



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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

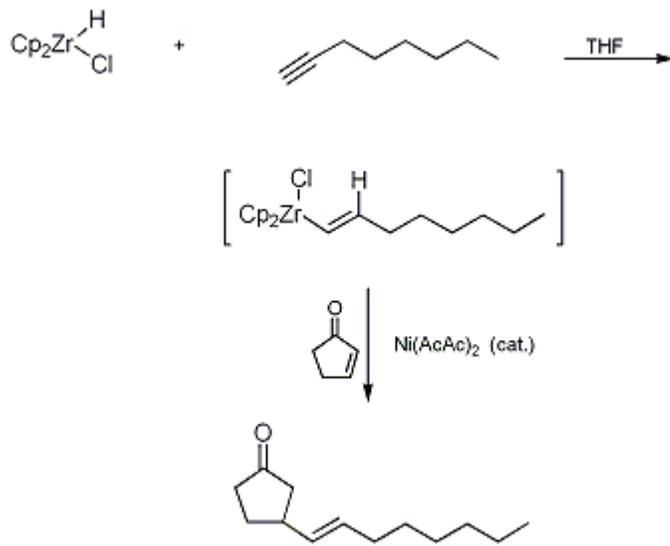
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

*Organic Syntheses, Coll. Vol. 9, p.640 (1998); Vol. 71, p.83 (1993).*

## CONJUGATE ADDITION OF A VINYLZIRCONIUM REAGENT: 3-(1-OCTEN-1-YL)CYCLOPENTANONE

[Cyclopentanone, 3-(1-octenyl)-, (E)-]



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### 1. Procedure

*3-(1-Octen-1-yl)cyclopentanone.*<sup>3</sup> A 38.7-g quantity (0.150 mol) of chlorobis( $\eta^5$ -cyclopentadienyl) hydrido-zirconium, Schwartz's reagent, (Note 1) is weighed into an oven-dried, 250-mL, three-necked flask. The flask, equipped with argon inlet and exit tubes, a thermometer and magnetic stirrer, is placed in an ice/water cooling bath. Under an atmosphere of argon, 50 mL of dry tetrahydrofuran (Note 2) and 23.6 mL (0.16 mol) of freshly distilled 1-octyne (Note 3) are added. The ice/water cooling bath is used to keep the temperature between 15°C and 25°C during the addition. Stirring is continued in the ice bath for 2 hr to control a mildly exothermic reaction; then the flask is wrapped in aluminum foil and stirred overnight at room temperature (elapsed time is 18 hr). At this point, 10.9 mL (0.130 mol) of freshly distilled 2-cyclopentenone (Note 3) is added and the reaction mixture is chilled in an ice bath for 10 min. To the cooled reaction mixture a total of 3.34 g (0.0130 mol) of vacuum-sublimed (at 180°C), powdered, solid nickel acetylacetonate (Note 3),(Note 4) is added in three portions at 10-min intervals, keeping the temperature of the reaction mixture below 50°C (Note 5),(Note 6).

The mixture is stirred for 2 hr in the ice bath and for 2 hr at room temperature, then poured into a large Erlenmeyer flask containing 150 mL of 1 N hydrochloric acid and 200 mL of ice/water mixture. Hexane (400 mL) is added and the quenched reaction mixture is stirred for 30 min. Solid material is removed by vacuum filtration (Note 7) and the solids are washed with hexane (3 × 70 mL). The combined filtrates are transferred to a separatory funnel and the organic layer is removed. The aqueous layer (Note 7) is extracted with 300 mL of hexane and the extract is combined with the original organic layer. After the organic layer is washed successively with 300-mL portions of saturated sodium bicarbonate solution and brine, it is dried over sodium sulfate and concentrated under reduced pressure to give 24.8 g of crude product. The crude product is placed on a chromatography column prepared from 550 g of silica gel and hexane. The column is eluted with 2% ethyl acetate in hexane until 3.5 L of eluant has been collected. Then 4% ethyl acetate in hexane is used. The fractions containing the product (TLC) are combined and evaporated, finally under high vacuum, to afford 15.4 g (61%) of a very pale yellow liquid (Note 8). GC analysis of this product on an OV17 50-m capillary column (100°C to 200°C

at 5°C/min) shows it to be 98.2% pure.

The material is distilled in a Kugelrohr apparatus at 0.15 mm and an oven temperature of 95–105°C to give 15.0 g (59% overall yield) of material with GC purity of 98.3% (Note 9).

## 2. Notes

1. Chlorobis( $\eta^5$ -cyclopentadienyl)hydrido­zirconium was prepared by lithium aluminum hydride reduction of the dichloro compound using the procedure of Buchwald and co-workers.<sup>4</sup> When carried out using chlorobis( $\eta^5$ -cyclopentadienyl)-hydrido­zirconium obtained from a commercial source, the procedure afforded only a 28% yield of final product.
2. Tetrahydrofuran was distilled from sodium/benzophenone before use.
3. 1-Octyne, cyclopentenone, and nickel acetylacetonate were purchased from the Aldrich Chemical Company, Inc. The checkers recrystallized the latter compound from anhydrous methanol followed by azeotropic drying with hot toluene.
4. For some applications of this chemistry, it may be preferable first to reduce the nickel catalyst with DIBAL.<sup>3</sup>
5. The checkers observed a significant induction period prior to onset of the exothermic reaction. Care must be taken to avoid addition of the nickel acetylacetonate too rapidly initially or temperature control becomes difficult.
6. In several separate small scale experiments, it was noted that the coupling reaction was not impeded by adding pyridine, triethylamine, t-butyl alcohol, chlorotrimethylsilane, or diisopropylamine to the reaction mixture before adding the nickel catalyst. These results suggest that a variety of functional groups can be present in the enone partner of the coupling reaction. In addition toluene can be used instead of tetrahydrofuran as the solvent.
7. Disposal of waste materials containing nickel salts should be carried out in an environmentally acceptable manner.
8. The checkers employed a flash chromatography technique, and 4% ethyl acetate/hexanes as the TLC solvent system to monitor the chromatographic separation.
9. The NMR spectrum of the product [<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ ] showed a characteristic set of multiplets from 0.8 to 2.9 ppm and olefinic protons at 5.43 (dd, 1 H, J = 15.4 and 6.4) and 5.49 ppm (dt, 1 H, J = 15.4 and 5.8); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ : 14.0, 22.6, 28.7, 29.3, 29.9, 31.6, 32.4, 38.1, 39.7, 44.9, 130.6, 131.9, 219.0; IR (neat) cm<sup>-1</sup>: 1743; MS m/e 194 (M<sup>+</sup>). Anal. Calcd for C<sub>13</sub>H<sub>22</sub>O: C, 80.35; H, 11.41. Found: C, 80.40; H, 11.35. The checkers employed a 30-m Durawax DX3 column for the GC analysis and found a purity of 97%.

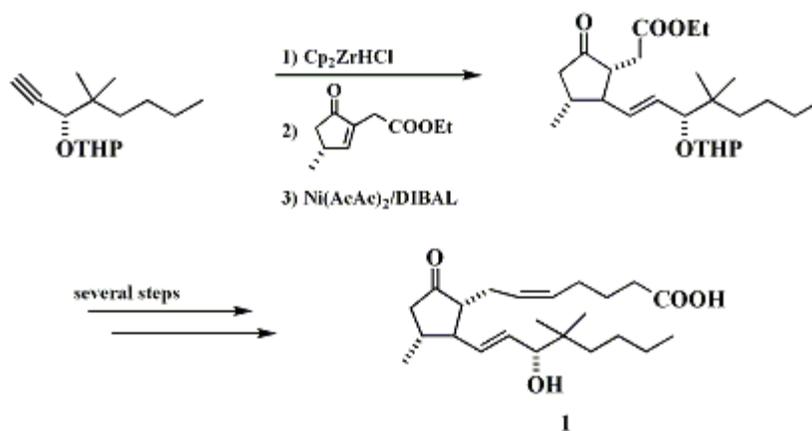
## Waste Disposal Information

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

## 3. Discussion

This example does not illustrate the highest yield application of this chemistry. Coupling of 1-octyne and cyclopentenone was selected because these materials are commercially available and because this coupling exemplifies, in a prototypical fashion, the application of this powerful chemistry to prostaglandin synthesis. Several additional examples are presented in the original publication.<sup>3</sup>

A closely related coupling reaction is a key step in a synthesis of the anti-ulcer prostaglandin **1**, a synthesis that was developed for large scale preparation of this compound.<sup>5</sup>



The simplicity of operation and flawless rendering of (E)-geometry make this an attractive alternative to vinylcuprate additions.

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 9, 162](#)

## References and Notes

1. Chemistry Research Department, Hoffmann-La Roche Inc., Nutley, NJ 07110.
2. Department of Chemistry, Princeton University, Princeton, NJ 08544.
3. Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333.
4. Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895; *Org. Synth., Coll. Vol. IX* **1998**, 162.
5. Coffen, D. L.; Manchand, P. S.; Truesdale, L. K.; Eur. Pat. Appl. Ep 153 689, 1985 (to Hoffmann-La Roche & Co.); *Chem. Abstr.* **1986**, *104*, 186231v.

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

hexanes

brine

chlorobis( $\eta^5$ -cyclopentadienyl)hydrido­zirconium, Schwartz's reagent

Chlorobis( $\eta^5$ -cyclopentadienyl)hydrido­zirconium

chlorobis( $\eta^5$ -cyclopentadienyl)-hydrido­zirconium

[hydrochloric acid](#) (7647-01-0)

[ethyl acetate](#) (141-78-6)

methanol (67-56-1)  
sodium bicarbonate (144-55-8)  
sodium sulfate (7757-82-6)  
aluminum (7429-90-5)  
nickel (7440-02-0)  
pyridine (110-86-1)  
toluene (108-88-3)  
Benzophenone (119-61-9)  
sodium (13966-32-0)  
Tetrahydrofuran (109-99-9)  
lithium aluminum hydride (16853-85-3)  
hexane (110-54-3)  
triethylamine (121-44-8)  
argon (7440-37-1)  
t-butyl alcohol (75-65-0)  
2-Cyclopentenone,  
cyclopentenone (930-30-3)  
1-OCTYNE (629-05-0)  
diisopropylamine (108-18-9)  
CHLOROTRIMETHYLSILANE (75-77-4)  
3-(1-Octen-1-yl)cyclopentanone (64955-00-6)  
Cyclopentanone, 3-(1-octenyl)-, (E)- (64955-00-6)  
nickel acetylacetonate (3264-82-2)