**Experiment 5: Green Aqueous Suzuki Coupling**

**Objectives**

 -Perform a Suzuki Coupling

 -Practice the technique of column chromatography

 -Practice characterization via NMR and IR and melting point.

 -Calculate % yield, % atom economy, and the E factor of a reaction

**Readings**

 Techniques in Organic Chemistry 3rd Ed.

 Technique 18: Liquid Chromatography pgs. 235-251.

**Materials**

***Reagents and Solvents***

 Phenylboronic acid [98-80-6]

 Ethyl 4-bromophenylacetate [14062-25-0]

 Palladium acetate [3375-31-3]

 Tetrabutylammonium bromide [1643-19-2]

 Potassium carbonate [584-08-7]

 Sodium carbonate

 Sodium sulfate

 Sand

 Silica Gel

 Acetone

 Diethyl ether

 Ethyl acetate

 Hexanes

***Equipment and Supplies***

25 mL round-bottom flask

 Stirbar

 Condenser

 Sand bath

 Ring stand

 Clamps

Centrifuge tubes

 50 mL Erlenmeyer flask

 50 mL round-bottom flask

 Flash column

 Test tubes

 250 mL round-bottom flask

**Introduction**

**The Suzuki Reaction**

One of the primary objectives of organic chemistry is the synthesis of complex targets. Essential to the synthesis of larger molecules from simple starting materials is the formation of carbon-carbon bonds. Multiple Nobel prizes have been have been awarded for novel reactions which achieve this important task. In 2010 Heck, Negishi and Suzuki won a Nobel for their development of palladium-catalyzed cross-coupling reactions. In the Suzuki coupling in today’s experiment an aryl halide is coupled with an arylboronic acid to form a biaryl derivative.

**Measures of Reaction Efficiency**

 While chemists often use percent yield to quantify the efficiency of the reaction. There are other measures that more fully account for the waste generated in the reaction. Two of these are percent experimental atom economy and Efactor. Each of these is calculated as follows:

% Experimental Atom Economy = (theoretical yield/total reactant mass) \* 100

E-factor = (total mass of waste/ mass of desired product)

***Reaction Scheme 1***



***Reagent Table 1***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reagent** | **MW (mg/mmol)** | **mmol****Theor.** | **Mass (mg)****Theor.** | **Density****(mg/L)** | **Vol. (L)** | **mp (oC)** |
| Ethyl 4-bromophenylacetate | 243.10 | 0.600 | 145 | 1.46 | 0.100 | 29-33 |
| Phenylboronic acid | 121.93 | 0.900 | 110 |  |  |  |
| Palladium acetate, Pd(OAc)2 | 224.51 | 0.090 | 20.0 |  |  |  |
| Tetrabutylammonium bromide, TBAB | 322.37 | 0.610 | 197 |  |  |  |
| Potassium carbonate,K2CO3 | 138.21 | 1.500 | 207 |  |  |  |
| Water, H2O |  |  |  |  | 5 |  |
| Ethyl (4-phenylphenyl)acetate | 240.30 | 0.600 | 144 |  |  |  |

***Reaction Scheme 2***



***Reagent Table 2***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reagent** | **MW (mg/mmol)** | **mmol****Theor.** | **Mass (mg)****Theor.** | **Density****(mg/L)** | **Vol. (mL)** | **mp (oC)** |
| Ethyl 4-bromophenylacetate | 243.10 | 0.600 | 145 | 1.46 | 0.100 | 29-33 |
| Phenylboronic acid | 121.93 | 0.900 | 110 |  |  |  |
| Palladium acetate | 224.51 | 0.03 | 7 |  |  |  |
| Sodium carbonate | 105.99 | 1.200 | 127 |  |  |  |
| Acetone |  |  |  |  | 2.3 |  |
| Water |  |  |  |  | 2.7 |  |
| Ethyl (4-phenylphenyl)acetate | 240.30 | 0.600 | 144 |  |  |  |

**Procedures**

***Part 1A: Suzuki Coupling with TBAB***

**1)** To a 25mL round-bottom flask charged with a stirbar add Pd(OAc)2, phenylboronic acid, TBAB, K2CO3 and degassed H2O.

**2)** Then have your instructor add the ethyl 4-bromophenylacetate via microliter syringe.

**3)** Equip the round-bottom flask with a water condenser and heat the reaction to 105 oC for 1 hr.

***Part 1B: Suzuki Coupling with Acetone/Water***

**1)** To a 25 mL round-bottom flask charged with a stirbar add Pd(OAc)2, phenylboronic acid, Na2CO3 , acetone and degassed H2O.

**2)** Then have your instructor add the ethyl 4-bromophenylacetate via a microliter syringe.

**3)** Equip the round-bottom flask with a water condenser and heat the reaction to 45 oC for 1 hr.

***Part 1A and 1B:***

**4)** After the 1 hr reaction time, allow the mixture to cool to room temperature. While you are waiting for the reaction to cool, take a TLC of

***Part 2: Reaction Workup***

**5)** Add 5 mL of diethyl ether to the cooled reaction mixture and transfer the resulting mixture to a centrifuge tube or test tube. Mix the two layers with a pipette and allow the layers to separate. Remove the top layer and transfer it to a 50 mL Erlenmeyer flask.

**6)** Add 5 mL of diethyl ether to the reaction flask and swirl to dissolve any residual product. Transfer this to the centrifuge tube containing the aqueous solution. Mix the two layers with a pipette and allow the layers to separate. Remove the top layer and transfer it to a 50 mL Erlenmeyer flask. Do this step once more.

**7)** Prepare a TLC comparing the starting material to the crude extract from your reaction mixture. Run this TLC using 10% ethyl acetate: 90% hexanes as the eluent. After evaporating off the solvent, visualize the plate using UV light and KMnO4 stain. Record the TLC plate and the Rf values in your lab notebook.

**8)** Dry the combined organic layers with sodium sulfate while you run the TLC plate.

**9)** Transfer the dried extracts to a ***tared*** 50 mL round bottom flask and remove the solvent en vacuo. Weigh the flask with the crude product and calculate the crude yield.

***Part 3: Purification***

**10)**Using your crude yield calculate how much silica gel you need for your flash column. Use about 20 times as much silica gel by weight as your crude mass. If your calculated amount is outside the 2-4 g range consult with your instructor.

**11)** Prepare the column as follows: First add a small ball of cotton to the bottom of the column and clamp your column to the ring stand. Next add 5 mm of sand and fill the column half full with the 10:90 EtOAc:Hexanes eluent. Then add the calculated amount of silica gel as a slurry with this eluent. After the silica gel has settled, add 3-4 mm of sand on top of the silica gel. ***NEVER*** let the silica gel column run dry until after the purification is completed.

**12)** Add the crude product to the column and run the column monitoring its progress by TLC.

**13)** Isolate the product from the solvents.

**Results and Calculations**

**1)** Calculate the ***crude percent yield***, the ***isolated percent yield***, the ***experimental atom economy***, the ***percent experimental atom economy***, and the ***E factor*** for your reaction.

**2)** Obtain an ***NMR*** spectrum for your reaction. Draw the structure of your product on the NMR and label it. Label the TMS peak and assign all peaks that you can in the spectrum. Also assign all protons in your product to peaks. You may group the aromatic peaks together.

**3)** Obtain an ***IR*** spectrum of your product. Label all significant peaks that are indicative of functional groups in your product such as carbonyl stretches, C(sp2)-H stretches etc.

**4)** Obtain a ***melting point*** of your product. Record the melting point as a range and include the unitis.

**Waste**

**1)** The aqueous layer from the reaction workup, the product, and the solvent from the column chromatography will go in the container labeled “CY315 Exp. 5 Halogenated Waste”.

**2)** The silica gel and sand from the column will go in the container labeled “CY 315 Exp. 5 Halogenated Solid Waste”.

The lab was adapted by Jonathan Fritz in November 2012 from the following reference.

Costa, N.E.; Pelotte, A.L.; Simard, J.M.; Syvinski, C.A.; Ceveau, A.M. *J. Chem. Educ.* **2012**, *89*, 1064-1067.