Synthesis of *N*-Alkenyl 2-Pyridonyl Ethers via a Au(I)-Catalyzed Rearrangement of 2-Propargyloxypyridines

Evan O. Romero and Dr. Carolyn E. Anderson*

Calvin College, Department of Chemistry and Biochemistry, 1726 Knollcrest Circle SE, Grand Rapids, MI 49546

INTRODUCTION

N-Alkyl pyridones have been of interest to the synthetic community in recent years because of their presence in natural products[1] and pharmacologically important targets (Figure 1).[2] Due to the relevance of this motif, our lab seeks to develop methods for the preparation of a variety of *N*-alkyl pyridones.

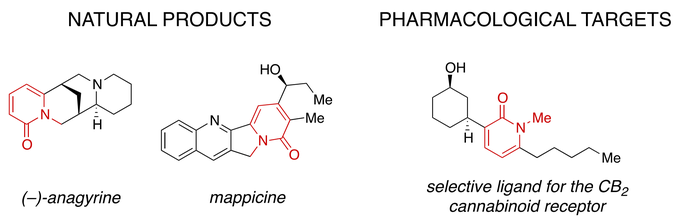
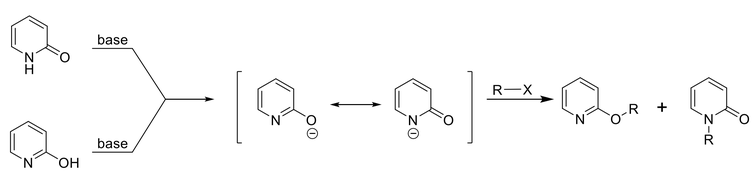


Figure 1. Examples of targets containing *N*-alkyl 2-pyridones.

CHALLENGE

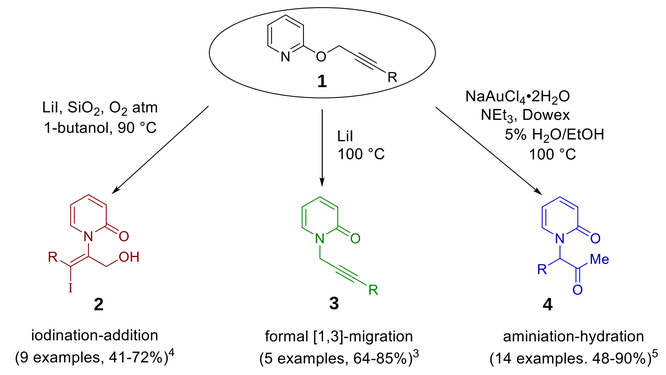
The direct nitrogen alkylation of both 2-hydroxypyridine and 2-pyridone has been explored extensively; selectivity for *N*- versus *O*-alkylation is a constant challenge due to the aromatic character of 2-oxypyridine anions (Scheme 1).



Scheme 1. Rationale for mixtures of *N*- and *O*-alkylated products.

INITIAL REACTION DEVELOPMENT

Our lab has focused on the development of a variety of methods for selective nitrogen alkylation of 2-pyridone systems via either alkyl migration or rearrangement (Scheme 2).



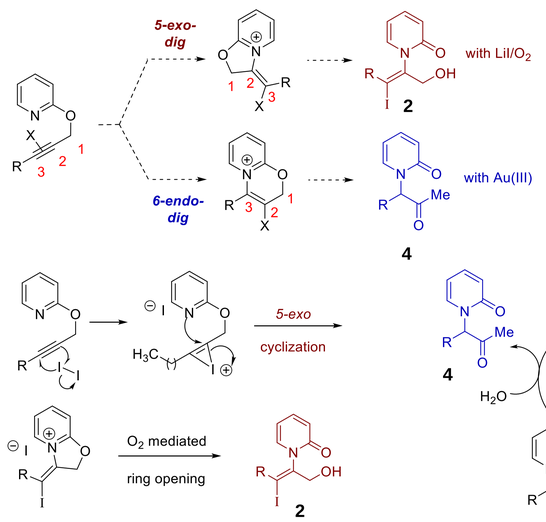
Scheme 2. Methods for nitrogen selective alkylation.

REFERENCES

1. Representative examples include: (a) Wall, M. E.; Wani, M. C. *J. Ethnopharmacol.* **1996**, 51, 239-253. (b) Gray, D.; Gallagher, T. *Agnew. Chem. Int. Ed.* **2006**, 45, 2419-2423. (c) Govindachari, T. R.; Ravindranath, K. R.; Viswanathan, N. *J. Chem. Soc., Perkin Trans.* **1974**, 1, 1215-1217.
2. Representative examples include: (a) Huffman, J. W.; Lu, J.; Hynd, G.; Wiley, J. L.; Martin, B. R. *Bioorg. Med. Chem.* **2001**, *9*, 2863-2870. (b) Parlow, J. J.; South, M. S. *Tetrahedron* **2003**, *59*, 7695-7701.
3. Tasker, S. Z.; Bosscher, M. A.; Shandro, C. A.; Lanni, E. L.; Ryu, K. A.; Snapper, G. S.; Utter, J. M.; Ellsworth, B. A.; Anderson, C. E. *J. Org. Chem.* **2012**, 77, 8220-8230.
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.
5. Romero, N. A.; Klesper, B. M.; Anderson, C. E. *Org. Lett.* **2012**, 14, 874-877.
6. (a) Fuerstner, A.; Davies, P. W. Angew. *Chem., Int. Ed.* **2007**, 46, 3410−3449. (b) Fuerstner, A. *Chem. Soc. Rev.* **2009**, 38, 3208−3221 (c) Housecroft, C. E. *Coord. Chem. Rev.* **1993**, 127, 187−221.
7. Romero, E. O.; Reidy, C. P.; Bootsma, A. N.; PreFontaine, N. M.; Vryhof, N. W.; Wierenga, D. C.; Anderson, C. E. *J. Org. Chem.* **2016**, *ASAP*.

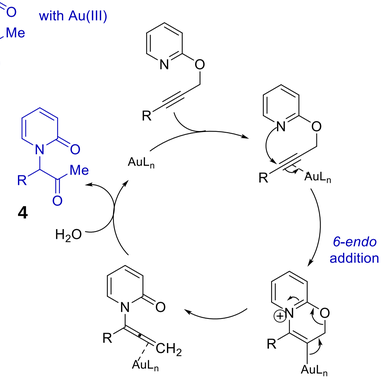
5-EXO VS. *6-ENDO*

Pyridones **2** and **4** result from *5-exo* versus *6-endo* addition to the alkyne (Schemes 3-5). Because LiI-mediated rearrangements are slow and yields are modest, an alternative means of accessing the 5-*exo* manifold was desired. Consequently, a Au(I) catalyzed rearrangement was evaluated.



Scheme 3. 5-*exo* and 6-*endo* cyclization manifolds.

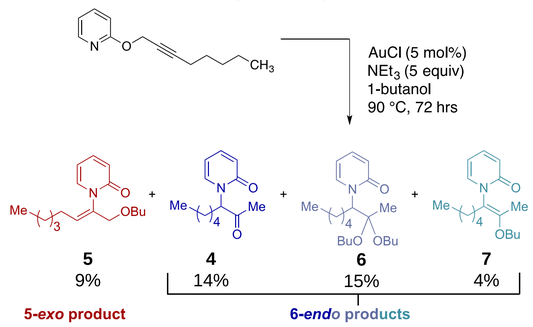
Scheme 4. Mechanism of LiI-mediated 5-*exo* rearrangement.



Scheme 5. Mechanism of Au(III)-mediated 6-*endo* rearrangement.

INITIAL AU(I) STUDIES

Upon treatment of pyridine **1** with AuCl four different pyridone products are produced: allylic ether **5**, ketone **4,** and the related ketal **6** and enol ether **7** (Scheme 6). This was the first time that both the 5-*exo* and 6-*endo* manifolds had been observed simultaneously from this starting material. Product ratios were determined by analysis of the ^{1}H NMR of the crude reaction mixtures (Figure 2).



Scheme 6. Formation of 2-pyridones

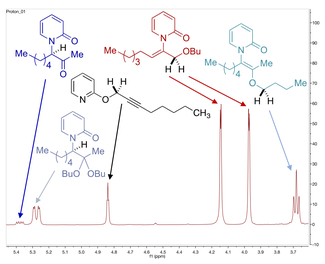


Figure 2. Determination of products ratios by ^{1}H NMR.

OPTIMIZATION

With the goal of increasing *5-exo* selectivity, a number of parameters were evaluated, including: Au(I) source, additives, Ag(I) salts, and temperature (Figure 3). Adjusting these conditions afforded significantly higher yields of the *5-exo* product, while simultaneously reducing the reaction time from 72 hours to four hours or less. Additionally, several Pt(II) catalysts were screened as they have been show to have similar reactivity to Au(I).[6] All catalysts evaluated resulted in a similar distribution of products, but Au(I) catalyst **11** gave the best selectivity. Optimal conditions are shown in Scheme 7.

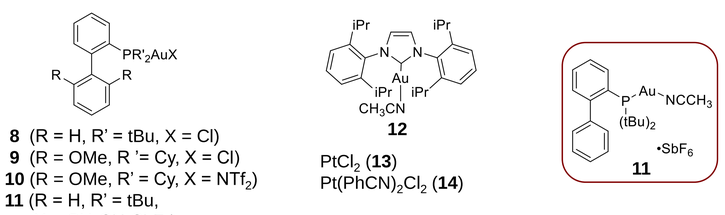
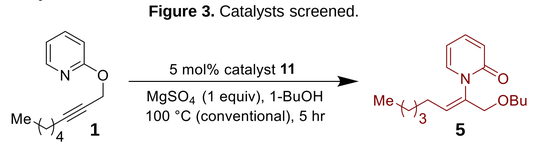


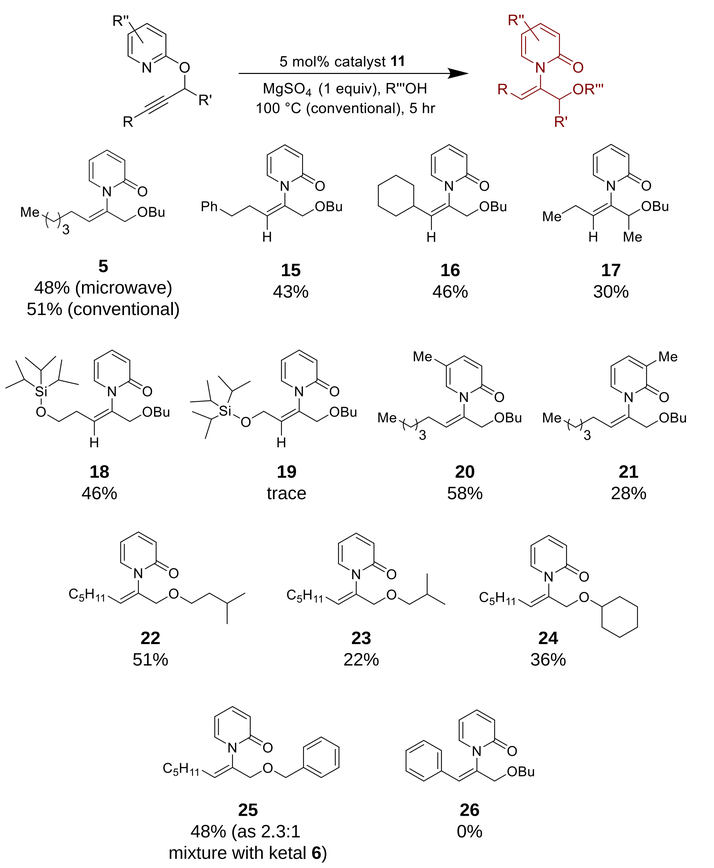
Figure 3. Catalysts screened.



Scheme 7. Optimized conditions.

SCOPE

Under the optimized reaction conditions, a variety of substituted 2-propargyloxypyridines were subjected to the Au(I)-catalyzed rearrangement (Scheme 8).



Scheme 8 . Evaluation of the substrate scope.

Alkyl sidechains were generally well tolerated, even with the sterically large cyclohexyl group, and provided 2-pyridones **5** and **15-18** in 30-51% yields. However, substrates with siloxane groups gave mixed results. With a two-carbon linker, the desired 2-pyridone **18** was formed in 46% yield, whereas with a one-carbon linker, desired ether **19** was not observed at all. Interestingly similar reactivity was our earlier Au(III) amination-hydration chemistry, in which only the two-carbon linked substrate was active.[5] 5-Me and 3-Me substitution on the pyridine ring was also acceptable in the reaction. Further it was found that a wide range of alcohols could be incorporated into the allylic ether products **22-25** .

Although phenyl pyridonyl ether **26** was not observed, *E* and *Z* isomers **27** and **28** were isolated in a combined 86% yield. This is in contrast to the aliphatic case where the enol ether was isolated as a minor byproduct and as a single geometric isomer.

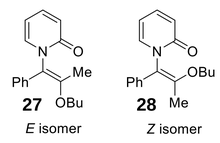


Figure 4. *E* and *Z* isomers of phenyl substituted pyridone (R=Ph).

SUMMARY

Biaryl catalyst **11** was found to provide selectivity for the *5-exo* product, converting a variety of propargylic and aryl substituted pyridines to 2-pyridonyl ethers in 22-58% yield. While yields were moderate, the method we have presented represents an important entry point for introducing the pyridone structure into more complex scaffolds. A manuscript detailing this work has recently appeared.[7]

ACKNOWLEDGMENTS

Connor Reidy
Noah PreFontaine
Nicholas Vryhoff
David Wierenga
Andrea Bootsma