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Metal-free Michael addition initiated multicomponent oxidative cyclodehydration route to polysubstituted pyridines from 1,3-dicarboxyls†

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A simple metal-free, step-economic and selective access to pyridines from readily available substrates is reported, involving a flexible 4 Å molecular sieves-promoted Michael addition initiated domino three-component reaction between a 1,3-dicarbonyl, a Michael acceptor and a synthetic equivalent of ammonia.

Pyridines are one of the most important nitrogen heterocycles found in numerous natural and synthetic pharmaceutical agents. These scaffolds are also of widespread interest in coordination and supramolecular chemistry, as well as for materials science. The synthesis of these heterocycles has long been an area of intense interest resulting in the development of a wide range of synthetic methods. Among them, the direct condensation of carbonyl compounds with a source of ammonia is well documented, but still suffers from some limitations in the substrates, or involves an oxidative agent or an elimination step. Thereby, development of valuable synthetic pathways still remains an industrial as well as an academic challenge.

In this context, the metal-catalysed [2+2+2] cycloisomerisation of alkenes with nitriles largely leads the way nowadays. However, despite recent spectacular advances, the low availability of some catalysts and substrates associated with the lack of regioselectivity constitute major drawbacks.

In the course of our studies on the development of new domino multicomponent reactions (MCRs) for creation of molecular complexity and diversity whilst combining economic aspects with environmental ones, we recently reported molecular sieves-promoted transformations of various 1,3-dicarboxyls for the stereoselective synthesis of a series of heterocycles. In this context, herein we wish to report on a simple metal-free, step-economic and selective access to pyridines from readily available substrates. Thus, we have now designed a flexible domino three-component reaction involving the direct condensation of 1,3-dicarboxyls with Michael acceptors and a synthetic equivalent of ammonia, under heterogeneous catalysis by 4 Å molecular sieves (MS), providing after in situ oxidation the corresponding pyridine derivatives in a single operation (Scheme 1).

Due to the nature of the three partners, this strategy may be viewed as a Michael addition initiated biomimetic approach previously formulated by Baldwin and Marazano for natural 3-alkylpyridinyls.

Preliminary experiments were conducted with easily available acyclic 1,3-dicarboxyls 1a–e and Michael acceptors 2a–c. Under optimised conditions, NH₂OAc proved to be the best source of ammonia and the corresponding pyridines 4a–j were obtained by simply heating a toluene solution of the three partners in the presence of 4 Å MS, acting both as dehydrating agent and as heterogeneous catalyst as shown before.

The general applicability is clearly seen from the results reported in Table 1. Acrolein (2a) (entries 1, 4, 8, 10) and methacrolein (2b) (entries 2, 5, 7) may be used, as well as methyl vinyl ketone (2c) (entries 3, 6, 9). Similarly, diversity may be accessed through the use of Fig. 1 of either acetylnicotone (1a) (entries 1–3), methyl acetooctate (1b) (entries 4–6) or ethyl 4,4,4-trifluoroacetooctoate (1c) (entry 7). Interestingly enough, β-ketoamide 1d led to the expected pyridines 4h and 4i (entries 8 and 9), making this transformation a direct and user-friendly one-pot access to nicotinamide derivatives. Finally, this multicomponent reaction appears as a promising new strategy for the direct metal-free synthesis of biaryl compounds.

**Scheme 1** MCR synthesis of polysubstituted pyridines 4.

**Fig. 1** Acyclic 1,3-dicarboxyl substrates 1 for the MCR.

**Fig. 2** Bi- and tricyclic pyridines from the MCR.
compounds from substrates such as 1e (entry 10), opening the way to a flexible design of atropoisomers of bi-aryl ligands.\textsuperscript{23}

To further demonstrate the versatility of the method, we then examined the use of cyclic 1,3-dicarbonyls such as dimesdone (1f) or indane-1,3-dione (1g) in the sequence, and some representative bi- and tricyclic pyridines are shown in Fig. 2. In all cases, products are obtained with a total regioselectivity. Of particular interest is the one-pot synthesis of 4-azafluorenones 4m and 4n, which are common skeletons in natural products and molecules of pharmacological interest,\textsuperscript{24} and generally accessed \textit{via} multistep sequences.\textsuperscript{25}

The neutral heterogeneous reaction conditions are also suitable with sensitive Michael acceptors such as \textit{a}-exo-methylketones 2d–f,\textsuperscript{26} leading to bi- and tricyclic pyridines 4o–q in acceptable yields (Fig. 3).

From a mechanistic point of view, two multistep sequences have been preliminarily explored. Both evolve through a 1,4-dihydropyridine intermediate 7 which suffers an \textit{in situ} oxidative aromatisation to the corresponding pyridine.\textsuperscript{27} We initially postulated that the first step of the sequence may be the molecular sieves promoted Michael addition between substrates 1 and acceptors 2. The corresponding adduct 5 may then react with ammonium acetate (3) leading to the dihydropyridine \textit{via} an intramolecular dehydrative cyclisation sequence. As a validation of this first hypothesis, pyridine 4c was isolated by mixing the Michael adduct 5a\textsuperscript{28} with 3 under standard conditions (Scheme 2). Alternatively, a more conventional mechanistic pathway could involve the preliminary formation of an enamino ketone intermediate 6, which may lead to the final product \textit{via} a Hantzsch-type reaction.\textsuperscript{29}

Interestingly enough, when 6, independently prepared from NH\textsubscript{2}OAc and acetylacetone (1a), was reacted with methyl vinyl ketone (2c), pyridine 4c was not formed and starting materials were recovered even after 24 hours (Scheme 2). These preliminary results support our original mechanistic proposal involving a 4 Å MS initiated Michael addition\textsuperscript{30} as the first step of the sequence.\textsuperscript{31}

In conclusion, we have developed a regioselective, user-friendly and mechanistically original three-component reaction for the one-pot synthesis of polysubstituted pyridines from readily accessible substrates. The biomimetic like sequence does not require any harmful reagents or metal-based catalysts, and allows construction of highly functionalised heterocycles of both biological and synthetic interest. This pyridine approach should be a good and complementary substrate directed synthetic alternative to other well known methods.

### Notes and references


