Organic
Syntheses

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). 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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

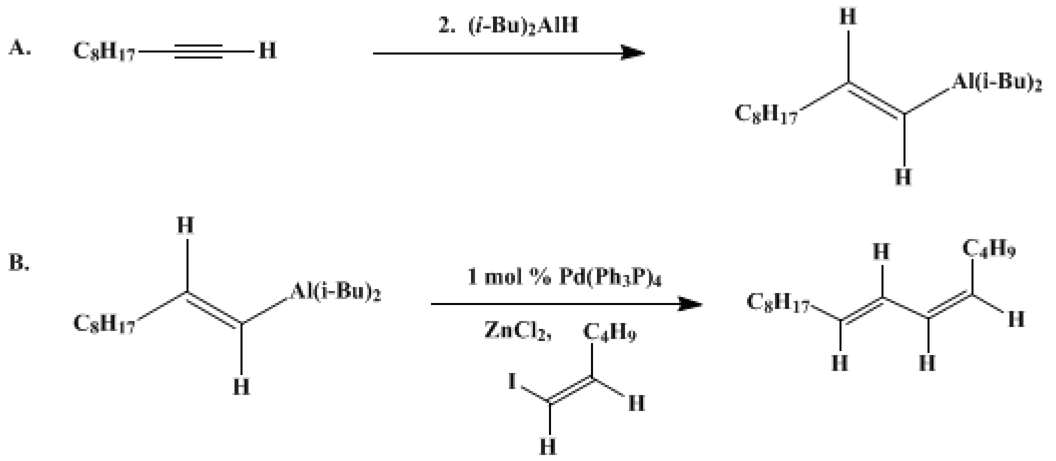
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.066.0060

Organic Syntheses, Coll. Vol. 8, p.295 (1993); Vol. 66, p.60 (1988).

PALLADIUM-CATALYZED SYNTHESIS OF CONJUGATED DIENES: (5*Z*,7*E*)-5,7-HEXADECADIENE

[5,7-Hexadecadiene, (*Z*, *E*)-]



Submitted by Ei-Ichi Negishi, Tamotsu Takahashi, and Shigeru Baba[1].
Checked by Masako Ohta and Ryoji Noyori.

1. Procedure

Caution! Organoaluminum compounds are pyrophoric. They must be kept and used with caution under a nitrogen atmosphere.

A. *(E)-1-Decenyldiisobutylalane*. An oven-dried, 300-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum inlet, and an outlet connected to a mercury bubbler is flushed with nitrogen, immersed in a water bath kept at room temperature, and charged with 22.6 mL (125 mmol) of 1-decyne (Note 1) and 80 mL of hexane (Note 2). To this flask is added dropwise, with stirring, 22.3 mL (125 mmol) of diisobutylaluminum hydride (Note 3) using a syringe (Note 4). After the addition has been completed, the water bath is replaced with an oil bath kept at 50–60°C, and the reaction mixture is stirred for 6 hr at this temperature (Note 5).

B. *(5Z, 7E)-5,7-Hexadecadiene.* To a mixture of 21.0 g (100 mmol) of (*Z*)-1-hexenyl iodide (Note 6), 13.6 g (100 mmol) of zinc chloride (Note 7), and 1.15 g (1 mmol) of tetrakis(triphenylphosphine) palladium (Note 8) in 100 mL of tetrahydrofuran (Note 9) is added the solution of (*E*)-1-decenyldiisobutylalane prepared as described above, while the reaction temperature is controlled with a water bath at room temperature. After the reaction mixture is stirred for 6 hr at room temperature, it is slowly transferred into a mixture of 300 mL of ice-cooled 3 *N* hydrochloric acid and 100 mL of pentane via a double-ended needle under a positive pressure of nitrogen. The organic layer is separated, and the aqueous layer is extracted twice with 100 mL of pentane. The combined organic layer is washed with 100 mL of water, followed by 100 mL of saturated aqueous sodium bicarbonate, and then dried over anhydrous magnesium sulfate. After filtration, the solvent is removed using a rotary evaporator. Hydroquinone (30 mg) is added and the residue is distilled (Note 10) to give 14.3–15.8 g [64–66% based on (*Z*)-1-hexenyl iodide] of (5*Z*,7*E*)-5,7-hexadecadiene as a colorless liquid, bp 116–119°C (1 mm) (Note 11) and (Note 12).

2. Notes

1. The submitters used 1-decyne from Farchan Laboratories, Inc. without further purification. The checkers used the material purchased from Aldrich Chemical Company, Inc. and Tokyo Kasei Kogyo Company.

2. Hexane available from Fisher Scientific Company was purified by distillation from sodium. The checkers used the solvent from Wako Pure Chemical Industries, Ltd. after distillation from sodium and benzophenone or calcium hydride under argon.

3. The submitters used neat diisobutylaluminum hydride obtained from Ethyl Corporation. The checkers used the material from Aldrich Chemical Company, Inc.

4. The submitters used a 50-mL syringe with a Luer-lock and a long (≥6-in.) 18-gauge needle, the plunger of which was lightly greased with a silicone grease. For a larger-scale operation, it is advisable to use a septum-capped graduated cylinder and a double-ended needle in place of a syringe.

5. GLC analysis of a small aliquot after iodinolysis with iodine dissolved in tetrahydrofuran indicated the formation of (*E*)-1-decenyldiisobutylalane (ca. 80%), 1-decynyldiisobutylalane (7–8%), and 1-decene (5%), together with 1-decyne (ca. 10%).

6. (*Z*)-1-Hexenyl iodide was prepared by treating acetylene with lithium dibutylcuprate followed by iodine according to an *Organic Syntheses* procedure.[2]

7. Zinc chloride available from Mallinckrodt, Inc. was flame-dried under a slow stream of nitrogen. The checkers used the material from Wako Pure Chemical Industries, Ltd. after heating under vacuum (1 mm).

8. Tetrakis(triphenylphosphine)palladium was prepared according to an *Inorganic Syntheses* procedure.[3] The submitters used a freshly prepared, shiny yellow crystalline sample of the palladium complex. On standing for an extended period of time (more than a few weeks), its color gradually darkens. The checkers used tetrakis(triphenylphosphine)palladium purchased from Aldrich Chemical Company, Inc.

9. Tetrahydrofuran available from Fisher Scientific Company or Wako Pure Chemical Industries, Ltd. was distilled from sodium and benzophenone.

10. Hydroquinone was added to avoid polymerization of the diene product.

11. Gas chromatographic examination of the reaction mixture using a 2-ft column of 20% SE-30 on Chromosorb W with undecane as an internal standard (200°C) indicates that (5*Z*,7*E*)-5,7-hexadecadiene is formed in 86–90% yield, based on (*Z*)-1-hexenyl iodide. The product obtained by this procedure shows the following properties: n_{D}^{23} 1.4662; IR (neat) cm^{-1}: 1630 (w), 1370 (w), 978 (m), 943 (m), 720 (m); ^{1}H NMR [CCl_4, $(CH_3)_4Si$] δ: 0.8–1.0 (m, 6 H), 1.15–1.5 (m, 16 H), 1.9–2.3 (m, 4 H) m, 5.15 (dt, 1 H, *J* = 10, 8), 5.61 (dt, 1 H, *J* = 14, 7) 5.92 (dd, 1 H, *J* = 10, 11), 6.30 (dd, 1 H, *J* = 11, 14).

12. (5*E*,7*E*)-5,7-Hexadecadiene can be prepared in the same manner as described except that (*E*)-1-hexenyl iodide is used in place of its (*Z*) isomer. The (*E*) iodide is obtainable by treating (*E*)-1-hexenyldiisobutylalane, prepared from 1-hexyne and diisobutylaluminum hydride, with iodine in tetrahydrofuran.[4] The (*E,E*) diene prepared by this procedure shows the following properties: n_{D}^{23} 1.4671; IR (neat) cm^{-1}: 1370 (w), 982 (m), 722 (m); ^{1}H NMR [CCl_4, $(CH_3)_4Si$] δ: 0.89 (t, 6 H, *J* = 6), 1.15–1.7 (m, 16 H), 1.8–2.2 (m, 4 H), 5.2–6.15 (m, 4 H): ^{13}C NMR [$CDCl_3$, $(CH_3)_4Si$] δ: 13.93, 14.06, 22.34, 22.76, 29.40, 29.62, 31.16, 31.78, 32.03, 32.37, 32.72, 130.59, 132.19, 132.26.

3. Discussion

The procedure described here is based on two reports by Negishi and his co-workers.[5,6] The original procedure[5] did not use zinc chloride as the second catalyst and required ca. 5 mol% of $Pd(PPh_3)_4$. The preparation of (*E*)-1-alkenylalane via hydroalumination was first reported by Wilke and Müller.[7] The procedure used here is essentially that which was described by Zweifel.[8]

The first highly stereoselective and satisfactory syntheses of conjugated dienes of general applicability are those based on organoboron chemistry reported by Negishi for (*E,E*) dienes[9] and (*E,Z*) dienes[10] as well as by Zweifel for (*Z,Z*) dienes.[11]

The method described here represents the first highly selective and general cross-coupling procedure for preparing conjugated dienes.[5,6] Subsequently, several variations of the above-described method have been published by Negishi and others. Some salient features of these investigations are as follows. First, palladium–phosphine complexes, such as $Pd(PPh_3)_4$, are preferred to nickel complexes,[5] which tend to reduce stereoselectivity. Second, all three possible stereoisomers may be prepared using this methodology. Third, in addition to Al, Zr,[12] Mg,[13] [14] B,[15] and Cu[16] have been shown to participate in Pd-catalyzed alkenyl–alkenyl cross-coupling. Fourth, the reaction is markedly accelerated by the addition of zinc and cadmium halides, such as $ZnCl_2$, $ZnBr_2$, and $CdCl_2$,[6] at least in cases where organometals containing Al,[6] Zr,[6] and Cu[16] are used. This and other observations suggest that alkenylzinc derivatives are probably the most reactive organometals in this reaction,[6] although no systematic comparisons have been made so far. Otherwise, the choice of metal depends on the stereochemistry of the desired product the required chemoselectivity, and other factors. For example, (*E*)-alkenyl metals are most directly available via hydroalumination,[8] carboalumination,[17] [18] hydroboration,[19] or hydrozirconation[20] of alkynes. In cases where the use of such derivatives is desirable, Al. B. or Zr should be considered first. On the other hand, (*Z*)-alkenyl metals are often readily available via carbocupration[21] of alkynes, and they may be used directly or via formation of the corresponding (*Z*)-alkenyl iodide.

Together with the organoboron procedures mentioned above, the Pd-catalyzed cross coupling procedures have been applied to the synthesis of a wide variety of insect pheromones, terpenoids, and carotenoids.

References and Notes

1. Department of Chemistry, Purdue University, West Lafayette, IN 47907.
2. Alexakis, A.; Cahiez, G.; Normant; J. F. *Org. Synth., Coll. Vol. VII* **1990**, 290.
3. Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.
4. Zweifel, G.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 2753.
5. Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729.
6. Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254.
7. Wilke, G.; Müller, H. *Chem. Ber..* **1956**, *89*, 444.
8. Zweifel, G.; Miller, J. A. *Org. React.* **1984**, *32*, 375.
9. Negishi, E.; Yoshida, T. *J. Chem. Soc., Chem. Commun.* **1973**, 606.
10. Negishi, E.; Lew, G.; Yoshida, T. *J. Chem. Soc., Chem. Commun.* **1973**, 874.
11. Zweifel, G.; Polston, N. L. *J. Am. Chem. Soc.* **1970**, *92*, 4068.
12. Okukado, N.; Van Horn, D. E.; Klima, W. L.; Negishi, E. *Tetrahedron Lett.* **1978**, 1027.
13. Dang, H. P.; Linstrumelle, G. *Tetrahedron Lett.* **1978**, 191;
14. Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 315.
15. Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron Lett.* **1981**, *22*, 127.
16. Jabri, N.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1981**, *22*, 959; **1982**, *23*, 1589.
17. Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252;
18. For a review, see Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333.
19. Brown, H. C. "Hydroboration," Benjamin: New York, 1962.
20. Schwartz, J. *J. Organometal Chem. Library* **1976**, *1*, 461.
21. Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

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

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

hydroquinone (123-31-9)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

iodine (7553-56-2)

Benzophenone (119-61-9)

sodium (13966-32-0)

palladium (7440-05-3)

zinc chloride (7646-85-7)

1-Decyne (764-93-2)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

iodide (20461-54-5)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

1-Hexyne (693-02-7)

argon (7440-37-1)

calcium hydride (7789-78-8)

diisobutylaluminum hydride (1191-15-7)

undecane (1120-21-4)

1-decene (872-05-9)

Tetrakis(triphenylphosphine)palladium (14221-01-3)

(Z)-1-hexenyl iodide (16538-47-9)

lithium dibutylcuprate

1-decynyldiisobutylalane

(5Z,7E)-5,7-Hexadecadiene,
(5Z, 7E)-5,7-Hexadecadiene,
5,7-Hexadecadiene, (Z, E)- (86883-79-6)

(E)-1-Decenyldiisobutylalane (107441-86-1)

(5E,7E)-5,7-Hexadecadiene

(E)-1-hexenyl iodide

(E)-1-hexenyldiisobutylalane