Synthesis of *N*-Alkenylated 2-Pyridone Containing Isoquinoline Alkaloids

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Introduction

Isoquinoline alkaloids are found frequently in pharmaceutical targets,[1] and throughout nature.[2] Morphine and berberine, seen in Figure 1, are two of the more well-known medicinal examples. Biological studies into the enzymes responsible for the biosynthesis of isoquinoline alkaloids have led to the isolation of many more.[2] In order for a compound to be considered an isoquinoline alkaloid, the compound must be derived from a benzopyridine ring system.[3] The prevalence of this motif makes the development of methods for their preparation an important synthetic goal.

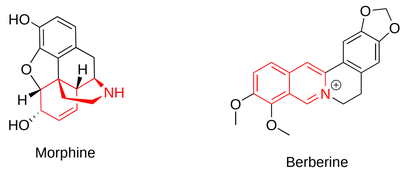
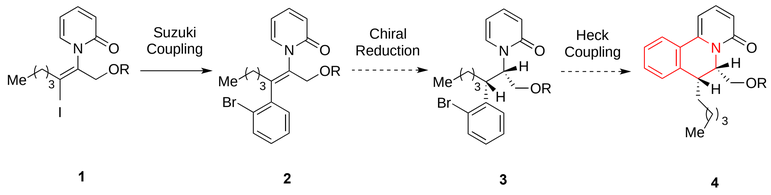


Figure 1: Examples of Medicinal Isoquinoline Analogues

With the goal of extending the methodology developed in our group for the preparation of β-iodo *N*-alkenyl 2-pyridones **1** and accessing highly functionalized isoquinoline alkaloid derivatives, we began to pursue the synthetic approach outlined in scheme 1. The ability to prepare isoquinoline **4** in an asymmetric fashion hinges on the stereoselective reduction of the tetrasubstituted alkene in compound **2**.

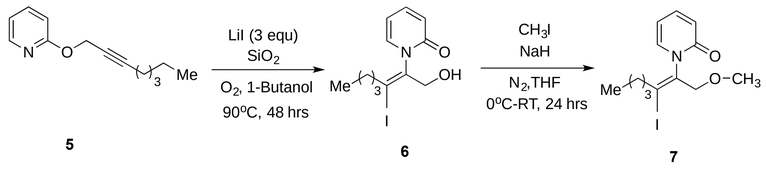


Scheme 1: Synthetic Approach to Isoquinoline **4**

Initially, a Suzuki coupling of vinyl iodide **1** with 2-bromophenyl boronic acid in the presence of a palladium catalyst is expected to install the required aryl bromide.[4] Subsequent asymmetric reduction of the tetrasubstituted alkene in compound **2** is then required. The resulting compound **3** is expected to be able to adopt the necessary conformation such that a Heck coupling may occur between the aryl bromide and the pyridine ring to close the desired central ring.[5]

Synthesis of β-Iodo *N*-Alkenyl 2-Pyridones

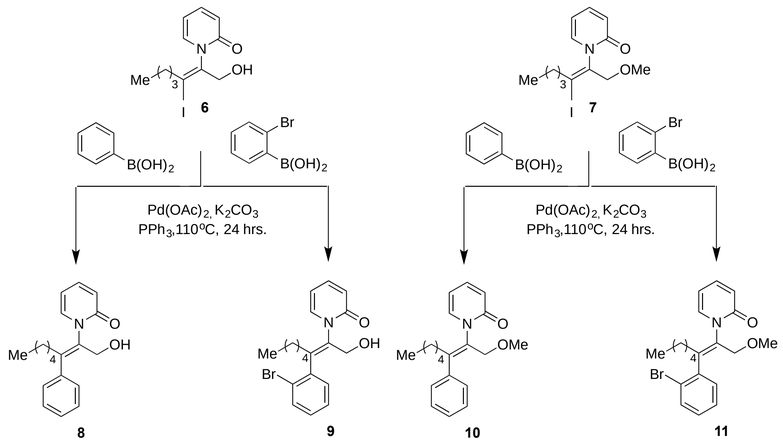
The Anderson lab has successfully synthesized both unprotected ß-iodo-*N*-alkyl 2-pyridone **6** and methyl ether **7** from *O*-propargyloxypyridine **5 (**Scheme 2). The initial rearrangement of the alkyne upon treatment with LiI under an oxygen atmosphere has been reported previously.[4] Product **6** was synthesized in up to 64% yield. The preparation of compound **6** was dependent on the amount of O_2 that the reaction mixture was exposed to over its duration. As such, the reaction can not be scaled-up and many individual runs had to be performed. Methylation of alcohol **6** then occurred upon treatment with CH_3I and NaH in up to 92% yield.



Scheme 2: Rearrangement and Methylation Reaction Conditions

Suzuki Coupling

Compounds **6** and **7** were then subjected to Pd(II) catalyzed Suzuki coupling with either phenyl boronic acid or 2-bromophenyl boronic acid. This resulted in a new sp^2-sp^2 carbon-carbon bond between the aryl ring and the *N*-alkenyl 2-pyridone depicted below in Scheme 3. Both the brominated and unsubstituted boronic acids were successfully coupled to compounds **6** and **7** (Scheme 3). Product **9**was isolated in 38% yield, while methylated analogue could be prepared in up to 83% yield.

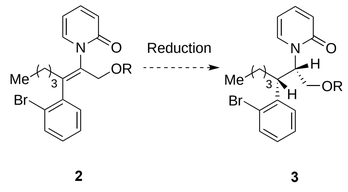


Scheme 3: Suzuki Coupling Conditions

This strategy allows for a variety of aryl substituents to be incorporated, further enhancing the range of analogues that should be accessible utilizing this method.

Achiral Reduction

Prior to the final Heck reaction, reduction of the tetrasubstituted alkene is required. While it is hoped that this reduction will be accomplished in an asymmetric manner during the final synthesis of isoquinoline target **4**, a racemic sample of compound **3** is required initially for chiral HPLC analysis.



Scheme 4: Reduction of *N*-Alkenyl Pyridone **2**

Though the alkene of interest is tetrasubstituted, making it sterically difficult to reduce, the first racemic attempts focused on hydrogenation in the presence of Pd/C. Methanol and ethyl acetate were evaluated as solvents and the reaction temperature was varied between 25°C and 50°C. Under these conditions, it appears that trace amounts of compound **3** was produced, as determined by evaluation of the 1H NMR of the crude reaction mixture. Unfortunately, compound **3** was never isolated from these reactions.

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NMR Analysis of Reaction Mixture

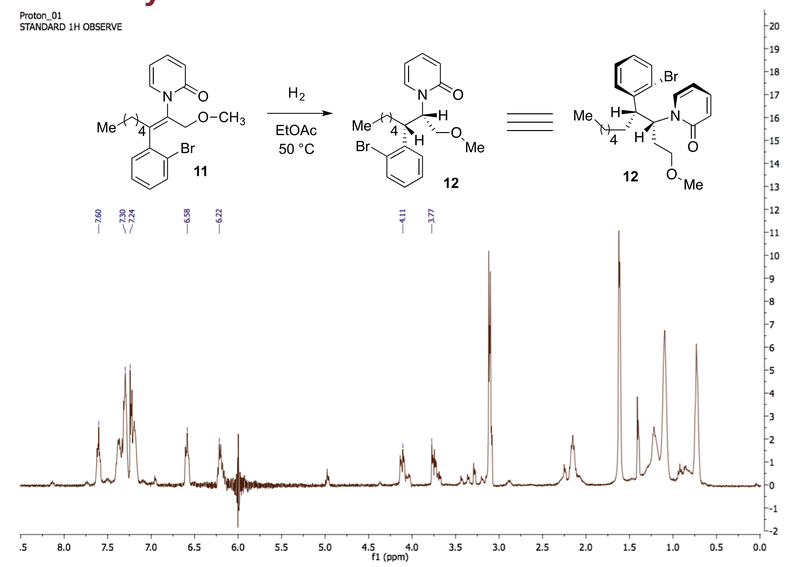
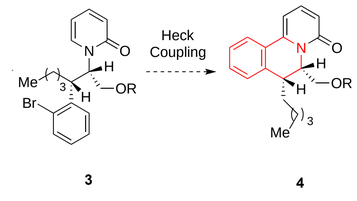


Figure 2: ^{1}H NMR of Crude Reaction Mixture

The ^{1}H NMR, shown above, reveals a series of secondary shoulders that appear slightly upfield of those for starting material **11** (Figure 2). This could be a result of the differing conformations available to compound **12** relative to the alkene **11**. Compound **11** exists as a mostly planar species while, upon reduction of the alkene, compound **12** can rotate freely around the central C-C bond. This could allow for the hydrogens of the aryl-bromide and pyridine rings to interact differently, causing the slight shifts in the NMR spectra that suggest that a small amount of compound **12** may be present. The inconclusiveness of these results, however, call for continued inquiry in order to find a more effective catalyst.

Future Directions

Attempts to accomplish the alkene reduction under both achiral and chiral conditions will continue to be pursued. Once this is achieved, the resulting compound **3** will be subject to Heck coupling conditions in an attempt to access isoquinoline **4** (Scheme 5).



Scheme 5: Final Step in Proposed Synthesis

Summary

An aryl bromide has been successfully installed at the β-position of *N*-alkenyl 2-pyridones **6** and **7**. Initial attempts to reduce the tetrasubstituted alkene **11** are promising, however, further effort in this area are ongoing.

References

(1) Bhadra, K.; Kumar, G. S. Therapeutic Potential of Nucleic Acid-Binding Isoquinoline Alkaloids: Binding Aspects and Implication for Drug Design. *Med. Res. Rev.* **2011**, 6, 821-862.
(2) Civjan, N. *Natural Products in Chemical Biology*; John Wiley & Sons, Inc.: New Jersey, 2012, pp 209-237.
(3) Majumdar, K. C.; Chattopadhyay, S. A. *Heterocycles in Natural Product Synthesis*,; 1st ed.; Wiley-VCH: New Jersey, 2011, pp 299-339.
(4) Tasker, S. Z.; Brandsen, B. M.; Ryu, K. A.; Snapper, G. S.; Staples, R. J.; DeKock, R. L.; Anderson, C. E. *Org. Lett.* **2011**, *13*, 6224-6227.
(4) Suzuki, A.; Diederich, F.; Stang, P. J. Metal-catalyzed Cross-coupling Reactions; Wiley- VCH: New York, **1998**, 49-97.
(5) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. Advances in the Heck Chemistry of Aryl Bromides and Chlorides. *Tetrahedron* **2001**, 57, 7449-7476.