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of Reliable Methods
for the Preparation
of Organic Compounds

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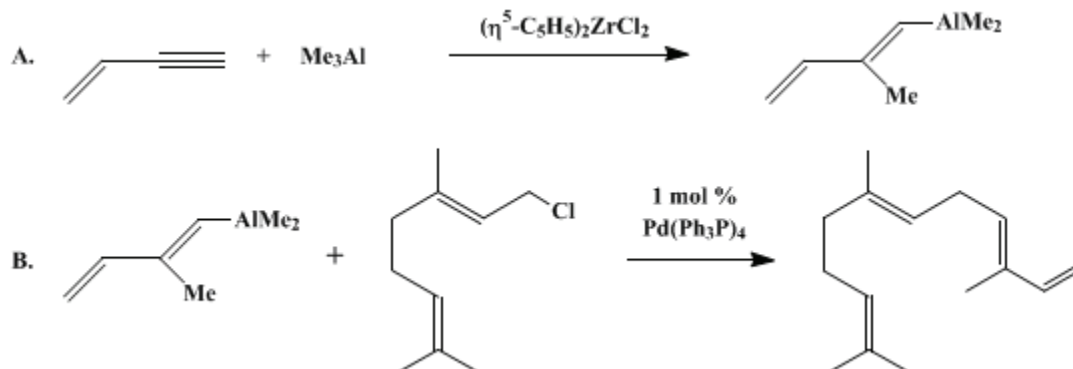
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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PALLADIUM-CATALYZED SYNTHESIS OF 1,4-DIENES BY ALLYLATION OF ALKENYLALANES: α -FARNESENE

[1,3,6,10-Dodecatetraene, 3,7,11-trimethyl-]



Submitted by Ei-ichi Negishi¹ and Hajime Matsushita².
Checked by Pauline J. Sanfilippo and Andrew S. Kende.

1. Procedure

Caution! Trimethylalane (Note 1) is highly pyrophoric. It must be kept and used under a nitrogen atmosphere.

A. *(E)*-2-Methyl-1,3-butadienyl dimethylalane. An oven-dried, 1-L, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an outlet connected to a mercury bubbler is charged with 7.01 g (24 mmol) of dichlorobis(η^5 -cyclopentadienyl)zirconium (Note 2) and flushed with nitrogen. To this are added sequentially at 0°C 100 mL of 1,2-dichloroethane (Note 3), 12.48 g (120 mmol) of a 50% solution of 1-buten-3-yne in xylene (Note 4), and 120 mL (240 mmol) of a 2 M solution of trimethylalane in toluene (Note 1). The reaction mixture is stirred for 12 hr at room temperature and used in the next step without further treatment (Note 5).

B. *(3E, 6E)*-3,7,11-Trimethyl-1,3,6,10-dodecatetraene (α -farnesene). To the solution of *(E)*-2-methyl-1,3-butadienyl dimethylalane prepared above are added 17.25 g (100 mmol) of geranyl chloride (Note 6) and 1.15 g (1 mmol) of tetrakis(triphenylphosphine)palladium (Note 7) dissolved in 100 mL of dry tetrahydrofuran (Note 8), while the reaction temperature is controlled below 25–30°C with a water bath. After the reaction mixture is stirred for 6 hr at room temperature, 250 mL of 3 N hydrochloric acid is slowly added at 0°C. The organic layer is separated and the aqueous layer is extracted twice with pentane. The combined organic layer is washed with water, saturated aqueous sodium bicarbonate, and water again. After the organic extract is dried over anhydrous magnesium sulfate, the solvent is removed thoroughly using a rotary evaporator (15–20 mm), and the crude product is passed through a short (15–20-cm) silica gel column (60–200 mesh) using hexane as an eluent (Note 9). After the hexane is evaporated using a rotary evaporator, the residue is distilled using a 12-cm Vigreux column to give 16.70 g (83% based on geranyl chloride) of α -farnesene as a colorless liquid, bp 63–65° (0.05 mm) (Note 10).

2. Notes

- The submitters used trimethylalane available in a cylinder from Ethyl Corporation. Both neat trimethylalane and its 2 M solution in toluene gave comparable results. The toluene solution of trimethylalane is also available from Aldrich Chemical Company.
- The submitters used dichlorobis(η^5 -cyclopentadienyl)zirconium available from Aldrich Chemical Company. This chemical is sufficiently air-stable to be handled in air.

3. The 1,2-dichloroethane available from Aldrich Chemical Company was distilled from phosphorus pentoxide before use. Although less effective, dichloromethane may also be used in the carbometallation step.
4. The submitters used a 50% solution of 1-buten-3-yne in xylene, available from Chemical Samples Company. For transferring this solution, the following procedure may be recommended. An ampule containing the solution is cooled with an ice-salt bath, opened, and capped with a rubber septum. A weighed measuring flask capped with a rubber septum is cooled with the ice-salt bath. To this is introduced the cooled solution by means of a double-tipped needle, and the weighed solution is then introduced to the reaction flask by means of a double-tipped needle.
5. The reaction mixture containing (*E*)-(2-methyl-1,3-butadienyl)dimethylalane may be stored at room temperature for at least a few days. Although it appears to be stable at room temperature for a much longer period of time, its thermal stability has not been carefully determined. The cross-coupling reaction in Section B should require only one equivalent of the alkenylalane, and its yield by gas chromatographic examination is 90–100%. It is practical, however, to use ca. 20% excess of 1-buten-3-yne for preparing the alkenylalane so as to achieve a high-yield conversion of geranyl chloride into α -farnesene.
6. Geranyl chloride was prepared by treating geraniol, available from Aldrich Chemical Company, with carbon tetrachloride and triphenylphosphine according to an *Organic Syntheses* procedure (Calzada, J. G.; Hooz, J. *Org. Synth., Coll. Vol. VI* **1988**, 634).
7. Tetrakis(triphenylphosphine)palladium was prepared by treating palladium chloride, available from Matthey Bishop, Inc., with hydrazine hydrate in the presence of triphenylphosphine 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. Even such samples are effective in many palladium-catalyzed cross-coupling reactions,^{4,5} but have not been tested in this reaction. Tetrakis(triphenylphosphine)palladium is also available from Aldrich Chemical Company.
8. Tetrahydrofuran available from Aldrich Chemical Company was distilled from sodium and benzophenone.
9. The main purpose of this filtration is to remove traces, if any, of palladium-containing compounds that might induce undesirable transformations, such as isomerization and polymerization, during the subsequent distillative workup.
10. The submitters reported bp 73–75°C (0.05 mm). Gas chromatographic examination of the reaction mixture with a hydrocarbon internal standard indicates that α -farnesene is formed in 98% yield, based on geranyl chloride, essentially as a single product (>98%). The product obtained by this procedure shows the following properties: n_D^{23} 1.4977; IR (neat) cm^{-1} : 3080(w), 2960(s), 2900(s), 1664(w), 1635(m), 1601(m), 981(m), 883(s); ^1H NMR [CDCl_3 , $(\text{CH}_3)_4\text{Si}$] δ : 1.59 (s, 3 H), 1.63 (s, 3 H), 1.66 (s, 3 H), 1.74 (s, 3 H), 2.03 (m, 4 H), 2.82 (t, $J = 6$, 2 H); ^{13}C NMR [CDCl_3 , $(\text{CH}_3)_4\text{Si}$] δ : 11.62, 16.07, 17.63, 25.69, 26.89, 27.35, 39.88, 110.37, 122.36, 124.50, 131.10, 131.74, 133.79, 135.55, 141.69.

3. Discussion

This procedure for the synthesis of α -farnesene⁶ is representative of the palladium-catalyzed stereo- and regio-specific coupling of allylic derivatives with alkenyl- and arylmetals.⁷ The use of neryl chloride in place of geranyl chloride gives the 6-*Z* isomer of α -farnesene in 77% yield (>98% isomeric purity).⁷ The high stereo- and regio-specificity (>98%) has been observed only with γ,γ -disubstituted allylic electrophiles. With γ -monosubstituted allylic derivatives, varying amounts of stereo- and regioisomers have been observed.⁸

Various allyl derivatives, such as those containing acyloxy, dialkylaluminumoxy, and trialkylsilyloxy groups, also react with alkenylalanes in the presence of a palladium-phosphine catalyst,⁸ and the synthesis of α -farnesene has been achieved by using geranyl acetate. Although the observed yields are ca. 20% lower than those observed with geranyl chloride, a careful comparison of the two derivatives has not been performed. In general, the order of reactivity of various leaving groups is: $-\text{Cl} > -\text{OAc} > -\text{OPO}(\text{OR})_2 > -\text{OSiR}_3$.

In addition to alkenylalanes, readily obtainable by either hydroalumination⁹ or carboalumination¹⁰ of alkynes, alkenylzirconium derivatives,^{7,11} obtainable by hydrozirconation¹² of alkynes, undergo a

related alkenyl-allyl coupling reaction. In a related aryl-allyl coupling reaction catalyzed by palladium complexes, arylmetals containing magnesium, zinc, and cadmium, in addition to those containing aluminum and zirconium, give the expected cross-coupled products. The yields with zinc or cadmium tend to be higher than those with aluminum or zirconium, whereas magnesium, in this respect, is inferior to aluminum or zirconium.⁸ Related reactions of alkenylboranes¹³ and alkenylmercury compounds¹⁴ are also known, but their applicability to the selective synthesis of 1,4-dienes of terpenoid origin, such as α -farnesene, is unknown.

The synthesis of 1,4-dienes via cross-coupling can, in principle, be achieved by either the reaction of allylmetals with alkenyl electrophiles or by the reaction of alkenylmetals with allyl electrophiles. The reaction of π -allylnickel derivatives with alkenyl halides¹⁵ represents the former approach and can be highly regioselective. Stereo- and regiodefined alkenylmetals containing aluminum,^{16 17 18 19} boron,²⁰ silicon²¹ and copper^{22 23 24 25} have been reported to react with allylic electrophiles producing 1,4-dienes. With the possible exception of the organocopper reaction, the scope of these uncatalyzed reactions is practically limited to γ -unsubstituted allylic halides. Finally, the nickel-catalyzed reaction of Grignard reagents with allylic electrophiles²⁶ is also known, but the reaction is generally nonselective. Nor does it appear that the reaction has been applied to the synthesis of 1,4-dienes.

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

α -Farnesene

dichlorobis (η^5 -cyclopentadienyl)zirconium

6-Z isomer of α -farnesene

(α -farnesene)

hydrochloric acid (7647-01-0)

sodium bicarbonate (144-55-8)

carbon tetrachloride (56-23-5)

1,2-dichloroethane (107-06-2)

nitrogen (7727-37-9)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

xylene (106-42-3)

hydrazine hydrate (7803-57-8)

Pentane (109-66-0)

dichloromethane (75-09-2)

palladium chloride (7647-10-1)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

1-Buten-3-yne (689-97-4)

hexane (110-54-3)

geraniol (106-24-1)

triphenylphosphine (603-35-0)

Trimethylalane (75-24-1)

Geranyl chloride (5389-87-7)

neryl chloride

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

1,3,6,10-Dodecatetraene, 3,7,11-trimethyl-

(E)-(2-Methyl-1,3-butadienyl)dimethylalane

geranyl acetate (105-87-3)

phosphorus pentoxide (1314-56-3)

(3E, 6E)-3,7,11-Trimethyl-1,3,6,10-dodecatetraene (502-61-4)