general methodology developed by Clark and Heathcock.<sup>3,4</sup> The β-chlorine can also be replaced with a variety of carbon- and heteronucleophiles,<sup>8</sup> and β-chloroenones can be easily reduced by

zinc/silver couple to the corresponding enone.<sup>4</sup>

The formation of 1,4-dilithiobutane (2) was first described by West and Rochow.<sup>9</sup> The original procedure was modified by Whitesides, et al., in their pioneering studies on the synthesis and reactivity of metallocyclopentanes.<sup>5,10</sup> The methodology described in Section B is general for the synthesis of a variety of 1,4- and 1,5-dilithioalkanes, as evident in the Table below.<sup>6,7</sup>

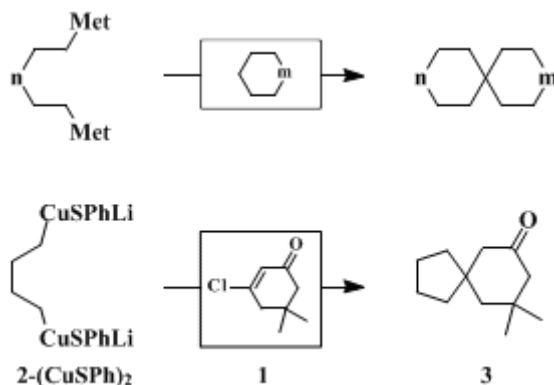
TABLE I  
SPIROANNELATION USING ORGANOBIS(CUPRATES)

Reagent M = CuSPh	Equiv.	Substrate	Product	Time hr	Yield %
	1.1	<b>1</b>	<b>3</b>	1	(96)
<b>4</b>	1.1			1	(85)
<b>4</b>	1.1			1	(80)
<b>4</b>	1.1			18	(93)
<b>4</b>	1.1			1	(87)
<b>4</b>	1.1			1	(76)
	4.0	<b>5</b>		1	(74)
	1.2	<b>5</b>		1	(49)
	3.0	<b>5</b>		2	88
	3.0	<b>5</b>		2	39
	10.0	<b>5</b>		2	94



Yields in parantheses were determined by internal standard gas chromatographic analysis.

The synthesis of 9,9-dimethylspiro[4.5]decan-7-one (**3**) uses the organobis(cuprate) derived from 1,4-dilithiobutane (**2**) as a bis(nucleophile) component, which is added to the bis(electrophile) 3-chloro-5,5-dimethylcyclohex-2-en-1-one (**1**).



This methodology provides for spiroannulation at a carbon beta to the ketone, and is a complementary protocol for the cyclization of  $\alpha,\omega$ -dihaloalkanes to the kinetic enolates of 1,3-cycloalkanedione enol ethers (at the alpha position).<sup>11</sup>

The methodology has been successfully extended with modifications to both the bis(nucleophile) and the bis(electrophile) components, as shown in the Table.<sup>6,7</sup>

## References and Notes

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8. For example, see (a) Sato, N.; Ishiyama, T.; Miyaura, N.; Suzuki, A. *Bull. Soc. Chem. Jpn.* **1987**, 60, 3471; Kienzle, F.; Minder, R. E. *Helv. Chim. Acta* **1987**, 70, 1537.

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**Appendix**  
**Chemical Abstracts Nomenclature (Collective Index Number);**  
**(Registry Number)**

sodium-benzophenone ketyl

chloroeneone

$\beta$ -chlorine

$\beta$ -chloroeneones

organobis(cuprate)

Benzene (71-43-2)

ether,  
diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

copper(I) oxide

toluene (108-88-3)

zinc (7440-66-6)

sodium (13966-32-0)

ethylene glycol (107-21-1)

menthol (15356-60-2)

Thiophenol (108-98-5)

silver (7440-22-4)

lithium (7439-93-2)

dimedone (126-81-8)

Tetrahydrofuran (109-99-9)

1,4-dichlorobutane (110-56-5)

oxalyl chloride (79-37-8)

hexane (110-54-3)

t-butyl alcohol (75-65-0)

diphenyl disulfide (882-33-7)

sec-butyl alcohol (78-92-2)

1,10-phenanthroline (66-71-7)

copper(I) thiophenoxide (34012-88-9)

9,9-Dimethylspiro[4.5]decan-7-one,  
Spiro[4.5]decan-7-one, 9,9-dimethyl- (63858-64-0)

3-Chloro-5,5-dimethylcyclohex-2-en-1-one (17530-69-7)

1,4-Dilithiobutane

copper thiophenoxide