Propargyloxypyridines as Precursors to Trisubstituted Indolizines

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INTRODUCTION

Indolizines are a versatile heterocyclic core found frequently in pharmaceutical targets for a wide variety of therapeutic areas, including: anti-bacterial[2] and anti-tumor,[3] in addition to targets against Alzheimer's disease,[4] asthma,[5] erectile dysfunction[6] and inflammation related to respiratory or cardiovascular disease (Figure 1).[7]

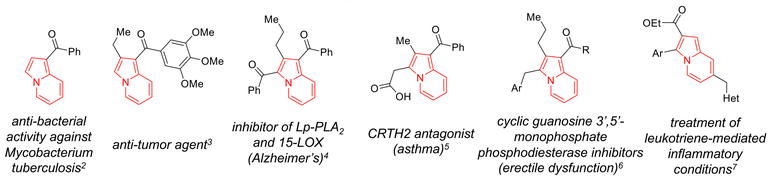
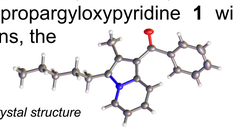
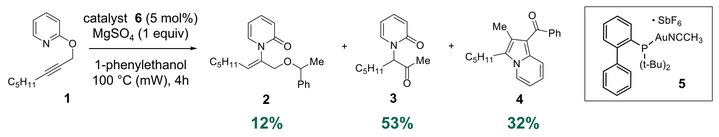


Figure 1. *Relevant Pharmaceutical Targets With Indolizine Cores*

While evaluating the scope of the Au(I)-catalyzed rearrangement of 2-propargyloxypyridine **1**,[1] the Anderson lab discovered substituted indolizine **4** as a byproduct (Scheme 1). We first observed the formation of indolizine **4** upon treatment of propargyloxypyridine **1** with catalyst **5** in 1-phenylethanol (Scheme 1). Under these conditions, the expected aliphatic ether **2** and ketone **3** were also observed. The structure of indolizine **4** was confirmed by NMR and X-ray analysis.

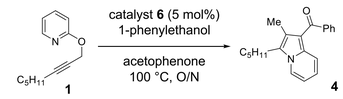




Scheme 1. *Formation of Indolizine By-Product*

KEY REAGENT

Given our inability to explain this unexpected outcome, the purity of the 1-phenylethanol solvent was investigated by NMR and shown to be contaminated with approximately 10% acetophenone. Using acetophenone-free 1-phenylethanol (confirmed by NMR) as the solvent, indolizine **4** was not observed (Table 1, entry 1). With the goal of replicating and improving upon the original reaction conditions, acetophenone was systematically added back to the reaction. As the amount of acetophenone was increased, the yield improved (Table 1). Further, by using acetophenone as the solvent, it was possible to increase the yield of indolizine **4** to 42% (entry 7). It was determined that using 5 equivalents of 1-phenylethanol in 0.5 M acetophenone is optimal for the formation of indolizine **4**. Further, $MgSO_4$ was found to be unnecessary.

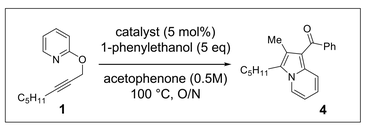


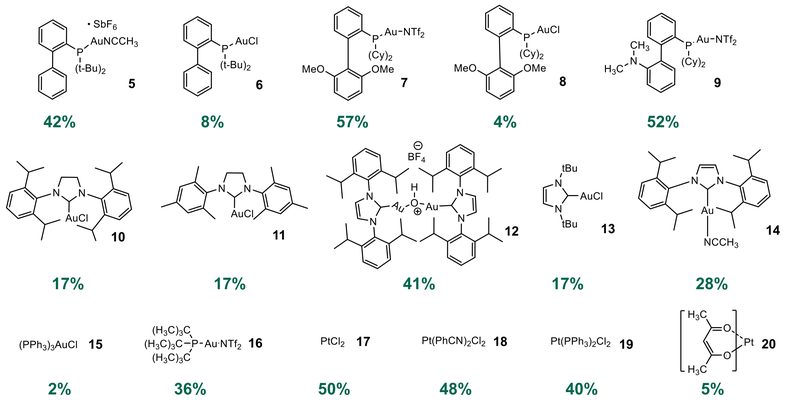
entry	1-phenylethanol	acetophenone	yield **4** (%)
1	0.5 M	-	0
2	0.5 M	0.5 equiv	20
3	0.5 M	1 equiv	23
4	0.5 M	1.5 equiv	24
5	0.5 M	3 equiv	34
6	0.5 M	5 equiv	33
7	**5 equiv**	**0.5 M**	**42**
8	2.5 equiv	0.5 M	39
9	-	0.5 M	20

Table 1. *Importance of Acetophenone*

CATALYST SCREEN

Utilizing the optimized solvent conditions, a thorough screening of Au(I) and Pt(II) catalysts was undertaken (Scheme 2). This exploration showed Au(I) catalyst **7** and $PtCl_2$ (**17**) to be promising, leading to yields of 57% and 50%, respectively. These catalysts were then used in further experiments.

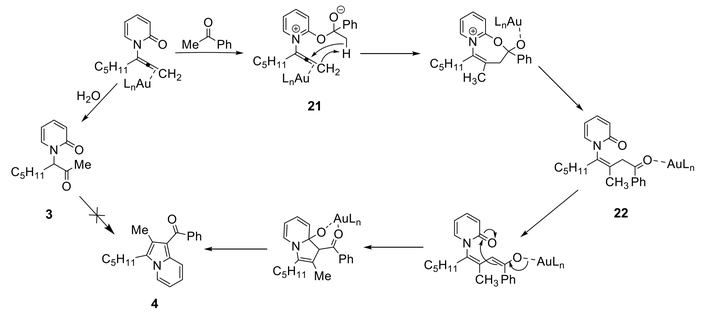




Scheme 2. *Catalyst Screen*

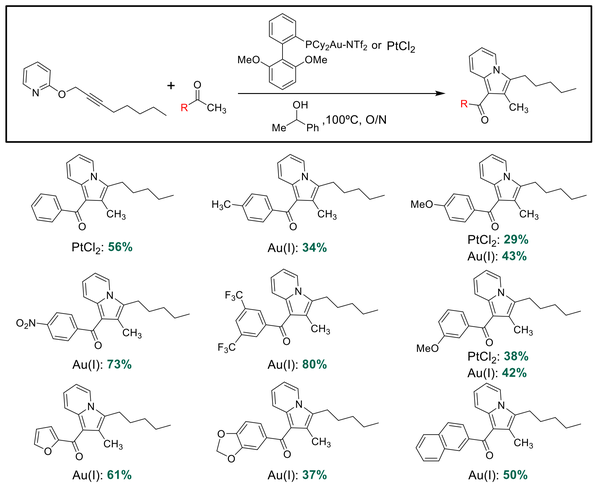
PROPOSED MECHANISM

It was originally thought that indolizine **4** was formed via ketone **3** (Scheme 3). However, upon subjecting ketone **3** to the reaction conditions, no indolizine **4** was produced. Adding a small amount of starting material **1**, along with ketone **3**, provided indolizine **4** in amounts proportional to the amount of starting material **1** added.



Scheme 3. *Proposed Mechanism for Indolizine Formation*

As ketone **3** is not a key intermediate, other possible intermediates were hypothesized, such as hemi-acetal **21**. To test the plausibility of this pathway, aromatic methyl ketones bearing various electron donating and withdrawing substituents were subjected to otherwise normal reaction conditions to see which substituent gave the highest yield.

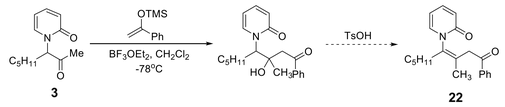


Scheme 4. *Screen of Aromatic Methyl Ketones*

The improved yields observed with more electron poor methyl ketones suggests that the mechanism may indeed go through hemi-acetal **21,** as this intermediate is expected to be stabilized by the para electron withdrawing group on the acetophenone.

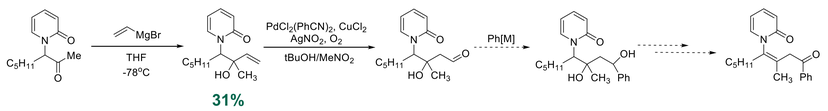
PROPOSED INTERMEDIATE SYNTHESIS

To support this finding and the mechanism proposed in Scheme 3, the synthesis of ketone **22** was pursued. A two step synthesis was proposed (Scheme 5).[7]



Scheme 5. *Proposed Synthesis for Mechanism Intermediate*

However, attempts at the first step produced no product. This is likely due to the steric hindrance present in ketone **3**. Alternatively, addition of a vinyl Grignard followed by aldehyde-selective Wacker oxidation[8] was attempted (Scheme 6). Further efforts will continue in this direction and may include epoxidation, rather that Wacker oxidation.



Scheme 6. *Modified Synthesis of Proposed Intermediate* ***22***

ISOTOPE STUDY

An isotope study using trideuterated acetophenone was done to test the validity of the proposed C-H activation (shown in Scheme 3, compound **21**). The NMR showed a difference of one proton on the methyl group of indolizine **5**, which supports the current mechanism (Figure 2).

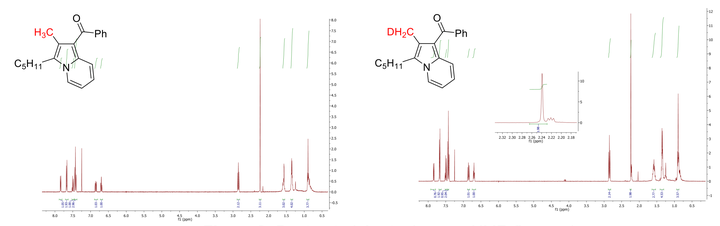
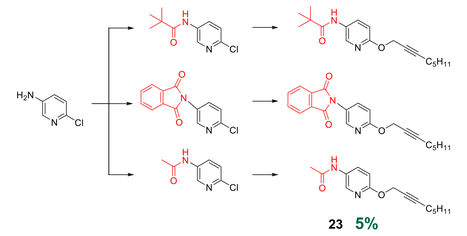


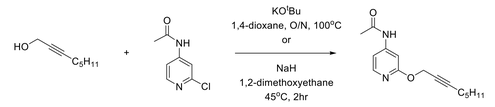
Figure 2: *Deuterated-Acetophenone NMR Comparison*

SUBSTITUTED PYRIDINES

Hemi-acetal **21** should be further stabilized by the addition of electron donating groups on the pyridine ring of propargyloxypyridine **1**. However, coupling of electron rich 2-halopyridines to propargyl alcohols has been a challenge (Scheme 7). As such, installation of an electron withdrawing protecting group, specifically acetyl, pivaloyl, or phthalimide, is being pursued (Scheme 9).



Scheme 7. *Protecting Group Strategy for Aminopyridines*

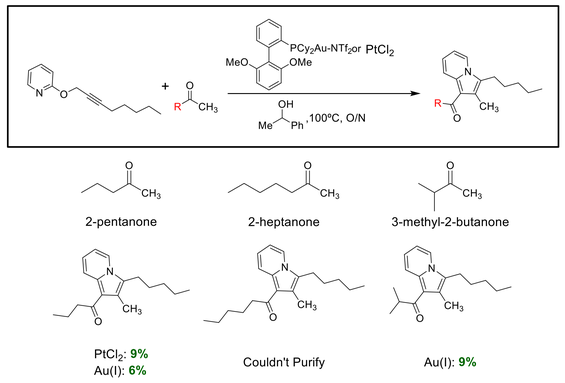


Scheme 8. *Coupling Reactions for Aminopyridines*

Unfortunately, the protecting groups that have been tried thus far introduce additional complications. Either, the amide carbonyl competes with the ring as an electrophile during the coupling, as in the acetyl case, leading to only low yields of compound **23**, or the protecting group is not stable under the coupling conditions. Attempts to broaden the range of protecting groups to try and avoid these issues are underway.

ALIPHATIC RESULTS

Evaluation of aliphatic methyl ketones, in place of aromatic methyl ketones, in the formation of indolizines was also undertaken (Scheme 9). Unlike the aromatics, the aliphatic indolizines were only formed in low yields, and were found to be less stable than their aromatic analogues, leading to problems with purification. Potential axial chirality, present in the final product, may also be causing the compounds to look impure by NMR.



Scheme 9. *Aliphatic Methyl Ketone Results*

SUMMARY

A new method for the synthesis of substituted indolizines has been discovered. Preliminary optimization has revealed promising Au(I) and Pt(II) catalysts. Additionally, altering the electronics of the solvent can substantially increase the yield. In the future, the Anderson lab will continue working to understand the mechanism, in order to fully leverage the possibilities of this new reaction.

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