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

Frédéric Liéby-Muller, Christophe Allais, Thierry Constantieux* and Jean Rodriguez*

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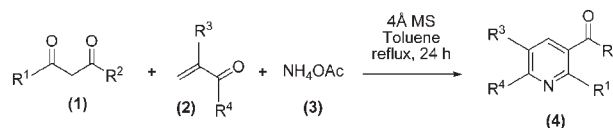
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A simple metal-free, step-economic and selective access to pyridines from readily available substrates is reported, involving a flexible 4 Å molecular sieves promoted Michael addition initiated domino three-component reaction between a 1,3-dicarbonyl, 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 agent⁶ 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 regioselectivity¹¹ constitute major drawbacks.

In the course of our studies on the development of new domino¹² multicomponent reactions (MCRs)¹³ for creation of molecular complexity and diversity¹⁴ whilst combining economic aspects¹⁵ with environmental ones,¹⁶ we recently reported molecular sieves-promoted transformations of various 1,3-dicarbonyls¹⁷ 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),



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

providing after *in situ* oxidation the corresponding pyridine derivatives **4** in a single operation (Scheme 1).¹⁹

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 Marazano²⁰ 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, NH₄OAc proved to be the best source of ammonia²¹ 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 accessed 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

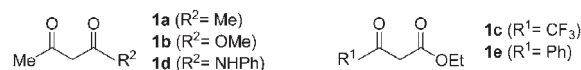


Fig. 1 Acyclic 1,3-dicarbonyl substrates **1** for the MCR.

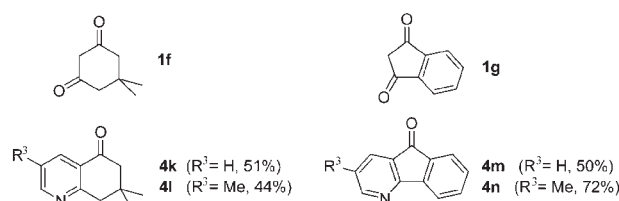


Fig. 2 Bi- and tricyclic pyridines from the MCR.

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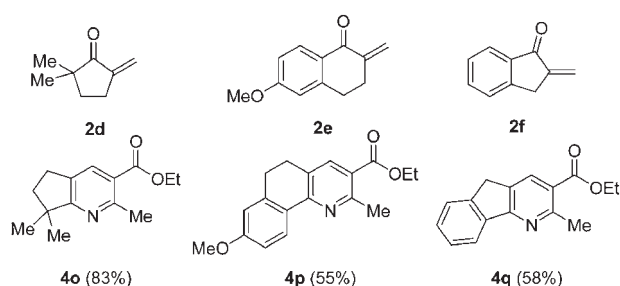
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Table 1 Pyridine synthesis from acyclic 1,3-dicarbonyls

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.

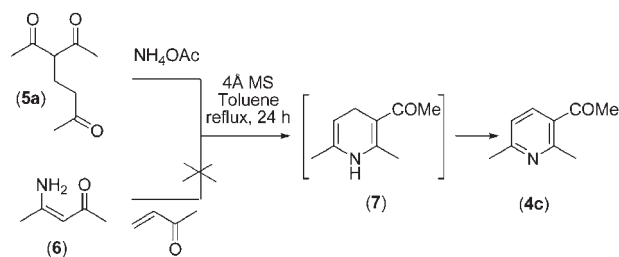
**Fig. 3** Pyridines from sensitive Michael acceptors.

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**

**Scheme 2** Mechanistic investigations.

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 addition³⁰ as the first step of the sequence.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.

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