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

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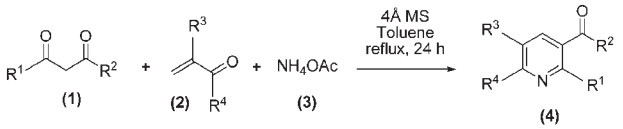
A simple metal-free, step-economic and selective access to pyridines from readily available substrates is reported, involving a flexible 4 Å molecular sieves promoted Michael addition initiated domino three-component reaction between a 1,3-dicarbonyl, a Michael acceptor and a synthetic equivalent of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

Pyridines are one of the most important nitrogen heterocycles found in numerous natural and synthetic pharmaceutical agents.[1] These scaffolds are also of widespread interest in coordination and supramolecular chemistry, as well as for materials science.[2] The synthesis of these heterocycles has long been an area of intense interest resulting in the development of a wide range of synthetic methods.[3] Among them, the direct condensation of carbonyl compounds with a source of ammonia is well documented,[4] but still suffers from some limitations in the substrates,[5] or involves an oxidative agent[6] or an elimination step.[7] Thereby, development of valuable synthetic pathways still remains an industrial as well as an academic challenge.[8] In this context, the metal-catalysed [2 + 2 + 2] cycloisomerisation of alkynes with nitriles largely leads the way nowadays.[9] However, despite recent spectacular advances,[10] the low availability of some catalysts and substrates associated with the lack of regioselectivity[11] constitute major drawbacks.

In the course of our studies on the development of new domino[12] multicomponent reactions (MCRs)[13] for creation of molecular complexity and diversity[14] whilst combining economic aspects[15] with environmental ones,[16] we recently reported molecular sieves-promoted transformations of various 1,3-dicarbonyls[17] for the stereoselective synthesis of a series of heterocycles.[18] 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-dicarbonyls **1** with Michael acceptors **2** and a synthetic equivalent of ammonia **3**, under heterogeneous catalysis by 4 Å molecular sieves (MS), providing after *in situ* oxidation the corresponding pyridine derivatives **4** in a single operation (Scheme 1).[19]



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

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[20] for natural 3-alkylpyridinium salts.

Preliminary experiments were conducted with easily available acyclic 1,3-dicarbonyls **1a–e** and Michael acceptors **2a–c**. Under optimised conditions, NH_4OAc proved to be the best source of ammonia[21] 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,[22] acting both as dehydrating agent and as heterogeneous catalyst as shown before.[18a] 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 acceded through the use (Fig. 1) of either acetylacetone (**1a**) (entries 1–3), methyl acetoacetate (**1b**) (entries 4–6) or ethyl 4,4,4-trifluoroacetoacetate (**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 bi-aryl

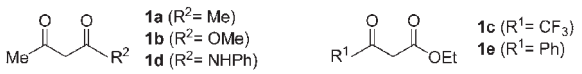


Fig. 1 Acyclic 1,3-dicarbonyl substrates **1** for the MCR.

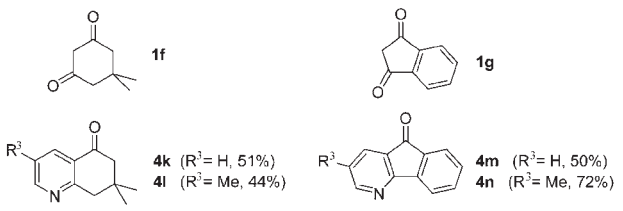


Fig. 2 Bi- and tricyclic pyridines from the MCR.

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Table 1 Pyridine synthesis from acyclic 1,3-dicarbonyls

Entry	Substrate **1**	R^3	R^4	Product	Yield (%)[a]
1	**1a**	H	H	**4a**	52
2	**1a**	Me	H	**4b**	65
3	**1a**	H	Me	**4c**	62
4	**1b**	H	H	**4d**	56
5	**1b**	Me	H	**4e**	44
6	**1b**	H	Me	**4f**	65
7	**1c**	Me	H	**4g**	70
8	**1d**	H	H	**4h**	61
9	**1d**	H	Me	**4i**	42
10	**1e**	H	H	**4j**	65

[a] Isolated yield after flash chromatography.

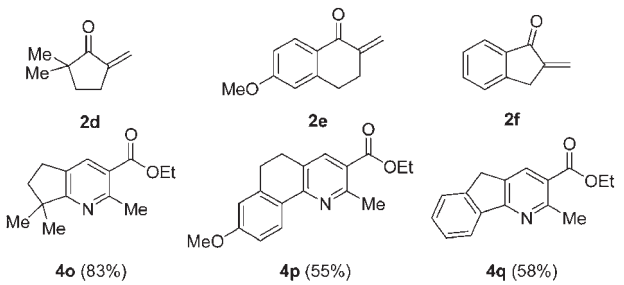


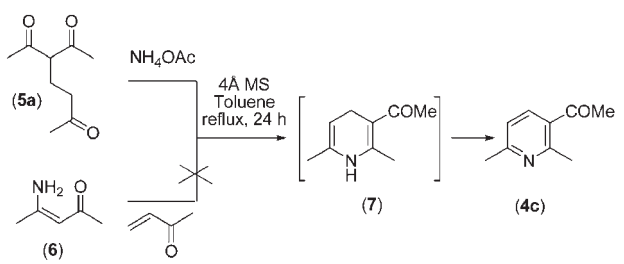
Fig. 3 Pyridines from sensitive Michael acceptors.

compounds from substrates such as **1e** (entry 10), opening the way to a flexible design of atropoisomers of bi-aryl ligands.[23]

To further demonstrate the versatility of the method, we then examined the use of cyclic 1,3-dicarbonyls such as dimedone (**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,[24] and generally accessed *via* multistep sequences.[25]

The neutral heterogeneous reaction conditions are also suitable with sensitive Michael acceptors such as α-*exo*-methylene ketones **2d–f**,[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 *in situ* oxidative aromatisation to the corresponding pyridine.[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 **7** *via* an intramolecular dehydrative cyclisation sequence. As a validation of this first hypothesis, pyridine **4c** was isolated by mixing the Michael adduct **5a**[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 *via* a Hantzsch-type reaction.[29] Interestingly enough, when **6**, independently prepared from NH_4OAc 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[30] as the first step of the sequence.[31]



Scheme 2 Mechanistic investigations.

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.

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