Phidianidine Analogs Containing Furan Ring Structures and a Biaryl Ring System

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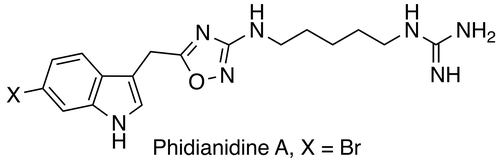
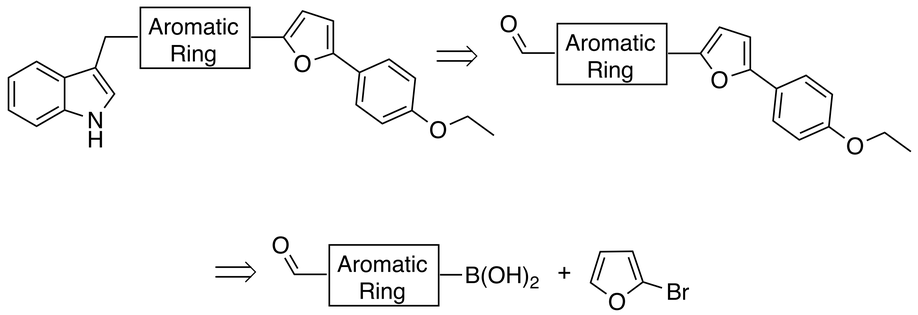
Introduction

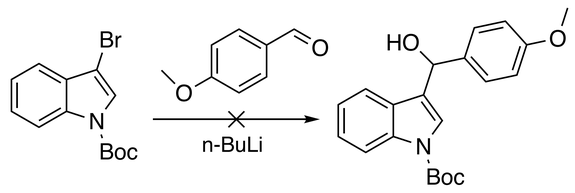
Phidianidines A & B were isolated from a shell-less mollusk, *Phidiana militaris*. These molecules are comprised of a 1,2,4-oxadiazole ring flanked by an indole ring and an aminoalkylguanadio group. Researchers were drawn to the compound for its similarities to quisqualic acid which has been shown to have agonistic effects against group I metabotropic glutamate receptors. The similarities between these compounds is mainly due to the structure of the 1,2,4-oxadiazole ring as these two compounds are one of few known compounds to naturally produce these rings. However, despite their structural similarities, upon testing, phidianidines were shown to be selective to the μ-opioid receptor which regulates the bodies response to pain stimulus. Additionally, this receptor has been known to bind to exogenous molecules which include but are not limited to strong pain-relieving compounds like hydrocodone, codeine, and illegal substances like heroin. This project was designed to synthesize phidianidine analogs with an ability to vary atoms on the central ring, indole, and vary the side chain. It has been shown that when the phidianidine indole is brominated it has significantly more biological activity than if the indole is hydrogenated. This relationship, while naturally occurring, raises the question could different substitutions cause a more active phiainidine thus allowing the compound to have either a smaller dosage or be a more effective treatment. Our group has worked on developing a synthesis to test this hypothesis.



Retrosynthesis



Addition of Indole to Furaldehyde



Ar	Conditions	Result
4-methoxy benzene	Cs_2CO_3, DMF	No Alcohol
4-methoxy benzene	Cs_2CO_3, DMF, 100 °C	Alcohol by IR
5-bromofuran	1) TMSOTf, i-Pr_2NEt, Et_2O, -78 °C 2) Pyridine 3) TBAF, THF	Alcohol by IR

Acknowledgements

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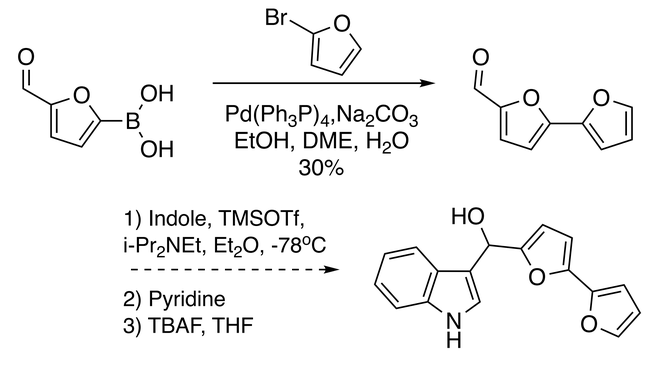
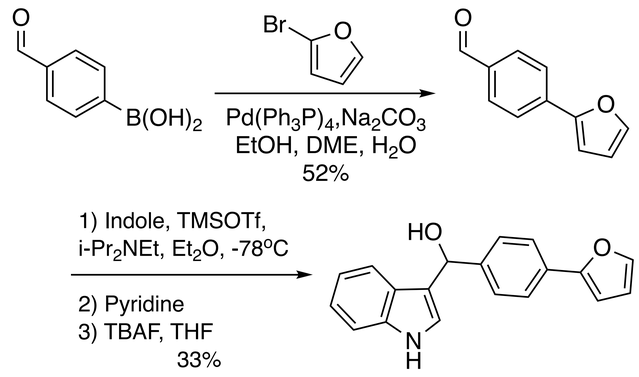
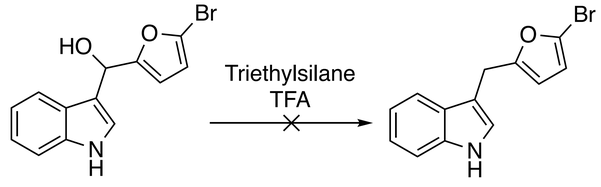
Synthesis and Addition of Biaryl Aldehydes





Reduction of alcohol



Conclusion

We have found that TMSOTf promotes the addition of indole to aromatic aldehydes like those needed to construct phidianidine analogs. We are now working to identify conditions to reduce the alcohol present after the addition. In the future, we hope to use these conditions to synthesize phidianidine analogs that vary the substituents of indoles to determine the impact on biological activity.