Exploring Green Aqueous Suzuki Coupling Reactions for the Undergraduate Laboratory: The Synthesis of Ethyl-(4-Phenylphenyl) Acetate, A Biologically Active Biaryl With Anti-Arthritic Potential

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ABSTRACT

Suzuki couplings are powerful chemical reactions commonly employed in academic and industrial research settings to generate functionalized biaryls. We have developed a discovery-based lab for the organic chemistry undergraduate laboratory that explores green Suzuki coupling using water as a solvent, and exposes students to the professional responsibilities of a pharmaceutical researcher. Specifically, students take on the role of a medicinal chemist striving to identify the greenest and most cost-effective method out of three proposed synthetic approaches to make ethyl-(4-phenylphenyl)acetate, **1**. Biaryl **1** demonstrates promise as a lead compound in the discovery of new non-steroidal anti-inflammatory drugs, and scale-up of this compound is necessary for future studies. In our work, the development and implementation of green aqueous Suzuki coupling experiments in a traditional introductory organic chemistry course is described.

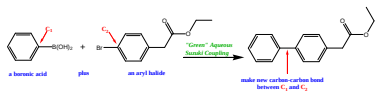

Figure 1. Overall reaction to make a new C-C bond via Suzuki Coupling and synthesize **1**, ethyl-(4-phenylphenyl)acetate.

BACKGROUND & SIGNIFICANCE

- Green chemistry is a rapidly growing research area that is consistently mindful of environmental consequences and generally advocates for the reducing, reusing, and recycling of chemicals whenever possible.[1-13]
- Recently there has been great interest in developing green chemical reactions that make carbon-carbon bonds using water as a solvent and applying these reactions in academic and industrial lab settings.[1,4-6,10]
- We are striving to expose students to powerful carbon-carbon bond forming reactions, like the Suzuki cross coupling.
- Suzuki cross couplings date from 1979[13] and:
  - are employed in many syntheses of biaryl molecules that have interesting medicinal properties
  - are widely used in synthetic chemistry research but not typically covered in sophomore organic
  - are catalyzed by palladium (Pd^0) join a aryl halide and an aryl boronic acid together by a new C-C bond
  - can be made "greener" by 1) adjusting the catalyst amounts, 2) using non-volatile solvents like water or ionic liquid, and 3) employing "ligand-free" conditions.[5-7,10,11]
- In our research we have developed an experiment for the undergraduate organic chemistry teaching lab.
  - Students function as medicinal chemistry research teams and strive to synthesize biaryl compound **1** according to the "green chemistry" principles adopted by their company. (Figure 4)
  - Students learn that derivatives of **1** are already under patent by their company as novel non-steroidal anti-inflammatory drugs for treating arthritis.[3] They are given a one week deadline to develop a high yielding, green synthesis of their target compound. Students are required to employ a Suzuki coupling and to start from commercially available starting materials to make target molecule **1**.
  - Students are then given, or alternatively research, three aqueous Suzuki coupling approaches in the primary literature that employ palladium acetate ($Pd(OAc)_2$) as a catalyst and are devoid of a phosphine ligand.[4-6] These methods also vary by their solvent mixtures and the type/amount of base used. (Figure 4)

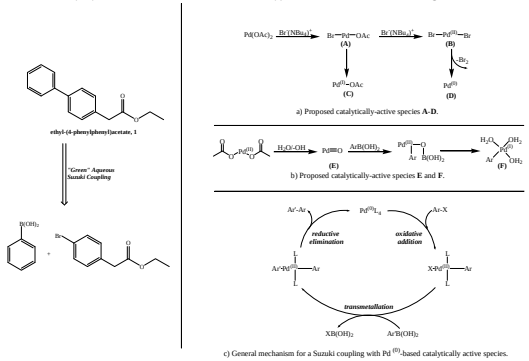

Figure 2. (left) Basic bond formation executed with a Suzuki Coupling reaction; (right) proposed catalytic species using $Pd(OAc)_2$.

RESEARCH GOALS

Global Goals Our Research

- To develop a new lab for our sophomore organic sequence employing "greener" Suzuki couplings
- To teach students some fundamental principles of green chemistry, including atom economy, solvent choice and catalysis.
- To expose students to a role-playing scenario as pharmaceutical researchers so that they may gain insights into the research process and into chemistry as a career

Specific Aims of the Student Lab Experiment

- To work in teams and synthesize a biaryl molecule **1** via an aqueous Suzuki coupling reaction using three different solvent systems
- To analyze the three approaches based on established green principles and determine which synthetic method is the "greenest"

SYNTHETIC METHODOLOGY: COMPARING THREE GREEN APPROACHES & PROOF OF CONCEPT

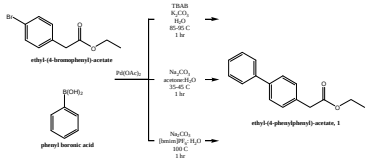

Figure 4. Synthesis of 1 via three "greener" aqueous Suzuki coupling reactions.

EXPERIMENTAL PROCEDURE AND REACTION DATA

Using Bmim[PF_6] / Water:
Place ethyl-4-bromophenylacetate (0.060mmol, 10µl), Phenyl Boronic Acid (0.135mmol, 0.017g), Na_2CO_3 (0.120 mmol, .0126mg), $Pd(OAc)_2$ (1.8mol %) and [bmim]PF_6 : H_2O:0.24mL:0.26mL in a 5 mL round bottom flask. Equip the flask with a magnetic stir bar and a water condenser, and heat your reaction to 100-105°C for 60 minutes.

Using Acetone / Water:
Place ethyl-(4-phenylphenyl)acetate (0.060mmol, 10µl), Phenyl Boronic Acid (0.135mmol, 0.017g), Na_2CO_3 (0.120 mmol, .0126mg) $Pd(OAc)_2$ (0.5mol %), and acetone:H_2O:0.23mL:0.27mL, in a 5 mL round bottom flask. Equip the flask with a magnetic stir bar and a water condenser, and heat your reaction to 40-45°C for 60 minutes.

Using Water with TBAB:
Place ethyl-(4-phenylphenyl)acetate (0.060mmol, 10µl), Phenyl boronic acid (0.094mmol, 0.012g), TBAB (0.060mmol, 0.0190g), K_2CO_3 (.15mmol, .0247g), $Pd(OAc)_2$ (0.009mmol), and 0.5mL of H_2O in a round bottom flask. Equip the flask with a magnetic stir bar and a water condenser, and heat your reaction to 90-95°C for 60 minutes.

General Workup, Purification, and Characterization:
Reaction progress was monitored using thin layer chromatography (Figure 9) in a 9:1: hexanes: ethyl acetate solvent system. The reactions were cooled to room temperature, extracted with three portions of diethyl ether, and dried with magnesium sulfate. Purification was achieved via column chromatography (Figure 9) in a 1:1: hexanes: ethyl acetate solvent system. Spectra were obtained on a Jeol ECX 300 MHz or a Jeol ECS 400 MHz NMR spectrometer. (Figures 6, 7, 8)

Solvent System	% yield*	Reaction Temperature	% Atom Economy	Cost per Experiment
Water	83%	85°C	28.9%	$0.96
Acetone / water	90%	35-50°C	51.2%	$0.58
Bmim[PF_6] / water	75%	100°C	51.2%	$2.13
Recycled Bmim[PF_6] / water	74%	100°C	51.2%	$0.48 †

*Percent yield is the average of three experiments. Scale is 60 mmol based on ethyl-(4-bromophenyl)-acetate
† Calculated for one recycle However, over multiple recycles the cost would be even lower.

Figure 5. Synthesis of 1 via three "greener" aqueous Suzuki coupling reactions.

REPRESENTATIVE NMR DATA FOR ETHYL-(4-PHENYLPHENYL)-ACETATE, (1)

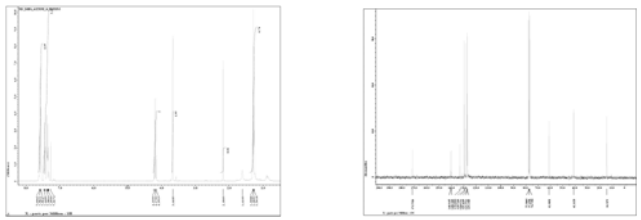

Figure 6. Proton (^1H, left) and carbon (^{13}C, right) NMR spectra of compound (1). NMR experiments were completed in $CDCl_3$ using a 300 MHz Jeol ECX300 NMR Spectrometer.

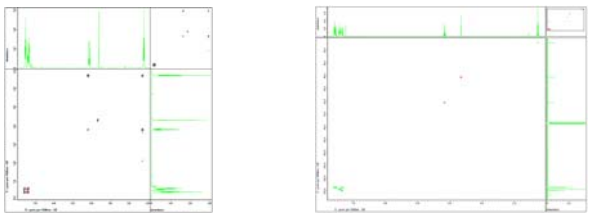

Figure 7. COSY of compound (1) was completed in $CDCl_3$ using a 300 MHz Jeol ECX300 NMR Spectrometer.

Figure 8. HETCOR of compound (1) was completed in $CDCl_3$ using a 400 MHz Jeol ECS NMR Spectrometer.

PART II: EXTENSION TO THE UNDERGRADUATE ORGANIC LABORATORY

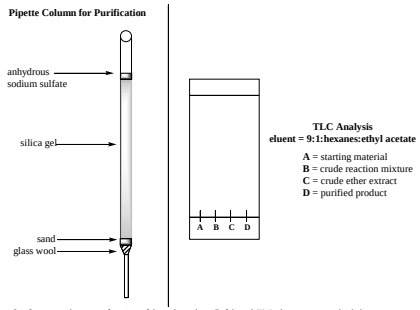

Figure 9. Pipette column purification of biaryl product (left) and TLC plate overview (right).

H_2O			Ionic Liquid			Acetone		
Average % yield	Mixed*	Pure	Average % yield	Mixed*	Pure	Average % yield	Mixed*	Pure
39.1	6	9	38.7	17	5	48.6	23	2

* Integrations of 1HNR spectra are currently being calculated to determine percent starting material that remains.

Figure 10. Undergraduate laboratory results

CONCLUSIONS

Part I: Proof of Concept
We have demonstrated that **1** can be synthesized via a Suzuki coupling. All solvent systems proved to be effective, giving significant yields (Figure 5). Based on atom economy (Figure 5) , both the ionic liquid in water and acetone in water demonstrated to be a better system over water alone with the TBAB additive. However, when looking at cost per student, the acetone in water was the most cost effective method (Figure 5). Acetone also resulted in the highest percent yield. Although the ionic liquid was the most expensive, it is also important to note that the solvent with catalyst can be recycled thus reducing experimental costs. (Figure 5) In general, both water and ionic liquids are attractive solvents because they are non-volatile.

Part II: Undergraduate Laboratory Data
We were successful at implementing the aqueous Suzuki coupling into the Organic II undergraduate laboratories at our University. Results yielded mixed data (Figure 10) . While some students achieved 100% conversion, some had starting material left. Currently, we are determining the percent of starting material remaining using NMR integration. We also wonder if increasing the scale from 0.060 mmol (proof of concept) to 0.090 mmol (student lab) is causing the reaction to not complete in the one hour alloted reaction time.

FUTURE DIRECTIONS

- To have organic students run the experiment on a 0.060 mmol scale and compare results to the 0.090 mmol class data.
- To complete the evaluation of student NMRs. Specifically, use the integration data of the -CH_2- singlets in mixed products to determine the amounts of starting material remaining.
- To run a student lead laboratory using the recycled ionic liquid and compare these results to current data.

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