

Synthesis of Multiply Functionalized Isoquinuclidines through Dearomatization of Pyridines

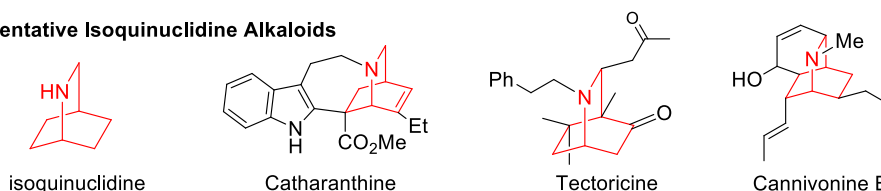
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Keywords: Pyridine; Dearomatization; Isoquinuclidine; Diels–Alder Reaction

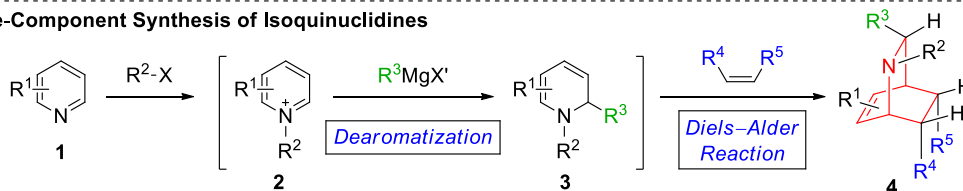
Isoquinuclidine is a scaffold found in many natural products and has been constructed through the Diels–Alder reaction of dihydropyridines. The dihydropyridines are prepared through cyclization of imines with alkynes¹ or aldehydes²; however, there is still room for improvement with regard to the synthesis of multiply functionalized isoquinuclidines.

Herein, we report a three-component synthesis of isoquinuclidines using dihydropyridines obtained through dearomatization of pyridines. Pyridine derivative **1** underwent alkylation or acylation to afford the corresponding pyridinium salt **2**, which reacted with a Grignard reagent to generate dihydropyridine **3**. Subsequent Diels–Alder reaction with a dienophile to provide isoquinuclidine derivative **4**. The structure of cycloadduct **4** was identified by NMR analysis and X-ray crystallography. Using this method, a range of isoquinuclidine derivatives were prepared in good to excellent yields with *endo* selectivity. In this presentation, the substituent effect of the nitrogen on the Diels–Alder reaction will be also discussed.

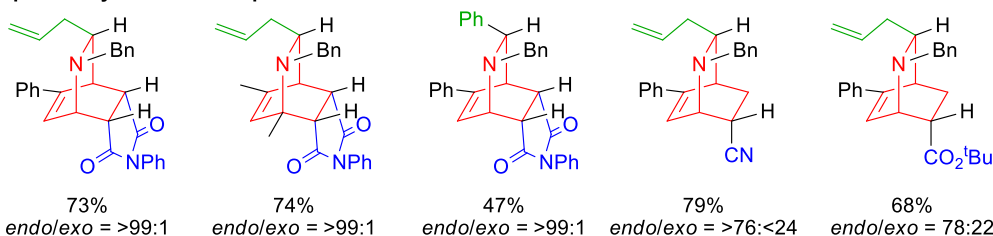
Representative Isoquinuclidine Alkaloids



Three-Component Synthesis of Isoquinuclidines



Examples of Synthesized Isoquinuclidine Derivatives



1) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2013**, 15, 444. 2) Ramaraju, P.; Pawar, A. P.; Iype, E.; Mir, N. A.; Choudhary, S.; Sharma, D. K.; Kant, R.; Kumar, I. *J. Org. Chem.* **2019**, 84, 12408.