



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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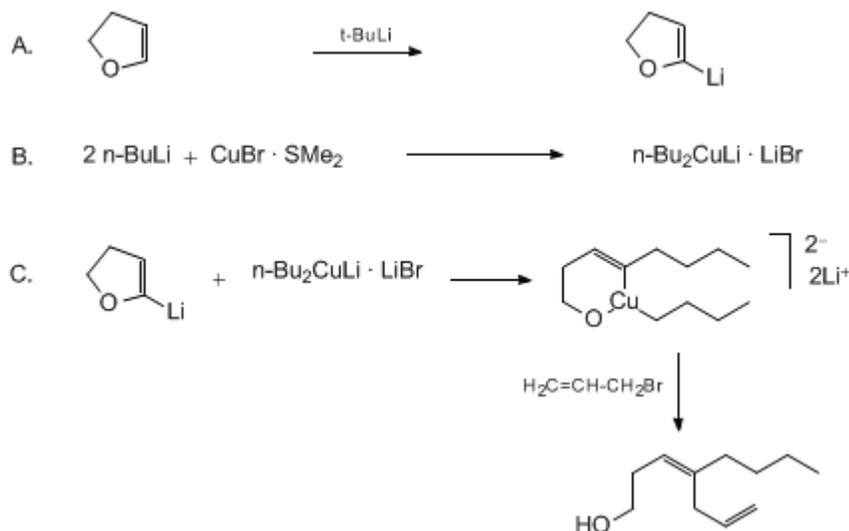
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

Organic Syntheses, Coll. Vol. 10, p.662 (2004); Vol. 79, p.11 (2002).

1,2-METALLATE REARRANGEMENT: (Z)-4-(2-PROPENYL)-3-OCTEN-1-OL

[3-Octen-1-ol, 4-(2-propenyl)-, (Z)-]



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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].

A. *2,3-Dihydro-5-furyllithium*. A 250-mL, three-necked, round-bottomed flask (Note 1) equipped with a thermometer, Teflon-coated magnetic stirring bar (Note 2) and a nitrogen inlet is charged with a solution of 2,3-dihydrofuran (3.15 g, 3.4 mL, 45 mmol) (Note 3) in tetrahydrofuran (THF, 6.13 g, 6.9 mL, 90 mmol) (Note 4). The magnetically stirred solution is cooled in a liquid nitrogen-ethyl acetate cooling bath to an internal temperature of -85°C whereupon tert-butyllithium (26.5 mL, 45 mmol, 1.7 M solution in pentane) (Note 5) is added dropwise via a syringe during 10 min (Note 6). After the addition the yellow semi-solid mixture is placed in an ice bath, stirred at $0\text{-}3^{\circ}\text{C}$ for 30 min and diluted with 20 mL of diethyl ether (Note 4) to give a thick yellow suspension of 2,3-dihydro-5-furyllithium.²

B. *Lithium dibutylcuprate*. A 250-mL, three-necked, round-bottomed flask, equipped with a thermometer, Teflon-coated magnetic stirring bar and a nitrogen inlet is charged with freshly recrystallized copper bromide-dimethyl sulfide complex (10.2 g, 49.5 mmol) (Note 7) and anhydrous diethyl ether (85 mL). To this suspension, cooled to -80°C in a liquid nitrogen-ethyl acetate bath, is added dropwise via syringe during 20 min a solution of n-butyllithium (44.4 mL, 99 mmol, 2.23 M solution in hexanes) (Notes 5 and 8). When the addition is complete, the reaction mixture is placed in an ice bath and stirred at $0\text{-}3^{\circ}\text{C}$ for 6 min to give a brown solution of lithium dibutylcuprate.

C. *(Z)-4-(2-Propenyl)-3-octen-1-ol*. The solution of lithium dibutylcuprate is cooled to -80°C and transferred by cannula (Note 9) under nitrogen pressure over 10 min to the stirred suspension of 2,3-dihydro-5-furyllithium cooled to -85°C (Note 10). After the transfer, the flask containing the cuprate is washed with 5 mL of diethyl ether. The temperature of the light brown suspension is allowed to rise slowly to 0°C over 3 hr (Note 11) and stirred at $0\text{-}3^{\circ}\text{C}$ for 30 min. The brown solution is cooled to -80°C and a solution of allyl bromide (17.9 g, 12.8 mL, 148 mmol) (Note 3) in diethyl ether (20 mL) is added dropwise during 10 min via syringe (Note 12). The black mixture is left in the cooling bath to warm gradually to rt overnight (12 hr). The resultant dark gray suspension is treated with an aqueous saturated solution of ammonium chloride (50 mL) and aqueous ammonia (20 mL, 30% in water). The organic layer is separated and the water

layer extracted with ether (2×75 mL). The combined organic extracts are dried with sodium sulfate, filtered, and concentrated under reduced pressure using a cold water bath (10-20°C). The crude product (light brown oil) is purified by flash chromatography on silica (150 g) (Note 13) eluting first with hexanes-diethyl ether (5:1, 500 mL followed by 1:2, 700 mL). The residue obtained from evaporation of the second fraction is distilled using a Kugelrohr oven to give the product as a colorless oil (6.39 g, 84%), bp 150°C (bath)/0.01 mm) (Notes 14, 15, 16).

2. Notes

1. All glassware was dried for at least 8 hr at 80°C, assembled hot, flame-dried, and allowed to cool under nitrogen.
2. Because of the semi-solid nature of the reaction mixture the use of a large football stirring bar (19 × 51 mm) or a mechanical stirrer is recommended.
3. 2,3-Dihydrofuran was purchased from Aldrich Chemical Company, Inc., and freshly distilled from calcium hydride under nitrogen.
4. Tetrahydrofuran was distilled from sodium/benzophenone ketyl or potassium/benzophenone under nitrogen.
5. tert-Butyllithium was purchased from Aldrich Chemical Company, Inc., and titrated using 1,3-diphenylacetone tosylhydrazine.³
6. During the addition the temperature should not be allowed to rise above -68°C.
7. Commercial copper bromide or its dimethyl sulfide complex contains impurities that are deleterious to the reaction. Therefore, the copper(I) bromide-dimethyl sulfide complex is prepared according to the method of House⁴ from copper(I) bromide generated by reduction of copper(II) bromide (Aldrich Chemical Company, Inc., 99%) with sodium sulfite.⁵ Best results are obtained using copper(I) bromide-dimethyl sulfide complex freshly recrystallized according to the following procedure. A 100-mL conical flask equipped with a condenser and a nitrogen inlet is charged with copper(I) bromide-dimethyl sulfide complex (15 g). Anhydrous dimethyl sulfide (50 mL) is added via syringe and the mixture heated gently until all the solid dissolves. The heating bath is removed and pentane (25 mL) is added to the warm solution. The solution is cooled in an ice bath until crystallization is complete. The product is collected by filtration under nitrogen using a sintered glass funnel. The complex is washed with 7.5 mL of dimethyl sulfide-pentane solution (2:1, v/v) and dried at rt under a stream of nitrogen for 1 hr to give 11.35 g of pure copper(I) bromide-dimethyl sulfide complex as a white solid.
8. During the addition, the temperature should not be allowed to rise above -58°C.
9. Because of the viscosity of the solution the size of the cannula is important. A cannula with an internal diameter of 2 mm was made from stainless steel HPLC tubing.
10. During the addition the temperature should not be allowed to rise above -76°C.
11. It is important to increase the temperature slowly to minimize the formation of by-products. The checkers found that this was most easily performed using a dry ice-acetone bath.
12. During the addition the temperature should not be allowed to rise above -30°C, and the mixture turns black.
13. MN Kieselgel 60, 230-400 mesh, purchased from Machery-Nagel GmbH & Co. was used. The checkers used ICN 32-63 D 60 Å, purchased from ICN Pharmaceuticals, Inc.
14. The spectral properties are as follows: ¹H NMR (400 MHz, CDCl₃) δ: 0.90 (t, 3 H, J = 7.2), 1.24-1.44 (comp m, 4 H), 1.64 (br s, 1 H), 2.02 (t, 2 H, J = 7.2), 2.31 (dt, 2 H, J = 6.6, 7.1), 2.81 (d, 2 H, J = 6.5), 3.64 (t, 2 H, J = 6.5), 5.00 (ddt, 1 H, J = 1.5, 1.7, 10.0), 5.04 (dq, 1 H, J = 1.5, 17.1), 5.22 (t, 1 H, J = 7.3), 5.76 (ddt, 1 H, J = 6.5, 10.2, 17.0); ¹³C NMR (100 MHz, CDCl₃) δ: 14.1, 22.6, 30.4, 31.5, 35.0, 37.0, 62.7, 115.3, 121.1, 136.4, 140.8; IR (neat) cm⁻¹: 3340, 3072, 2928, 2866, 1631, 1456, 1052, 913; MS (CI+) m/z: 169.1586 (C₁₁H₂₀O + H requires 169.1592), 169, 151, 127 (base), 109; Anal. Calcd. for C₁₁H₂₀O: C, 78.51; H, 11.98%. Found C, 78.43; H, 11.83%.
15. Capillary gas chromatography indicated a purity of 94%: DB 225 (30 m × 0.32 mm × 0.25 μm); 100°C (2 min) temperature programmed at 8°C/min to 160°C; He carrier 2.3 mL/min.
16. The submitters have found recently that the same result can be obtained using 1 equiv of dihydrofuran, 1.1 equiv of butyllithium, and 1.1 equiv of commercial copper(I) cyanide.

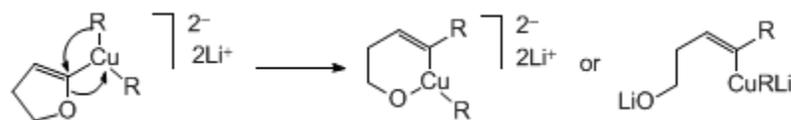
Waste Disposal Information

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

3. Discussion

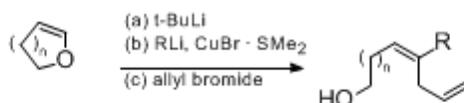
The preparation of (Z)-4-(2-propenyl)-3-octen-1-ol described here illustrates the use of 1,2-metallate rearrangements of metal carbenoids for the stereoselective synthesis of trisubstituted alkenes.⁶ 1,2-Metallate rearrangements of boronate

carbenoids are well known to proceed with inversion of stereochemistry at sp^3 hybridized carbon.⁷ Examples involving cuprates,⁸ manganates⁹ and zincates¹⁰ are also known. The present reaction, a rare example of a 1,2-metallate rearrangement involving inversion of stereochemistry at sp^2 hybridized carbon, was discovered during an investigation of the Cu(I)-catalyzed ring scission of 2,3-dihydro-5-furyllithium by butyllithium first described by Fujisawa and co-workers.¹¹ A mechanism involving the 1,2-metallate rearrangement of a higher order organocuprate intermediate has been postulated.¹²



The reaction has broad scope: 5-, 6-, and 7-membered ring metallated enol ethers participate equally well as do organocuprates derived from MeLi, PhLi, sec-BuLi, tert-BuLi, Me₃SnLi, and PhMe₂SiLi among others. The reaction also works with Grignard reagents.¹³ Some examples are given in the Table.

TABLE
DIENOLS VIA Cu(I)-MEDIATED 1,2-METALLATE REARRANGEMENT^a



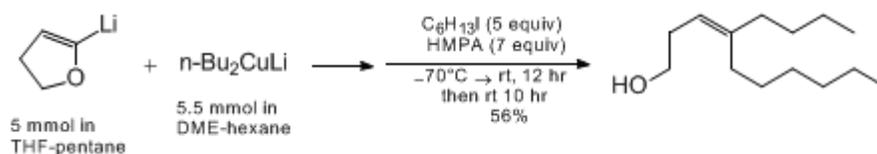
Entry	n	R	Time (min) ^b	Yield (%)
1	1	Me	30	81
2		Ph		81
3		sec-Bu		90
4		tert-Bu		90
5	2	n-Bu	180 ^c	79
6		sec-Bu		82
7		tert-Bu		87

^a The reactions were performed on a 5-mmol scale.

^b Time of stirring the reaction mixture at 0–3°C after transferring the solution of the cuprate to the lithiated enol ether and warming to 0°C.

^c Dihydropyran (n = 2) is less reactive than dihydrofuran (n = 1) and requires a longer reaction time.

The final step in the sequence can be accomplished with less reactive halides such as hexyl iodide with two modifications to the reaction conditions: the lithium dialkylcuprate must be generated in 1,2-dimethoxyethane instead of diethyl ether and HMPA must be added along with the alkylating agent as illustrated in the following example:



References and Notes

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

(Z)-4-(2-Propenyl)-3-octen-1-ol:
3-Octen-1-ol, 4-(2-propenyl)-, (Z)- (12); (119528-99-3)

2,3-Dihydro-5-furyllithium:
Lithium, (4,5-dihydro-2-furanyl)- (9); (75213-94-4)

2,3-Dihydrofuran:
Furan, 2,3-dihydro- (8,9); (1191-99-7)

tert-Butyllithium:
Lithium, tert-butyl- (8);
Lithium, (1,1-dimethylethyl)- (9); (594-19-4)

Copper (I) bromide-dimethyl sulfide complex:
Copper, bromo[thiobis[methane]]- (9); (54678-23-8)

Allyl bromide:
1-Propene, 3-bromo- (8,9); (106-95-6)

Dimethyl sulfide:
Methyl sulfide (8);
Methane, thiobis- (9); (75-18-3)

Butyllithium:
Lithium, butyl- (8,9); (109-72-8)