

Synthèses originales de cyclopenténones spirocycliques par réaction d'aza-Piancatelli

Aza-Piancatelli Reactions for the Synthesis of New Spirocyclic Cyclopentenones

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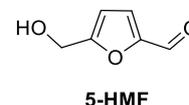
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Biomass is a natural renewable carbon source distinct from oil and coal, which has already been widely exploited for the production of chemicals and fuels. 5-Hydroxymethylfurfural (HMF) is regarded as one of the most promising biomass-derived platform chemicals thanks to a readily availability from carbohydrates such as fructose, glucose, sucrose, cellulose and inulin but also a great chemical intrinsic potential through a C-2 and C-5 bi-functionalization. In the continuity of on-going projects building on HMF, and expanding the scope of its use towards fine chemicals, we recently reported the possibility to involve it in multi-component reactions.¹

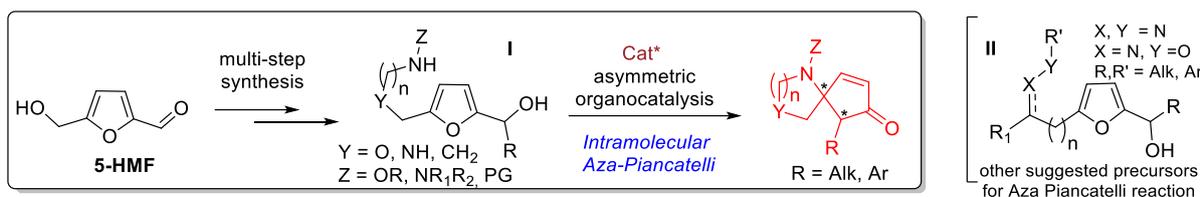


The Piancatelli rearrangement is a 45 years old reaction, which consists in the direct conversion of 2-hydroxyalkylfurans to cyclopentenones under acidic conditions, through a dehydration/water-addition/ring opening/electrocyclization sequence. Among applications in the synthesis of diverse natural and bioactive products, the reaction was a key step to build the cyclopentane cores of prostaglandin derivatives. The variant aza-Piancatelli was also developed with nitrogen nucleophiles both in intermolecular and intramolecular versions.²

We propose a functionalisation of 5-HMF to provide a diversity of substrates (**I**) for Piancatelli-type rearrangements (Scheme 1). To expand the scope of nitrogen nucleophiles, we suggest the elaboration of a functionalized lateral chain of the hydroxymethyl furan core, leading to two precursors **I** and **II** (variation of X, Y and Z in the scheme below). Some of these transformations will lead to new families of spirocycles. In addition to the methodological study, we will tackle the use of enantioselective organocatalysis to apply an underexploited intramolecular aza-Piancatelli rearrangement. Covalent and non-covalent organocatalysis by amines or acids will be explored to provide a series of spirocyclic cyclopentenones. Targeting complex polycyclic molecules, featuring multi-stereogenic centers to be controlled, while starting from 5-HMF, will be a great challenge.

¹ Fan, W.; Queneau, Y.; Popowycz, F. *Green Chem.* **2018**, *20*, 485 ; Fan, W.; Queneau, Y.; Popowycz, F. *RSC Adv.* **2018**, *8*, 31496 ; Fan, W.; Verrier, C.; Queneau, Y.; Popowycz, F. *Curr. Org. Synth.* **2019**, *16*, 583.

² Verrier, C.; Moebis-Sanchez, S.; Queneau, Y.; Popowycz, F. *Org. Biomol. Chem.* **2018**, *16*, 676.



Scheme 1. Targeting spirocycles from 5-HMF using an aza-Piancatelli reaction

5-HMF features the required 2-hydroxyalkylfuran core and could be suitably functionalized either in C-2 or C-5 positions but has never been involved as a precursor Piancatelli-type reaction. Moreover, many different nucleophiles could be used in this reaction, especially in intramolecular processes. The diversity of the protecting groups substituting nitrogen nucleophiles was limited, narrowing the actual scope of the reaction applications. Several advantages can already be pointed out about the intramolecular aza-Piancatelli reaction:

- this rearrangement is by definition a high **atom economic** transformation
- a wide variety of substrates could be prepared through the functionalization of 5-HMF, meaning that this process is suitable for **diversity-oriented synthesis**.
- complex molecules difficult to synthesize using described chemistry might be accessible using this strategy.

During this contract, the PhD student will gain major skills in synthetic methodology through multi-step synthesis with diverse type of reactions and characterization of complex chiral molecules. Although in full charge of the operational part, he or she will benefit from a participatory, reliable and guiding management from a close-knit team, with common processes and attached with the same care for quality. This constant support to autonomy and innovation will be reinforced by written and oral communication competencies, in a multi-cultural team.