Cobalt Porphyrin Catalyzed Intramolecular Cyclopropanation of *N*-Alkyl Indoles/Pyrroles with Alkylcarbene

Annapureddy Rajasekar Reddy, Fei Hao, Kai Wu, Cong-Ying Zhou*, Chi-Ming Che*
The HKU Shenzhen Institute of Research & Innovation, Shenzhen, China
**Corresponding author: E-mail address:* cyzhou@hku.hk; cmche@hku.hk

Abstract: A protocol on chemo-selective cobalt(II) porphyrin-catalyzed intramolecular cyclopropanation of N-alkyl indoles/pyrroles with alkylcarbene has been developed. The reaction enables the rapid construction of a range of nitrogen-containing polycyclic compounds in moderate to high yields from readily accessible materials. These N-containing polycyclic compounds can be converted to a variety of N-heterocycles with potential synthetic and biological interest. Compared to their N-tosylhydrazone counterparts, the use of bulky N-2,4,6-triisopropylbenzenesulfonyl hydrazones as carbene precursors allows the cyclopropanation to occur under milder reaction conditions.

Keywords: alkylcarbene • cyclopropanation • cobalt porphyrin

1. Introduction

Transition metal catalyzed reactions of hetero-aromatics with α-diazocarbonyl compounds are powerful methods which can be used both to construct diverse heterocycles and in natural product synthesis.[1] However, the reactions involving alkyldiazomethanes are underexplored. Herein are described the findings on cobalt porphyrin catalyzed intramolecular cyclopropanation of *N*-alkyl indoles/pyrroles with alkyldiazomethanes *in situ* generated from hydrazones.[2] The reaction enables rapid construction of a range of nitrogen-containing polycycles in good yields from readily accessible materials. These polycycles can be readily converted to a variety of N-heterocycles with potential biological interest.

2. Experimental (or Theoretical)

A reaction vessel was charged with *N*-tosylhydrazone (0.5 mmol), potassium carbonate (3 equiv.), [Co(F_{20}-TPP)] (10 mg, 2 mol%) and dry dioxane (3.0 mL). The mixture was stirred under reflux until the reaction was completed. The reaction mixture was cooled to room temperature and filtered, the filtrate was concentrated, and the residue was purified by silica gel column chromatography to give corresponding products.

3. Results and discussion

A range of *N*-tosylhydrazones derived from different indoles underwent intramolecular cyclopropanation to give corresponding tetracyclic cyclopropane-fused indolines in moderate to high yields (Table 1). The reaction was observed to tolerate a variety of functionalities including halo, nitro, methoxy, and ester groups. The catalysis is also applicable for intramolecular cyclopropanation of pyrroles to synthesize cyclopropane-fused pyrrolines (Table 1). The Co(II)-catalyzed cyclopropanation is compatible with di-substituted and tri-substituted pyrroles to give corresponding multi-substituted polycycles in good yields. This efficient approach to generate multi-substituted polycycles is appealing since the starting material hydrazones can be readily synthesized in two steps (Michael addition and condensation) from readily accessible substituted pyrroles.

The as obtained cyclopropanation products could be converted to a range of N-heterocycles of interest in medicinal chemistry. For example, cyclopropane-fused pyrrolines can readily undergo cyclopropane ring opening to generate 5,7a-dihydro-3H-pyrrolizine which can be converted to poly-substituted pyrrolizidine by hydrogenation or to 3H-pyrrolizine by oxidation (Figure 1).

Table 1. [Co(F_{20}-TPP)]-catalyzed Intramolecular Cyclopropanation of N-Alkyl Indoles/Pyrroles with Alkylcarbene

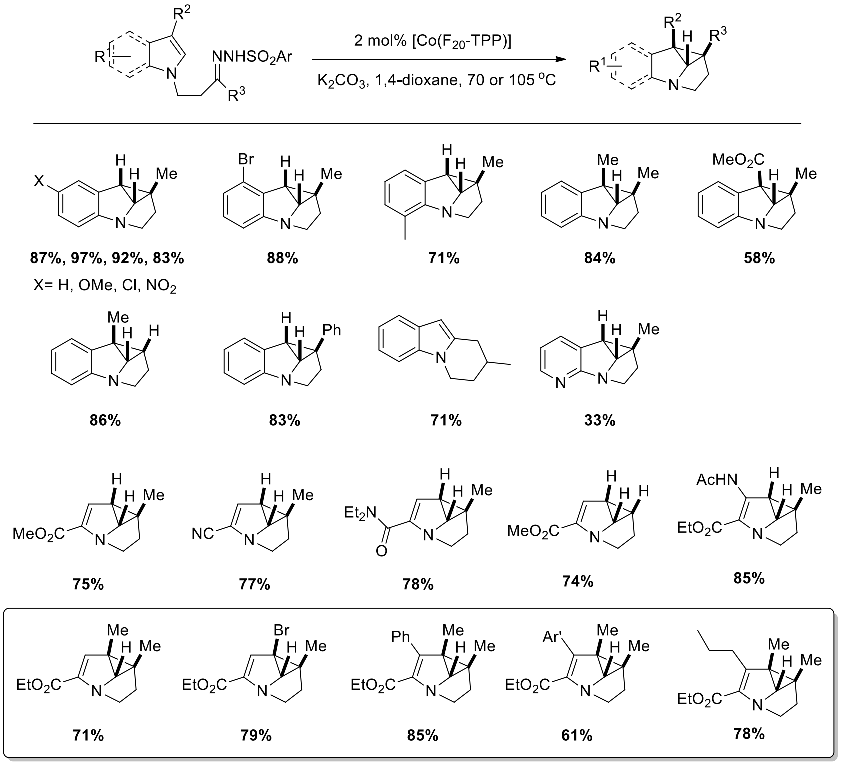
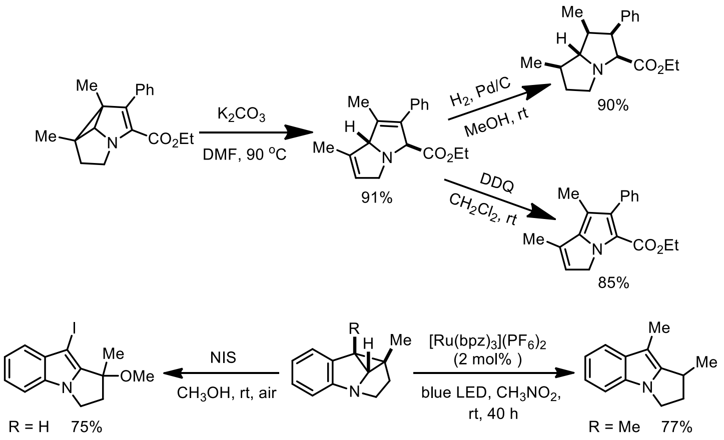


Figure 1. Transformations of cyclopropane-fused pyrrolines



4. Conclusions

In conclusion, we have developed an efficient method for rapid construction of a range of nitrogen-containing polycycles from simple starting materials by a cobalt(II) porphyrin catalyzed intramolecular cyclopropanation of *N*-alkyl indoles/pyrroles with alkyldiazomethanes *in situ* generated from hydrazones. A series of polycyclic cyclopropane-fused indolines and pyrrolines were obtained in moderate to high yields and with high chemo-selectivity. Further elaboration of the as obtained polycycles opens straightforward access to a variety of N-heterocycles, including polysubstituted pyrrolizidines and other complex N-heterocycles.

References

1. H. M. L. Davies, S. J. Hedley, *Chem. Soc. Rev.* **2007**, *36*, 1109.
2. A. R. Reddy, F. Hao, K. Wu, C.-Y. Zhou, C.-M. Che, *Angew. Chem., Int. Ed.* 2016, *55*, 1810.