



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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.

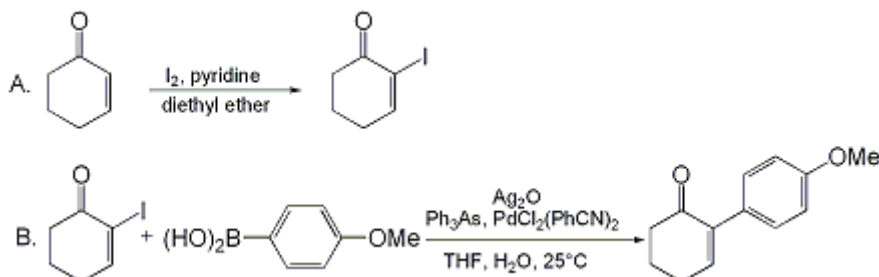
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

Organic Syntheses, Coll. Vol. 10, p.467 (2004); Vol. 75, p.69 (1998).

2-(4-METHOXYPHENYL)-2-CYCLOHEXEN-1-ONE: PREPARATION OF 2-iodo-2-cyclohexen-1-one AND SUZUKI COUPLING WITH 4-METHOXYPHENYLBORONIC ACID

[2-Cyclohexen-1-one, 2-(4-methoxyphenyl)- and 2-Cyclohexen-1-one, 2-iodo-]



Submitted by Frederic S. Ruel, Matthew P. Braun, and Carl R. Johnson¹.
Checked by Alain Zakarian and David J. Hart.

1. Procedure

Caution! This procedure involves volatile and toxic reagents and should be conducted in an efficient fume hood.

A. *2-Iodo-2-cyclohexen-1-one*. A 500-mL, three-necked, round-bottomed flask equipped with a 1.5-in. Teflon-coated magnetic stirring bar, glass stopper, 50-mL addition funnel, and a reflux condenser is charged with a 1:1 mixture of 75 mL of anhydrous *diethyl ether* (Note 1) and 75 mL of *pyridine*. With vigorous stirring, 53 g (0.21 mol) of *iodine* (Note 2) is added slowly. At the completion of the addition, the dark brown mixture is stirred an additional 10–20 min until complete dissolution is obtained.

The addition funnel is charged with 9.53 mL (9.46 g, 98.4 mmol) of *2-cyclohexen-1-one* (Note 3). After addition of approximately 2 mL of the enone, the flask is quickly immersed in an ice bath (Note 4) and the remainder of the enone is added dropwise to the cooled, stirred, dark-brown solution over a 10-min period. At the completion of the addition, the ice bath is removed and the mixture is stirred an additional 2.5 hr. The reaction mixture is poured into a 1-L separatory funnel and the round-bottomed flask is washed with two 200-mL portions of *diethyl ether* that are added to the separatory funnel. The mixture is washed successively with two 150-mL portions of 2N *hydrochloric acid* to remove *pyridine* (Note 5), three 150-mL portions of aqueous 20% *sodium thiosulfate* (Na₂S₂O₃) (Note 6) and 100 mL of brine. The resulting organic phase is dried over anhydrous *magnesium sulfate*, filtered, and evaporated at reduced pressure to give a yellow-orange solid.

This material is recrystallized from *diethyl ether*/*pentane* (2:1) to give 15.1 g (69%) of *2-iodo-2-cyclohexen-1-one* as a pale yellow solid, mp 48.5–49°C (Note 7). If desired, an additional 2.4 g (11%; mp 48–49°C) can be isolated by concentration of the mother liquor, column chromatography of the residue on 40 g of silica gel eluting with a mixture of 10% *ethyl acetate* in petroleum ether, and recrystallization of the collected iodoenone from *pentane*.

B. *2-(4-Methoxyphenyl)-2-cyclohexen-1-one*. A 500-mL, round-bottomed flask, equipped with a 1.5-in. Teflon-coated magnetic stirring bar and an argon inlet adaptor, is charged with 10.02 g (45.1 mmol) of *2-iodo-2-cyclohexen-1-one*, 10.69 g (70.4 mmol, 1.56 eq) of *4-methoxyphenylboronic acid* (Note 8), 16.72 g (72.1 mmol, 1.6 eq) of *silver(I) oxide* (Ag₂O) (Note 9), 0.85 g (2.8 mmol, 6 mol %) of *triphenylarsine* (Note 10), 0.53 g (1.4 mmol, 3 mol %) of *palladium(II) bis(benzonitrile)dichloride* (Note 11), 200 mL of *tetrahydrofuran* (THF) and 25 mL of water (Note 12). The reaction mixture, flushed

with **argon**, is stirred for 1 hr and then quenched by the addition of 125 mL of saturated aqueous **ammonium chloride**. After the solution is stirred for 1 hr, the resulting two-phase mixture is poured into a 2-L separatory funnel. The upper (organic) and lower (aqueous) phases are separated. The aqueous phase is extracted twice with 300-mL portions of **diethyl ether**. The combined organic phases are washed successively with two 500-mL portions of water and 200 mL of brine. The resulting organic phase is dried over anhydrous **magnesium sulfate**, filtered, and concentrated at reduced pressure to give a pale yellow solid.

The resulting product is purified by column chromatography on 90 g of silica gel eluting with a mixture of 30% **ethyl acetate** in petroleum ether (**Note 13**). The chromatographed material is further purified by recrystallization from **diethyl ether/pentane** (2:1) to give 7.1 g (78%) of **2-(4-methoxyphenyl)-2-cyclohexen-1-one** as a pale yellow solid, mp 58-59°C (**Note 14**). An additional 1.6 g (18%; mp 58-59°C) can be isolated by concentration of the mother liquor and column chromatography of the residue on 30 g of silica gel eluting with a mixture of 10% **ethyl acetate** in petroleum ether.

2. Notes

1. Unless otherwise indicated, the solvents are reagent grade and are used without further purification.
2. **Iodine** certified A.C.S. was purchased from Fisher Scientific Company.
3. **2-Cyclohexen-1-one** (97%) was purchased from Aldrich Chemical Company, Inc. *Caution! This chemical is highly toxic; glove protection is recommended.*
4. The reaction is exothermic. The first addition of 2 mL of the enone is necessary to avoid formation of aggregates that occurs if the mixture is cooled before this initial addition is made.
5. These first washes are very important; less acidic washes can promote reversal of the reaction from **pyridine** left in the medium.
6. These washes remove the brown color of the upper (organic) phase. The aqueous solution of **sodium thiosulfate** is 20% by weight.
7. Spectral data for **2-iodo-2-cyclohexen-1-one** follow: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 2.07 (quint, 2 H, $J = 6.3$), 2.43 (dt, 2 H, $J = 5.4, 5.8$), 2.64 (apparent t, 2 H, $J = 6.3$), 7.76 (t, 1 H, $J = 4.5$); $^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ : 22.7, 29.8, 37.1, 103.7, 159.5, 192.1.
8. **4-Methoxyphenylboronic acid** can be purchased from Aldrich Chemical Company, Inc.
9. **Silver(I) oxide**, 99+%, was purchased from Aldrich Chemical Company, Inc.
10. **Triphenylarsine**, 97%, was purchased from Aldrich Chemical Company, Inc.
11. **Palladium(II) bis(benzonitrile)dichloride** was purchased from Aldrich Chemical Company, Inc.
12. The dissolution of all solid chemicals may be slightly exothermic but this does not cause any build-up of pressure.
13. Insoluble by-products could be removed by hot filtration but with a significant loss of product. Chromatography is advised to optimize the isolated yield.
14. This material gave a satisfactory combustion analysis. Characterization data for **2-(4-methoxyphenyl)-2-cyclohexen-1-one** follow: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 2.09 (quint, 2 H, $J = 6.3$), 2.5-2.6 (m, 4 H), 3.80 (s, 3 H), 6.88 (d, 2 H, $J = 8$ Hz), 6.98 (t, 1 H, $J = 4.5$), 7.26 (d, 2 H, $J = 8$ Hz); $^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ : 22.9, 26.5, 39.0, 55.2, 113.4, 128.9, 129.7, 139.6, 146.9, 159.0, 198.2; Anal. calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2$: C, 77.20; H, 6.97. Found: C, 77.09; H, 7.01.

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

Cycloalkenones are ubiquitous as reactive intermediates and bioactive materials. Modification of a simple cycloalkenone by addition of a carbon substituent at the α -position should be a useful transformation, but one that is not readily accomplished by conventional enone chemistry. α -Substituted cycloalkenones could of themselves be of interest, but perhaps, of more general importance would be their use as intermediates for the production of substituted cycloalkanones or α,β -disubstituted cycloalkanones by a subsequent conjugate addition procedure.² These strategies avoid many of the

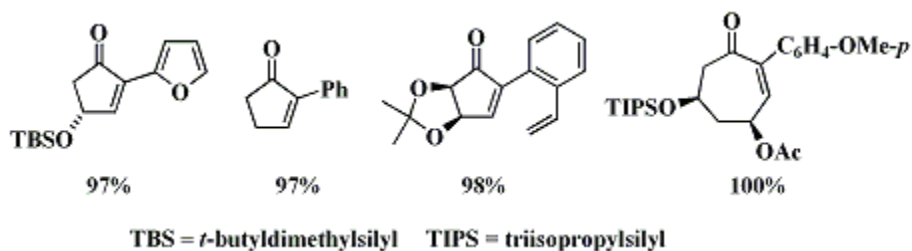
limitations attendant to the trapping of enolates with carbon electrophiles. The method of Kim involving treatment of enones with the combination of a dimethyl acetal, pyridine and trimethylsilyl triflates results in α -(1-methoxyalkyl)enones.³ The metallation of α -bromo-enones masked as ketals for α -functionalizations has been developed by Smith.⁴

This preparation illustrates an efficient two-step process for the transformation of a cycloalkenone to the corresponding α -substituted derivative. The first step involves the installation of an α -iodo substituent by a process thought to involve nucleophilic addition of pyridine, iodine capture of the resulting enolate, and pyridine-promoted elimination of pyridine.⁵ The resulting vinyl iodides are superior to other vinyl halides as participants in a variety of transition-metal catalyzed coupling reactions, illustrated here by the Suzuki coupling with an arylboronic acid. Other coupling partners that have been investigated in the laboratories of the submitters include alkenes, vinyl metals,⁶ arylstannanes,⁷ and alkyl-9-BBN's.²

Prior to our original report⁷ on this method, acceptable and general preparative routes to α -iodocycloalkenones had not been described. Treatment of a β -substituted cycloalkenone with trimethylsilyl azide and a mixture of iodine and pyridine sequentially in dichloromethane has now been reported as a method for the preparation of β -substituted- α -iodocycloalkenones.⁸ The combination of iodine and pyridinium dichromate has also been reported to provide α -iodoenones from enones⁹ as well as from ethynyl carbinols.^{9,10} Some successes have also been achieved with enones and iodine azide (IN₃)¹¹ and iodine/ceric ammonium nitrate.^{12,13,14} The submitters' first variant⁵ of the present procedure used carbon tetrachloride as a solvent. In this procedure this solvent has been replaced with the more benign diethyl ether.

The Suzuki coupling of 2-iodo-2-cyclohexen-1-one and 4-methoxyphenylboronic acid is achieved using silver(I) oxide as a suspension in aqueous THF as the base. Unlike earlier reports,^{15,16,17} in which up to 6 equiv of Ag₂O were used, we have found that 1.6 equiv is completely effective. Under these mild conditions, rapid conversion can be achieved at room temperature for a large variety of sensitively functionalized partners in near quantitative yields (see Table).¹⁸

TABLE
2-ARYL-2-CYCLOALKENONES FROM 2-iodo-2-CYCLOALKENONES



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 18. The development of this procedure was made possible by a grant from the National Science Foundation.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

2-(4-Methoxyphenyl)-2-cyclohexen-1-one:
2-Cyclohexen-1-one,2-(4-methoxyphenyl)- (10); (63828-70-6)

2-Iodo-2-cyclohexen-1-one:
2-Cyclohexen-1-one, 2-iodo- (8,9); (33948-36-6)

4-Methoxyphenylboronic acid:
Benzeneboronic acid, p-methoxy- (8),
Boronic acid,(4-methoxyphenyl)- (9); (5720-07-0)

Pyridine (8,9); (110-86-1)

Iodine (8,9); (7553-56-2)

2-Cyclohexen-1-one, HIGHLY TOXIC (8,9); (930-68-7)

Sodium thiosulfate:
Thiosulfuric acid, disodium salt (8,9); (7772-98-7)

Silver(I) oxide:
Silver oxide (8);
Silver oxide (Ag₂O) (9); (20667-12-3)

Triphenylarsine:
Arsine, triphenyl- (8,9); (603-32-7)

Palladium(II) bis(benzonitrile)dichloride:
Palladium, bis(benzonitrile)dichloro- (8,9); (14220-64-5)

