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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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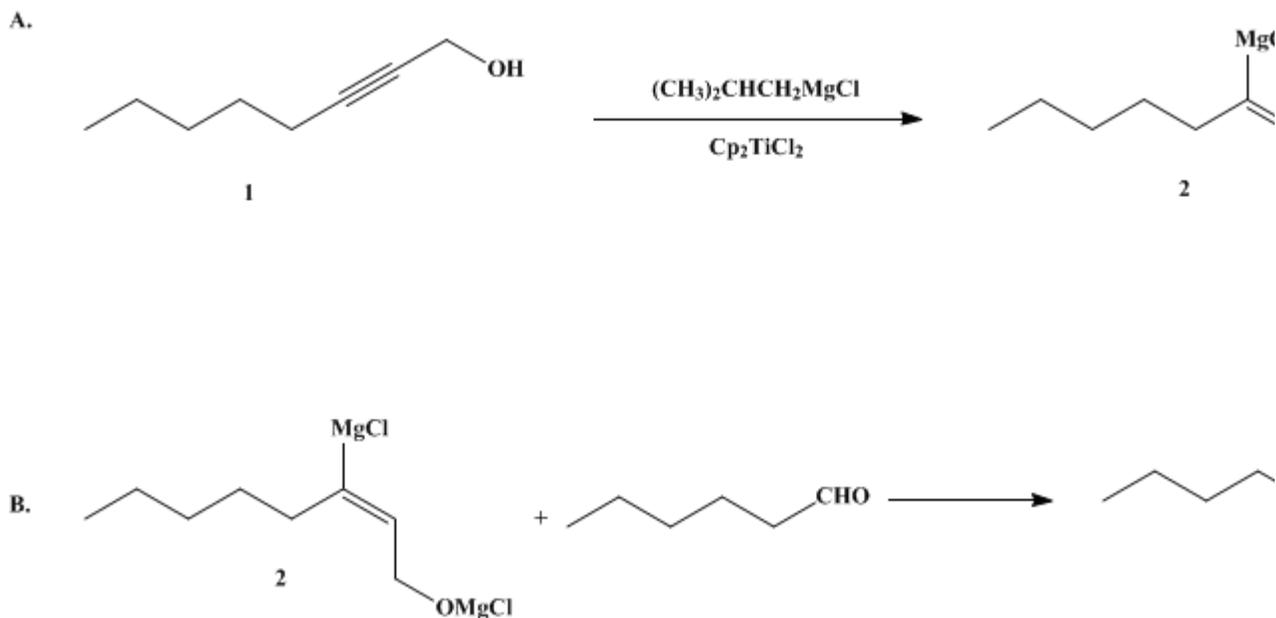
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 8, p.507 (1993); Vol. 69, p.106 (1990).

HYDROMAGNESIATION REACTION OF PROPARGYLIC ALCOHOLS: (*E*)-3-PENTYL-2-NONENE-1,4-DIOL FROM 2-OCTYN-1-OL



Submitted by Fumie Sato and Yuichi Kobayashi¹.
Checked by Zuliang Zhou and Ekkehard Winterfeldt.

1. Procedure

A. *The Grignard reagent 2.* A dry, 500-mL, three-necked, round-bottomed flask containing a magnetic stirring bar is equipped with a 100-mL pressure-equalizing dropping funnel, a glass stopper, and a two-way stopcock to which is attached a T-piece connected at one end to a supply of nitrogen, and at the other to an oil bubbler (Note 1). The flask is charged with a solution of isobutylmagnesium chloride in ether (320 mL, 0.75 M, 240 mmol) (Note 2) and (Note 3) and immersed in an ice-water bath. Titanocene dichloride (1.3 g, 5.2 mmol) (Note 4) is added at once and the resulting solution is allowed to stir at 0°C for 10 min. A solution of 2-octyn-1-ol (1) (13.2 g, 105 mmol) (Note 5) in ether (30 mL) (Note 3) is placed in the dropping funnel and added dropwise to the flask over 20 min at 0°C. The solution is stirred at room temperature for 4 hr to complete the reaction, affording Grignard reagent 2 (Note 6),(Note 7),(Note 8).

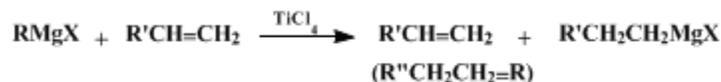
B. (*E*)-3-Pentyl-2-nonene-1,4-diol (4). Half the amount of the Grignard reagent 2 prepared according to Procedure A is diluted with ether (160 mL) and cooled in an ice-water bath to 0°C. A solution of hexanal (9.25 g, 92.5 mmol) (Note 9) dissolved in ether (30 mL) (Note 3) is added through the dropping funnel over 30 min with efficient stirring. After the addition is complete, the solution is stirred at 0–5°C for 2 hr and then poured into saturated ammonium chloride solution (300 mL). The mixture is stirred at 0°C for 1 hr. The resulting precipitate is removed by filtration through a pad of Celite (70 × 24 mm) under reduced pressure and the precipitate is washed with ethyl acetate (100 mL). The organic layer is separated and the aqueous phase is extracted with ethyl acetate (150 mL). The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to leave an oil that is purified by column chromatography on silica gel (Note 10) and (Note 11) to afford 4 (7.0–7.4 g, 59–62% yield) (Note 12).

2. Notes

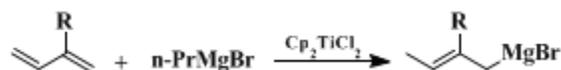
1. Reactions A and B are carried out under a nitrogen atmosphere. The submitters used argon.
2. A solution of isobutylmagnesium chloride in ether was prepared using isobutyl chloride (13.8 g, 150 mmol), magnesium turnings (4.05 g, 165 mg-atom), and ether (175 mL) according to the procedure for the preparation of *sec*-butylmagnesium chloride reported by Gilman and Kirby.² The checkers found that this solution contained about 145 mmol of isobutylmagnesium chloride.
3. Ether and tetrahydrofuran were distilled from benzophenone ketyl under an argon atmosphere.
4. Titanocene dichloride was purchased from Aldrich Chemical Company, Inc., and used without further purification.
5. Alcohol **1** was prepared according to the procedure of Rickards and Weiler³ and distilled under reduced pressure (102–108°C at 15 mm) before use. This material is also commercially available from Farchan Laboratories, Inc. The checkers obtained it from Lancaster Chemical Co.
6. The checkers found that Grignard reagent **2** could not be obtained quantitatively although all of the isobutylmagnesium chloride had reacted. The end point of the reaction was determined by TLC analysis of a small amount of reaction mixture after hydrolysis. 2-Octyn-1-ol (**1**) and (*Z*)-2-octen-1-ol (**3**), have R_f values of 0.53 and 0.47, respectively (using Silica Gel 60 F₂₅₄ precoated TLC aluminum sheets and benzene–ethyl acetate (1 : 1) as developing agent). If the reaction is not complete, an additional amount of titanocene dichloride should be added to the solution, which is cooled again to 0°C before the addition.
7. The submitters report that, if this solution is poured into 1 *N* hydrochloric acid and ice and worked up in the usual manner, (*Z*)-2-octen-1-ol (**3**) may be obtained in 86% yield by distillation, bp 97–101°C (12 mm). This product has the following spectra: IR (neat) cm^{-1} : 3290, 1457, 1014; ¹H NMR (90 MHz, CCl₄, (CH₃)₄Si, D₂O) δ : 0.88 (t, 3 H, $J = 6$), 1.05–1.57 (m, 6 H), 1.85–2.22 (m, 2 H), 4.03 (d, 2 H, $J = 5$), 5.27–5.65 (m, 2 H).
8. The submitters report that, if this solution is concentrated, then dissolved in tetrahydrofuran and treated with methyl iodide, (*Z*)-3-methyl-2-octen-1-ol (**5**) may be obtained after silica gel chromatography using hexane–ether as eluent. The product has the following spectra: IR (neat) cm^{-1} : 3305, 1447, 1000; ¹H NMR (90 MHz, CCl₄, (CH₃)₄Si, D₂O) δ : 0.88 (t, 3 H, $J = 6$), 1.1–1.6 (m, 6 H), 1.68 (s, 3 H), 1.9–2.2 (m, 2 H), 3.99 (d, 2 H, $J = 6$), 5.29 (t, 1 H, $J = 6$).
9. Hexanal was used as supplied by Tokyo Kasei Kogyo Co., Ltd. (Japan). The checkers obtained it from Aldrich Chemical Company, Inc.
10. Silica gel (100–200 mesh) was purchased from Wako Pure Chemical Industries, LTD (Japan).
11. A silica gel column (225 g, 60 × 210 mm) is used with a mixture of benzene and ethyl acetate as an eluent [R_f value (benzene–ethyl acetate = 1 : 1): **3**, 0.47; **4**, 0.23]. Distillation of product **4** under reduced pressure caused partial decomposition (bp 120–155°C/0.25 mm).
12. Diol **4** has the following spectra: IR (neat) cm^{-1} : 3300, 1468, 1020; ¹H NMR (90 MHz, CDCl₃, (CH₃)₄Si, D₂O) δ : 0.89 (t, 6 H, $J = 6$), 1.1–1.7 (m, 14 H), 1.9–2.2 (m, 4 H), 4.02 (m, 1 H), 4.20 (d, 2 H, $J = 6$), 5.63 (t, 1 H, $J = 6$). With D₂O exchange there is a change in the range of δ 1.9–2.2 (m, 2 H).

3. Discussion

In 1962 Cooper and Finkbeiner reported the titanium chloride (TiCl₄)-catalyzed exchange reaction of an alkyl Grignard reagent (RMgX) having β -hydrogen(s) with olefins (Eq. 1).⁴ In this reaction, RMgX can be formally regarded as a source of HMgX that adds to the olefins, and hence this reaction is known as the hydromagnesiation reaction.



Since then, hydromagnesiation of other unsaturated hydrocarbons such as conjugated dienes and acetylenes has been investigated intensively.^{5,6} Hydromagnesiation of 2-alkyl substituted 1,3-butadienes has been shown to proceed regioselectively by using Cp₂TiCl₂ as a catalyst to afford the corresponding allylic Grignard reagent shown in Eq. 2 quantitatively.⁷

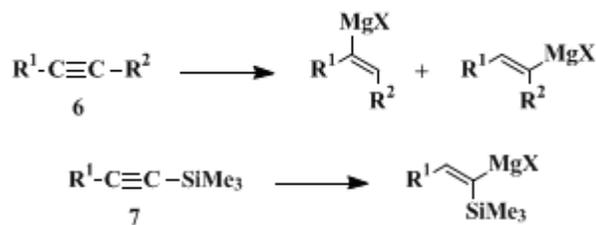


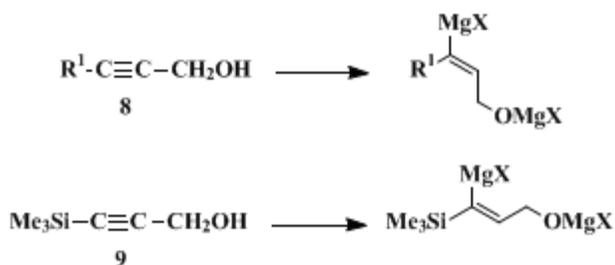
Cp₂TiCl₂-catalyzed hydromagnesiation of acetylenes with isobutyl Grignard reagents has also been

shown to provide a convenient and practical method for preparation of various vinyl Grignard reagents. The acetylenes so far examined include 1,2-dialkylacetylenes **6** (Eq. 3), 1-(trimethylsilyl)acetylenes **7** (Eq. 4),⁸ propargyl alcohols **8** (Eq. 5),⁹ and 3-(trimethylsilyl)propargyl alcohol (**9**) (Eq. 6).¹⁰ Although the reaction occurs with low regioselectivity for unsymmetric dialkylacetylenes **6**, high regioselectivity is attained in the case of **7**, **8**, and **9**. Acetylenes **6**, **7**, and **8** afford the corresponding vinylmagnesium halides in which HMgX adds in a *syn* pathway to the triple bond, while **9** affords the *anti*-addition product. In the latter case, hydromagnesiation follows the *syn* pathway to yield the corresponding (*Z*)-alkenyl Grignard reagent first, which, however, isomerizes rapidly under the reaction conditions to the (*E*)-alkenyl Grignard reagent. Since the hydromagnesiation reaction of **7**, **8**, and **9** proceeds highly regio- and stereo-selectively, the reaction has become a powerful synthetic tool for utilization in organic syntheses. Some of the examples are given in Table I.

TABLE I

Starting Acetylene	i-BuMgX X	Vinylmagnesium Halide	Electrophile	Product
	Br		I ₂	
	Br		/CuI	
	Cl		I ₂	
	Cl		MeI	
	Br			
	Br		EtCN	





This preparation is referenced from:

- [Org. Syn. Coll. Vol. 9, 510](#)

References and Notes

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Appendix

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

benzophenone ketyl

Cp₂TiCl₂

1-(trimethylsilyl)acetylenes

Br

Cl

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

isobutyl chloride (513-36-0)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

titanium chloride (7550-45-0)

argon (7440-37-1)

3-(trimethylsilyl)propargyl alcohol (5272-36-6)

Hexanal (66-25-1)

2-OCTYN-1-OL (20739-58-6)

isobutylmagnesium chloride (5674-02-2)

Titanocene dichloride (1271-19-8)

(E)-3-Pentyl-2-nonene-1,4-diol (138149-15-2)

sec-butylmagnesium chloride (15366-08-2)

(Z)-2-octen-1-ol (26001-58-1)

(Z)-3-methyl-2-octen-1-ol (30804-78-5)