Nickel-Catalyzed Suzuki-Miyaura Coupling of Heterocycles in Green Solvents

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INTRODUCTION

The Suzuki-Miyaura reaction is a cross-coupling synthetic technique for organic halides and organic boronic acids, which are activated by a basic reagent.[1] This reaction generally uses a palladium catalyst, which are both expensive and dangerous due to high toxicity. Additionally, they are often performed in solvents that are hazardous to both the chemist and the environment. "Green" solvents are that which require small amounts of energy to produce, can be recycled by purification, and pose less environmental, health, and safety risks including water/air pollution, persistency, volatility, toxicity, irritation, and flammability.[2] Heterocyclic compounds are coupled in this reaction as they are common building blocks of drug discovery. They manipulate lipophilicity, polarity and hydrogen bonding in biological molecules as they simulate the structure of natural heterocyclic compounds such as nucleic acids and amino acids. These molecules improve the pharmacological, pharmacokinetic, toxicological and physiochemical properties of drugs.[3] . In the special project study, a less expensive and less hazardous nickel catalyst and a "green" solvent, t-amyl alcohol, will be utilized.[4]

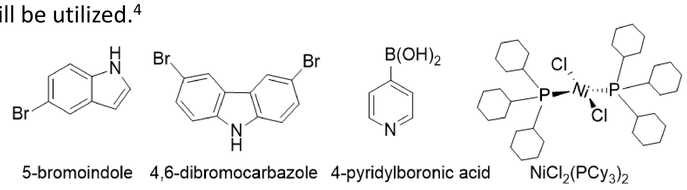


Figure 1: Reagents used in following project

EXPERIMENTAL

The general reaction scheme is shown below in *Figure 2*. An additional proof of concept was performed, shown in *Figure 3.*

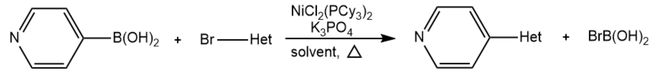


Figure 2: General Suzuki-Miyaura reaction scheme used in project for trials 1-7[4,5]

Cross-coupling reactions were run under multiple conditions, changing solvent, heating apparatus, and substrate.

1 5-bromoindole, 4-pyridyl boronic acid, potassium phosphate(K_3PO_4) and $NiCl_2(PCy_3)_2$ were heated in t-amyl alcohol in an oil bath for 1 hour at 80°C.

2 4,6-dibromocarbazole, 4-pyridyl boronic acid, K_3PO_4 and $NiCl_2(PCy_3)_2$ were heated in a microwave reactor at 150°C for 30 minutes in t-amyl alcohol.

3 5-bromoindole, 4-pyridyl boronic acid, K_3PO_4 and $NiCl_2(PCy_3)_2$ were heated in THF in an oil bath for 12 hours at 80°C.

4/6 5-bromoindole, 4-pyridyl boronic acid, K_3PO_4 and $NiCl_2(PCy_3)_2$ were heated in t-amyl alcohol in a metal heating block for 12 hours at 120°C.

5 4,6-dibromocarbazole, 4-pyridyl boronic acid, K_3PO_4 and $NiCl_2(PCy_3)_2$ were heated in t-amyl alcohol in a metal heating block for 12 hours at 120°C.

7 5-bromoindole, 4-pyridyl boronic acid, K_3PO_4 and $NiCl_2(PCy_3)_2$ were heated in a microwave reactor at 150°C for 30 minutes in THF.

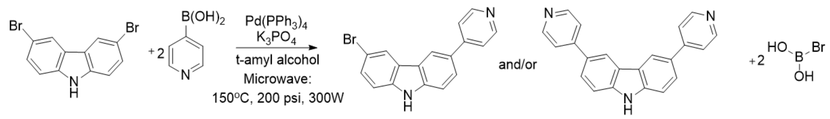


Figure 3: Suzuki-Miyaura reaction scheme used in trial 8

8 4,6-dibromocarbazole, 4-pyridyl boronic acid, K_3PO_4 and $NiCl_2(PCy_3)_2$ were heated in a microwave reactor at 150°C for 30 minutes in EtOH.

All reactions followed the same workup of quenching with 1M HCl, extraction with EtOAc, washing with 1M NaOH and brine, drying over $MgSO_4$, filtering and concentrating.

RESULTS

Starting Materials Galore!!

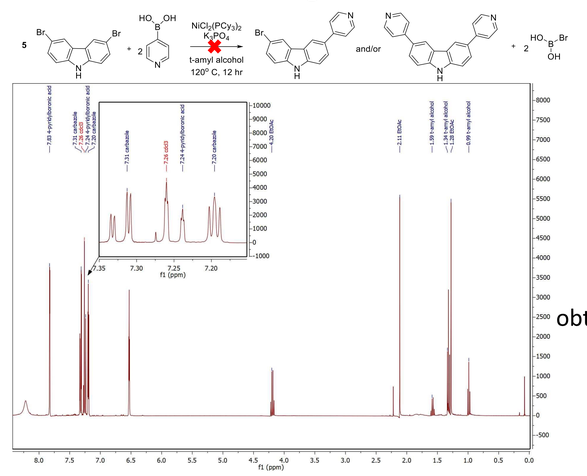


Figure 3: ^{1}H NMR obtained from reaction **5**

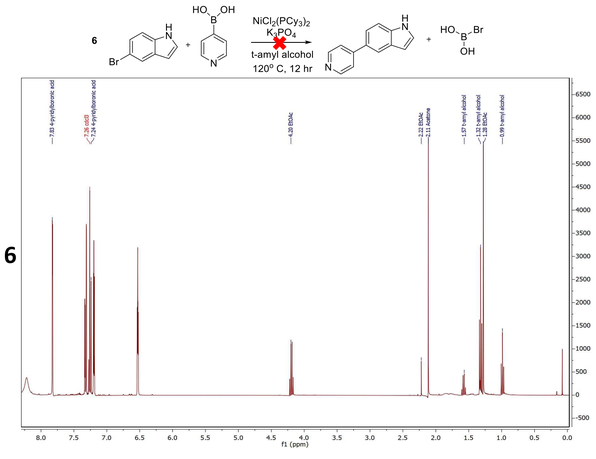


Figure 4: ^{1}H NMR obtained from reaction **6**

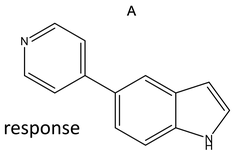
CONCLUSION

The experiments were unsuccessful in synthesizing the proposed products. Solubility of the starting materials in the solvents was a consistent issue as well as finding the appropriate heating method for the reactions. The possible product formations could have been decomposed if the temperatures were too high or the reactions were run for too long. The proof of concept reaction utilizing a traditional Suzuki-Miyaura Pd catalyst was unsuccessful being performed in the microwave as a result of high pressure buildup. Optimization of reaction conditions were unsuccessful but could be improved through future experimentation.

FUTURE WORK

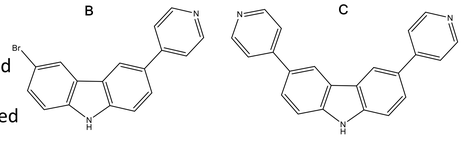
Optimization of the synthetic conditions could allow for product formation and characterization. Different solvents, heating methods and reaction times could be altered. Additionally, coupling of other substrates with different reactivity and structure could be attempted as a proof of concept and for the formation of new heterocyclic molecules.

Product **A:**



- Likely result of coupling of 4-pyridylboronic acid and 5-bromoindole
- Potential applications as a receptor antagonist for dopamine, meaning it blocks or dampens a biological response by binding or blocking a receptor
- It could be developed as a treatment for central nervous system disorders, including depression, anxiety, OCD, PTSD, ADHD, schizophrenia and substance addictions.[6]

Products **B** and **C:**



- Possible products of the coupling of 4-pyridylboronic acid and 4,6-dibromocarbazole.
- Not successfully been synthesized through a batch method.
- Said to exhibit electroluminescent properties, which emit light in response to an electric current or field. These compounds and other derivatives can
- Could demonstrate strong brightness, heat resistance, efficiency and a long lifetime.[7]

Constructing a simple batch synthesis of these three products will allow for the advancement of heterocyclic compounds with commercial applications.

REFERENCES

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[3] Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H. M.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; Mcelroy, C. R.; Sherwood, J. *Sustainable Chemical Processes* **2016**, *4* (7).
[4] Hie, L.; Chang, J. J.; Garg, N. K. *Journal of Chemical Education* **2014**, *92* (3), 571–574.
[5] Ramgren, S. D.; Hie, L.; Ye, Y.; Garg, N. K. *Organic Letters* **2013**, *15* (15) 3950– 3953.
[6] Kong, J.; Park, W.; Cho, H.; Jeong, D. Piperazinyl-propyl-pyrazole Derivatives as Dopamine D4 Receptor Antagonists. U.S. Patent 8,236,806, August 7, 2012.
[7] Gao, C.; Cui, D.; Wang, K.; Sun, Y. Preparation of 1,3-bis(carbazol-9-yl)-5-aryloxybenzene as organic electroluminescent material, December 4, 2015.