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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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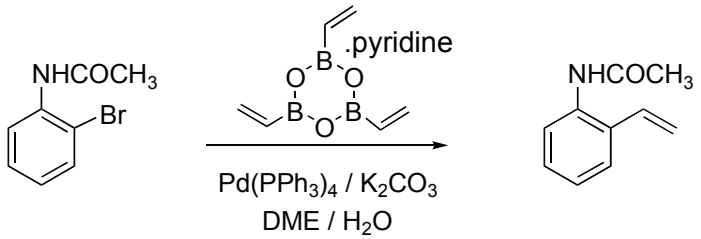
# SUZUKI-MIYAURA CROSS-COUPLING: PREPARATION OF 2'-VINYLACETANILIDE
## [*N*-(2-Ethenylphenyl)acetamide]




Submitted by Bertrand Cottineau, Albane Kessler and Donal F. O'Shea.[1]
Checked by Anuradha Gupta and Marvin J. Miller.
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## 1. Procedure

A 500-mL, two-necked, round-bottomed flask covered in tin-foil and is equipped with a stirring bar, a reflux condenser fitted with a nitrogen inlet, and a stopper. The flask is charged with *N*-(2-bromophenyl)acetamide (10.0 g, 46.6 mmol, Note 1), ethylene glycol dimethyl ether (180 mL) (Note 2), and tetrakis(triphenylphosphine)palladium(0) (1.08 g, 0.9 mmol) (Note 3). The apparatus is maintained under an atmosphere of nitrogen during the course of the reaction. The mixture is stirred at room temperature for 20 min then potassium carbonate (6.44 g, 46.6 mmol) (Note 4) dissolved in distilled water (55 mL) is added via funnel, followed by 2,4,6-trivinylcyclotriboroxane-pyridine complex (5.6 g, 23.3 mmol) (Note 5). The reaction mixture is stirred and heated at reflux in an oil bath for 20 h, then cooled to ambient temperature. Distilled water (75 mL) is added via a funnel, and the resulting mixture is filtered on a Büchner funnel. The filtrate is transferred to a separatory funnel and extracted with diethyl ether (3 x 100 mL) (Note 6). The combined organic phases are dried over sodium sulfate, filtered on filter paper and concentrated to dryness by rotory evaporation (30 °C, 25 mmHg). The resulting yellow solid is purified by column chromatography (Note 7) affording *N*-(2-vinylphenyl)acetamide (5.9 g, 37.3 mmol) as a pale yellow solid. The solid is dissolved in a hot mixture of cyclohexane:dicholoromethane (4:1) (55 mL) and the warm mixture is filtered through a Büchner funnel. The filtrate is allowed to cool to room temperature for 20 min. The flask is immersed for 30 min in an ice bath in order to complete precipitation. The resulting crystals are collected by

suction filtration on a Büchner funnel, washed with cyclohexane (10 mL), and dried under reduced pressure (15 h at 0.1 mmHg) to provide *N*-(2-vinylphenyl)acetamide (5.30 g, 71%) as a white solid (Note 8).

## 2. Notes

1. *N*-(2-Bromophenyl)acetamide (96%) was purchased from Aldrich Chemical Company, Inc. and was used without purification.

2. Ethylene glycol dimethyl ether (DME) was purchased from Aldrich Chemical Company, Inc. and passed through a column of Merck aluminium oxide 90 (30 g) immediately prior to use.

3. Tetrakis(triphenylphosphine)palladium(0) was used as received from Aldrich Chemical Company, Inc.

4. Potassium carbonate (99%) was used as received from Aldrich Chemical Company, Inc.

5. 2,4,6-Trivinylcyclotriboroxane-pyridine complex (purity not indicated) was used as received from Frontier Scientific, Inc.

6. Diethyl ether was used as received from Aldrich Chemical Company, Inc. (HPLC grade).

7. The yellow solid, dissolved in 20 mL of dichloromethane, was applied to 4.5 cm diameter column packed with 600 g of flash silica gel (Merck silica 60 mesh 0.040−0.063 mm). The product was eluted with diethyl ether/cyclohexane (9:1) (3.5 L). $R_f$ of 2'-vinylacetanilide: 0.26 using the same eluting solvent and TLC aluminium sheets with silica gel $60F_{254}$ (received from Aldrich Chemical Company, Inc.). Dichloromethane, diethyl ether and cyclohexane were used as received from Aldrich Chemical Company, Inc. (HPLC grade).

8. Analytical data: $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 2.05 (s, 3 H), 5.30 (dd, $J$ = 11.0, 1.1 Hz, 1 H), 5.77 (dd, $J$ = 17.5, 1.1 Hz, 1 H), 6.89 (dd, $J$ = 17.5, 11.0 Hz, 1 H), 7.16–7.27 (m, 2 H), 7.37 (d, $J$ = 7.9 Hz, 1 H), 7.61 (d, $J$ = 7.8 Hz, 1H), 9.52 (bs, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 23.1, 115.3, 125.2, 125.4, 126.2, 127.9, 131.5, 132.4, 135.1, 168.5; mp: 94–95 °C (lit.[3a] 89–90 °C); IR (KBr) cm$^{-1}$: 3228.8, 1648. MS (ES$^-$) *m/z* 160.1; Anal. required for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69; Found: C, 74.44; H, 6.99; N, 8.61. HPLC analysis [column: Atlantis$^{TM}$ $C_{18}$ 5 μm 4.6 x 250 mm, elution: 80% $CH_3CN$ 20% $H_2O$ (pH = 4, adjusted with 100 μL of $HCO_2H$ in 1.1 L of water), 1 mL/min, 1300 psi, retention time 3.6 min] gives 100% purity at 200 and 254 nm.

## Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

## 3. Discussion

We have previously reported a synthetic methodology for the generation of substituted styrene derivatives using 2,4,6-trivinylcyclotriboroxane-pyridine complex as the vinyl source in a Suzuki-Miyaura cross-coupling protocol.[2] Functionalized styrenes are of considerable synthetic importance as key synthetic intermediates and for the generation of new polymeric materials. Specifically *N*-(2-vinylphenyl)-acetamide is an intermediate used for the synthesis of the indole ring system.[3]

Numerous palladium-catalyzed methods have been described in which aryl halides are utilized as starting substrates in reactions with a variety of reagents as sources of the alkene functionality. To date the most commonly utilized approaches have been the Heck[4] and Stille[5] methodologies, which use ethene and tributyl(vinyl)tin, respectively, as the vinyl provider. Vinylmagnesium bromide,[6] trimethylvinylsilane,[7] vinyltrimethylsiloxane,[8] vinylpolysiloxanes,[9] potassium vinyltrifluoroborate,[10] vinylboronic acid dibutyl ester,[11] trivinylindium,[12] vinylbromide,[13] and divinylaluminium-2-dimethylaminoethanolate[14] have also been demonstrated as coupling reagents.

Aryl halides with *ortho*-subsituents are known to be challenging substrates for cross-coupling reactions of boronic acids, therefore we chose *N*-(2-bromophenyl)acetamide as a test substrate.[15] The target product has been previously synthesised by the coupling of ethene with *N*-(2-bromophenyl)acetamide using a high pressure Heck protocol.[3a]

In our reaction the cross-coupling proceeds efficiently by using a standard coupling procedure without the need of specialized catalysts. The reaction is successful with 0.5 mole equivalent of the trivinylboronic anhydride indicating that the anhydride provides more than one of the vinyl groups for reaction. In summary, 2,4,6-trivinylcyclotriboroxane-pyridine complex serves as a versatile coupling partner with aryl halides for the generation of substituted styrenes.

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## Appendix
## Chemical Abstracts Nomenclature (Registry Number)

*N*-(2-Bromophenyl)acetamide; (614-76-6)
Tetrakis(triphenylphosphine)palladium(0); (14221-01-3)
2,4,6-Trivinylcyclotriboroxane-pyridine complex: Boron, ethenyl[(ethenylboronic acid-κ*O*) bimol. monoanhydridato(2-)] (pyridine)-; (95010-17-6)
*N*-(2-Vinylphenyl)acetamide: Acetamide, *N*-(2-ethenylphenyl)-; (29124-68-3)