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of Organic Compounds

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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.

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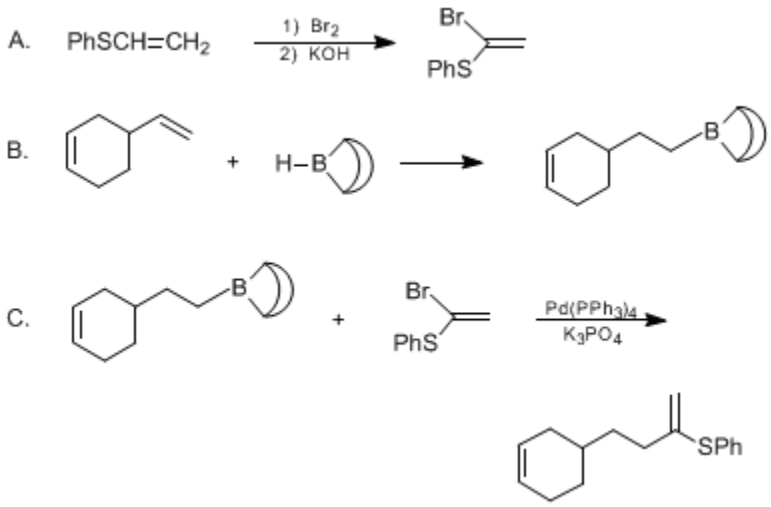
PALLADIUM(0)-CATALYZED REACTION OF 9-ALKYL-9-BORABICYCLO[3.3.1]NONANE WITH 1-BROMO-1-PHENYLTHIOETHENE: 4-(3-CYCLOHEXENYL)-2-PHENYLTHIO-1-BUTENE



Submitted by Tatsuo Ishiyama, Norio Miyaura, and Akira Suzuki[1].
Checked by Ron J. Graham and Leo A. Paquette.
Discussion Addendum *Org. Synth.* **2011**, *88*, 207

1. Procedure

A. *1-Bromo-1-phenylthioethene.* A 300-mL, two-necked, round-bottomed flask is fitted with a magnetic stirring bar, pressure-equalizing dropping funnel, and a reflux condenser to which a nitrogen inlet tube and an oil bubbler are attached, and flushed with nitrogen (Note 1). In the flask are placed 13.6 g (100 mmol) of phenyl vinyl sulfide (Note 2) and 80 mL of ether (Note 3), which are then cooled to ca. −78°C with a dry ice-methanol bath. Bromine (16.0 g, 100 mmol) is added dropwise over 30 min to the stirred solution. After the solution is warmed to room temperature, 40 mL of absolute ethanol, followed by a solution of 8.0 g (140 mmol) of potassium hydroxide in 80 mL of absolute ethanol is added dropwise to the resulting slightly red solution over 30 min. The light brown solution containing a white precipitate of potassium bromide is stirred at room temperature for 2 hr. The precipitate is removed by filtration and the filtrate is concentrated by rotary evaporation. The residue is treated with 200 mL of ether and 200 mL of water. The organic layer is separated, washed with brine (50 mL), and dried over anhydrous magnesium sulfate. After rotary evaporation of the solvent, the residual oil is distilled under reduced pressure to give 17.2 g (80% yield) of 1-bromo-1-phenylthioethene (Note 4) as a colorless liquid, bp 49–50°C (0.07 mm).

B. *9-[2-(3-Cyclohexenyl)ethyl]-9-BBN.* A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, thermometer, reflux condenser, and a pressure-equalizing addition funnel capped with a rubber septum. The apparatus is connected through the condenser to a nitrogen source and an oil bubbler and flushed with nitrogen. The flask is charged with 35 mL of tetrahydrofuran (Note 5) and 8.32 g (77.0 mmol) of 4-vinyl-1-cyclohexene (Note 6) and cooled to 0°C. A 0.5 M solution of 9-BBN (9-borabicyclo[3.3.1]nonane) in tetrahydrofuran (154 mL, 77.0 mmol) (Note 7) is transferred via cannula to the addition funnel and is added dropwise with stirring over 1 hr maintaining the temperature at 0–5°C. The reaction mixture is stirred for 1 hr at 0°C and for 1.5 hr at room temperature. The solution obtained is used in the next step without further treatment (Note 8).

C. *4-(3-Cyclohexenyl)-2-phenylthio-1-butene.* To the above solution of the borane derivative, 0.809 g (0.700 mmol) of tetrakis(triphenylphosphine)palladium(0) (Note 9), 1.47 g (5.60 mmol) of

triphenylphosphine (Note 10), 35 mL of 3 M potassium phosphate in water (Note 11), and finally 15.1 g (70.0 mmol) of 1-bromo-1-phenylthioethene are added and the resulting mixture is heated at reflux for 3 hr with stirring. The light brown solution is cooled to room temperature and treated with 6.4 g (100 mmol) of ethanolamine (Note 12) for 1 hr. Then 100 mL of hexane and 100 mL of water are added. The organic layer is separated, washed with 100 mL of water, and dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated by rotary evaporation. The addition of 250 mL of hexane to the residual viscous oil, containing some solid, precipitates the 9-BBN/ethanolamine complex. The solid is removed by filtration and is washed with hexane (50 mL × 3), and the filtrate is concentrated using a rotary evaporator. The crude product is passed through a short silica gel column (60–200 mesh, 60 g) using hexane as an eluent (Note 13). After removal of the hexane, the residue is distilled under reduced pressure to give 12.5–13.9 g (73–81%) of 4-(3-cyclohexenyl)-2-phenylthio-1-butene as a colorless liquid, bp 114–116°C (0.04 mm) (Note 14).

2. Notes

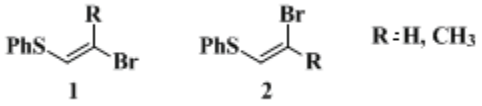
1. All glassware was pre-dried in an oven at 120°C for 2 hr, assembled while hot, and allowed to cool under a stream of nitrogen.
2. The preparation of phenyl vinyl sulfide is described *Org. Synth., Coll. Vol. VII* **1990**, 453 and in this volume on pp. 662. The compound is also available from Aldrich Chemical Company, Inc.
3. Ether was distilled from benzophenone ketyl under nitrogen before use.
4. The product is labile at room temperature and should be stored in a freezer. Spectral data are as follows: IR (neat) cm^{-1}: 3076, 3060, 1583, 1477, 1440, 1069, 752, 689; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.73 (d, 1 H, J = 2.3), 5.83 (d, 1 H, J = 2.3), 7.23–7.46 (m, 5 H).
5. Tetrahydrofuran is distilled from benzophenone ketyl under nitrogen before use.
6. 4-Vinyl-1-cyclohexene was obtained from Aldrich Chemical Company, Inc., and distilled it prior to use.
7. A 0.5 M solution of 9-BBN in tetrahydrofuran was purchased from Aldrich Chemical Company, Inc., and was used without additional purification. The preparation[2] of the reagent by hydroboration of 1,5-cyclooctadiene with borane/tetrahydrofuran complex is reported.
8. If necessary, 9-[2-(3-cyclohexenyl)ethyl]-9-BBN[3] can be purified by removal of the solvent and vacuum distillation under nitrogen [bp 103°C (0.035 mm)].
9. The preparation of tetrakis(triphenylphosphine)palladium(0) is described.[4] It is also available from Aldrich Chemical Company, Inc.
10. Triphenylphosphine was obtained from Nakarai Chemicals, Japan. When the reaction is carried out without additional triphenylphosphine, the yield of coupling product may drop to 60–70% and the product is accompanied by the by-products, phenyl vinyl sulfide and 4-vinyl-1-cyclohexene, derived from β-hydride elimination.
11. The solution is prepared by dissolving 22.3 g (105 mmol) of potassium phosphate (Nakarai Chemicals, Japan) in water and adjusting the final volume to 35 mL. The original method[5] used sodium hydroxide as base; potassium phosphate is desirable for the extension of the present procedure to base-sensitive compounds. Under such conditions, the reaction with 9-(10-carbomethoxydecanyl)-9-BBN proceeds similarly without saponification of the ester group.
12. Ethanolamine was purchased from Nakarai Chemicals, Japan. The reagent reacts with the resulting 9-BBN residue to give an air stable 1:1 adduct[6] that is insoluble in hexane.
13. This operation effectively removes the remaining palladium-containing compounds, phosphine derivatives, and borane residues.
14. Gas chromatographic analysis of the product (Finnigan ITD 800-fused silica capillary, SE 30 column, 0.35 mm × 25 m, column temperature 80–250°C, injection temperature 250°C) shows that the chemical purity is 94–98.5%. The spectral data are as follows: IR (neat) cm^{-1}: 3030, 2920, 1615, 1590, 1480, 1440, 750, 690; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.00–1.90 (m, 6 H), 1.90–2.20 (m, 3 H), 2.20–2.50 (m, 2 H), 4.88 (s, 1 H), 5.15 (s, 1 H), 5.64 (s, 2 H), 7.20–7.50 (m, 5 H). The product deteriorates at room temperature and should be stored in the freezer.

Waste Disposal Information

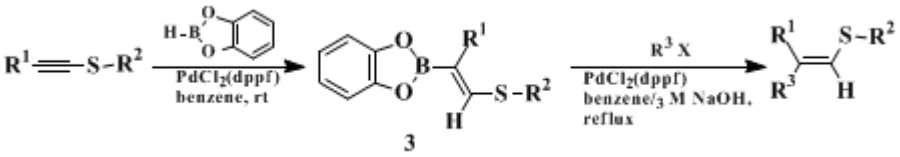
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The reaction described here is a method for the synthesis of alkenyl sulfides via the palladium-catalyzed cross-coupling reaction of 9-alkyl-9-BBN.[5] Bromo(phenylthio)ethene has several advantages in terms of its practical use for the cross-coupling reaction. The coupling occurs at the bromine position, but no coupling products at the sulfur position are obtained even under conditions using an excess of 9-alkyl-9-BBN. Thus, the formation of dialkylation products is completely avoided. The reaction is highly stereoselective and readily extended to the coupling with (E)- and (Z)-2-bromo-1-phenylthio-1-alkenes (**1** and **2**).[7] The reactions of (E)-, (Z)-1-alkenyl, or 1,3-alkadienylboronic esters with **1** or **2** provide simple routes for the stereoselective syntheses of 1,3-alkadienyl and 1,3,5-alkatrienyl phenyl sulfides.[8] Another route to vinylic sulfides involves the cross-coupling of 1-alkenyl halides with lithium, tin, and boron thioalkoxides.[9] These routes are convenient when the corresponding alkenyl halides are easily available.

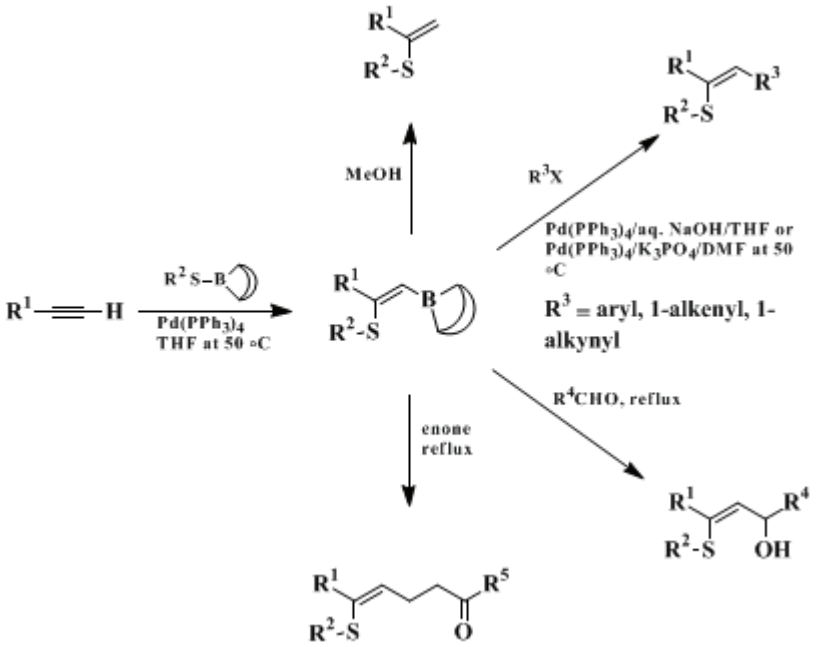


The ready availability of 2-(organothio)-1-alkenylboron compounds, obtained by the catalytic hydroboration of 1-organothio-1-alkynes (eq. 1) or the thioboration of 1-alkynes (Scheme 1), may offer other flexible and reliable routes to such stereodefined alkenyl sulfides in combination with the cross-coupling reaction with organic halides. The catalytic hydroboration of thioalkynes with catecholborane in the presence of $NiCl_2$(dppe) or $PdCl_2$(dppf) regio- and stereoselectively gives **3**. [10]The sequential catalytic hydroboration and cross-coupling reactions with a common palladium catalyst allows the one-pot synthesis of 1-alkenyl sulfides (eq. 1).[11]



When a solution of terminal alkyne and 9-RS-9-BBN in THF is heated at 50°C for 3 hr in the presence of $Pd(PPh_3)_4$ (3 mol %), the cis-addition of the B-S bond to alkyne proceeds regio- and stereoselectively (Scheme 1).[12] The adduct **4** is susceptible to C-B bond breaking or stereochemical isomerization, but the in situ preparation and subsequent cross-coupling with organic halides gives a variety of alkenyl sulfides retaining the original configuration of **4**. The vinylboranes thus obtained have unusually high nucleophilicity due to the activation by an electron-donating β-organothio group. The protodeboronation proceeds instantaneously with methanol to provide the thiol adducts. The addition to aldehydes and the Michael addition to α,β-unsaturated ketones or aldehydes at the refluxing temperature of THF afford various vinyl sulfides.[13]

The synthesis of vinylic sulfides via the cross-coupling reaction of organoboron compounds and other related reactions were recently reviewed.[14]



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

benzophenone ketyl

brine

9-BBN

9-[2-(3-Cyclohexenyl)ethyl]-9-BBN

9-BBN (9-borabicyclo[3.3.1]nonane)

9-(10-carbomethoxydecanyl)-9-BBN

NiCl

PdCl

$Pd(PPh_3)_4$

ethanolamine complex

ethanol (64-17-5)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

bromine (7726-95-6)

nitrogen (7727-37-9)

sulfur (7704-34-9)

potassium hydroxide (1310-58-3)

palladium (7440-05-3)

potassium bromide (7758-02-3)

magnesium sulfate (7487-88-9)

ethanolamine (141-43-5)

borane (7440-42-8)

Tetrahydrofuran,
THF (109-99-9)

hexane (110-54-3)

triphenylphosphine (603-35-0)

1,5-cyclooctadiene

4-vinyl-1-cyclohexene

CATECHOLBORANE (274-07-7)

tetrakis(triphenylphosphine)palladium(0) (14221-01-3)

Phenyl vinyl sulfide (1822-73-7)

1-BROMO-1-PHENYLTHIOETHENE (80485-53-6)

4-(3-Cyclohexenyl)-2-phenylthio-1-butene (155818-88-5)

Bromo(phenylthio)ethene

potassium phosphate (7778-53-2)