Synthesis of Substituted Indolizine Structures via Au(I) and Pt(II) Catalysis

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INTRODUCTION

While evaluating the scope of the Au(I)-catalyzed rearrangement of 2-propargyloxypyridines, the Anderson lab discovered a new pathway for making substituted indolizine structures. Indolizines are a versatile heterocyclic core found frequently in pharmaceutical targets and have been shown to be active in a wide variety of therapeutic areas, including: anti-bacterial,[1] and anti-tumor,[2] in addition to targets against Alzheimer's disease,[3] asthma,[4] erectile dysfunction[5] and inflammation related to respiratory or cardiovascular disease (Figure 1).[6]

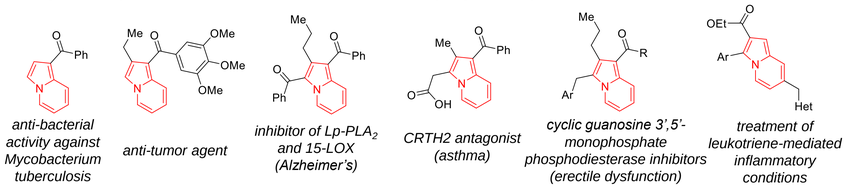
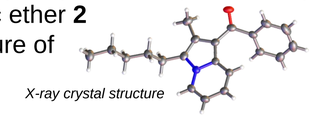
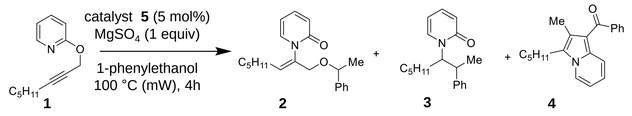


***Figure 1**. Relevant Pharmaceutical Targets With Indolizine Cores*

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*

INITIAL OPTIMIZATION

Given our inability to explain this unexpected outcome, the purity of the 1-phenylethanol solvent was investigated by NMR and was shown to be contaminated with about 10% acetophenone. An additional test reaction was done with pure 1-phenylethanol (confirmed by NMR) that failed to produce any significant quantities of indolizine **4**. With the goal of reenacting and improving upon the original reaction conditions, acetophenone was systematically added back into reaction run in pure 1-phenylethanol. As increasing equivalents of acetophenone were added to the reactions, the yields were found to increase. (Figure 2). Further, by using acetophenone as the solvent instead of 1-phenylethanol, it was possible to increase the yield of indolizine **4** to 42% (Figure 3).

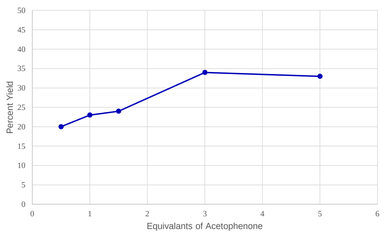


***Figure 2.** Yields of Indolizine Product (0.5M alcohol)*

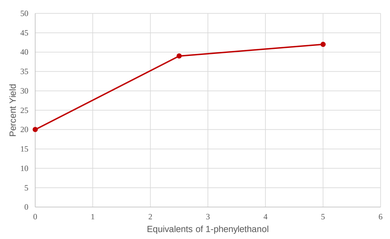
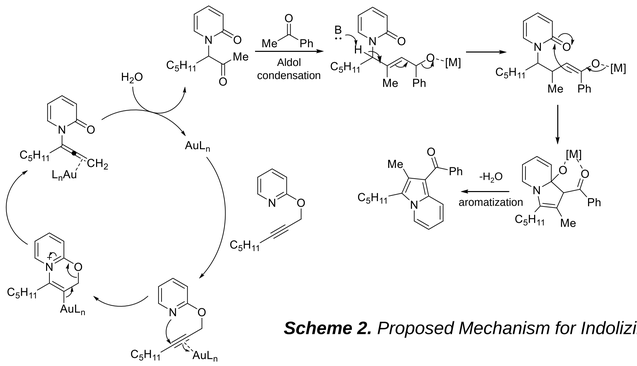


***Figure 3.** Yields of Indolizine Product (0.5M acetophenone)*

It was determined that the optimal solvent for the reaction was 5 equivalents of 1-phenylethanol in 0.5M acetophenone (Scheme 3). Also, throughout the course of the investigations, it was determined that $MgSO_4$ was not required for the reaction.

PROPOSED MECHANISM

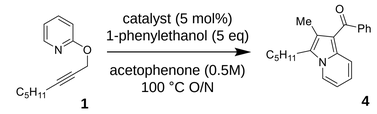
It is proposed that ketone **3** is formed initially, followed by an Aldol condensation in the presence of acetophenone, facilitated by the presence of the metal (Scheme 2). Subsequent deprotonation and enolate addition to the pyridine carbonyl, again mediated by the metal, would then lead to the formation of the observed ring system. Aromatization upon loss of water would then result in the formation of indolizine **4**.



***Scheme 2.** Proposed Mechanism for Indolizine Formation*

CATALYST SCREEN

Utilizing the optimized solvent conditions, a thorough screening of Au(I) and Pt(II) catalysts was undertaken (Table 1). This exploration showed catalysts **7** and **18** to be promising for the reaction, leading to yields of 57% and 50% respectively. These catalysts were then used in further optimization experiments.



***Scheme 3.** Standard Conditions for Catalyst Screen*

5	42%	11	41%
6	8%	12	17%
7	**57%**	13	28%
8	4%	14	12%
9	52%	15	17%
10	38%	16	2%
17	**5%**	18	**50%**
19	40%	20	46%

***Table 1.** Catalyst Screen*

FURTHER OPTIMIZATION

Having investigated potential catalysts, focus shifted back towards the reaction conditions of temperature, amounts of reactants, and impact of additives (Table 2).

7	Variant Conditions Standard Conditions: 5 mol% catalyst, 0.5M acetophenone, 100°C	$PtCl_2$ 18
57%		50%
42%	160°C	44%
50%	2.5 mol%	48%
53%	10 mol%	31%
53%	0.25M	51%
51%	1.0M	45%
34%	Cl analogue + $AgNTf_2$	N/A

***Table 2.** Optimization*

Overall, each of the changes surveyed allowed for the formation of indolizine **4**, however, none of these variations provided any improvement in yield. It is interesting to note that generating catalyst **7** from chloride analogue **8** and silver triflate significantly decreased the yield, suggesting that silver chloride is detrimental to the transformation.

SUMMARY

A new method for the synthesis of substituted indolizines has been discovered. Preliminary optimization has revealed promising Au(I) and Pt(II) catalysts. In the future, the Anderson lab looks to continue optimization work with additives, as well as doing experiments to confirm the proposed mechanism.

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