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# The Use of 5-Hydroxymethylfurfural (5-HMF) in Multi-component Hantzsch Dihydropyridine Synthesis

Jingjing Jiang,<sup>[a]</sup> Yves Queneau<sup>[a]\*</sup> and Florence Popowycz<sup>[a]\*</sup>

[a] INSA Lyon, Université Lyon 1, CNRS, CPE, UMR 5246, ICBMS, 1 rue Victor Grignard,  
F-69621 Villeurbanne Cedex

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## Abstract:

The renewable 5-hydroxymethylfurfural (5-HMF) has gained a wide interest from the chemistry community as a valuable biobased platform opening the way to further functionalization. Despite an impressive number of publications reporting either its preparation or its functionalization, its direct use in fine chemistry, and especially in multi-component reaction (MCR), is less reported. Here, we report a complete study of the use of 5-HMF in the Hantzsch dihydropyridines synthesis. The strategy was applied to a scope of  $\beta$ -dicarbonyl molecules (including  $\beta$ -ketoesters and 1,3-diketones) in a 3-component procedure leading to a series of symmetrical 1,4-dihydropyridines derived from 5-HMF in excellent yields. The study was extended to the 4-component protocol using one equivalent of a  $\beta$ -ketoester and one equivalent of 5,5-dimethyl-1,3-cyclohexanedione (dimedone), which efficiently provided the corresponding unsymmetrical dihydropyridines.

**Keywords:** 5-HMF, MCR, Hantzsch, 1,4-dihydropyridines, ammonium acetate, solvent-free.

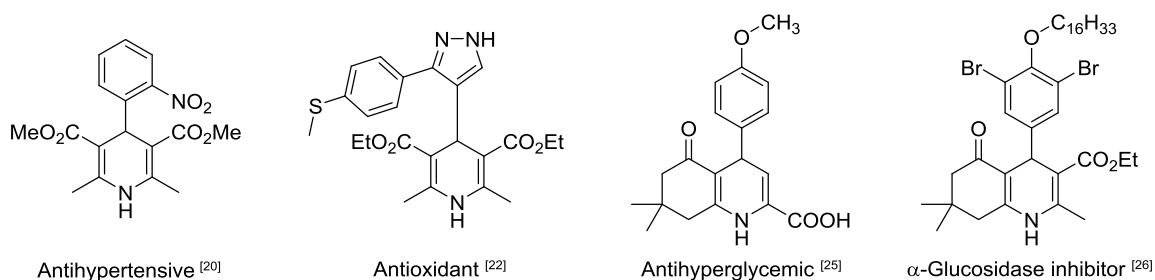
## Introduction

5-Hydroxymethylfurfural (5-HMF) is becoming an increasingly popular starting chemical.<sup>[1]</sup> A first reason is the continuously improving efficiency of its preparation from biomass resources, notably hexoses (glucose, fructose), polysaccharides (cellulose, inulin...) or agricultural and forestry residues and food wastes,<sup>[2]</sup> thanks to progress in the choice of reaction media (like deep eutectic solvents, ionic liquids, biobased solvents), catalysts, and purification methods.<sup>[3]</sup> A second reason is the developing interest for its upgrading towards industrially relevant targets such as polymers, fuels and solvents,<sup>[4]</sup> benefiting from more diverse methodologies including photocatalysis, electrocatalysis, thermocatalysis, biocatalysis.<sup>[5]</sup> In particular, the oxidation of HMF into 2,5-furandicarboxylic acid (FDCA)<sup>[6]</sup> or its hydrogenation towards various diols,<sup>[7]</sup> is now expanding in the field of biobased polymers.<sup>[8]</sup> HMF acetals and ethers, or derivatives such as dimethylfuran also contribute to this development, including in the field of biofuels.<sup>[9]</sup>

What is remarkable in 5-HMF is the number of functional entities, OH, CHO, furan, ready for a wide range of chemical transformations enabling significant innovation in organic molecular design. Furanic aldehydes like HMF become thus nowadays also attractive candidates as building blocks in fine chemistry,<sup>[10]</sup> in a general trend to switch from fossil to renewable resources.<sup>[11]</sup> In recent years, our group investigated several multi-component reactions involving 5-HMF, such as the Biginelli reaction,<sup>[12]</sup> Kabachnik-Fields reaction,<sup>[13]</sup> nitron dipolar cycloaddition<sup>[14]</sup> and [4+2+1] cycloaddition reaction.<sup>[15]</sup> In our investigation of the 5-HMF Biginelli reaction, we found that very small quantities of the Hantzsch product was actually

observed as an undesired by-product.<sup>[12]</sup> Indeed, ammonia can be produced from urea, triggering the possible Hantzsch pathway when the Biginelli one is slow.<sup>[12,16]</sup> Considering the interest of these Hantzsch dihydropyridines, we investigated their formation more closely for widening the scope of the uses of 5-HMF in the design of fine chemicals.

The Hantzsch pyridine synthesis, described by Arthur Hantzsch in 1882,<sup>[17]</sup> is a reaction involving generally an aldehyde, two equivalents of a  $\beta$ -ketoester and a nitrogen source, providing 1,4-dihydropyridines, recognized as an important class of nitrogen-containing compounds.<sup>[18,19]</sup> These molecules are renowned for a wide range of biological applications: first of all as a calcium antagonist used in cardiovascular, cerebrovascular and antihypertensive drugs,<sup>[20]</sup> but also as antibacterial, antioxidant, antidiabetic, insecticidal compounds,  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitors, or as reagents application in protein conjugation, formaldehyde detection and bacterial anti-adhesion.<sup>[21-26]</sup> Examples of biologically relevant molecules including the 1,4-dihydropyridine skeleton are depicted in Figure 1.



**Figure 1.** Examples of biologically active molecules built on the 1,4-dihydropyridine scaffold.

Since our earlier report showing the presence of Hantzsch dihydropyridines as by-products of the Biginelli reaction involving HMF, other pieces of work have only discussed the viewpoint of

the use of complex catalysts and solvents<sup>[27-31]</sup> Up to now, no detailed study of the scope of the reaction of HMF with respect to the other partners of the reaction, in particular its application to three-component and four-component approaches has been reported yet. Here, we report the first complete study of the use of 5-HMF in the Hantzsch reaction, and its application to a scope of  $\beta$ -ketoesters/ $\beta$ -diketones.

## Results and Discussion

We initiated our study by checking which nitrogen source (“N”) would be the most appropriate for a solvent-free Hantzsch dihydropyridine synthesis using 5-HMF. Among classically reported conditions<sup>[32-34]</sup> we focused on the simplest ones avoiding the use of complex catalysts or solvents. Ammonia, used in the original Hantzsch protocol can be substituted by several other reagents. In order to develop the cleanest and mildest conditions, we focused on systems able to play both the role of the nitrogen source and a neutral promoter, and making possible to run the reaction in clean solvent or even under no-solvent conditions. Thus, the survey was performed by reacting 5-HMF **1a** (1 eq.) with ethyl acetoacetate **2a** (2 eq.) and a “N” source (1 eq.) under solvent-free conditions, and assessing the outcome of the reaction by NMR of the crude complete mixture in the presence of 1,3,5-trimethoxybenzene as internal standard. The results are summarized in Table 1. The best “N” source was clearly  $\text{NH}_4\text{OAc}$ , leading to the expected 1,4-dihydropyridine **3a** in 90% NMR yield at 90°C after 1 hour in the absence of any additional catalysts (Table 1, entry 1). Using  $(\text{NH}_4)_2\text{CO}_3$  (Table 1, entry 2) led to a significantly

lower yield of 37% of target product (conversion of 83% of 5-HMF and more than 20% of the starting amount ethyl acetoacetate remaining), as well as 15% yield in Knoevenagel intermediate (intermediate I, see mechanism section). Intermediate I was fully characterized and structurally identified as the Knoevenagel compound by 1D and 2D NMR as well as mass spectroscopy (see SI). Using ammonium formate ( $\text{NH}_4\text{HCO}_2$ ) under neat conditions (Table 1, entry 3) led to a messy mixture with only a 40% yield of compound **3a** together with some Knoevenagel intermediate I (ca. 12%) though all 5-HMF was consumed. No 1,4-dihydropyridine product **3a** was generated either when ammonium halides (I, Cl, Br) or ammonium sulfate were tested (Table 1, entries 4 and 5). In these cases, NMR of the crude mixture showed essentially starting materials without any by-product, except for  $\text{NH}_4\text{I}$  which gave a messy mixture of unconverted reagents, together with some unidentified by-products. A few sets of conditions using nitrogen source commercially available in solution were also tested. Interestingly, an ammonia solution (30% in  $\text{H}_2\text{O}$ ) led to a 70% yield of **3a** (Table 1, entry 6) while the dioxane solution was ineffective (entry 7). A solution of ammonium formate ( $\text{NH}_4\text{HCO}_2$ ) in EtOH provided **3a** in 74% yield (Table 1, entry 8). Based on this first set of experiments,  $\text{NH}_4\text{OAc}$  as nitrogen source was selected under solvent-free conditions for the next step of the study.

The counterion associated with the ammonium cation has obviously an important effect. Although the complexity of the mechanism with the different stages and intermediates makes it difficult to fully explain these differences, we can propose some hypotheses. The counterion

can first influence the solubility and stability of the ammonium ion. Ammonium acetate is generally more soluble in an organic medium than ammonium carbonate. This decreased solubility of ammonium carbonate appears here as a real handicap as already mentioned in literature.<sup>[35]</sup> In our case, significant formation of a white solid is observed at the upper part of the reaction vessel. Literature examples also show that ammonium carbonate is more efficient in aqueous media,<sup>[35-36]</sup> whereas here, without any solvent, the medium is organic. Another explanation can be ascribed to the difference of acidity, resulting from the use of a salt derived from a weak acid (acetic acid) (entry 1) or a stronger acid, like with hydrochloric acid (entry 4). This is consistent with reports on the Hantzsch reaction of benzaldehyde and ethyl acetoacetate which proceeds slower using ammoniums salts derived from stronger acids.<sup>[35]</sup> Furthermore, in reactions using HMF, which is acid sensitive, a less acidic or polar environment is preferred. The availability of ammonia in the medium can also vary. For example, ammonium chloride is reported to be moderately active in aqueous Hantzsch reactions, while no reaction is observed here in a solvent-free medium.<sup>[35-36]</sup>

**Table 1.** Comparison of nitrogen sources in the Hantzsch 1,4-dihydropyridine synthesis.

Entry	nitrogen source	NMR yield <sup>a</sup> (%)
1	NH <sub>4</sub> OAc, solvent-free	90
2	(NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub> , solvent-free	37
3	NH <sub>4</sub> HCO <sub>2</sub> , solvent-free	40
4	NH <sub>4</sub> I, NH <sub>4</sub> Cl or NH <sub>4</sub> Br, solvent-free	0

5	(NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub> , solvent-free	0
6	Ammonia solution (30% in H <sub>2</sub> O)	70
7	Ammonia solution (0.5 M in dioxane)	0
8	NH <sub>4</sub> HCO <sub>2</sub> (1 M in EtOH)	74

<sup>a</sup> Yields are expressed in mol%. Reaction conditions: 5-HMF **1a** (1.0 mmol), ethyl acetoacetate **2a** (2.0 mmol), "N" source (1.0 mmol), stirred at 90 °C for 1 h in a screw-cap tube. NMR yield using 1,3,5-trimethoxybenzene as internal standard.

The appropriate amount of ammonium acetate, the reaction temperature and time were then optimized (Table 2). The reaction of 5-HMF with ethyl acetoacetate in the presence of ammonium acetate was performed at 90°C for 1 hour. A small increase of the yield of 1,4-dihydropyridine **3a** was observed when a slight excess of ammonium acetate (1.2 to 1.5 equiv.) was introduced (Table 2, entries 2-3), with a maximum yield of 94% reached for 1.5 equivalents. Adding more ammonium acetate (1.8 equiv.) did not lead to a better yield (Table 2, entry 4). Regarding the reaction time, a similar yield (93%) was obtained already after only 25 minutes (Table 2, entry 5). Regarding the reaction temperature, a good 84% yield of **3a** was already obtained at 50°C (Table 2, entry 6), and excellent yields were found when the reaction run for 1 hour from 60°C to 90°C (Table 2, entries 7-9), with the highest yield (94%) for the reaction conducted at 80°C (Table 2, entry 9). Extending the reaction time at 70°C had no effect on the yield (entries 8/10), whereas a decrease was observed at 80°C (entries 9/11).

This decrease in the yield was clearly related to the stability of both the starting material HMF and the 1,4-dihydropyridine products in the reaction conditions. This was investigated by measuring the quantity of remaining HMF or 1,4-dihydropyridine **3a** when heated at 80°C in presence of ammonium acetate, or a mixture of ammonium acetate and acetic acid (since acetic acid is produced in the reaction), using the same NMR yield method based on



1,3,5-trimethoxybenzene as internal standard. Both sets of conditions indicated extensive decrease of the HMF amount after a few hours at 80°C (Table S1). The 1,4-dihydropyridine **3a** appeared much more stable, though when acetic acid is present, some limited but consistently increasing degradation was noticed (Table S2), in levels which are consistent with the decrease in the yields observed in the Hantzsch reaction. Since water is also formed in the reaction, the influence of the presence of small amounts of water on 1,4-dihydropyridine **3a** stability was also checked, showing slightly more degradation (see details in Table S1 and S2 in supplementary information).

Overall, it is important to note that the reaction can proceed also at room temperature, requiring however a longer reaction time for reaching good yields (Table 2, entry 12-14). Actually, all conditions used in this study resulted in high or excellent yields, in a very clean reaction allowing to run it under a wide range of temperatures.

**Table 2.** Optimization of three-component Hantzsch 1,4-dihydropyridine synthesis.

Entry	NH <sub>4</sub> OAc (x mmol)	Temperature	Time	NMR Yield (%) <sup>a</sup>
1	1.0	90 °C	1 h	90
2	1.2	90 °C	1 h	91
3	1.5	90 °C	1 h	94
4	1.8	90 °C	1 h	91
5	1.5	90 °C	25 min	93

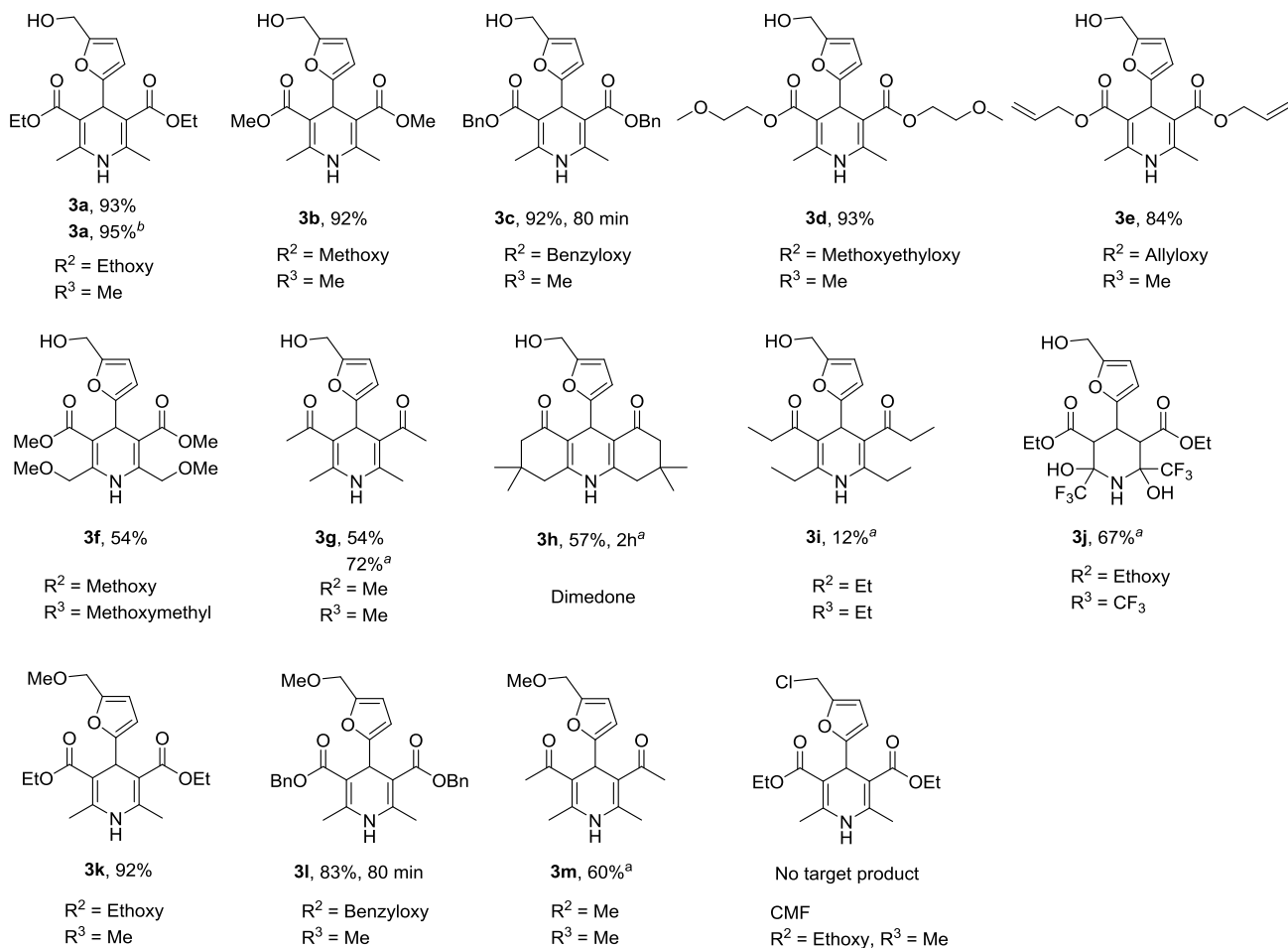
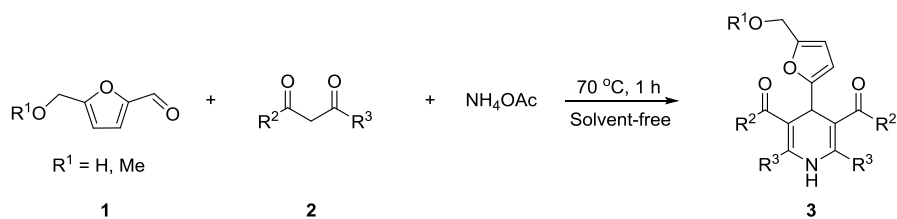
6	1.5	50 °C	1 h	84
7	1.5	60 °C	1 h	90
8	1.5	70 °C	1 h	93
9	1.5	80 °C	1 h	94
10	1.5	70 °C	15 h	92
11	1.5	80 °C	15 h	76
12	1.5	rt	1 h	66
13	1.5	rt	4 h	75
14	1.5	rt	22 h	74

<sup>a</sup> Yields are expressed in mol%. Reaction conditions: 5-HMF **1a** (1.0 mmol), ethyl acetoacetate **2a** (2.0 mmol), NH<sub>4</sub>OAc (x mmol), solvent-free, screw-cap tube. NMR yield: using 1,3,5-trimethoxybenzene as internal standard.

Choosing the optimal conditions (1.5 equiv. of ammonium acetate, 70 °C, 1 hour), we further investigated the generality of the Hantzsch reaction of 5-HMF using nine differently substituted dicarbonyl substrates including the initial ethyl acetoacetate reactant. As shown in Figure 2, we found that all the alkyl acetoacetates gave the corresponding 1,4-dihydropyridines in excellent yields. The (ethyl, methyl and benzyl esters) provided respectively 93%, 92%, and 92% of the corresponding target products (**3a-3c**). The methoxyethyl and allyl esters also performed well, providing 93% and 84% of the targeted products (**3d-3e**). The reaction was easily scaled-up starting from 2g of 5-HMF, producing the desired compound **3a** on a more than 5 gram scale after 2h at 70 °C (95% yield). Switching to the methyl 4-methoxyacetoacetate led to a significantly reduced yield (**3f** compared with **3b**). This can be due to a lower reactivity of the last intermediate before cyclization, with the electron-donating methoxymethyl group making the carbonyl less electrophilic, or to a H-bonding interaction of the quaternary OH with the

methoxy group, slowing down the final dehydration step.  $\beta$ -Diketones were also pertinent substrates in the reaction though giving more complex results as compared with  $\beta$ -ketoesters. Acetylacetone provided product **3g** in 54% yield at 70°C, and 72% yield upon increasing the temperature to 90°C. 5,5-Dimethyl-1,3-cyclohexanedione (dimedone) provided 57% of the target product **3h** at 90°C as well as unidentified impurities. 3,5-Heptanedione proved much less efficient with only 12% of product **3i** at 90 °C, together with about 40 % of the Knoevenagel intermediate but no remaining HMF or diketone. Diketones are thus less reactive, although the formation of the Knoevenagel intermediate appears easier (as seen by control experiments, *vide infra*). Therefore the decrease in reactivity must occur at a later stage of the sequence, possibly at the stage of the cyclization, due to a lower nucleophilic power of the enamine nitrogen due to presence on the enamine double bond of a more electron-withdrawing ketone group vs the ester one. The  $\beta$ -keto-ester bearing a strong electron-withdrawing group  $\text{CF}_3$  could be used but led to the formation of the undehydrated product **3j** like what we observed in the Biginelli products in our earlier work.<sup>[12]</sup> Finally, among HMF analogs, similar results were found using 5-methoxymethylfurfural, leading to the products **3k**, **3l** and **3m** whereas chloromethylfurfural (CMF)<sup>[37]</sup> failed to be used in this reaction likely due to the ability of the C-Cl linkage to compete as electrophilic function.

All new products were purified by chromatography for full structural characterization purposes, however, it is worth to mention that the products with high NMR yield can be obtained in high purity after simple treatment of the crude mixture with ice water and extraction in ethyl acetate. Overall, these are very clean and simple reaction and purification conditions providing high yields of 1,4-dihydropyridines exhibiting high purity (Figure 2).

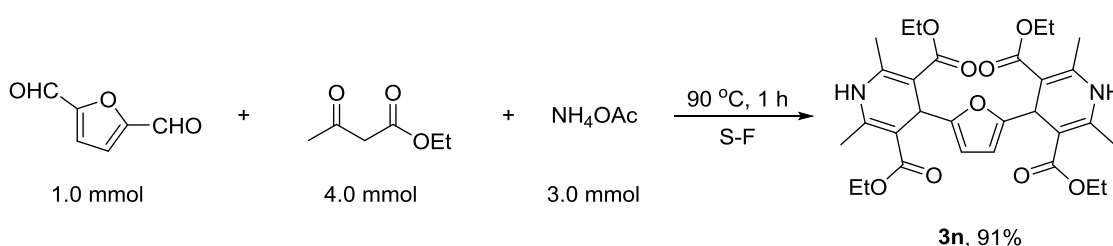


Reaction conditions: Aldehydes **1** (1.0 mmol),  $\beta$ -ketoesters or  $\beta$ -diketones **2** (2.0 mmol),  $\text{NH}_4\text{OAc}$  (1.5 mmol), stirred at 70 °C for 1 h unless indicated time, isolated yield. <sup>a</sup> Stirred at 90 °C for 1 h unless indicated time. <sup>b</sup> Scale-up reaction: HMF (15.9 mmol), ethyl acetoacetate (31.8 mmol),  $\text{NH}_4\text{OAc}$  (23.9 mmol), stirred at 70 °C for 2 h.

**Figure 2.** Synthesis of 1,4-dihydropyridines through three-component Hantzsch 1,4-dihydropyridine synthesis.

The reaction was also applied to 2,5-furandicarboxaldehyde (DFF) which is the bis-aldehydic molecule obtained by oxidation of 5-HMF or from renewable carbohydrates. In addition to its typical reactivity as an aldehyde, DFF, involved in the production of furan-based chemicals, has

been used as a monomer in polymer chemistry and as intermediate for the design of biofuels, surfactants and functional materials.<sup>[38,39]</sup> Some examples of the use of bis-aldehydes in Hantzsch dihydropyridine synthesis or Hantzsch-like reactions have been reported, and some of them concern phenyl-bis-carboxaldehydes.<sup>[40-42]</sup> We therefore tested the furanic equivalent DFF in this reaction, which led to a 91% yield of the double 1,4-dihydropyridine structure **3n** under solvent-free conditions (Scheme 1).

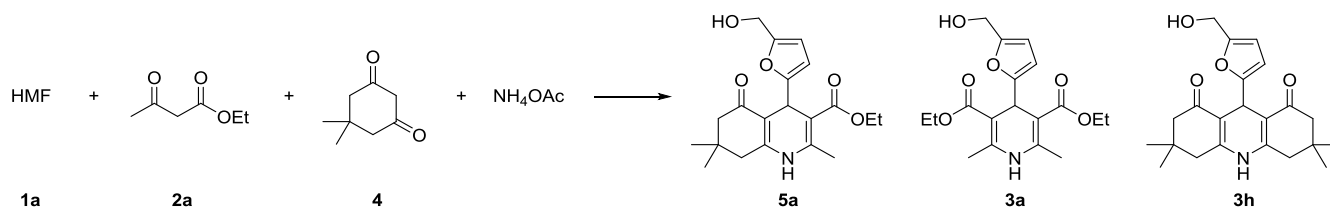


**Scheme 1.** Synthesis of double 1,4-dihydropyridine structure from DFF through Hantzsch dihydropyridine synthesis.

### *Synthesis of unsymmetrical dihydropyridines*

The Hantzsch reaction is actually a four-component reaction, in which most often, the two  $\beta$ -diketones are identical. However, two different di-carbonyl compounds can be used, making the approach a real four-component one.<sup>[18,19,33]</sup> In such a protocol, the reaction can provide either the unsymmetrical 1,4-dihydropyridine (here the polyhydroquinoline **5a**), or some symmetrical ones, combining either twice the ethyl acetoacetate (**3a**) or twice the diketone (**3h**). Unsymmetrical dihydropyridines are also biologically relevant compounds<sup>[21,25,26]</sup> and it was

thus interesting to extend our study accordingly. Here, we combined 5-HMF (**1a**) with 1 equivalent of 5,5-dimethyl-1,3-cyclohexanedione (**4**) and 1 equivalent of ethyl acetoacetate (**2a**) in the presence of ammonium acetate (1.5 equivalents), and reaction outcome was investigated (Scheme 2).



**Scheme 2.** Four-component Hantzsch protocol and possible products.

We used similar conditions as for the three-component reaction (solvent free, 1.5 equiv. of ammonium acetate) and compared to reactions performed in ethanol in a screw-cap tube. In all cases, the protocol underwent very selectively the four-component pathway leading to compound **5a**. A slightly better yield (84% vs 79%) was obtained in ethanol (Table 3, entries 1 and 2), possibly by facilitating the solubilisation of 5,5-dimethyl-1,3-cyclohexanedione which is a solid. Keeping ethanol as the solvent, increasing temperature or the amount of ammonium acetate did not improve the yield or even resulted in a gradual decrease (Table 3, entries 3-5). The reaction performed quite well even after 20 or 40 min (Table 3, entry 6-7). Regarding the concentration, the ethanol quantity could be halved without yield decrease (Table 3, entry 8). Overall, after screening the temperature, reaction time and the amount of solvent (Table 3, entries 6-12), we can consider that 1:1:1:1.5 of **1a/2a/4/NH<sub>4</sub>OAc** in 0.5 mL of ethanol at 80°C for 80 minutes as the optimal reaction conditions, with the highest yield of 88% obtained in the four-component reaction (Table 3, entry 9). The symmetrical product **3a** involving two

molecules of ethyl acetoacetate was observed in limited amount (0-8%), while the other symmetrical product **3h** involving two molecules of diketone was observed only as very small amounts (0-4%), consistently with what was observed when comparing the reactivity in the 3-CR protocol.

**Table 3.** Optimization of four-component Hantzsch 1,4-dihydropyridine synthesis using HMF with ethyl acetoacetate, 5,5-dimethyl-1,3-cyclohexanedione and ammonium acetate.

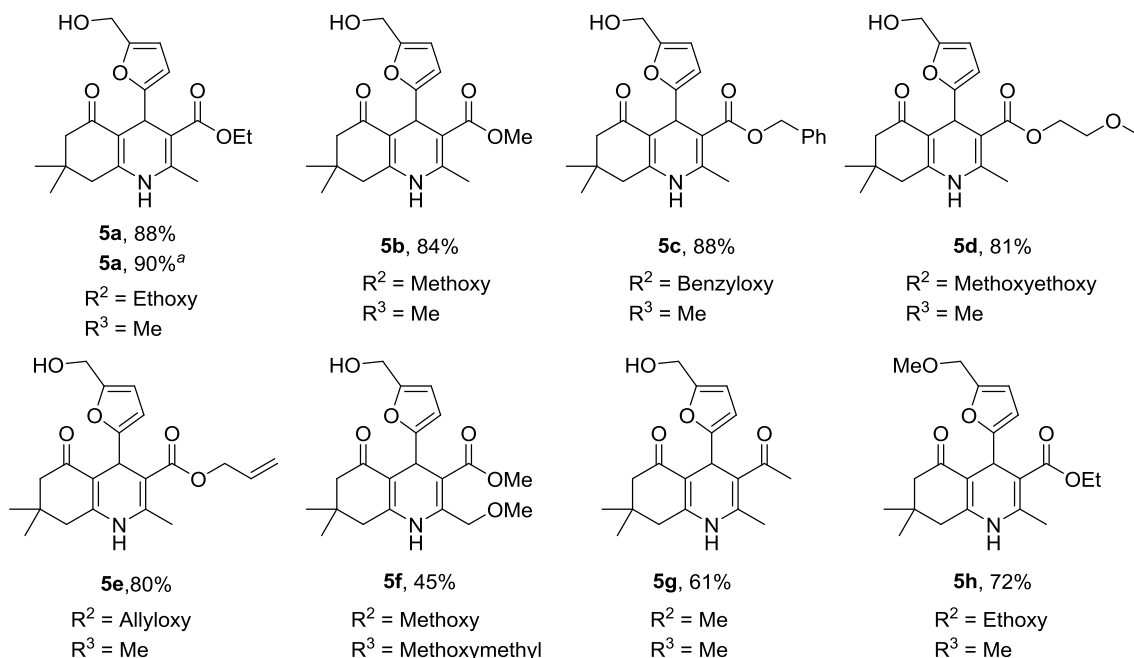
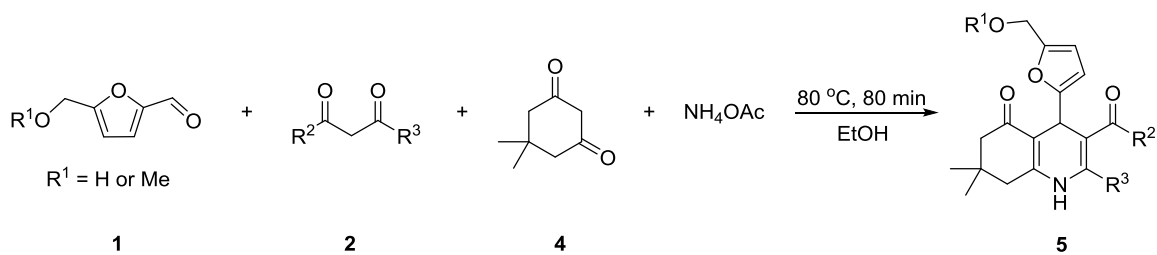
Entry	NH <sub>4</sub> OAc	Temperature	Time	Solvent	NMR Yield (%) <sup>a</sup>
1	1.5	80 °C	1 h	Solvent-free	79
2	1.5	80 °C	1 h	EtOH	84
3	1.5	90 °C	1 h	EtOH	84
4	2.0	90 °C	1 h	EtOH	83
5	2.5	90 °C	1 h	EtOH	81
6	1.5	80 °C	20 min	EtOH	73
7	1.5	80 °C	40 min	EtOH	81
8	1.5	80 °C	1 h	EtOH (0.5 mL)	85
<b>9</b>	<b>1.5</b>	<b>80 °C</b>	<b>80 min</b>	<b>EtOH (0.5 mL)</b>	<b>88</b>
10	1.5	80 °C	100 min	EtOH (0.5 mL)	85
11	1.5	70 °C	1 h	EtOH	79
12	1.5	50 °C	1 h	EtOH	58

<sup>a</sup> Yields are expressed in mol%. Reaction conditions: 5-HMF **1a** (1.0 mmol), ethyl acetoacetate **2a** (1.0 mmol), 5,5-dimethyl-1,3-cyclohexanedione **4** (1.0 mmol), NH<sub>4</sub>OAc (x mmol) in ethanol (1 mL unless otherwise marked), screw-cap tube. NMR yield using 1,3,5-trimethoxybenzene as internal standard.

These conditions were then applied to a short structural scope in which 5-HMF and 5,5-dimethyl-1,3-cyclohexanedione were condensed with a series of  $\beta$ -ketoesters or 1,3-diketones, leading to a family of unsymmetrical dihydropyridines shown in Figure 3. In

terms of comparative reactivity, the results are consistent with what was observed in the symmetrical examples, with acetoacetic esters working the best to afford the corresponding products in 80% to 88% yields (**5a-5e**). This four-component reaction could produce compound **5a** on a more than 5 gram scale starting from 2g of 5-HMF without decrease of the yield (90% yield, 80 °C, 2.5 h in EtOH). Methyl 4-methoxyacetoacetate led to only 45% yield (**5f**). When the  $\beta$ -diketone acetylacetone was used, **5g** was obtained in only 61% yield. Overall, a general preference for the formation of the unsymmetrical products was observed in all cases, with only trace amounts of symmetrical products observed. Replacing 5-HMF with 5-methoxymethylfurfural provided 72% of **5h**.





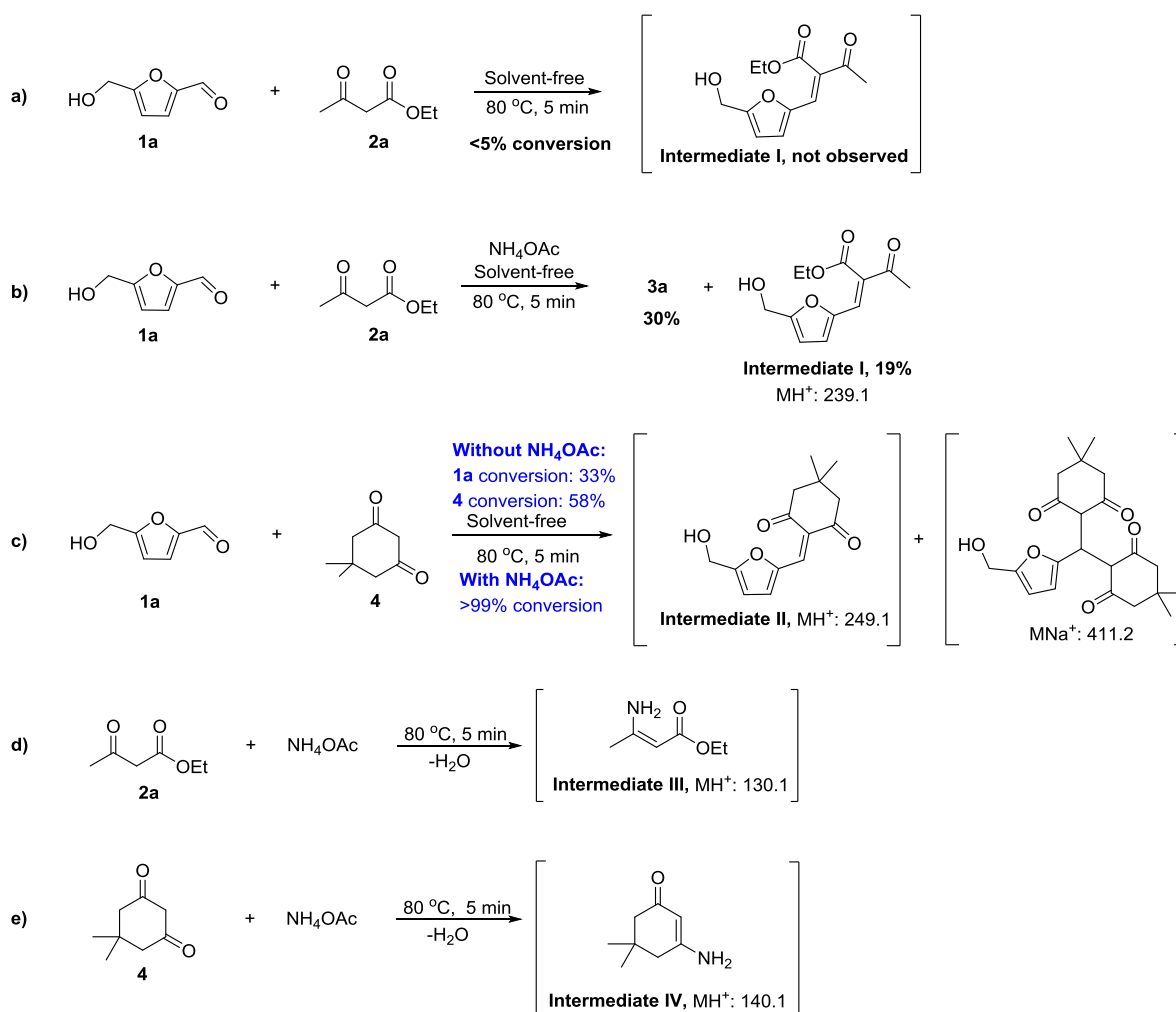
Reaction conditions: Aldehydes (**1**, 1.0 mmol),  $\beta$ -ketoesters or  $\beta$ -diketones (**2**, 1.0 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**4**, 1.0 mmol),  $\text{NH}_4\text{OAc}$  (1.5 mmol) in ethanol (0.5 mL), stirred at 80 °C for 80 min, isolated yield.<sup>a</sup> Scale-up reaction: HMF (15.9 mmol), ethyl acetoacetate (15.9 mmol), dimedone (15.9 mmol),  $\text{NH}_4\text{OAc}$  (23.9 mmol), EtOH (8.0 mL), stirred at 80 °C for 2.5 h .

**Figure 3.** Synthesis of unsymmetrical 1,4-dihydropyridines through four-component Hantzsch dihydropyridine synthesis.

### Control experiments

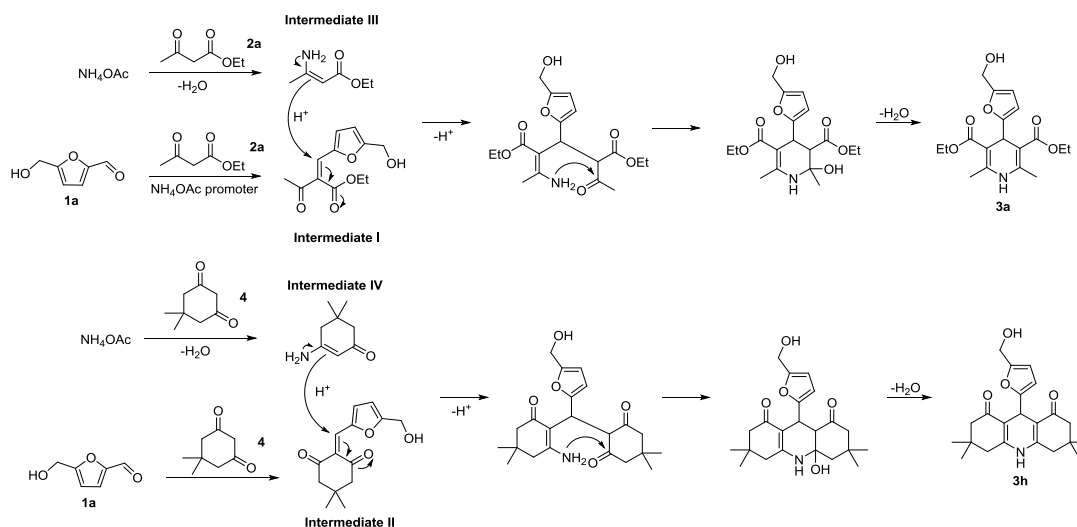
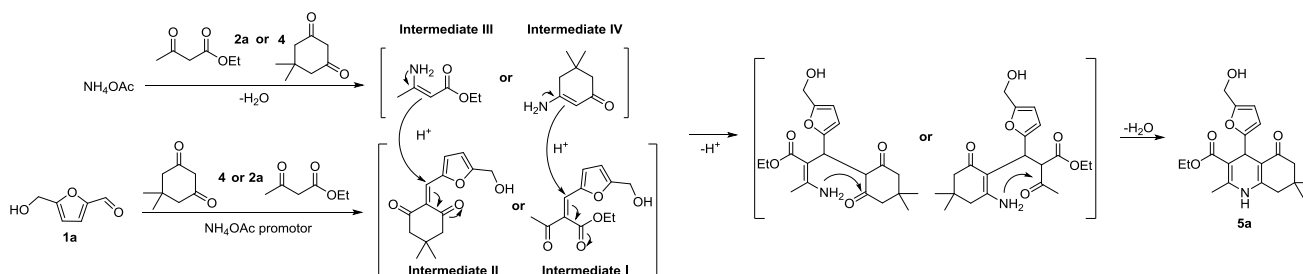
Control experiment in the absence of  $\text{NH}_4\text{OAc}$  show that in the reaction of HMF **1a** with ethyl acetoacetate **2a** at 80°C under solvent-free conditions (Scheme 3, a), no Knoevenagel condensation product was observed neither by mass spectrometry (MS) nor NMR analysis,

with essentially only starting materials remaining. However, addition of 1.5 equivalents of ammonium acetate to the mixture led to the complete conversion of the reactants within 5 minutes and generated 30% yield of the corresponding 1,4-dihydropyridine **3a** as well as the Knoevenagel condensation intermediate **I**, clearly identified by  $^1\text{H}$  NMR and by MS (molecular weight  $\text{MH}^+$ : 239.1) (Scheme 3, b). In the case of 5,5-dimethyl-1,3-cyclohexanedione **4**, presence of  $\text{NH}_4\text{OAc}$  clearly accelerates the conversion of the reactants, though the reaction can slowly proceed toward the formation of trace amount of Knoevenagel intermediate **II** ( $\text{MH}^+$ : 249.1) even in the absence of  $\text{NH}_4\text{OAc}$ . The bis-addition product arising from the addition of diketone **4** onto the Knoevenagel intermediate **II** was also identified by MS at  $\text{MNa}^+$  411.2 (Scheme 3, c). Control experiments in the absence of HMF show the formation of the expected enamines **III** ( $\text{MH}^+$ : 130.1) and **IV** ( $\text{MH}^+$ : 140.1) from ethyl acetoacetate and dimedone, respectively (Scheme 3, d and e). The overall outcome of HMF in the three- and the four-component reactions is depicted in Scheme 4.



Reaction conditions: 5-HMF **1a** (1.0 mmol), ethyl acetoacetate **2a** (1.0 mmol), 5,5-dimethyl-1,3-cyclohexanedione **4** (1.0 mmol),  $\text{NH}_4\text{OAc}$  (1.5 mmol).

### Scheme 3. Control experiments

**Three-component reaction:****Four-component reaction:**

**Scheme 4.** Formation of the 5-HMF based intermediates on the way to 1,4-dihydropyridines.

**Conclusion:**

A wide range of novel symmetrical and unsymmetrical 5-HMF derived 1,4-dihydropyridines were obtained for the first time in excellent yields using the very atom-economical Hantzsch dihydropyridine synthesis. The scope was extended to the three or four component approaches. The four-component route shows excellent selectivity towards the unsymmetrical 1,4-dihydropyridines, favoured compared to the also possible three-component reaction products. Remarkably mild, clean and easy to perform reaction conditions were used, namely

ammonium acetate as nitrogen source, neat or in ethanol, and absence of any additional catalyst or complex solvent, applicable on the multi-gram scale.

## Experimental section

All commercial materials and solvents were used without further purification and were supplied by Sigma-Aldrich, Acros Organics, Janssen Chimica, Alfa Aesar, Carlo Erba or TCI. HMF (min 97% purity GC), was purchased from Biosynth. Optimization reactions were performed in a 10 mL screw-cap tube using anhydrous solvents or without solvent. Gram scale reactions were performed in a 250 mL round bottom flask. NMR spectra were recorded on a Bruker AVL 300 ( $^1\text{H}$ : 300 MHz;  $^{13}\text{C}$ : 75 MHz) spectrometer using  $\text{DMSO-}d_6$ . The chemical shifts ( $\delta$  ppm) and coupling constants (Hz) are reported in the standard fashion. Additionally, 2D experiments were conducted, namely  $^1\text{H}$ - $^1\text{H}$  COSY,  $^1\text{H}$ - $^{13}\text{C}$  HSQC and  $^1\text{H}$ - $^{13}\text{C}$  HMBC spectra, to assign the peaks. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on an amaZon SL Bruker mass spectrometer. High-resolution mass spectra (HRMS) were recorded on Bruker QTOF Impact II spectrometer using ESI as ionization source. Analytical thin-layer chromatography was carried out on Macherey-Nagel silica gel 60 G/UV254 (0.20 mm). Flash chromatographies were performed on Macherey-Nagel silica 60 M (40-63  $\mu\text{m}$ ). Melting points were measured using a BUCHI Labortechnik AG B-540 apparatus and noted in  $^\circ\text{C}$ . The typical procedures and characterization data are described below for one example of symmetrical 1,4-dihydropyridine (compound **3a**) and one example of unsymmetrical 1,4-dihydropyridine (compound **5a**). The

supplementary information reports the data for all other compounds as well as the Tables S1 and S2 related to the experiments investigating the stability of HMF and of 1,4-dihydropyridine **3a**.

Typical solvent-free protocol for the synthesis of the symmetrical 1,4-dihydropyridines.

### Diethyl

#### 4-[5-(hydroxymethyl)furan-2-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3a**):

5-HMF (126 mg, 1.0 mmol, 1.0 equiv.), ethyl acetoacetate (255  $\mu$ L, 2.0 mmol, 2.0 equiv.) and ammonium acetate (118 mg, 1.5 mmol, 1.5 equiv.) were added to a 10 mL screw-cap tube. The tube was heated in oil bath at 70°C for 1 h. The reaction crude was dissolved with ethyl acetate (EA). The solution was concentrated under reduced pressure and purified by flash column chromatography on silica gel (n-pentane/EA = 1/1). The yellow solid product was obtained in 93% yield. The reaction could also be performed at the 2g scale in a 250 mL flask: HMF (15.9 mmol), ethyl acetoacetate (31.8 mmol), NH<sub>4</sub>OAc (23.9 mmol), stirred at 70°C for 2 h. High purity **3a** product (>95%) can be obtained by simple water washing. Further purification by silica gel chromatography provided the pure product **3a** in 95% yield. **3a**: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.88 (s, 1H, NH), 6.05 (d, *J* = 3.1 Hz, 1H, H<sub>4'</sub>), 5.74 (d, *J* = 3.1 Hz, 1H, H<sub>3'</sub>), 5.17-4.91 (m, 2H, H<sub>4</sub>, OH), 4.25 (d, *J* = 5.6 Hz, 2H, CH<sub>2</sub>OH), 4.21-3.88 (m, 4H, 2 CH<sub>2</sub>CH<sub>3</sub>), 2.25 (s, 6H, 2 CH<sub>3</sub>), 1.18 (t, *J* = 7.1 Hz, 6H, 2 CH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, DMSO)  $\delta$  166.8 (2 C=O), 158.2 (C<sub>2'</sub>), 153.6 (C<sub>5'</sub>), 146.3 (2 C<sub>2</sub>), 107.6 (C<sub>4'</sub>), 104.7 (C<sub>3'</sub>), 98.6 (2 C<sub>3</sub>), 59.1 (2 CH<sub>2</sub>CH<sub>3</sub>), 55.8 (CH<sub>2</sub>OH), 32.9 (C<sub>4</sub>), 18.2 (2 CH<sub>3</sub>), 14.3 (2 CH<sub>2</sub>CH<sub>3</sub>). HRMS (ESI) *m/z*: Calcd for [M+H]<sup>+</sup>

$C_{18}H_{24}NO_6 = 350.1598$ ; Found 350.1594. HRMS (ESI)  $m/z$ : Calcd for  $[M+Na]^+ C_{18}H_{23}NNaO_6 = 372.1418$ ; Found 372.1420.

**Typical protocol for the synthesis of the unsymmetrical 1,4-dihydropyridines in ethanol.**

***Ethyl 4-[5-(hydroxymethyl)furan-2-yl]-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydro-***

***quinoline-3-carboxylate (5a)***: 5-HMF (126 mg, 1.0 mmol, 1.0 equiv.), ethyl acetoacetate (128  $\mu$ L, 1.0 mmol, 1.0 equiv.), 5,5-dimethyl-1,3-cyclohexanedione (144 mg, 1.0 mmol, 1.0 equiv.), ammonium acetate (118 mg, 1.5 mmol, 1.5 equiv.) and ethanol (0.5 mL) were added to a 10 mL screw-cap tube. The tube was heated in oil bath at 80°C for 80 min. The reaction crude was dissolved with EA/MeOH. The solution was concentrated under reduced pressure and purified by flash column chromatography on silica gel (*n*-pentane/EA = 1/2). The yellow solid product was obtained in 88% yield. The reaction could also be performed on the 2g scale using a 250 mL flask: HMF (15.9 mmol), ethyl acetoacetate (15.9 mmol), dimedone (15.9 mmol),  $NH_4OAc$  (23.9 mmol), EtOH (8.0 mL), stirred at 80°C for 2.5 h, yield 90%. **5a**:  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  9.11 (s, 1H, NH), 6.04 (d,  $J = 3.0$  Hz, 1H,  $H_{4'}$ ), 5.75 (d,  $J = 3.1$  Hz, 1H,  $H_{3'}$ ), 5.04-4.94 (m, 2H,  $H_4$ , OH), 4.22 (d,  $J = 5.6$  Hz, 2H,  $\underline{CH_2OH}$ ), 4.16-3.97 (m, 2H,  $\underline{CH_2CH_3}$ ), 2.47-1.97 (m, 7H, 2  $CH_2$ ,  $CH_3$ ), 1.20 (t,  $J = 7.1$  Hz, 3H,  $\underline{CH_2CH_3}$ ), 1.03 (s, 3H,  $CH_3$ ), 0.96 (s, 3H,  $CH_3$ ).  $^{13}C$  NMR (75 MHz, DMSO)  $\delta$  194.1 ( $\underline{CO}$ ), 166.7 ( $\underline{COO}$ ), 157.8 ( $C_{2'}$ ), 153.2 ( $C_{5'}$ ), 150.5 ( $C_{8a}$ ), 145.6 ( $C_2$ ), 107.5 ( $C_{4'}$ ), 106.6 ( $C_{4a}$ ), 104.6 ( $C_{3'}$ ), 100.9 ( $C_3$ ), 59.1 ( $\underline{CH_2CH_3}$ ), 55.7 ( $\underline{CH_2OH}$ ), 50.3 ( $\underline{CH_2}$ ), 39.5 ( $\underline{CH_2}$ ), 32.1 ( $C_7$ ), 29.6 ( $\underline{C_4}$ ), 29.2 ( $\underline{CH_3}$ ), 26.3 ( $\underline{CH_3}$ ), 18.24 ( $\underline{CH_3}$ ), 14.3 ( $\underline{CH_2CH_3}$ ). HRMS (ESI)  $m/z$ : Calcd for  $[M+H]^+ C_{20}H_{26}NO_5 = 360.1805$ ; Found 360.1805. HRMS (ESI)  $m/z$ : Calcd for  $[M+Na]^+ C_{20}H_{25}NNaO_5 = 382.1625$ ; Found 382.1622.

## Conflicts of interest

There are no conflicts of interest to declare.

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