



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

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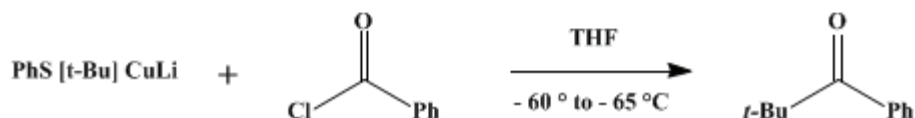
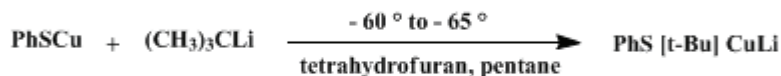
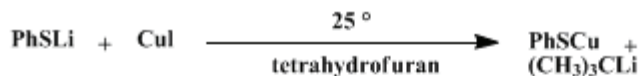
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 6, p.248 (1988); Vol. 55, p.122 (1976).*

## SECONDARY AND TERTIARY ALKYL KETONES FROM CARBOXYLIC ACID CHLORIDES AND LITHIUM PHENYLTHIO(ALKYL)CUPRATE REAGENTS: *tert*-BUTYL PHENYL KETONE

### [1-Propanone, 2,2-dimethyl-1-phenyl]



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Checked by Joyce M. Wilkins and Herbert O. House.

### 1. Procedure

*Caution! tert-Butyllithium is extremely pyrophoric and must not be allowed to come into contact with the atmosphere. This reagent should only be handled by individuals trained in its proper and safe use. It is recommended that transfers be carried out by using a 20-mL or smaller glass syringe filled to no more than 2/3 capacity, or by cannula. For a discussion of procedures for handling air-sensitive reagents, see Aldrich Technical Bulletin AL-134. [Note added August 2009].*

*Caution! Since the odor of the thiophenol (benzenethiol) used in this preparation is unpleasant, both steps of this preparation should be conducted in a hood and the glassware used should be washed before it is removed from the hood.*

A. *Lithium phenylthio(tert-butyl)cuprate.* A dry, 200-ml., round-bottomed flask is fitted with a magnetic stirring bar and a 100-ml., pressure-equalizing dropping funnel, the top of which is connected to a nitrogen inlet. After the apparatus has been flushed with nitrogen, 50 ml. of 1.60 M (0.080 mole) *n*-butyllithium (Note 1) solution is placed in the flask and cooled with an ice bath. Under a nitrogen atmosphere, a solution of 8.81 g. (0.0801 mole) of freshly distilled thiophenol (Note 2) in 30 ml. of anhydrous tetrahydrofuran (Note 3) is added dropwise to the cooled, stirred solution. An aliquot of the resulting solution (Note 4) is standardized by quenching in water, followed by titration with 0.10 N hydrochloric acid to a green end point with a bromocresol indicator. The concentration of lithium thiophenoxide prepared in this manner is typically 1.0 M.

A dry, 250-ml., three-necked round-bottomed flask is equipped with a sealed mechanical stirrer (Note 5), a glass stopper, and a rubber septum through which are inserted hypodermic needles used to evacuate the flask and to admit nitrogen. After the apparatus has been flushed with nitrogen, 4.19 g. (0.0220 mole) of purified copper(I) iodide (Note 6) is added, and while warming with a flame, the apparatus is evacuated, then refilled with nitrogen. After this procedure has been performed twice, the flask is allowed to cool, the stopper is replaced with a thermometer, and 45 ml. of anhydrous tetrahydrofuran is added (Note 3) with a hypodermic syringe. With continuous stirring, 22 ml. of 1.0 M (0.022 mole) lithium thiophenoxide solution is added with a syringe to the slurry of copper(I) iodide. After 5 minutes, the resulting yellow solution is cooled, with continuous stirring, to  $-65^\circ$  with an acetone-dry ice cooling bath. Some copper(I) thiophenoxide usually separates from solution at ca.  $-45^\circ$ . When the temperature of the mixture has reached ca.  $-65^\circ$ , 13.6 ml. (0.0218 mole) of 1.60 M *tert*-butyllithium (Note 7) solution is added with a syringe to the stirred mixture at such a rate

that the temperature of the mixture remains at  $-60^{\circ}$  to  $-65^{\circ}$ . The resulting cloudy yellow-orange solution of the cuprate reagent is stirred at  $-60^{\circ}$  to  $-65^{\circ}$  for 5 minutes (Note 8).

B. *tert-Butyl phenyl ketone*. With a syringe a solution of 2.81 g. (0.0200 mole) of freshly distilled benzoyl chloride (Note 9) in 15 ml. of anhydrous tetrahydrofuran (Note 3) is added dropwise, with stirring, to the cold solution ( $-60^{\circ}$  to  $-65^{\circ}$ ) of the cuprate reagent. The resulting yellow-brown solution is stirred for 20 minutes (at  $-60^{\circ}$  to  $-65^{\circ}$ ) and quenched by the addition, with a syringe, of 5 ml. of anhydrous methanol. The red-orange reaction mixture is allowed to warm to room temperature and then poured into 100 ml. of aqueous saturated ammonium chloride. The copious precipitate of copper(I) thiophenoxide is separated by suction filtration and washed thoroughly with several 50-ml. portions of diethyl ether. The combined filtrate is extracted with three 100-ml. portions of ether. The combined ethereal solution is washed with two 50-ml. portions of aqueous 1 N sodium hydroxide and with one 50-ml. portion of aqueous 2% sodium thiosulfate. Each of the aqueous washes is extracted in turn with a fresh 50-ml. portion of ether. The combined ethereal solution is dried with anhydrous magnesium sulfate, filtered, and concentrated by distillation through a short Vigreux column. The residual pale yellow liquid (Note 10) is distilled through a short column under reduced pressure, yielding 2.73–2.82 g. (84–87%) of *tert-butyl phenyl ketone* as a colorless liquid b.p.  $105\text{--}106^{\circ}$  (15 mm.),  $114\text{--}115^{\circ}$  (44 mm.),  $n_D^{20}$  1.5092,  $n_D^{25}$  1.5066 (Note 11).

## 2. Notes

1. Solutions containing approximately 1.6 M *n*-butyllithium in hexane were purchased either from Alfa Inorganics, Inc., or from Foote Mineral Company. The concentration of *n*-butyllithium in these solutions can be determined either by a double titration procedure<sup>2</sup> or by dilution with anhydrous tetrahydrofuran, followed by titration with 2-butanol<sup>3</sup> in the presence of a 2,2'-bipyridyl indicator [*Org. Synth., Coll. Vol. 6* 121 (1988)]. In either case the total base concentration in the reagent is determined by titration with standard aqueous acid.

2. Thiophenol, purchased from Aldrich Chemical Company, Inc., was redistilled before use; b.p.  $65\text{--}66^{\circ}$  (42 mm.).

3. Commercial anhydrous tetrahydrofuran was distilled from lithium aluminum hydride and stored under nitrogen.

4. The submitters report that this solution may be stored under nitrogen at  $0^{\circ}$  for several days without deterioration. Phenylthiocopper is now commercially available from the Alpha Division of the Ventron Corp., 152 Andover St., Danvers, Massachusetts 01923.

5. Although the submitters had recommended use of a magnetic stirring bar, the checkers encountered considerable difficulty in maintaining adequate stirring of the cold reaction mixture with a magnetic stirrer and recommend use of a sealed mechanical stirrer such as a Truebore® stirrer.

6. Copper(I) iodide, purchased from Fisher Scientific Company, was purified by continuous extraction with anhydrous tetrahydrofuran in a Soxhlet extractor for approximately 12 hours, to remove colored impurities. The residual copper(I) iodide was then dried under reduced pressure at  $25^{\circ}$  and stored under nitrogen in a desiccator.

7. A pentane solution of *tert*-butyllithium (purchased from either Alfa Inorganics, Inc., or Lithium Corporation of America, Inc.) was standardized by one of the previously described titration procedures (Note 1). If possible, it is desirable to use a freshly opened bottle of *tert*-butyllithium since previously used bottles of this reagent often contain lithium *tert*-butoxide, which will lead to formation of a contaminant in the final product (Note 10).

8. Although the submitters report that this reagent is stable at  $0^{\circ}$  (*i.e.*, still reactive toward benzoyl chloride) for periods of at least one hour under a nitrogen atmosphere,<sup>3,4</sup> the checkers repeatedly observed evidence of thermal decomposition when the solution was allowed to warm above  $-40^{\circ}$ . This decomposition was indicated by the appearance of a red-brown coloration as the reagent was warmed to  $-40^{\circ}$ ; as the temperature was raised further to  $-25^{\circ}$  and to  $0^{\circ}$ , the mixture progressively exhibited a darker brown color.

9. Benzoyl chloride (purchased from Eastman Organic Chemicals) was redistilled before use; b.p.  $35\text{--}36^{\circ}$  (0.5 mm.).

10. The checkers found that with previously opened bottles of *tert*-butyllithium, the crude product was often contaminated with *tert*-butyl benzoate (from lithium *tert*-butoxide; see (Note 7)). The presence of this impurity in the crude product may be detected either by the presence of an extra IR peak at  $1720\text{ cm}^{-1}$  (conjugated ester), or by GC analysis. On a 1.3-m. GC column, packed with silicone fluid, No. SE-52, suspended on Chromosorb P and operated at  $155^{\circ}$ , the retention time of *tert*-butyl phenyl ketone was 4.4 minutes, and the retention times of potential impurities, methyl benzoate and *tert*-butyl benzoate were 2.4 minutes and 7.8 minutes, respectively. If a small amount of *tert*-butyl benzoate is present in the crude product, it is most easily removed by heating a mixture of the crude product with 1% by weight of *p*-toluenesulfonic acid on a steam bath for 10 minutes followed by partitioning the product between ether and aqueous sodium hydrogen carbonate. After the resulting ether solution has been dried and distilled, pure *tert*-butyl phenyl ketone is obtained.

11. The product exhibits a single GC peak (see (Note 10)). The spectral properties of the product are as follows;

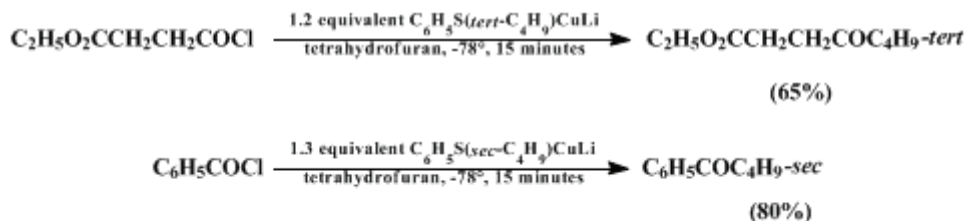
IR (CCl<sub>4</sub>) cm<sup>-1</sup>: 1680 (conjugated ketone), 1395 and 1370 [C(CH<sub>3</sub>)<sub>3</sub>]; <sup>1</sup>H NMR (CCl<sub>4</sub>), δ(multiplicity, number of protons, assignment): 1.30 [s, 9H, C(CH<sub>3</sub>)<sub>3</sub>], 7.2–7.9 (m, 5H, C<sub>6</sub>H<sub>5</sub>); UV (95% C<sub>2</sub>H<sub>5</sub>OH) nm. max. (ε): 237 (7350) and 272 (620); mass spectrum *m/e* (relative intensity): 162 (M,45), 106 (28), 105 (100), 77 (63), 57 (40), 51 (23), and 41 (30). The physical constants reported for the product are: b.p. 103–104° (13 mm.).<sup>5</sup> *n*<sub>D</sub><sup>20</sup> 1.5090.<sup>6</sup>

### 3. Discussion

*tert*-Butyl phenyl ketone has been prepared by the reactions of benzoic acid with *tert*-butyllithium,<sup>7</sup> of acetophenone with methyl iodide and base,<sup>5,9</sup> of benzaldehyde with *tert*-butylmagnesium chloride followed by oxidation,<sup>10</sup> and of 2,2-dimethylpropanoyl chloride with phenylmagnesium bromide.<sup>11</sup>

The procedure described here illustrates the preparation of mixed lithium arylhetero(alkyl)cuprate reagents and their reactions with carboxylic acid chlorides.<sup>4</sup> These mixed cuprate reagents also react with α,α'-dibromoketones,<sup>12</sup> primary alkyl halides,<sup>4</sup> and α,β-unsaturated ketones,<sup>4</sup> with selective transfer of the alkyl group.

Two limitations on the utility of organocopper reagents have often been the difficulty in using thermally unstable lithium *sec*- and especially *tert*-alkylcuprates<sup>13</sup> and the need for a large (*e.g.*, 300–500%) excess of an organocuprate to achieve complete conversion of substrate to product. Both of these limitations are circumvented by using lithium phenylthio(*tert*-alkyl)cuprates, which react with approximately equimolar amounts of carboxylic acid chlorides, forming the corresponding *tert*-alkyl ketones in high yield, even with the yield based on the transferred alkyl group. Furthermore, this alkyl group transfer can be achieved in the presence of other functional groups (*e.g.*, remote halogen or ester functionalities) in the carboxylic acid chloride substrate (Equation 1). Transfer of secondary alkyl groups can also be accomplished efficiently in this way (Equation 2).



The reaction of *tert*-alkyl Grignard reagents with carboxylic acid chlorides in the presence of a copper catalyst provides *tert*-alkyl ketones in substantially lower yields than those reported here.<sup>4,14</sup> The simplicity and mildness of experimental conditions and isolation procedure, the diversity of substrate structural type, and the functional group selectivity of these mixed organocuprate reagents render them very useful for conversion of carboxylic acid chlorides to the corresponding secondary and tertiary alkyl ketones.<sup>15</sup>

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 6, 137](#)

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### References and Notes

1. Department of Chemistry, the Johns Hopkins University, Baltimore, Maryland 21218; this work was supported by the National Science Foundation (GP-33667).
2. G. M. Whitesides, C. P. Casey, and J. K. Krieger, *J. Am. Chem. Soc.*, **93**, 1379 (1971).
3. For warning concerning 2-butanol, see *Chem. Eng. News*, **59**, (19), 3 (1981).
4. G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 7788 (1973).
5. A. Haller and E. Bauer, *C. R. Hebd. Seances Acad. Sci.*, **148**, 73 (1909).
6. C. Cherrier and J. Metzger, *C. R. Hebd. Seances Acad. Sci.*, **226**, 797 (1948).
7. Unpublished results of C. H. Heathcock and R. Radcliff as reported in Ref. <sup>8,8</sup>.
8. For a general discussion of ketone formation from carboxylic acids and organolithium reagents, see M. J. Jorgenson, *Org. React.*, **18**, 1 (1970).
9. J. U. Nef, *Justus Liebigs Ann. Chem.*, **310**, 316 (1900).
10. A. Favorskii, *Bull. Soc. Chim. Fr.*, **3**, 239 (1936).
11. J. Thiec, *Ann. Chim. (Paris)*, **9**, 51 (1954).
12. G. H. Posner and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 3076 (1973).
13. G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Am. Chem. Soc.*, **91**, 4871 (1969).
14. J. E. Dubois, M. Boussu, and C. Lion, *Tetrahedron Lett.*, **829** (1971) and references cited therein; J. A. MacPhee and J. E.

Dubois, *Tetrahedron Lett.*, 467 (1972).

15. For use of other organocopper reagents in converting carboxylic acid chlorides to ketones, see G. H. Posner and C. E. Whitten, *Tetrahedron Lett.*, 1815 (1973); G. H. Posner, C. E. Whitten, and P. E. McFarland, *J. Am. Chem. Soc.*, **94**, 5106 (1972). For a recent report on direct and convenient preparation of lithium phenylthio(alkyl)cuprate reagents, see G. H. Posner, D. J. Brunelle, and L. Sinoway, *Synthesis*, 662 (1974); G. H. Posner, "An Introduction to Synthesis Using Organocopper Reagents," Wiley, New York, 1980.

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

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether,  
diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

copper (7440-50-8)

benzaldehyde (100-52-7)

Acetophenone (98-86-2)

benzoyl chloride (98-88-4)

Methyl iodide (74-88-4)

Phenylmagnesium bromide (100-58-3)

methyl benzoate (93-58-3)

Pentane (109-66-0)

Thiophenol,  
Benzenethiol (108-98-5)

copper(I) iodide (7681-65-4)

magnesium sulfate (7487-88-9)

bromocresol

butyllithium,  
n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

2-Butanol (78-92-2)

2,2'-bipyridyl (366-18-7)

p-toluenesulfonic acid (104-15-4)

1-Propanone, 2,2-dimethyl-1-phenyl,  
tert-Butyl phenyl ketone (938-16-9)

lithium thiophenoxide

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

Phenylthiocopper

2,2-dimethylpropanoyl chloride (3282-30-2)

tert-Butyllithium (594-19-4)

tert-butylmagnesium chloride (677-22-5)

lithium tert-butoxide (1907-33-1)

tert-butyl benzoate (774-65-2)

Lithium phenylthio(tert-butyl)cuprate

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