

Preparation of pyrazolo[3,4-*b*]pyridines and integration in late-stage functionalization

Synthèse de pyrazolo[3,4-*b*]pyridines & Diversification à un stade avancé

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A multitude of aromatic heterocycles have a bicyclic nitrogen structure. Among these, the pyridine-*b*-bicyclic unit is extremely common, and consists of a pyridine fused to another aromatic ring. The pyrazolo[3,4-*b*]pyridine ring has a pyridine ring attached to a pyrazole. This motif is present in a multitude of compounds with biological activity, such as anxiolytics,¹ antifungals,² anti-leishmaniasis³ and even as anti-influenza agents⁴ (Figure 1). For our part, in collaboration with the Microbiology, Adaptation and Pathogenesis team (UMR5240), we have been able to show that certain molecules have bactericidal or bacteriostatic properties.

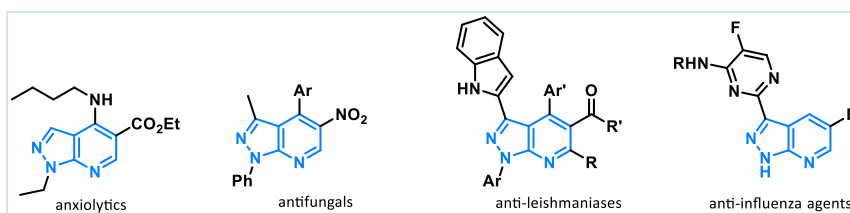


Figure 1. Examples of bio-active pyrazolo[3,4-*b*]pyridines

Despite the importance of the pyrazolo[3,4-*b*]pyridine nucleus present in many active pharmaceutical ingredients (APIs) covering a wide range of biological activities, synthetic transformations on this scaffold are few and far between. **Today's challenges lie on the development of more eco-compatible methods (saving steps and atoms) while offering more chemical diversity.** In response to this ambitious synthetic challenge and given the interest of these bicyclic nitrogen structures for the development of a drug candidate, this project will focus on the development of **innovative and direct metallo-catalysed late stage functionalization methodologies on this bicyclic scaffold** (Figure 2).

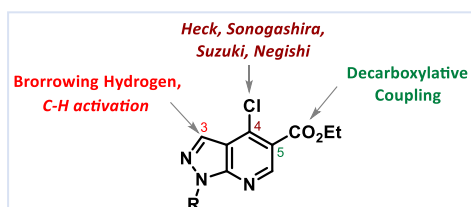
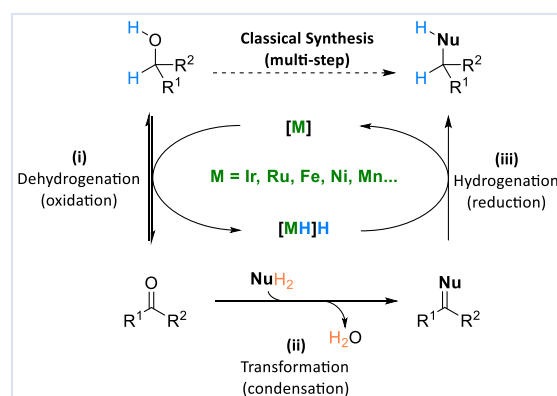


Figure 2. Pyrazolopyridine functionalizations

Finally, functionalization in C-3 position will be envisioned using the **borrowing hydrogen (BH) methodology** with various primary and secondary alcohols. This one-pot transformation has emerged as an attractive strategy for the construction of novel C-C bonds from an alcohol and a C-nucleophile.⁶ A first step of catalytic dehydrogenation converts an unreactive alcohol into the corresponding carbonyl. Subsequent aldol condensation with a C-nucleophile gives the corresponding α,β -unsaturated ketone which upon hydrogenation affords the expected C-alkylated compound (Scheme 1). We thus propose to take advantage of the pyrazolopyridine as a novel C-nucleophile.

Based on our preliminary work on Suzuki cross-coupling reaction on 4-chloro-5-carbomethoxy pyrazolopyridine,⁵ other pallado-catalyzed reactions such as **Sonogashira** and **Heck** will be examined for C-4 functionalization. Another part of the project, dedicated to the **decarboxylative coupling** in C-5 position will be performed in collaboration with COBRA-Rouen (Dr. C Schneider and Prof. C Hoarau).



Scheme 1. C-alkylation using the BH methodology

A wide range of late-stage transformations will be evaluated in the framework of this PhD program and the library of compounds will be integrated in the Chimiothèque Nationale for biological screening.

¹ (a) Patel, J. B.; Mallick, J. B.; Salama, A. I.; Goldberg, M. E. *Pharmacol. Biochem. Behav.* **1985**, *23*, 675–680. (b) Bare, T. M.; McLaren, C. D.; Campbell, J. B.; Friror, J. W.; Resch, J. F.; Walters, C. P.; Salama, A. I.; Meiners, B. A.; Patel, J. B. *J. Med. Chem.* **1989**, *32*, 2561–2573.
² Quiroga, J.; Villarreal, Y.; Gálvez, J.; Ortíz, A.; Insausti, B.; Abonia, R.; Raimondi, M.; Zacchino, S. *Chem. Pharm. Bull.* **2017**, *65*, 143–150.
³ Anand, D.; Yadav, P. K.; Patel, O. P. S.; Parmar, N.; Maurya, R. K.; Vishwakarma, P.; Raju, K. S. R.; Taneja, I.; Wahajuddin, M.; Kar, S.; Yadav, P. P. *J. Med. Chem.* **2017**, *60*, 1041–1059.
⁴ Bandarage, U. K.; Clark, M. P.; Perola, E.; Gao, H.; Jacobs, M. D.; Tsai, A.; Gillespie, J.; Kennedy, J. M.; Maltais, F.; Ledebor, M. W.; Davies, I.; Gu, W.; Byrn, R. A.; Nti Addae, K.; Bennett, H.; Leeman, J. R.; Jones, S. M.; O'Brien, C.; Memmott, C.; Bennani, Y.; Charifson, P. S. *ACS Med. Chem. Lett.* **2017**, *8*, 261–265.
⁵ Lavrard, H.; Popowycz, F. *Eur J Org Chem* **2017**, *2017*, 600–608.
⁶ François, J.; Rio, J.; Jeanneau, E.; Perrin, M.-È. L.; Jacolot, M.; Payard, P.-A.; Popowycz, F. *Org. Chem. Front.* **2023**, *10*, 4732–4739.