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From biobased sugar platforms towards new spirocycles or cylopenta[*b*]indoles: intra or intermolecular aza-Piancatelli reactions in action.

Biomass has been widely exploited for the production of chemicals and fuels as an alternative natural renewable carbon source to oil and coal. Biobased sugar platforms such as furfural or 5-hydroxymethylfurfural (HMF) are privileged candidates as primary renewable building blocks, readily available from fructose, glucose, sucrose, cellulose and inulin. Bifunctional HMF specially features an interesting intrinsic chemical potential. For several years, investigations in our team have been engaged on developing different reactions from biobased products, among HMF.[1]

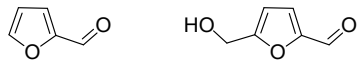
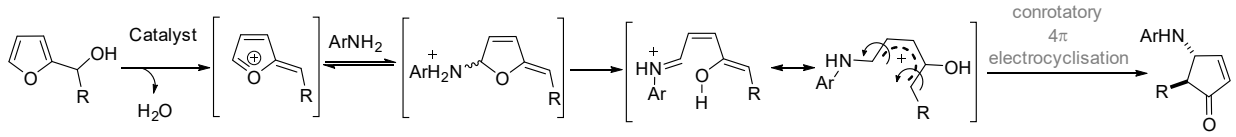


Figure 1. Furfural and 5-Hydroxymethylfurfural biobased sugar platforms

The Piancatelli rearrangement, known for 40 years, consists in the direct conversion of 2-hydroxyalkylfurans to cyclopentenones under acidic conditions, through a dehydration/water-addition/ring opening/electrocyclisation sequence. The aza-Piancatelli rearrangement from 2-furylcarbinols has also been developed (Scheme 1) with nitrogen nucleophiles, in inter- or intramolecular versions, and also associated with chiral catalysts to provide good enantiomeric excess.[2]



Scheme 1. Classical Aza-Piancatelli reaction

Aza-Piancatelli reaction was used as a key step to build the cyclopentane core of diverse nitrogen-containing complex heterocycles, natural and bioactive products. Cyclopenta[*b*]indoles represent a key structural motif of natural products which exhibit a wide range of biological activities such as bruceollines used to treat malaria and other parasitic diseases.[3] Their biological and synthetic interest has already called for the search of efficient

[1] W. Fan, C. Verrier, Y. Queneau and F. Popowycz, *Curr. Org. Synth.*, 2019, **16**, 583-614.; W. Fan, Y. Queneau and F. Popowycz, *RSC Adv.*, 2018, **8**, 31496-31501; W. Fan, Y. Queneau and F. Popowycz, *Green Chem.*, 2018, **20**, 485-492.
[2] C. Verrier, S. Moebs Sanchez, Y. Queneau and F. Popowycz, *Org. Biomol. Chem.*, 2018, **16**, 676-687.
[3] H. Chen, J. Bai, Z.-F. Fang, S.-S. Yu, S.-G. Ma, S. Xu, Y. Li, J. Qu, J.-H. Ren, L. Li, Y.-K. Si and X.-G. Chen, *J. Nat. Prod.*, 2011, **74**, 2438-2445.

strategies for their preparation,[4] generally based on the final cyclopentane ring formation from an indole-based intermediate.[5] The 1-azaspirocycle structural motif is also remarkable as embedded in natural products such as cephalotoxin (Figure2). Intramolecular aza-Piancatelli rearrangement was reported as an effective method for the synthesis of functionalized 1-azaspirocycles.[6] 5-HMF, as furfural, is not only a privileged precursor for the required 2-hydroxyalkylfuran core but also offers a more direct access to 2,5-bifunctionalized furanic substrates. This has been yet hardly exploited so far to provide aminocyclopentenones.[7]

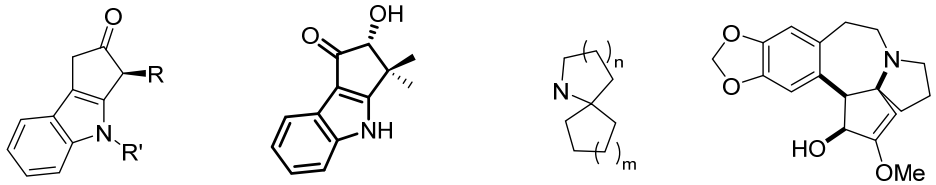


Figure 2. Key structural motifs

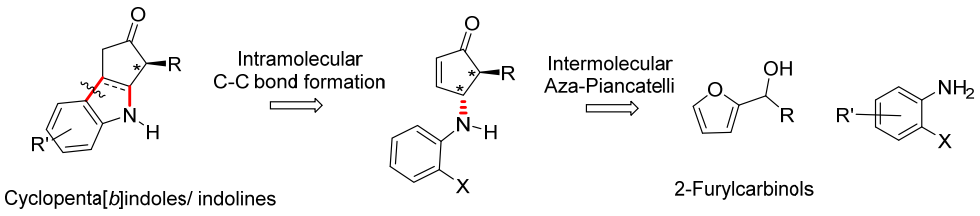
To supplement our current investigations towards the development of Piancatelli rearrangement from furfural and 5-hydroxymethylfurfural,[2,8] the project will revolve around two main axes :

- original syntheses of cyclopenta[*b*]indole nucleus from furfural
- the challenging access to novative intermediates and molecules from 5-HMF

On one hand, an original aza-Piancatelli / C-C coupling reaction sequence is proposed to prepare compounds featuring the cyclopenta[*b*]indole core. The access to nitrogen-containing complex heterocycles by combining the aza-Piancatelli reaction with another transformation is not unprecedented. In particular, the sequential combination of an aza-Piancatelli reaction with an intramolecular conjugate addition to the resultant cyclopentenone was exemplified with N,[9] O and S[10] nucleophiles. C-C bond formation was also reported *via* a Friedel-Crafts alkylation with a pyrrole appended feature leading to pyrrolo[*1,2-d*]benzodiazepine based cyclopentanones.[11] As the addition of sterically hindered anilines was shown to be feasible,[12] we envision that, once the aminocyclopentenone resulting from an (asymmetric) aza-Piancatelli reaction with a suitably substituted aniline is formed, the cyclopenta[*b*]indole nucleus could originally result from an intramolecular C-C bond

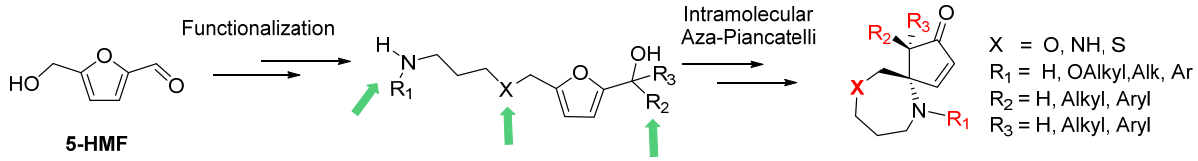
[4] a) T. Vivekanand, B. Satpathi, S. K. Bankar and S. S. V. Ramasastry, *RSC Adv.*, 2018, **8**, 18576-18588; b) J. A. Jordan, G. W. Gribble and J. C. Badenock, *Tetrahedron Lett.*, 2011, **52**, 6772-6774 and ref herein.
[5] a) S. Gandhi and B. Baire, *J. Org. Chem.*, 2019, **84**, 3904-3918; b) J. A. Jordan, G. W. Gribble and J. C. Badenock, *Tetrahedron Lett.*, 2011, **52**, 6772-6774 and ref herein.
[6] a) Z.-L. Xu, P. Xing and B. Jiang, *Org. Lett.*, 2017, **19**, 1028-1031 ; W.-B. Tang, K.-S. Cao, S.-S. Meng and W.-H. Zheng, *Synthesis*, 2017, **49**, 3670-3675; L. I. Palmer and J. Read de Alaniz, *Angew. Chem. Int. Ed.*, 2011, **50**, 7167-7170.
[7] R. F. A. Gomes, J. A. S. Coelho and C. A. M. Afonso, *ChemSusChem*, 2019, **12**, 420-425.
[8] Eman Dokmak, PhD contract 2018-2021
[9] a) K. Nayani, R. Cinsani, A. Hussaini Sd, P. S. Mainkar and S. Chandrasekhar, *Eur. J. Org. Chem.* , 2017, 5671-5678 ; b) J. Liu, Q. Shen, J. Yu, M. Zhu, J. Han and L. Wang, *Eur. J. Org. Chem.*, 2012, 6933-6939.
[10] B. V. S. Reddy, Y. V. Reddy, P. S. Lakshumma, G. Narasimhulu, J. S. Yadav, B. Sridhar, P. P. Reddy and A. C. Kunwar, *RSC Adv.*, 2012, **2**, 10661.
[11] a) Z. Wei, J. Zhang, H. Yang and G. Jiang, *Org. Lett.*, 2019, **21**, 2790-2794 (asymmetric); b) Y. P. Sarnikar, D. O. Biradar, Y. D. Mane and B. C. Khade, *J. Heterocycl. Chem.*, 2019, **56**, 1111-1116; c) B. V. Subba Reddy, Y. Vikram Reddy and K. K. Singarapu, *Org. Biomol. Chem.*, 2016, **14**, 1111-1116.
[12] a) L. Marin, R. Guillot, V. Gandon, E. Schulz and D. Leboeuf, *Org. Chem. Front.*, 2018, **5**, 640-647 ; b) L. I. Palmer and J. R. de Alaniz, *Synlett*, 2014, **25**, 8-11.

formation *via* a transition-metal catalyzed conjugate addition of aryl halide. Further functionalization of the obtained cyclopenta[*b*]indoles could then be envisioned.



Scheme 2. Retrosynthesis for a suggested formation of cyclopenta[*b*]indoles

On the other hand, based on the functionalization potential of HMF, an intramolecular aza Piancatelli-type rearrangement would convert this achiral scaffold into a three-dimensional chiral building block. So far only azaspirocycles with carbon skeleton were prepared using such a strategy.[6] HMF offers an intrinsic opportunity to introduce a heteroatom X while different amines than anilines can be considered.[13] Combining a biobased sugar platform, a high atom economic transformation, chiral organocatalysis,[14] new complex structures might be accessible to expand the scaffold diversity in the spirocyclic chemical space.[15]



Scheme 3. Toward the synthesis of novel azaspirocycles

The PhD contract will take place in a very enthusiast multicultural team, fluent in English, in a well-located brand new building with all the facilities to perform a high-level doctoral training in chemistry. The applicant must have a solid background in organic chemistry and NMR structural characterizations. A good motivation to learn and work in a multi-step synthesis program, strong communication skills, curiosity, and team spirit will be greatly appreciated.

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[15] G. Müller, T. Berkenbosch, J. C. J. Benningshof, D. Stumpfe and J. Bajorath, *Chem. Eur. J.*, 2017, **23**, 703-710.