Novel Tandem Reaction to Synthesize 2-Formalphenylboronic Acids

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Abstract and/or Background

Abstract: One of the most pressing issues that organic chemists face is the lack of resources such as time, money, and manpower needed to meet the demand for both novel and known organic compounds. A large amount of effort has been directed towards the elimination of wasted time and money while maintaining products with high yields. One target of these efforts is to streamline syntheses with multiple stages by combining steps in "one-pot" reactions, mitigating the amount of time and effort that is typically required by purification and isolation of intermediates. These reactions have their final products synthesized in the same container that the original reactants were introduced into and do not require purification of intermediate compounds. Our research focused on a novel method of one-pot synthesis of benzaldehyde derivatives with a specific focus on 2-formylphenylboronic acid. The strategy employed focused on directed metalation to target the desired benzaldehyde in the ortho position. N-[2-(Dimethylamino)ethyl]-N-methylformamide and phenyl lithium were used to initiate the process and form an alpha-amino alkoxide. This synthesis was completed under argon and at low temperatures, then purified via radial preparative layer chromatography (RPLC). The addition of butyllithium, followed by the addition of 2,4-dinitrophenylhydrazine (as the isolating agent), produced an ortho-substituted hydrazone of phenylboronic acid that was orange in color. The product was identified using melting point comparison, infrared (IR) spectrometry, and liquid-chromatography mass spectrometry (LC-MS) as confirmation that the desired products were acquired through the tandem reaction process.

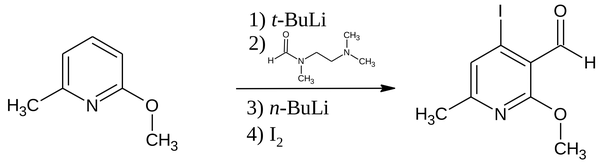
Introduction and/or Research Question

Tandem reactions involve the breakage and formation of several bonds in one pot without the need to isolate any intermediates. Comins and colleagues used this process in their synthesis of camptothecin (1). In the light of their discovery, these current experiments attempted to apply Comins' method in the synthesis of *ortho* substituted benzaldehyde. Positive results from this synthetic method could be applied to the synthesis of novel structures.

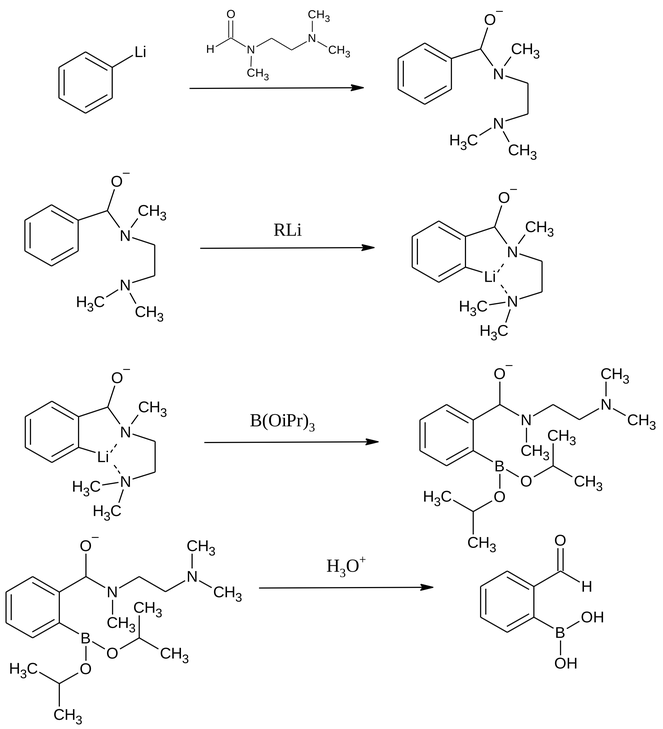
Methods

The formamide and tetrahydrofuran were cooled to -78° C in a round-bottom flask under an inert, argon atmosphere. Then, one equivalent of phenyl lithium was added, and the reaction was stirred for one hour. Three equivalents of n-butyl lithium were then added, followed by 30 minutes of stirring. The reaction was then placed in the freezer at -20° C overnight. Once the solution was cooled to -78° C, six equivalents of the electrophile were added, and the reaction was stirred for 30 minutes. Afterwards, the solution was warmed to room temperature with continuous stirring for 30 minutes. Hydrochloric acid (2 N) was added to the solution, which was then stirred for two hours. Ethyl acetate was added, and the layers were separated. The aqueous layer was extracted twice more using ethyl acetate. The combined organic layers were then washed with brine, dried using magnesium sulfate, and concentrated *in vacuo*. Initially the products were purified by radial preparative layer chromatography (RPLC).

Scheme 1: Synthesis of Camptothecin by Comins using tandem reactions.



Scheme 2: General sequence of steps in the tandem reaction.



Scheme 3: Method of Isolation.

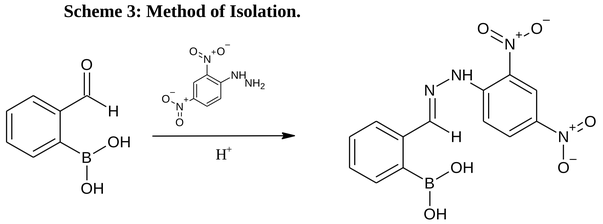


Figure 1: IR Spectra

Table 1: Metalation conditions

Entry	Electrophile (E^+)	Metalation conditions	Yield
1	$B(OiPr)_3$	Formamide, PhLi, n-BuLi, E^+, THF, -20 ˚C, overnight	68.97%

Table 2: Comparison of Melting Points

Entry	Melting Point Range (℃)	Note: Melting point difference may be due to recrystallization of compound 1 in ethanol, which increased pre-recrystallization melting point by ~20°C. Recrystallized control compound may yield similar results
Control	177.2-178.5	
1	186.6-188.5	

Results and/or Conclusion

Previous results have shown that this reaction works for all examples listed. However, according to the obtained NMR results, an acceptable purity was not obtained by RPLC. Other compounds were purified by extensive *concentration in vivo* under high vacuum. Products can be isolated under these conditions, but due to the volatile nature of these compounds, product is lost under high vacuum. Current compounds are being tested with the use of 2,4-dinitrophenylhydrazine to isolate the desired product more effectively.

Future Work

This experiment provided standardized conditions necessary for the tandem repeat reaction to work. The compounds synthesized through this method will need to undergo further purification steps. Those compounds will need to be characterized by using nuclear magnetic resonance (NMR). Furthermore, the method will need to be performed with other electrophiles in order to select the compatible electrophile groups that yield more pure and greater amounts of products. Once the products are characterized and synthesized in satisfactory yield and purity, this method will be used to expand the choices of electrophiles for the synthesis of more complex compounds.

References and/or Acknowledgments

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Acknowledgements
We would like to thank the Liberty University Department of Biology and Chemistry for providing laboratory space and financial resources for this research.
This research is made possible in part by support from the Provost Research Initiative, PR1827 and UR1931, Liberty University.