Synthesis and Characterization of Boronic acid appended diphenylimidazo [1,5-a] pyridine saccharide sensors

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♦ Abstract

Imidazopyridines are both an important and intriguing class of compounds due to their unique structural (π-conjugated system) and medicinal properties. Here, we report a direct cyclization of 2-benzoylpyridine with benzaldehyde and several of its boronic acid analogs, in the presence of ammonium acetate and acetic acid
The significance of this approach is that the reaction methodology is straightforward with only one step. The use of metal catalysts, highly sensitive Lewis acids or air sensitive reaction conditions is not needed. In addition, the reaction scope is significantly wide due to the reaction being tolerant to various aldehyde substrates.

♦ Introduction

Sugars play a major role in the process of metabolism in human bodies and excessive sugar levels have been shown to lead to harmful physiological conditions. Therefore, the monitoring of sugar levels is essential to human life. High levels of glucose, fructose and galactose have been shown to lead to diseases such as diabetes, heart disease and glaucoma. The tight control of sugar levels has been shown to dramatically reduce these complications that arise from diabetes, therefore, strict monitoring and control of sugar levels is vital. Saccharide sensors based on boronic acid-diol interactions have emerged as a new and promising class of sugar detectors. Boronic acids have been shown to bind with compounds which contain diol moieties with high affinity through reversible ester formation. This tight binding allows boronic acids to be used as the recognition moiety in the construction of sensors for saccharides

♦ Hypothesis

The reaction of boronic acid or boronic ester substituted benzaldehydes with 2-Benzoylpyridine and ammonium acetate in acetic acid should, according to our plausible mechanism (**Figure 1**), results in the formation of imidazo[1,5-a]pyridine appended boronic acids or boronic acid derivatives.

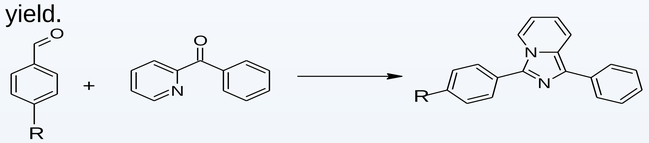
♦ Methods & Materials

Materials. Starting materials were reagent grade and were used without further purification unless otherwise indicated. Solvents were reagent grade and were used without further purification unless otherwise indicated.

Melting point determination was performed using a programmable melting temperature apparatus. Melting point determination conditions were as follows: Start temp-40 ^{o}C, Ramp rate- 5^{o}C/min and Stop temp- 150 ^{o}C.

♦ Synthesis/Results

Treatment of 2-Benzoylpyridine with benzaldehyde in the presence of ammonium acetate (**Scheme 1**) gave 1-Phenyl-3-phenyl[1,5-a]pyridine (entry 1) in 37.3% yield.



Scheme 1: *Reagent and Conditions*: 2-Benzoylpyridine (1 equiv), Benzaldehyde (2.0 equiv), NH_4OAc (5 equiv), acetic acid , 110^{o} C, 18 hr.

A plausible mechanism for the formation of 1-Phenyl-3-phenylimidazo[1,5-a]pyridine from the above reaction **Scheme 1** is given in **Figure 1**.

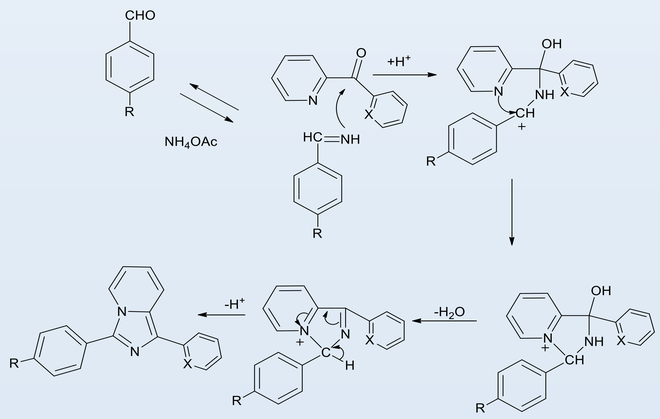
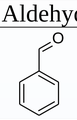
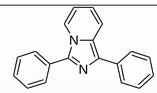
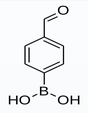
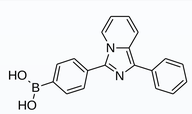
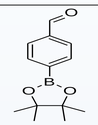
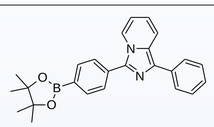


Figure 1: Plausible mechanism for imidazo[1,5-*a*]pyridine formation from the reaction of substituted benzaldehyde, 2-Benzoylpyridine and ammonium acetate in acetic acid.

♦ Synthesis/Results

Entry	Aldehyde	Product	Yield
1			1.209g
2			0.809g
3			0.395g

♦ Discussion

Treatment of benzaldehyde and substituted boronic acid derivatives with 2-benzoylpyridine in the presence of ammonium acetate leads to the formation of 1,3-substituted imidazo[1,5-a]pyridines **1,2** and **3**. This reaction was optimal yield information. It was determined that the ratio of substrates was the key. When the benzaldehyde, ketone , and ammonium acetate reached a molar ratio of 1:2:5, optimal yields were recorded for both reactions **1.** This optimal condition was applied to all other reactions when different aldehyde substrates used. The significance of this approach was as follows: (1) to determine the scope and limitations of the reaction and (2) determine the yield (efficiency) of the reaction for imidazo[1,5-a]pyridine production. Data indicated the reaction was not applicable to a the boronic acid aromatic aldehyde substrate. This was observed as the reaction mixture and isolated product showed signs of degradation. The boronic ester product **(2)** was isolated (in very low yields), which still requires additional purification (as indicated by the melting point. This new method is advantageous over previous approaches which involved the use of either n-BuLi or complex intermediates. However, modifications to the reaction conditions will be later explored.

♦ Conclusion

In conclusion, we have investigated the reaction between boronic acid and boronic ester substituted benzaldehydes and 2-benzoylpyridine with ammonium acetate in acetic acid. This synthetic methodology has demonstrated a potential to synthesize boronic ester appended Imidazo[1,5-a]pyridines
Further investigation and characterization on the esters will need to be done to optimize this reaction.

♦ References

1) Nazeeruddin, Md. K.; Kay, A.; Rodicio, I.; Humphry-Baker, R.;
Mu¨ ller, E.; Liska, P.; Vlachopoulos, N.; Gra¨ tzel, M. *J. Am. Chem. Soc*.
1993, *115*, 6382.
2) Rudmann, H.; Shimada, S.; Rubner, M. *J. Am. Chem. Soc*. **2002**,
124, 4918. Gao, F. G.; Bard, A. J. *J. Am. Chem. Soc*. **2000**, *122*, 7426.
3) Mizuno, T.; Wei, W.-H.; Eller, L. R.; Sessler, J. L. *J. Am. Chem.*
Soc. **2002**, *124*, 1134. Grigg, R.; Norbert, W. D. J. A. *J. Chem. Soc.,*
Chem. Commun. **1992**, 1300.
4) Hortholary, C.; Coudret, C. *J. Org. Chem*. **2003**, *68*, 2167.
5) Baxter, P.; Lehn, J.-M.; Decian, A.; Fischer, J. *Angew. Chem.,*
Int. Ed. **1993**, *32*, 69. Kra¨mer, R.; Lehn, J.-M.; De Cian, A.; Fischer, J.
Angew. Chem., Int. Ed. **1993**, *32*, 703.
6) Ligtenbarg, A. G.; Spek, A. L.; Hage, R.; Feringa, B. L. *J. Chem.*
Soc., Dalton Trans. **1999**, 659.
7) Bluhm, M. E.; Ciesielski, M.; Go¨rls, Walter, O.; Do¨ring, M. *Inorg.*
Chem. **2003**, *42*, 8878.
8) (a) Krapcho, A. P.; Powell, J. R. *Tetrahedron Lett*. **1986**, *27*, 3713.
(b) Grigg, R.; Kennewell, P.; Savic, V.; Sridharan, V. *Tetrahedron* **1992**,
48, 10423.
9) Bluhm, M. E.; Ciesielski, M.; Go¨rls, Walter, O.; Do¨ring, M.
Angew. Chem., Int. Ed. **2002**, *41*, 2962.
10) Wang, J.; Mason, R.; VanDerveer, D.; Feng, K.; Bu, X. R. *J.*
Org. Chem. **2003**, *68*, 5415.

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