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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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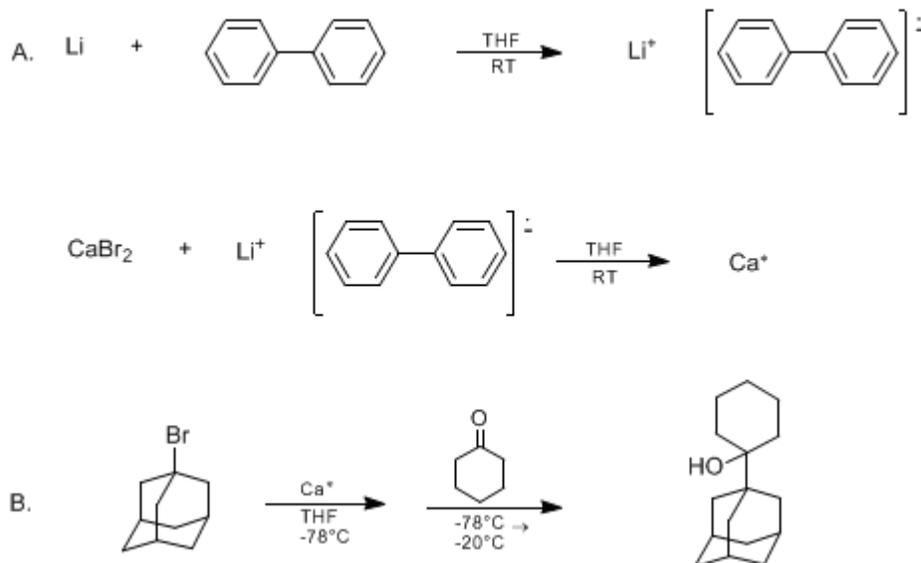
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

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HIGHLY REACTIVE CALCIUM FOR THE PREPARATION OF ORGANOCALCIUM REAGENTS: 1-ADAMANTYL CALCIUM HALIDES AND THEIR ADDITION TO KETONES: 1-(1-ADAMANTYL)CYCLOHEXANOL

[Cyclohexanol, 1-tricyclo[3.3.1.1^{3,7}]dec-1-yl]



Submitted by Reuben D. Rieke, Tse-Chong Wu, and Loretta I. Rieke¹.

Checked by Katsutaka Yasue and Hisashi Yamamoto.

1. Procedure

A. *Active calcium.* Freshly cut lithium (41.7 mg, 6.01 mmol) and biphenyl (1.020 g, 6.61 mmol) in freshly distilled tetrahydrofuran (THF, 15 mL) (Note 1) are vigorously stirred at room temperature under argon (Note 2) until the lithium is completely consumed (approx. 2 hr). The preformed lithium biphenylide is transferred via a cannula at room temperature to a well-dispersed suspension of calcium bromide (CaBr_2 , 1.213 g, 6.07 mmol) (Note 3) in freshly distilled THF (15 mL). The reaction mixture is stirred for 1 hr at room temperature prior to use (Note 4).

B. *1-(1-Adamantyl)cyclohexanol.* Activated calcium prepared from preformed lithium biphenylide and excess CaBr_2 in THF is cooled to -78°C (Note 5). 1-Bromoadamantane (543 mg, 2.52 mmol) (Note 6) in THF (10 mL) is added via a cannula at -78°C and the mixture is stirred at -78°C for 20 min (Note 7). Excess cyclohexanone (520 mg, 5.30 mmol) is added via a disposable syringe at -78°C . The resulting mixture is gradually warmed to -20°C and stirred at -20°C for 30 min. The reaction mixture is then quenched with water at -20°C (20 mL) and warmed to room temperature. At this temperature it is filtered through a small pad of Celite which is washed with diethyl ether (Et_2O , 100 mL). The aqueous layer is extracted with Et_2O (3×50 mL). The combined organic phases are washed with water (15 mL) and dried over anhydrous magnesium sulfate (MgSO_4). Removal of the solvent and flash-column chromatography on silica gel (150 g, 230–400 mesh, eluted sequentially with hexane/ EtOAc [0% to 15%]) affords reasonably pure 1-(1-adamantyl)cyclohexanol as a white solid. 1-(1-Adamantyl)cyclohexanol is recrystallized from hexanes as follows: The white crystals are dissolved in a limited amount of dichloromethane (CH_2Cl_2), hexane (15 mL) is added, the solvent is evaporated to 8 mL, more hexane (15 mL) is added, the solvent is evaporated to about 15 mL, and the solution is gradually cooled and allowed to stand for 24 hr to afford 469–476 mg (80–82% yield) of product as colorless needles, mp 169 – 171°C (Note 8),(Note 9).

2. Notes

1. **Lithium** was weighed out and charged into reaction flasks under **argon** in a Vacuum Atmospheres Company dry box. (The checkers did not use a dry box: **Lithium** was freshly cut in air, rinsed in **hexane**, and charged into reaction flasks under **argon**.) **Biphenyl** was purchased from Aldrich Chemical Company, Inc. **Tetrahydrofuran** anhydrous, 99.9% purity, was purchased from Aldrich Chemical Company, Inc. It was freshly distilled over Na/K alloy under **argon** before use.

2. All glassware, syringes, needles, and cannulas were kept in a 120°C oven overnight prior to use. All manipulations were carried out on a dual manifold vacuum/argon system. The Linde prepurified grade **argon** was further purified by passing it through a 150°C catalyst column (BASF R3-11), a phosphorus pentoxide column, and a column of granular potassium hydroxide. (The checkers used **argon** as received.)

3. Anhydrous **calcium(II) bromide** was purchased from Cerac, Inc. Commercially available reagents were used as received unless specially noted.

4. Good stirring is important for the preparation of highly reactive **calcium**. A Schlenk tube is better than a flask for the reactor. Excess **calcium** salt was present during the oxidative addition reaction with **1-bromoadamantane**.

5. Low-temperature reactions were performed using a Neslab endocal ULT-80 refrigerated circulating bath or a dry ice/acetone bath.

6. **1-Bromoadamantane**, 99%, was purchased from Aldrich Chemical Company, Inc.

7. The reaction was checked by GC; all the starting material was consumed.

8. Melting points were determined on a Thomas Hoover melting point apparatus or an Electrothermal melting point apparatus and are corrected.

IR spectra were taken on an Analect RFX-30 FTIR spectrophotometer neat between NaCl or KBr plates or as KBr disks. ¹H NMR spectra were recorded on a Nicolet NT-360 (360 MHz) or on a Varian VXR-200 (200 MHz) spectrometer. All chemical shifts are reported in parts per million (δ) downfield from internal **tetramethylsilane**. Fully decoupled ¹³C NMR spectra and DEPT experiments were recorded on a Varian VXR-200 (50 MHz) spectrometer. The center peak of CDCl₃ (77.0 ppm) was used as the internal reference.

9. The physical properties are as follows: IR (KBr) cm⁻¹: 3465, 2931, 2902, 2844, 1448, 1344, 980, 955, 935; ¹H NMR (200 MHz, CDCl₃) δ: 0.95–2.05 (m, 26 H); ¹³C NMR (50 MHz, CDCl₃) δ: 21.9, 26.0, 28.7, 29.8, 35.8, 37.3, 39.1, 74.6; MS (EI) m/e (relative intensity) 234 (M⁺, 0.2), 135 (26.0), 98 (100.0); HRMS calcd for C₁₆H₂₆O m/e 234.1984, found m/e 234.1982. Anal. Calcd: C, 81.99; H, 11.18. Found: C, 82.13; H, 11.41.

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 development of organocalcium chemistry has been slow compared with the extensive studies of organometallic reagents of other light metals,² due in part to the lack of a facile method of preparing organocalcium compounds. Direct oxidative addition to **calcium** has been limited by the reduced reactivity of **calcium** metal with organic substrates, presumably because of surface poisoning. The organocalcium derivatives RCaX were formed most readily when X = I; the preparation of RCaX (X = Br, Cl) usually required activated **calcium**. Few examples have been reported and overall yields tend to be low.² Although simple primary and secondary alkyl iodides react with **calcium** in reasonable yields,³ ⁴ tertiary alkylidocalcium compounds are very difficult to prepare and most workers have reported only trace amounts.⁵ ⁶ In contrast, the highly reactive **calcium** complexes reported here react readily with all these substrates to generate excellent yields of the corresponding organocalcium compounds.

Highly reactive **calcium** can be readily prepared by the reduction of **calcium** halides in **tetrahydrofuran** solution with preformed **lithium biphenylide** under an **argon** atmosphere at room temperature.⁷ This colored **calcium** species seems to be reasonably soluble in THF. However, the

reactive calcium complex prepared from preformed lithium naphthalenide was insoluble in THF solution and precipitated out of solution to give a highly reactive black solid. The exact nature of this black calcium complex has not been determined. Acid hydrolysis of the black material releases naphthalene as well as THF. Accordingly, the most likely structure of the black material is a Ca-naphthalene-THF complex similar in nature to the soluble magnesium-anthracene complex recently reported.^{8 9 10 11}

Highly reactive calcium was prepared by the lithium biphenylide reduction of calcium salts in THF. Both CaBr₂ and CaI₂ generate the reactive calcium species. The organocalcium compounds, prepared directly from this calcium complex and organic halides, were found to undergo Grignard-type reactions efficiently. Alkyl bromides and alkyl chlorides reacted rapidly with the calcium complex at temperatures as low as -78°C. 1-Chlorooctane gave 1-octylcyclohexanol in 83% yield.⁷ Similar results were noted for secondary halides. Bromocyclohexane reacted readily with the calcium species at -78°C and the resulting organocalcium reagent underwent carbonyl addition to give the alcohol in 75% yield. Significantly, the highly reactive calcium complex reacted rapidly with tertiary bromides at -78°C. For example, the Grignard-type reaction of 1-bromoadamantane with the reactive calcium afforded 1-(1-adamantyl)cyclohexanol in 80% yield. The direct reaction of 1-bromoadamantane with metals is known to yield mainly reductive cleavage or dimerization.¹² Accordingly, this method represents a significant new approach to the 1-metalloadamantane.

Reactions of aryl halides with the reactive calcium required slightly higher temperatures, up to -30°C for aryl bromides and up to -20°C for aryl chlorides.⁷ Surprisingly, the active calcium reacted readily with fluorobenzene at room temperature to form the corresponding organocalcium reagent in near quantitative yield.

Addition of copper(I) salts to the organocalcium reagents form novel organocalcium copper reagents that cross-couple with acid chlorides to yield ketones, and undergo conjugate addition to α,β -unsaturated ketones. The highly reactive calcium also reacts readily with 1,3-dienes to form bisorganocalcium complexes. Reaction of these calcium reagents with biselectrophiles generates a wide variety of complex cyclic hydrocarbons.⁷

References and Notes

1. Department of Chemistry, University of Nebraska, Lincoln, NE 68588-0304.
2. Lindsell, W. E. "Comprehensive Organometallic Chemistry"; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1982; Vol. 1, Chapter 4, pp. 223-228.
3. Kawabata, N.; Matsumura, A.; Yamashita, S. *Tetrahedron* **1973**, *29*, 1069;
4. Kawabata, N.; Matsumura, A.; Yamashita, S. *J. Org. Chem.* **1973**, *38*, 4268.
5. Gowenlock, B. G.; Lindsell, W. E. *J. Organomet. Chem. Libr.* **1977**, *3*, 1-73;
6. Bogatskii, A. V.; Chumachenko, T. K.; Derkach-Kozhukhova, A. E.; Lyamtseva, L. N.; Suprinovich, E. S. *Zh. Obshch. Khim.* **1977**, *47*, 2297; *Chem. Abstr.* **1978**, *88*, 37865d.
7. Wu, T.-C.; Xiong, H.; Rieke, R. D. *J. Org. Chem.* **1990**, *55*, 5045.
8. Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1983**, *48*, 879;
9. Raston, C. L.; Salem, G. J. *J. Chem. Soc., Chem. Commun.* **1984**, 1702;
10. Harvey, S.; Junk, P. C.; Raston, C. L.; Salem, G. J. *J. Org. Chem.* **1988**, *53*, 3134;
11. Bogdanovic, B. *Acc. Chem. Res.* **1988**, *21*, 261.
12. Dubois, J. E.; Bauer, P.; Molle, G.; Daza, J. *C.R. Hebd. Seances Acad. Sci., Ser. C* **1977**, *284*, 145.

Appendix

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

1-metalloadamantane
diethyl ether (60-29-7)
Cyclohexanone (108-94-1)
copper (7440-50-8)
calcium (7440-70-2)
Biphenyl (92-52-4)
Naphthalene (91-20-3)
bromocyclohexane (108-85-0)
dichloromethane (75-09-2)
lithium (7439-93-2)
magnesium sulfate (7487-88-9)
Fluorobenzene (462-06-6)
Tetrahydrofuran (109-99-9)
hexane (110-54-3)
argon (7440-37-1)
1-bromoadamantane (768-90-1)
tetramethylsilane (75-76-3)
1-ADAMANTYL CALCIUM
1-(1-Adamantyl)cyclohexanol,
Cyclohexanol, 1-tricyclo[3.3.1.1^{3,7}]dec-1-yl (84213-80-9)
Lithium biphenylide (34467-57-7)
calcium bromide,
calcium(II) bromide (7789-41-5)
lithium naphthalenide
1-Chlorooctane (111-85-3)
1-octylcyclohexanol