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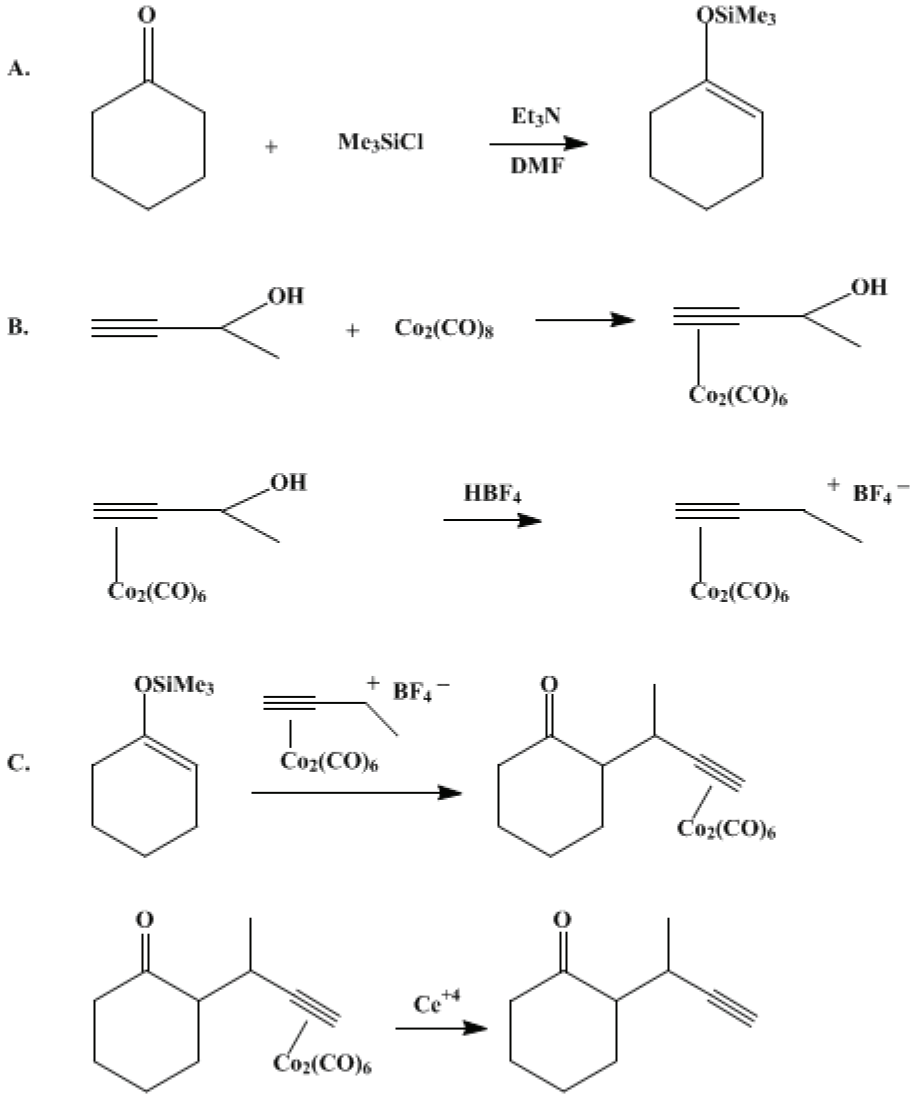
ALKYLATIONS USING HEXACARBONYL(PROPARGYLIUM) DICOBALT SALTS: 2-(1-METHYL-2-PROPYNYL) CYCLOHEXANONE

[Cyclohexanone, 2-(1-methyl-2-propynyl)-, (R^*,R^*) and (R^*,S^*)-]



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1. Procedure

Caution! Dicobalt octacarbonyl is highly toxic and air sensitive. All operations with this reagent should be carried out in an inert atmosphere and in a well-ventilated hood.

A. *1-Trimethylsiloxycyclohexene.*[2] A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser fitted with a nitrogen gas inlet tube that is attached to a mineral oil bubbler. The system is flushed with nitrogen and flame-dried, and while the system is maintained under a static pressure of nitrogen, the flask is charged with 300 mL of dry dimethylformamide (Note 1) and 110.3 g (1.1 mol) of triethylamine (Note 2); 58.3 (0.54 mol) of chlorotrimethylsilane (Note 3) is added by syringe. Cyclohexanone (40.0 g, 0.41 mol) (Note 4) is added and the mixture is refluxed with stirring for 48 hr. After the flask is cooled to room temperature, the contents are poured into 600 mL of pentane. The resulting mixture is transferred to a separatory funnel and washed with three 500-mL portions of cold aqueous sodium bicarbonate. The organic layer is washed rapidly in succession with 200 mL of cold 1.5*N* hydrochloric acid and 200 mL of cold aqueous sodium bicarbonate. The pentane solution is dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude product is distilled through a short Vigreux column to give 53–54 g (76–77%) of 1-trimethylsiloxycyclohexene as a colorless liquid, bp 75–80°C (20–21 mm) (Note 5).

B. *Hexacarbonyl(1-methyl-2-propynylium)dicobalt tetrafluoroborate* ***(1)***. A 2-L, two-necked, round-bottomed flask fitted with a magnetic stirring bar, a stopper, and a gas inlet T-tube that is attached to a mineral oil bubbler is flame-dried under a flow of nitrogen. The flask is charged with 200 mL of dry dichloromethane (Note 6) and 13.0 g (0.185 mol) of 3-butyn-2-ol (Note 7). After the mixture is stirred for 15 min, 65.0 g (0.19 mol) of dicobalt octacarbonyl (Note 8) is added in portions over a few minutes while maintaining a slow stream of nitrogen. Vigorous gas evolution (*carbon monoxide!*) is observed. The mixture is stirred for 4–5 hr, and the solvent is then removed under reduced pressure (20–25 mm). The residual solid (alkyne)$Co_2(CO_6)$ complex is dissolved in 40 mL of propionic anhydride under nitrogen and cooled to −45°C in a dry ice–acetonitrile bath. Tetrafluoroboric acid–dimethyl etherate (37.3 g, 0.28 mol) (Note 9) is added with stirring. After 30 min, 600–800 mL of anhydrous diethyl ether is added with continuous stirring. The burgundy-red salt that precipitates is isolated by filtration under a flow of nitrogen (Note 10) and is thoroughly washed with anhydrous diethyl ether to give 60–61 g (76–77%) of hexacarbonyl(1-methyl-2-propynylium)dicobalt tetrafluoroborate. This material is used immediately in the following step.

C. *2-(1-Methyl-2-propynyl)cyclohexanone.* A 2-L, two-necked, round-bottomed flask is equipped with a magnetic stirring bar, a stopper, and a pressure-equalizing dropping funnel fitted with a gas inlet T-tube that is connected to a mineral oil bubbler. The flask is flushed with nitrogen and charged with 150 mL of dry dichloromethane (Note 6) and 60.0 g (0.141 mol) of the salt from Part B. The mixture is stirred and cooled to −78°C in a dry ice/2-propanol bath, and 23.9 g (0.141 mol) of 1-trimethylsiloxycyclohexene (Part A) is added dropwise over a few minutes. The mixture is stirred at −78°C for 4 hr. After the solution is warmed to room temperature, dichloromethane is removed under reduced pressure and replaced with 400 mL of acetone. The dark-red solution of the alkyne complex is cooled to −78°C and 175 g (0.32 mol) of ceric ammonium nitrate (Note 11) is added in portions. The mixture is stirred until the gas evolution (carbon monoxide!) ceases (ca. 4 hr) (Note 12). The reaction mixture is warmed to room temperature, poured into 1 L of saturated brine solution, and extracted with four 250-mL portions of diethyl ether. The combined ether extracts are dried over magnesium sulfate, filtered, and concentrated on a rotary evaporator. The residual red oil is distilled at reduced pressure to afford 15.0–15.2 g (71–72%) of 2-(1-methyl-2-propynyl)cyclohexanone as a pale-yellow liquid, bp 57–60°C (10 mm) (Note 13).

2. Notes

1. Dimethylformamide, obtained from Aldrich Chemical Company, Inc., was vacuum distilled from calcium hydride, bp 44°C (25 mm), and stored over Linde 3A molecular sieves.
2. Triethylamine, obtained from the Aldrich Chemical Company, Inc., was distilled from potassium hydroxide prior to use.
3. Chlorotrimethylsilane, obtained from the Aldrich Chemical Company, Inc., was redistilled from calcium hydride before use.
4. Cyclohexanone was purchased from the Aldrich Chemical Company, Inc., redistilled, and stored over Linde 4A molecular sieves.
5. The product is over 99.5% pure by GLPC (6 ft × 1/8 in. 3% SP 2100 on 100–120-mesh Supelcoport column) and has the following spectral characteristics: ^{1}H NMR ($CDCl_3$) δ: 0.21 (s, 9 H), 1.55 (m, 2 H), 1.69 (m, 2 H), 2.05 (br d, 4 H), 4.88 (br s, 1 H).
6. Dichloromethane, obtained from the Aldrich Chemical Company, Inc., was distilled from calcium hydride and stored over Linde 4A molecular sieves.
7. 3-Butyn-2-ol was obtained from the Aldrich Chemical Company, Inc., and used without further

purification.

8. Dicobalt octacarbonyl was obtained from Alfa Products, Morton/Thiokol, Inc. It is best weighed in a nitrogen-filled polyethylene glove bag or in a dry box.

9. Tetrafluoroboric acid–dimethyl etherate (d 1.38 g/mL) was purchased from the Aldrich Chemical Company, Inc. The submitters note that a tetrafluoroboric acid–acetic acid mixture, which is prepared by carefully adding 49% aqueous tetrafluoroboric acid (50 g, 0.28 mol) to ice-cold acetic anhydride (30.6 g, 0.30 mol), also can be used.

10. The filtration under nitrogen is conveniently carried out in a Schlenk filter flask.[3]

11. Ceric ammonium nitrate was obtained from the Aldrich Chemical Company, Inc.

12. The disappearance of the dark red (alkyne)$Co_2(CO)_6$ complex can be monitored by TLC on silica gel with a 1 : 9 diethyl ether : petroleum ether solvent mixture.

13. The product is obtained as a 2 : 1 diastereomeric mixture and is over 99% pure by GLPC (6 ft × 1/8 in. 3% SP 2100 on 100–120-mesh Supelcoport column). It has the following spectral characteristics: IR (CCl_4) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.8–2.9 (br envelope, 10 H), 1.05 (d, 3 H, $J = 7$, minor diastereomer), 1.10 (d, 3 H, $J = 7$, major diastereomer), 2.15 (s, 1 H, both diastereomers); ^{13}C NMR ($CDCl_3$) δ: 16.3, 19.2, 24.2, 25.6, 24.7, 27.1, 28.4, 30.7, 41.7, 41.9, 54.1, 54.8, 68.2, 69.6, 86.3, 87.5, 209.7, 210.3; MS (70 eV) *m/e* 150, 121 (100%).

3. Discussion

In addition to their reactions with trimethylsilyl enol ethers, (propargylium)-$Co_2(CO)_6^+$ complexes react with a variety of other mild carbon nucleophiles including activated aromatic compounds,[4] β-dicarbonyl compounds,[5] other enol derivatives (enol acetates and ketones directly),[6] allylsilanes,[7] and alkyl- and alkynyl-aluminum reagents.[8,9] These reactions provide a flexible means of introducing the synthetically versatile propargyl function. Key features of propargylations using these complexes are (a) ready introduction and removal of the activating and directing -$Co_2(CO)_6$ group, (b) regiospecific attack by nucleophiles at the carbon α to the coordinated alkynyl group, giving propargyl products only (no allenic coproducts); and (c) very mild reaction conditions and good overall yields.

The method reported here appears to be the one of choice for the dependable, efficient α-propargylation of ketones. It can be applied to propargylate ketones regioselectively at either the less substituted α-position (via the trimethylsilyl enol ether) or the more substituted α-position (using the enol acetate or even the ketone directly[6]). The resulting α-propargylated ketones are very useful synthetic intermediates. They have been converted to chromanols,[10] furans,[11] other heterocycles,[11] and cyclohexenones,[12] and they undergo regiospecific hydration to 1,4-diketones that, in turn, can be converted to cyclopentenones.[13,14,15] More classical indirect ketone propargylations generally give low yields with substantial coproduction of allenic by-products, as with enamine[10,16] or acetoacetic ester propargylations.[11,17] Direct coupling of ketone enolates with propargyl halides or tosylates have rarely been attempted and can be expected to have the same limitations.

This preparation of 2-(1-methyl-2-propynyl)cyclohexanone appears to be the first reported.

References and Notes

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

petroleum ether

brine

Cyclohexanone, 2-(1-methyl-2-propynyl)-, (R^*,R^*) and (R^*,S^*)-

dimethyl etherate

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether,
diethyl ether (60-29-7)

acetic anhydride (108-24-7)

carbon monoxide (630-08-0)

sodium bicarbonate (144-55-8)

Cyclohexanone (108-94-1)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

carbon (7782-42-5)

potassium hydroxide (1310-58-3)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

propionic anhydride (123-62-6)

dimethylformamide (68-12-2)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

CHLOROTRIMETHYLSILANE (75-77-4)

1-Trimethylsiloxycyclohexene (6651-36-1)

ceric ammonium nitrate

2-(1-Methyl-2-propynyl)cyclohexanone (130719-24-3)

3-butyn-2-ol (2028-63-9)

Hexacarbonyl(1-methyl-2-propynylium)dicobalt tetrafluoroborate (62866-98-2)

tetrafluoroboric acid (16872-11-0)