Multicomponent synthesis of 3-aminopyridines under batch and flow conditions

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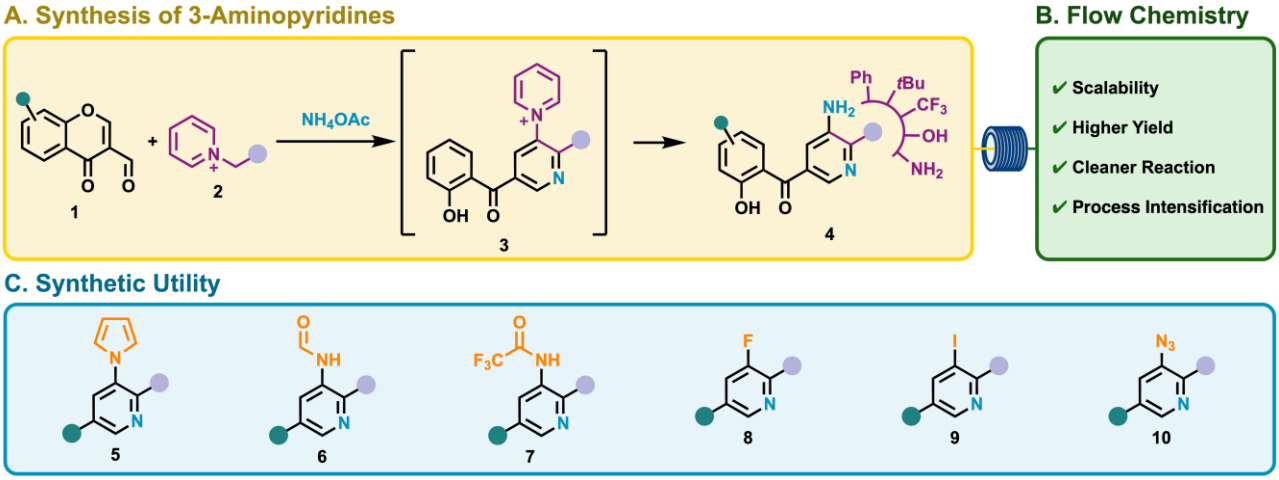
The Kröhnke pyridine synthesis is a commonly employed method for generating pyridine libraries. This process involves the interaction between an α,β-unsaturated carbonyl compound and an α-pyridinium methyl ketone salt in the presence of an ammonia source.[1–3] Whilst this reaction has demonstrated considerable efficacy in producing 2,4,6-trisubstituted pyridines, its scope is notably restricted, particularly regarding the range of substituents and functional groups that can be incorporated.[3] In the Kröhnke reaction, the crucial mechanistic stage involves the aromatisation of pyridine, which is primarily facilitated by the elimination of the pyridinium group.[1–3] Consequently, it is plausible that should the aromatisation of the pyridine be finalised whilst preserving the pyridinium group, this component could be utilised for additional modification.

In order to facilitate the aromatisation of pyridine without removing the pyridinium group, ether-tethered α,β-unsaturated carbonyl compounds **1** were chosen as Michael acceptors. This approach enables the formation of the pyridine framework through the cleavage of the ether linkage. In this context, pyridinium serves an alternative function as a leaving group during substitution with ammonia, facilitating the production of the hard-to-obtain 3-aminopyridines **4** (Scheme 1, A).

In contrast to the conventional Kröhnke reaction, our multi-component approach facilitates the production of pyridines featuring a substitution pattern at positions C-2, C-3, and C-5. This method accomplishes the functionalisation of electronically neutral carbon atoms within the pyridine structure. This approach was additionally investigated as a means for producing 3-aminopyridines **4** with bespoke functionalities at the C-2 position.

This talk will elucidate the synthetic potential of our approach and outline the confirmed reaction mechanism. Additionally, we will showcase research highlighting the feasibility of mass-producing 3-aminopyridines **4** using flow chemistry techniques (Scheme 1, B). Furthermore, we will demonstrate the practical applications of these compounds, with a particular focus on utilizing the attached amino group (Scheme 1, C).



Scheme 1: Schematic depiction the newly developed synthesis of 3-aminopyridines using a modified Kröhnke method (A), the advantages of the application in flow chemistry (B) and the representation compounds obtained in the post-functionalization studies (C).

References

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