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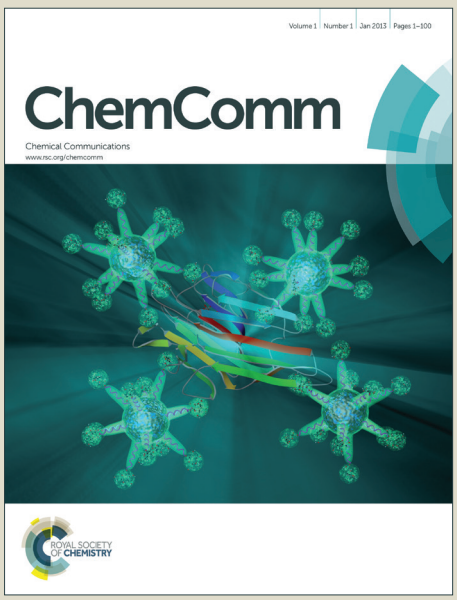

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A heavy metal- and oxidant-free, one-pot synthesis of pyridines and fused pyridines based on a Lewis acid-catalyzed multicomponent reaction

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The $InCl_3$-catalyzed sequential multicomponent reaction between 2-furfurylamine, β-dicarbonyl compounds and α,β-unsaturated aldehydes in ethanol, followed by microwave irradiation in solvent-free conditions, afforded good to excellent yields of highly substituted pyridines, with loss of the 2-furylmethyl side chain. The method was also adapted to the synthesis of quinolones, isoquinolines, phenanthridines and more complex fused pyridine systems.

Pyridine is one of the best-studied nitrogen heterocycles due to the importance of its derivatives in many fields of academic and industrial reasearch. Mono-, bi- and terpyridine scaffolds are widely employed in coordination chemistry, giving chelates that often have good catalytic properties.[1] Pyridines are also important in supramolecular chemistry[2] and in the science of polymers,[3] surfaces[4] and materials[5]. Pyridine substructures are also present in many natural products[6] and in a large number of bioactive compounds, and hence pyridine can be regarded as a privileged structure in drug discovery.[7] Furthermore, pyridine derivatives are also widely employed in agricultural chemistry as herbicides, insecticides and antifungals, and they also are important synthetic intermediates.

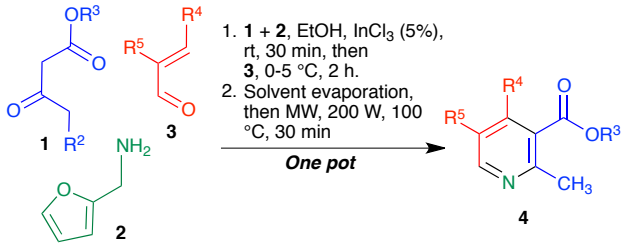
Because of the immense importance of pyridines, synthetic chemists have developed a large number of methods for their preparation.[8,9] Among them, those involving the use of multicomponent reactions to create the pyridine ring are particularly efficient thanks to the generation of several bonds in a single operation. These methods are also preferable from the environmental point of view, since avoiding workup and purification steps leads to a greatly diminished generation of waste from organic solvents and chromatographic stationary phases. In spite of recent progress, the development of chemo- and regioselective multicomponent routes to functionalized pyridines and their fused derivatives remains challenging.

Some multicomponent pyridine syntheses including, among others, the Bönnemann cyclization *i.e.* the [2+2+2] cycloaddition of alkynes with nitriles, require the use of transition metals.[10] Besides the need for expensive and toxic catalysts, these methods sometimes suffer from a lack of regioselectivity. While many of the multicomponent methods leading to the pyridine ring that do not require heavy metals are known,[11] the ones most closely related to our work start from β-dicarbonyl compounds and involve the intermediacy of β-enaminones, *via* a [3+3] mechanism. This is the case of the Hantzsch synthesis, that can be coupled with a sequential or *in situ* oxidation to afford pyridines,[12] the Bohlmann-Rahtz synthesis and related transformations.[13] Recently, it has been found that β-dicarbonyl compounds, α,β-unsaturated aldehydes or α,β-unsaturated α-ketoesters or amides and ammonia can give pyridines, in a Michael-initiated process that furnishes a 1,5-dicarbonyl that then reacts with ammonia.[14]

In this context, we have recently described a room-temperature, four-component reaction between β-dicarbonyl conpounds, α,β-unsaturated aldehydes, primary amines and alcohols in the presence of Ce(IV) ammonium nitrate as catalyst, that affords excellent yields of 1-alkyl-6-alkoxy-1,4,5,6-tetrahydropyridines bearing alkyl groups at C-2 and an ester function at C-3.[15] We became interested in extending this methodology to the preparation of pyridines, but found that the replacement of primary amines by ammonia failed to give the desired products. Thus, the only remaining option was to perform the multicomponent reaction from a primary amine whose substituent could act as a leaving group. Furthermore, in order to achieve a more general access to pyridine derivatives, we also needed to increase the scope of our reaction to include more varied substitution patterns and types of substituents, since the original process allows only simple alkyls at C-2 and methyl groups at either C-4 or C-5, but not at both positions. Regarding the first goal, we achieved limited success by using dimethylhydrazine as the amino component, but the scope of the reaction was very narrow, allowing substitution only at C-2 and C-3, and the average yield was only 66%.[16]

We now report a satisfactory solution to both problems, which has led to a one-pot synthesis of highly substituted pyridines and several families of their fused derivatives from simple,

readily available starting materials. Our method is based on the spontaneous loss of the 2-furylmethyl substituent from an 1-(2-furylmethyl)-6-ethoxy-1,4,5,6-tetrahydropyridine intermediate under microwave irradiation. Benzyl leaving groups were also assayed, but led to complex mixtures. As shown in Scheme 1, the sequential multicomponent reaction between β-ketoesters **1**, 2-furylamine **2** and unsaturated aldehydes **3** was performed under modified conditions (0-5 °C, $InCl_3$ as catalyst) and, without isolation of the tetrahydropyridine product, the solvent was evaporated and the residue was submitted to microwave irradiation (200 W, 100 °C) to give pyridines **4** in a one-pot protocol.



Scheme 1. Synthesis of polysubstituted pyridines

Under these improved conditions the scope of the multicomponent reaction was considerably expanded in comparison to the published method and hence a wide range of pyridines were accesible, as summarized in Figure 1. These include di-, tri- and tetrasubstituted pyridines bearing alkyl or aryl substituents at C-4,5. Furthermore, the C-2 position was readily amenable to the introduction of complex substituents containing a variety of functional groups, including thioether and ester groups and alkene or diene fragments.

A rationalization of the pyridine synthesis is shown in Scheme 2. As previously reported,[15] the initial four- component reaction proceeds *via* a sequence of β-enaminone formation, Michael addition, intramolecular 6-*exo*-*trig* cyclization and hydroxy-alkoxy exchange *via* an intermediate iminium intermediate, to give compound **5**. We propose that microwave irradiation of the latter induces its S_N1-type degradation to give ethoxide anion and **6**, a benzylic cation stabilized by the furan oxygen, that then combine to furnish 2-ethoxymethylfuran, which was detected in the crude reaction mixtures. In the last step, air oxidation of **6** affords the final products **4** without the need for addition of other oxidants, which is relevant in view of the fact that redox reactions are often difficult to scale up and are often undesirable from an environmental point of view, which has led to the concept of redox economy as a desirable feature of synthetic routes.[17] In agreement with this proposal, starting compounds bearing primary N-alkyl substituents, which cannot generate stable carbocations, failed to give pyridine products. Interestingly, the microwave-assisted reactions showed a divergent behaviour when carried out under conventional heating. Thus, the reaction starting from ethyl 3-oxohept-6-enoate afforded compound **4d** under microwave conditions, while its reflux in toluene gave a 1-(2-furylmethyl)-1,4-dihydropyridine derivative that was rather unstable but could nevertheless be identified by its NMR data (see the Supporting Information). This observation is consistent with the proposed mechanism, since microwave irradiation is known to stabilize polar transition states such as those involved in the transformation of **5** into **6**.[18]

The method also worked well for the preparation of fused pyridines (Figure 2). Thus, the use of cyclohexene-1-

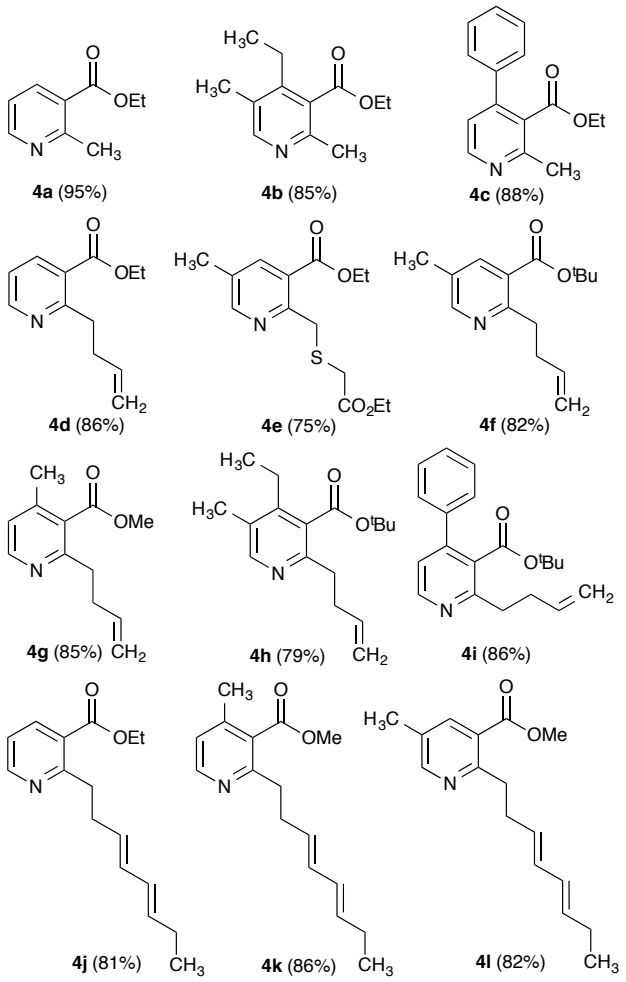
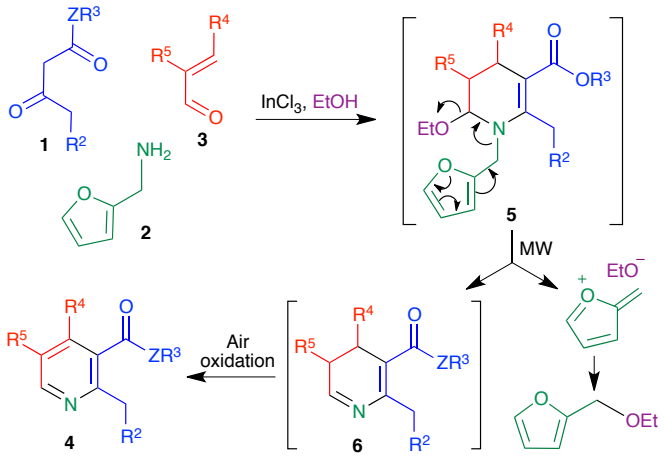


Figure 1. Scope of the pyridine synthesis



Scheme 2. Mechanistic rationalization of the pyridine synthesis

carbaldehyde as the α,β-unsaturated aldehyde component allowed the synthesis of isoquinoline derivatives **7a-d**. Quinolines were also accessible, by employing 1,3-cyclohexanediones as the β-dicarbonyl component (compound **7e**). Furthermore, we found that β-tetralone was sufficiently reactive to replace the usual β-dicarbonyl derivative, and this modification of the method allowed the preparation of benzo[*f*]quinolines such as **7f** and **7g**. Finally, we were able to

combine the strategies leading to isoquinolines and quinolines, furnishing more complex fused systems such as phenanthridine **7h** and benzo[*a*]phenanthridine **7i**.

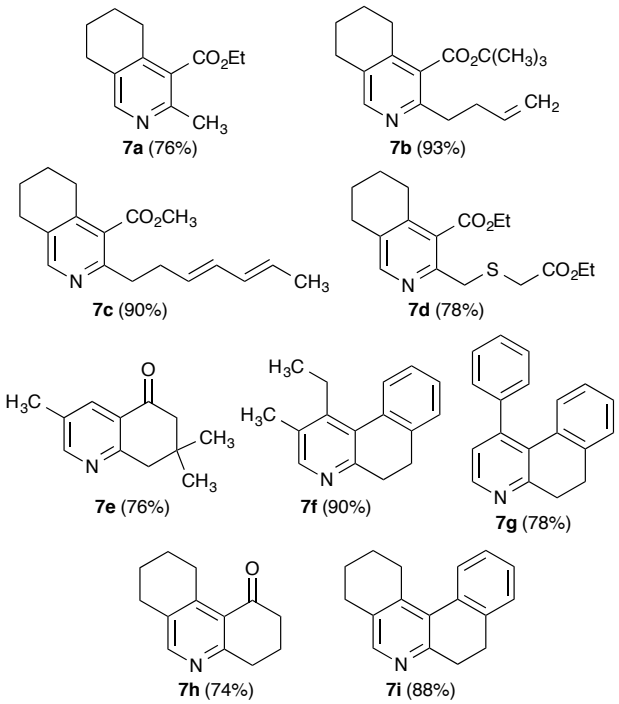


Figure 2. Synthesis of fused pyridines

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Conclusions

In conclusion, we have developed a one-pot protocol that affords good to excellent yields of pyridines and several types of their fused derivatives, including quinolin-5-ones, isoquinolines, phenanthridines and more complex tetracyclic systems, from simple and inexpensive starting materials and catalysts, on the basis of a sequence of reactions initiated by a multicomponent reaction. This one-pot process does not require the purification of intermediates nor the use of toxic transition metal-based catalysts or oxidants other than air, rendering it attractive from the point of view of green chemistry. It generates one C-C and two C-N bonds *via* a cascade of seven individual reactions and is mechanistically novel in that it involves a fragmentation reaction that allows the unprecedented use of 2-furylmethyl as a nitrogen protecting group.

Notes and references

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Electronic Supplementary Information (ESI) available: Copies of spectra of all compounds. See DOI: 10.1039/c000000x/

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