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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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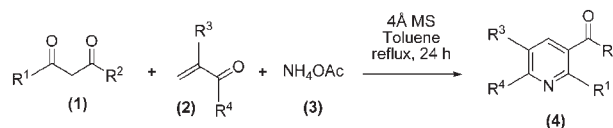
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A simple metal-free, step-economic and selective access to pyridines from readily available substrates is reported, involving a flexible 4 Å molecular sieves promoted Michael addition initiated domino three-component reaction between a 1,3-dicarbonyl, 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.<sup>1</sup> These scaffolds are also of widespread interest in coordination and supramolecular chemistry, as well as for materials science.<sup>2</sup> The synthesis of these heterocycles has long been an area of intense interest resulting in the development of a wide range of synthetic methods.<sup>3</sup> Among them, the direct condensation of carbonyl compounds with a source of ammonia is well documented,<sup>4</sup> but still suffers from some limitations in the substrates,<sup>5</sup> or involves an oxidative agent<sup>6</sup> or an elimination step.<sup>7</sup> Thereby, development of valuable synthetic pathways still remains an industrial as well as an academic challenge.<sup>8</sup> In this context, the metal-catalysed [2+2+2] cycloisomerisation of alkynes with nitriles largely leads the way nowadays.<sup>9</sup> However, despite recent spectacular advances,<sup>10</sup> the low availability of some catalysts and substrates associated with the lack of regioselectivity<sup>11</sup> constitute major drawbacks.

In the course of our studies on the development of new domino<sup>12</sup> multicomponent reactions (MCRs)<sup>13</sup> for creation of molecular complexity and diversity<sup>14</sup> whilst combining economic aspects<sup>15</sup> with environmental ones,<sup>16</sup> we recently reported molecular sieves-promoted transformations of various 1,3-dicarbonyls<sup>17</sup> for the stereoselective synthesis of a series of heterocycles.<sup>18</sup> 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).<sup>19</sup>

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<sup>20</sup> 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<sub>4</sub>OAc proved to be the best source of ammonia<sup>21</sup> 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,<sup>22</sup> acting both as dehydrating agent and as heterogeneous catalyst as shown before.<sup>18a</sup> 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

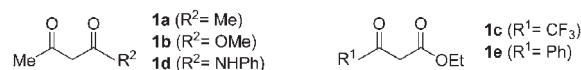


Fig. 1 Acyclic 1,3-dicarbonyl substrates **1** for the MCR.

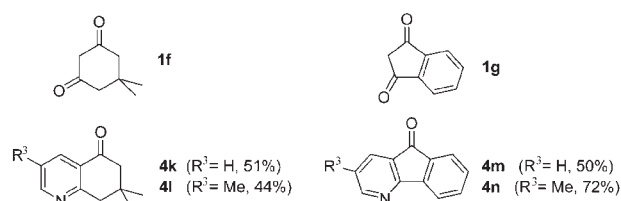


Fig. 2 Bi- and tricyclic pyridines from the MCR.

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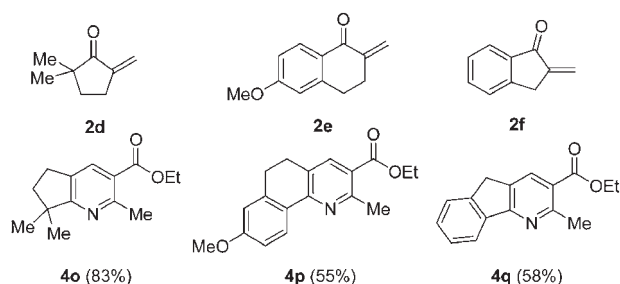
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**Table 1** Pyridine synthesis from acyclic 1,3-dicarbonyls

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

<sup>a</sup> Isolated yield after flash chromatography.

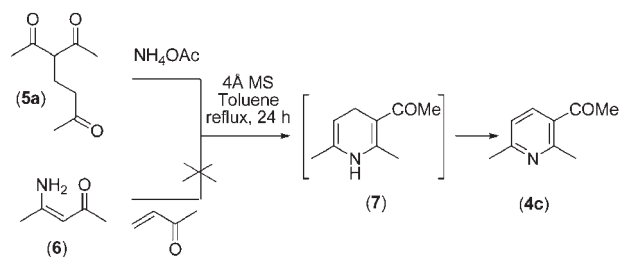
**Fig. 3** Pyridines from sensitive Michael acceptors.

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

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,<sup>24</sup> and generally accessed *via* multistep sequences.<sup>25</sup>

The neutral heterogeneous reaction conditions are also suitable with sensitive Michael acceptors such as  $\alpha$ -*exo*-methylene ketones **2d–f**,<sup>26</sup> 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.<sup>27</sup> 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**<sup>28</sup> 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.<sup>29</sup> Interestingly enough, when **6**, independently prepared from NH<sub>4</sub>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<sup>30</sup> as the first step of the sequence.<sup>31</sup>

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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