A revisit to the Hantzsch reaction: Unexpected products beyond 1,4-dihydropyridines†

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A novel green and efficient one-pot three-component synthesis of 2-aryl-pyridines in good to excellent yields has been reported. The methodology initially involved the formation of 1,2-dihydropyridine intermediates *via* reaction of a variety of aromatic aldehydes with ethyl (methyl) acetoacetate and ammonium acetate, which were the same starting materials as the Hantzsch reaction, under solvent-, catalyst- and heat-free (at room temperature) conditions, followed by air oxidation for 72 hours. In this paper, we also systematically reinvestigated the classic Hantzsch reaction under different reaction conditions, analyzed the main products as well as byproducts, corrected some mistakes in the literature and elucidated the reaction mechanism.

Introduction

There is always something new on the old topic of the Hantzsch reaction since Arthur Hantzsch first reported it in 1882.[1] This is mainly due to the fact that it offers an efficient way to prepare the 1,4-dihydropyridines (1,4-DHPs) which exhibit significant biological activities in the treatment of cardiovascular disease as calcium channel blockers. More than twelve commercial, clinically important drugs such as Amlodipine, Nifedipin, Nimodipin, Felodipine, Isradipine, and Nicardipine containing the 1,4-dihydropyridine parent nucleus have been manufactured and used worldwide.[2] Up till now, numerous literature citations exist relating to various attempts to improve the Hantzsch reaction using alternative catalysts and greener methods.[3] Almost all of the new methodologies of organic synthesis, for instance, microwave-assisted synthesis,[4] the promotion of solar thermal energy[5] and ultrasound irradiation,[6] the replacement of the organic solvents by ionic liquids or water[7] and the use of a variety of metal halides or triflates as Lewis catalysts[8] have been employed for the synthesis of 1,4-DHPs. However, most of the research has been focused on the modification and optimization of the Hantzsch reaction to maximize reaction conversion, minimize reaction time and offer high purity 1,4-DHPs. At the same time, the oxidative aromatization of 1,4-DHPs to corresponding pyridines has also been extensively studied. A plethora of oxidants including air, catalyzed by $RuCl_3$ or Pd/C have been applied in the aromatization reactions.[9] All of these studies seem to indicate that the reaction conditions, products and mechanism of the Hantzsch reaction have been well understood.

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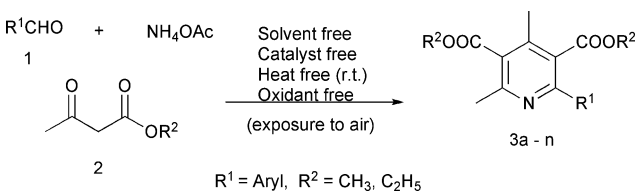
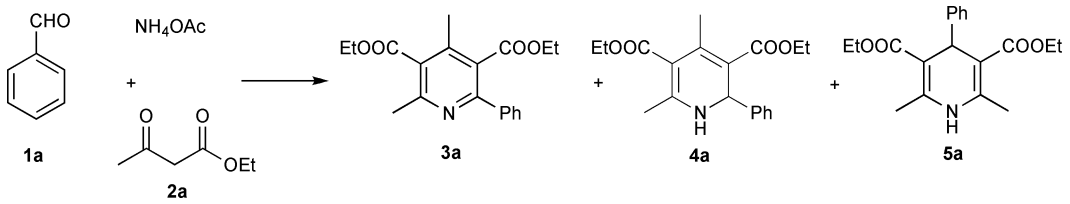
Our group has devoted much effort over the years to multi-component reactions under solvent-free conditions.[10] Although care needs to be taken as the solvent is often the heat sink that absorbs the heat from exothermic reactions, for reactions without a strong exotherm, solvent-free conditions offer environmental advantages and will be safe and efficient. Recently, we have surprisingly found that the unsymmetric 2-arylpyridine **3** could be obtained as a major product by the one-pot multicomponent reaction of benzaldehyde, ethyl acetoacetate and ammonium acetate under solvent-free, heat-free, catalyst-free and oxidant-free conditions, whereas only trace amounts of classic Hantsch products were detected (Scheme 1).



Scheme 1 Synthesis of 2-arylpyridine **3a**–**n** under mild reaction conditions.

2-Arylpyridines have received significant attention in the fields of biologically active molecules and supramolecular coordination chemistry.[11] One of the most commonly used methods for the synthesis of 2-arylpyridines is based on the metal-catalyzed cross-coupling reactions of aryl- or pyridylhalide. However, one has to introduce functional groups after the cross-coupling because of the low compatibility of the organometallic intermediates with many substituents.[12] Thus, there is still a need for a straightforward and "green" approach to 2-arylpyridines. In this paper, we would like to report a new efficient and green method to synthesize 2-arylpyridine derivatives.

Due to some contradictory results and the wrong interpretation of the product structure published over the years and even recently,[13–15] it is timely for chemists to present a comprehensive research study on the Hantzsch reaction. This motivates us to



Scheme 2 Model reaction for the synthesis of 2-arylpyridines.

experimentally reexamine the title reaction thoroughly in the second section of this paper.

Results and discussion

As part of our drug discovery efforts, we recently were required to prepare a number of 1,4-DHPs. According to the literature procedure,[15] the reaction of benzaldehyde, ethyl acetoacetate and ammonium acetate was performed at 80 °C under solvent-free conditions. However, in contrast to the results of the previous report, the reaction did not afford the desired 1,4-DHP product in high yield (**5a**, 1.5 h, 93%), instead, 1,2-DHP (**4a**) was obtained as the main product with a small amount of other isomers (^{1}H NMR analysis indicated a mixture of two isomers in a 3:1 ratio).[16] Much to our surprise, the aromatic oxidative product, unsymmetric 2-arylpyridine **3a**, was obtained by prolonging the reaction time to 12 h (Scheme 2). Encouraged by this result, benzaldehyde, ethyl acetoacetate and ammonium acetate (1:2.4:1.2) were selected as representative reactants for further optimization of the reaction conditions.

For our initial studies, the effects of the temperature on the reaction were examined under solvent-free, catalyst-free conditions in an air atmosphere with different reaction times. The ratio of two products (**3a** and **5a**) was strongly dependent on the temperature. A mixture of **3a** and **5a** was formed in the ratio of 42:58 at 120 °C, whereas at 20 °C the final ratio of the two products was 94:6, which indicated that the formation of the desired product, 2-arylpyridine **3a**, was highly favored by a decrease in reaction temperature. The results are shown in Table 1.

After the preliminary investigations, our efforts were directed towards the evaluation of the solvent in the synthesis of 2-arylpyridine using the same substrates after stirring for 72 h in an air atmosphere under optimized temperature conditions (Table 2). Only acetic acid afforded a good yield (70.7%) of the expected product **3a**, whereas a mixture of 1,4- and 1,2-DHPs was obtained in other solvents (Entry 1–6) and no oxidative products were observed even after prolonged reaction time. Finally, to our delight, the best results (**3a** as the only major product) were obtained when the reaction was conducted in the absence of solvent at 20 °C.

Table 1 Effect of the reaction temperature on the ratio of the products under solvent-free, catalyst-free conditions in an air atmosphere

Entry	Temperature (°C)	Time (h)[a]	Ratio[b]	Yield[c]
1	120	7	**3a**:**5a** = 42:58	40.5
2	80	12	**3a**:**5a** = 69:31	67.4
3	65	14	**3a**:**5a** = 72:28	70.2
4	50	24	**3a**:**5a** = 77:23	76.6
5	20	72	**3a**:**5a** = 94:6	93.5

[a] The reaction time was monitored by TLC and similar results were obtained by prolonging the reaction time. [b] Yields and ratios were based on GC analysis. [c] Yields referred to the desired product **3a**.

Table 2 Effects of the solvents on the reaction under catalyst-free conditions in an air atmosphere at 20 °C

Entry	Solvent	Ratio[a]	Yield[b]
1	CH_3OH	**4a**:**5a** = 57:43	40.2
2	THF	**4a**:**5a** = 60:40	55.5
3	EtOH	**4a**:**5a** = 62:38	55.7
4	CH_2Cl_2	**4a**:**5a** = 59:41	37.2
5	CH_3CN	**4a**:**5a** = 69:31	35.7
6	DMSO	**4a**:**5a** = 26:74	43.2
7	AcOH	**3a**:**5a** = 90:10	70.7
8	None	**3a**:**5a** = 94:6	93.5

[a] Yields and ratios were based on GC analysis. [b] Yields in Entry 1–6 referred to **4a** and in Entry 7–8 referred to **3a**.

Table 3 Effect of catalyst on the product selectivity under solvent-free conditions in an air atmosphere at 20 °C

Entry	Catalyst[a]	Ratio[b]	Time (h)	Yield[c]
1	None	**3a**:**5a** = 94:6	72	93.5
2	Piperidine	**3a**:**5a** = 89:11	72	88.3
3	$Yb(PFO)_3$	**3a**:**5a** = 90:10	72	87.2
4	$InCl_3{\cdot}4H_2O$	**3a**:**5a** = 94:6	72	78.6

[a] 10 mol% of catalysts were used. [b] Yields and ratios were based on GC analysis. [c] Yields referred to the desired product **3a**.

Usually, catalyst plays an important role in the synthesis of 1,4-DHPs.[17] Accordingly, piperidine, $Yb(PFO)_3$ (ytterbium perfluorooctanoate) and $InCl_3{\cdot}4H_2O$ were selected to investigate the effect of catalysts on ratio of products under solvent-free conditions at 20 °C (Table 3). However, the results indicated little influence of catalyst on ratio of product. The classical Hantzsch product 1,4-DHP **5a** was produced as a minor product.

Under these optimized reaction conditions, the generality and scope of this new one-pot three-component protocol was then explored. A range of structurally diverse aldehydes, ethyl (methyl) acetoacetate and ammonium acetate were subjected under solvent-free, catalyst-free conditions in an air atmosphere at 20 °C to produce the corresponding 2-arylpyridine derivatives (Table 4). Substituted benzaldehydes afforded high to excellent yield of 2-arylpyridine derivatives irrespective of electronic effects. Pyridine aldehydes also worked well with this protocol (Compounds **3g** and **3j**). However, when furan aldehyde, thiophene aldehyde and aliphatic aldehydes were used as substrates, the main products obtained by this new method were the classical 1,4-DHPs, few desired products were observed.

Table 4 Synthesis of 2-arylpyridines **3a**–**n** under solvent-free, catalyst-free conditions in an air atmosphere at 20 °C

Comp.	R^1	R^2	Yield[a]
3a	C_6H_5	C_2H_5	93.5
3b	4-$NO_2C_6H_4$	C_2H_5	75.4
3c	4-$CH_3C_6H_4$	C_2H_5	82.5
3d	C_6H_5	CH_3	90.2
3e	4-BrC_6H_4	C_2H_5	79.3
3f	4-CNC_6H_4	CH_3	80.8
3g	3-Pyridinyl	C_2H_5	69.0
3h	4-$OCF_3C_6H_4$	CH_3	87.1
3i	4-$OCH_3C_6H_4$	CH_3	68.2
3j	3-(6-ClPyridinyl)	CH_3	81.8
3k	3-BrC_6H_4	C_2H_5	82.5
3l	4-$CH_3C_6H_4$	CH_3	84.1
3m	4-FC_6H_4	C_2H_5	82.3
3n	4-ClC_6H_4	CH_3	85.9

[a] Yields were based on GC analysis.

After the successful synthesis of a series of 2-arylpyridines under these new reaction conditions, we next turned our attention to present comprehensive results from the experimental research on the reactivity and selectivity of the Hantzsch reaction. In order to verify the results of the literature, some important reported procedures were repeated and several parameters, including solvent, catalyst (piperidine), temperature and reaction time were reexamined. The detailed results are summarized in Scheme 3. Generally speaking, low temperature and solventless reaction conditions were favorable for forming 1,2-DHP (**C**). Once the intermediate 1,2-DHP was formed, the oxidation product 2-arylpyridine was generated easily in situ by air oxidation after stirring for a prolonged period (72 h) at 20 °C in high yield. The reaction was also performed under an argon atmosphere and gave mixtures of 1,4-DHP (**A**) and 1,2-DHP(**C**) (32:68), no 2-arylpyridine was detected. This result further verified that the air played a key role in the oxidation of 1,2-DHPs. The acetic acid was a unique solvent for this reaction. At 20 °C, the 1,2-DHP and its oxide (**D**) were favored, whereas in the refluxing HOAc, a higher percentage of Hantzsch 1,4-DHP was observed, and unexpectedly a small amount of the oxidative product of 1,4-DHP (**B**) was also detected.

In order to explain the formation of the different products, 1,4-DHPs and 2-arylpyridines (**3**), a mechanism is suggested in Scheme 4. The so-callled "twin-reactions" use almost similar types of two-step mechanisms. The initial step is the same in two reaction conditions. At this stage, the reaction involves a Knoevenagel condensation of the 1,3-dicarbonyl compound with the aldehyde to give an α,β-unsaturated carbonyl compound **7** and a condensation of ammonia with another equivalent of the 1,3-dicarbonyl compound to afford an enamine **6**.[18] The rate determining step is the Michael addition of the enamine to the α,β-unsaturated carbonyl compound. However, unlike the previously known mechanism of the Hantzsch reaction, the enamine intermediate prefers to attack on the carbon atom of the C=O double bond (carbon b of **7**) instead of the carbon atom of the C=C double bond (carbon a of **7**). Subsequently, the intermediate **9** undergoes an intramolecular addition of the amino to the carbon–carbon double bond to afford the 1,2-dihydropyridine **4**, which can be further oxidized to the desired pyridines **3** in air.

Conclusions

In summary, we have developed a novel, efficient and environmentally friendly one-pot three-component method for the synthesis of the 2-arylpyridines in air at room temperature. The methodology does not require the use of any organic solvent, catalyst and additional oxidant, thus eminently meeting green chemistry objectives. To minimize misunderstandings and confusions with earlier publications, this paper also introduced the details of experimental research of the classical and improved Hantzsch reaction. Our aim is to provide an intuitional picture for describing this chemical reaction. These studies will be important for the understanding of the process. However, these efforts do not mean that everything is known, and there is still a lot to learn about this fascinating and useful reaction.

Experimental

Materials and methods

All chemicals were purchased commercially and used without further purification. Melting points were measured in an open capillary using Büchi melting point B540 apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz and 100 MHz, respectively) using TMS as internal standard. Gas chromatography (GC) was recorded on a HP 6890 Plus GC instrument and high-resolution mass spectra (HRMS) were recorded under electron impact conditions using a MicroMass GCT CA 055 instrument.

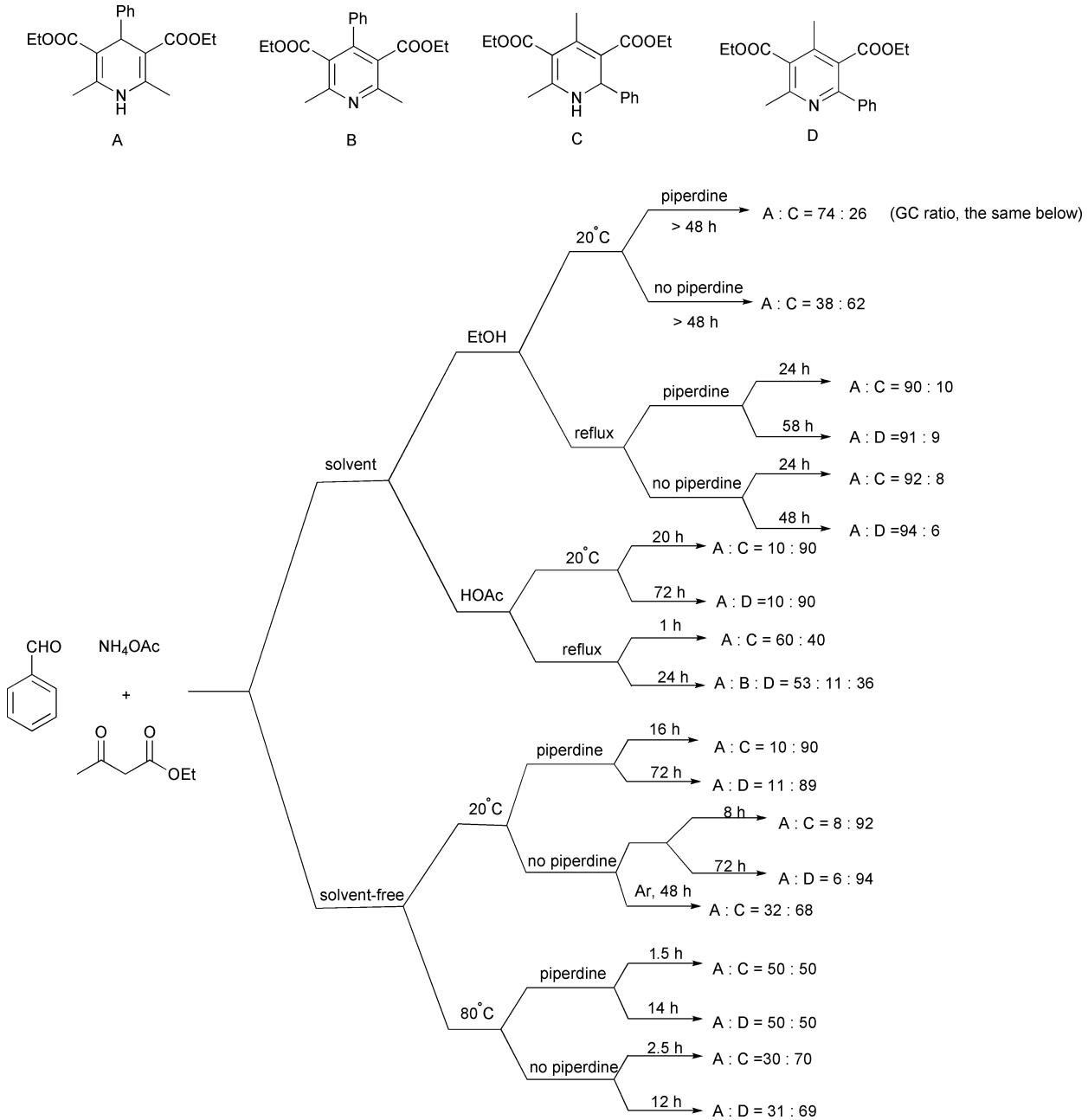
General procedure for the synthesis of substituted pyridines

A 10 mL round-bottomed flask was charged with aldehyde (1 mmol), 1,3-dicarbonyl compound (2.4 mmol) and ammonium acetate (1.2 mmol). The mixture was stirred at 20 °C until the reaction was completed (monitored by TLC). The reaction mixture was treated with brine solution, extracted with ethyl acetate and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to leave the crude product which was purified by chromatography over silica gel.

Spectroscopic data for compounds 3a–n

Diethyl 2-phenyl-4,6-dimethylpyridine-3,5-dicarboxylate (3a). Yield 82% (isolated yield and the same below); colorless oil; δ_H (400 MHz, $CDCl_3$): 7.59–7.57 (2H, m, Ph*H*), 7.45–7.42 (3H, m, Ph*H*), 4.48 (2H, q, J = 7.2 Hz, 3-$CO_2CH_2CH_3$), 4.12 (2H, q, J = 7.2 Hz, 5-$CO_2CH_2CH_3$), 2.64 (3H, s, 6-CH_3), 2.38 (3H, s, 4-CH_3), 1.44 (3H, t, J = 7.2 Hz, 3-$CO_2CH_2CH_3$), 1.00 (3H, t, J = 7.2 Hz, 5-$CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 168.2 (*C*=O), 168.1 (*C*=O), 156.3 (*C*-6), 155.1 (*C*-2), 142.7 (*C*-4), 139.6 (Ph-*C*), 128.7 (Ph-*C*), 128.4 (Ph-*C*), 128.2 (Ph-*C*), 128.1 (*C*-3), 127.2 (*C*-5), 61.5 (–O*C*H_2CH_3), 61.4 (–O*C*H_2CH_3), 23.0 (6-*C*H_3), 16.7 (4-*C*H_3), 14.1 (–OCH_2CH_3), 13.5 (–OCH_2CH_3); HRMS: calc. for $C_{19}H_{21}NO_4$ (M^+): 327.1471, found: 327.1472.

Diethyl 2-(4-nitrophenyl)-4,6-dimethylpyridine-3,5-dicarboxylate (3b). Yield 60%; colorless crystal; mp: 47.1–48.5 °C; δ_H (400 MHz, $CDCl_3$): 8.27–8.23 (2H, m, Ph*H*), 7.75–7.72 (2H, m, Ph*H*), 4.45 (2H, q, J = 7.2 Hz, 3-$CO_2CH_2CH_3$), 4.13 (2H, q,

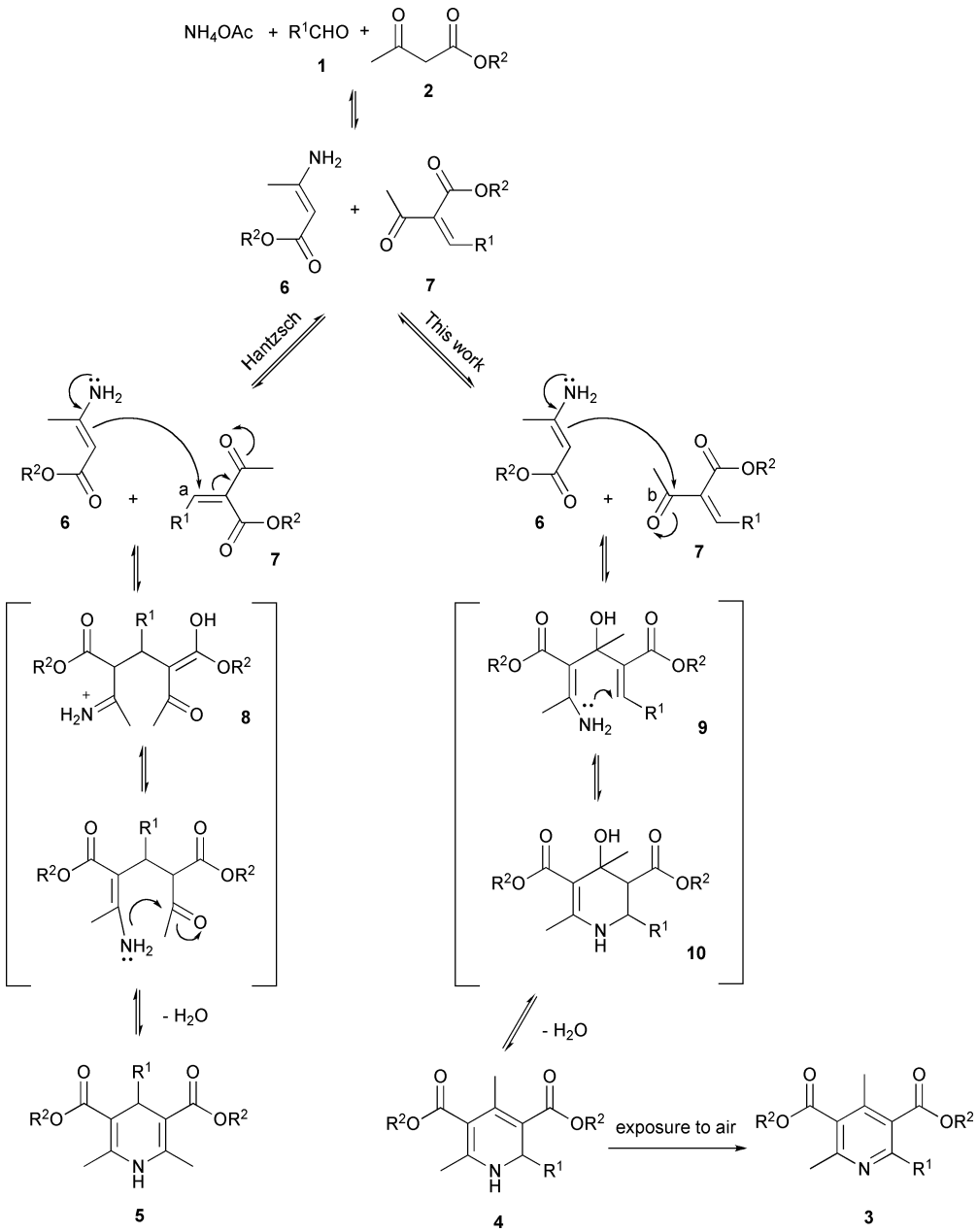


Scheme 3 A survey of the reaction of benzaldehyde with ethyl acetoacetate and ammonium acetate under different reaction conditions.

J = 7.2 Hz, 5-$CO_2CH_2CH_3$), 2.59 (3H, s, 6-CH_3), 2.36 (3H, s, 4-CH_3), 1.40 (3H, t, J = 7.2 Hz, 3-$CO_2CH_2CH_3$), 1.03 (3H, t, J = 7.2 Hz, 5-$CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 167.8 (*C*=O), 167.7 (*C*=O), 155.7 (*C*-6), 153.8 (*C*-2), 148.0 (*C*-4), 145.8 (*C*-NO_2), 143.4 (Ph-*C*), 129.6 (Ph-*C*), 129.4 (*C*-3), 127.5 (*C*-5), 123.5 (Ph-*C*), 61.9 (–O*C*H_2CH_3), 61.8 (–O*C*H_2CH_3), 23.0 (6-*C*H_3), 16.9 (4-*C*H_3), 14.1 (–OCH$_2$*C*H_3), 13.7 (–OCH$_2$*C*H_3); HRMS: calc. for $C_{19}H_{20}N_2O_6$ (M^+): 372.1321, found: 372.1308.

Diethyl 2-(4-methylphenyl)-4,6-dimethylpyridine-3,5-dicarboxylate (3c). Yield 73%; light-yellow crystal; mp: 49.1–50.3 °C; δ_H (400 MHz, $CDCl_3$) 7.49–7.47 (2H, m, Ph*H*), 7.24 (1H, s, Ph*H*), 7.22 (1H, s, Ph*H*), 4.46 (2H, q, J = 7.2 Hz, 3-$CO_2CH_2CH_3$), 4.15 (2H, q, J = 7.2 Hz, 5-$CO_2CH_2CH_3$), 2.61 (3H, s, 6-CH_3), 2.39 (3H, s, CH_3Ph), 2.36 (3H, s, 4-CH_3), 1.43 (3H, t, J = 7.2 Hz, 3-$CO_2CH_2CH_3$), 1.06 (3H, t, J = 7.2 Hz, 5-$CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 168.6 (*C*=O), 168.4 (*C*=O), 156.4 (*C*-6), 155.2 (*C*-2), 142.7 (*C*-4), 138.8 (Ph-*C*), 136.8 (Ph-*C*), 129.0 (Ph-*C*), 128.2 (Ph-*C*), 128.1 (*C*-3), 127.1 (*C*-5), 61.7 (–O*C*H_2CH_3), 61.5 (–O*C*H_2CH_3), 23.1 (6-*C*H_3), 21.3 (Ph-*C*H_3), 16.9 (4-*C*H_3), 14.1 (–OCH$_2$*C*H_3), 13.7 (–OCH$_2$*C*H_3); HRMS: calc. for $C_{20}H_{23}NO_4$ (M^+): 341.1627, found: 341.1627.

Dimethyl 2-phenyl-4,6-dimethylpyridine-3,5-dicarboxylate (3d). Yield 79%; colorless crystal; mp: 85.0–86.2 °C; δ_H (400 MHz, $CDCl_3$): 7.61–7.57 (2H, m, Ph*H*), 7.50–7.41 (3H, m, Ph*H*), 3.99 (3H, s, 3-CO_2CH_3), 3.65 (3H, s, 5-CO_2CH_3), 2.62 (3H, s, 6-CH_3), 2.36 (3H, s, 4-CH_3); δ_C (100 MHz, $CDCl_3$):



Scheme 4 Proposed mechanisms for the synthesis of 2-arylpyridines.

168.9 (*C*=O), 168.8 (*C*=O), 156.4 (*C*-6), 155.6 (*C*-2), 143.1 (*C*-4), 139.4 (Ph-*C*), 130.1 (Ph-*C*), 129.0 (Ph-*C*), 128.4 (Ph-*C*), 128.2 (*C*-3), 127.0 (*C*-5), 52.6 (–O*C*H$_3$), 52.4 (–O*C*H$_3$), 23.2 (6-*C*H$_3$), 17.1 (4-*C*H$_3$); HRMS: calc. for $C_{17}H_{17}NO_4$ (M^+): 299.1158, found: 299.1160.

Diethyl 2-(4-bromophenyl)-4,6-dimethylpyridine-3,5-dicarboxylate (3e). Yield 70%; colorless oil; δ_H (400 MHz, $CDCl_3$): 7.57 (2H, d, J = 8.8 Hz, Ph*H*), 7.47 (2H, d, J = 8.4 Hz, Ph*H*), 4.47 (2H, q, J = 7.2 Hz, 3-$CO_2CH_2CH_3$), 4.16 (2H, q, J = 7.2 Hz, 5-$CO_2CH_2CH_3$), 2.62 (3H, s, 6-CH_3), 2.37 (3H, s, 4-CH_3), 1.43 (3H, t, J = 7.2 Hz, 3-$CO_2CH_2CH_3$), 1.08 (3H, t, J = 7.2 Hz, 5-$CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 168.0 (*C*=O), 167.9 (*C*=O), 155.3 (*C*-6), 154.9 (*C*-2), 142.9 (*C*-4), 138.5 (Ph-*C*), 131.4 (Ph-*C*), 130.0 (Ph-*C*), 128.7 (*C*-3), 127.1 (*C*-5), 123.3 (Ph-*C*), 61.7 (–O*C*H$_2$CH$_3$), 61.6 (–O*C*H$_2$CH$_3$), 23.0 (6-*C*H$_3$), 16.8 (4-*C*H$_3$), 14.1 (–OCH$_2$*C*H$_3$), 13.6 (–OCH$_2$*C*H$_3$); HRMS: calc. for $C_{19}H_{20}NO_4Br$ (M^+): 405.0576, found: 405.0578.

Dimethyl 2-(4-cyanophenyl)-4,6-dimethylpyridine-3,5-dicarboxylate (3f). Yield 72%; colorless crystal; mp: 112.1–112.6 °C; δ_H (400 MHz, $CDCl_3$): 7.76–7.73 (2H, m, Ph*H*), 7.71–7.69 (2H, m, Ph*H*), 4.00 (3H, s, 3-CO_2CH_3), 3.68 (3H, s, 5-CO_2CH_3), 2.62 (3H, s, 6-CH_3), 2.37 (3H, s, 4-CH_3); δ_C (100 MHz, $CDCl_3$): 168.4 (*C*=O), 168.3 (*C*=O), 156.0 (*C*-6), 154.3 (*C*-2), 143.8 (*C*-4), 143.6 (Ph-*C*), 132.2 (Ph-*C*), 129.2 (Ph-*C*), 129.0 (*C*-3), 127.1 (*C*-5), 118.5 (–*C*N), 112.7 (*C*-CN), 52.7 (–O*C*H$_3$), 52.6 (–O*C*H$_3$), 23.1 (6-*C*H$_3$), 17.1 (4-*C*H$_3$); HRMS: calc. for $C_{18}H_{16}N_2O_4$ (M^+): 324.1110, found: 324.1112.

Diethyl 4,6-dimethyl-2,3′-bipyridine-3,5-dicarboxylate (3g). Yield 58%; light-yellow oil; δ_H (400 MHz, $CDCl_3$): 8.69–8.68 (2H, m, Py*H*), 7.49–7.48 (2H, m, Py*H*), 4.46 (2H, q, J = 7.2 Hz, 3-$CO_2CH_2CH_3$), 4.14 (2H, q, J = 7.2 Hz, 5-$CO_2CH_2CH_3$), 2.61 (3H, s, 6-CH_3), 2.37 (3H, s, 4-CH_3), 1.42 (3H, t, J = 7.2 Hz, 3-$CO_2CH_2CH_3$), 1.03 (3H, t, J = 7.2 Hz, 5-$CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 167.7 (*C*=O), 167.5 (*C*=O), 155.7 (*C*-6), 153.5 (*C*-6′), 149.7 (*C*-2, *C*-2′), 147.0 (*C*-4), 143.2 (*C*-3′, *C*-4′), 129.5 (*C*-3), 127.3 (*C*-5), 122.8 (*C*-5′), 61.8 (–OCH_2CH_3), 61.7 (–OCH_2CH_3), 23.0 (6-CH_3), 16.8 (4-CH_3), 14.1 (–OCH_2CH_3), 13.4 (–OCH_2CH_3); HRMS: calc. for $C_{18}H_{20}N_2O_4$ (M^+): 328.1423, found: 328.1424.

Dimethyl 2-(4-trifluoromethoxyphenyl)-4,6-dimethylpyridine-3,5-dicarboxylate (3h). Yield 76%; colorless crystal; mp: 60.4–60.9 °C; δ_H (400 MHz, $CDCl_3$): 7.62 (2H, d, J = 8.8 Hz, Ph*H*), 7.28 (2H, d, J = 8.4 Hz, Ph*H*), 3.99 (3H, s, 3-CO_2CH_3), 3.67 (3H, s, 5-CO_2CH_3), 2.61 (3H, s, 6-CH_3), 2.35 (3H, s, 4-CH_3); δ_C (100 MHz, $CDCl_3$): 168.6 (*C*=O), 168.5 (*C*=O), 155.7 (*C*-6), 154.8 (*C*-2), 149.7 (*C*-OCF_3), 143.3 (*C*-4), 138.1 (Ph-*C*), 129.8 (Ph-*C*), 128.5 (*C*-3), 126.9 (*C*-5), 120.7 (Ph-*C*), 120.4 (–OCF_3), 52.5 (–OCH_3), 52.3 (–OCH_3), 23.0 (6-CH_3), 16.9 (4-CH_3); HRMS: calc. for $C_{18}H_{16}NO_5F_3$ (M^+): 383.0981, found: 383.0982.

Dimethyl 2-(4-methoxyphenyl)-4,6-dimethylpyridine-3,5-dicarboxylate (3i). Yield 59%; oil; δ_H (400 MHz, $CDCl_3$): 7.57 (2H, d, J = 8.8 Hz, Ph*H*), 6.96 (2H, d, J = 8.4 Hz, Ph*H*), 3.98 (3H, s, 3-CO_2CH_3), 3.86 (3H, s, PhOCH_3), 3.70 (3H, s, 5-CO_2CH_3), 2.62 (3H, s, 6-CH_3), 2.34 (3H, s, 4-CH_3); δ_C (100 MHz, $CDCl_3$): 169.2 (*C*=O), 168.8 (*C*=O), 160.3 (*C*-6), 155.8 (*C*-OCH_3), 155.4 (*C*-2), 143.0 (*C*-4), 131.9 (Ph-*C*), 129.6 (Ph-*C*), 127.6 (*C*-3), 126.5 (*C*-5), 113.9 (Ph-*C*), 55.3 (Ph-OCH_3), 52.5 (–OCH_3), 52.4 (–OCH_3), 23.2 (6-CH_3), 17.0 (4-CH_3); HRMS: calc. for $C_{18}H_{19}NO_5$ (M^+): 329.1263, found: 329.1265.

Dimethyl 6′-chloro-4,6-dimethyl-2, 3′-bipyridine-3,5-dicarboxylate (3j). Yield 73%; colorless crystal; mp: 70.1–70.4 °C; δ_H (400 MHz, $CDCl_3$): 8.59 (1H, d, J = 2.4 Hz, 2′- Py*H*), 7.92 (1H, dd, J = 8.4, 2.4 Hz, 4′-Py*H*), 7.41(1H, d, J = 8.4 Hz, 5′- Py*H*), 3.99 (3H, s, 3-CO_2CH_3), 3.75 (3H, s, 5-CO_2CH_3), 2.62 (3H, s, 6-CH_3), 2.36 (3H, s, 4-CH_3); δ_C (100 MHz, $CDCl_3$): 168.2 (*C*=O), 168.1 (*C*=O), 156.1 (*C*-6), 151.8 (*C*-Cl), 148.9 (*C*-2), 143.5 (*C*-4), 138.5 (*C*-2′), 134.1 (*C*-4′), 129.0 (*C*-5, *C*-3′), 127.1 (*C*-3), 123.9 (*C*-5′), 52.6 (–OCH_3), 52.5 (–OCH_3), 23.0 (6-CH_3), 17.0 (4-CH_3); HRMS: calc. for $C_{16}H_{15}N_2O_4Cl$ (M^+): 334.0720, found: 334.0718.

Diethyl 2-(3-bromophenyl)-4,6-dimethylpyridine-3,5-dicarboxylate (3k). Yield 72%; light-yellow oil; δ_H (400 MHz, $CDCl_3$): 7.75 (1H, t, J = 1.6 Hz, Ph*H*), 7.56–7.54 (1H, m, Ph*H*), 7.52–7.49 (1H, m, Ph*H*), 7.30 (1H, t, J = 8.0 Hz, Ph*H*), 4.47 (2H, q, J = 7.2 Hz, 3-$CO_2CH_2CH_3$), 4.18 (2H, q, J = 7.2 Hz, 5-$CO_2CH_2CH_3$), 2.62 (3H, s, 6-CH_3), 2.37 (3H, s, 4-CH_3), 1.43 (3H, t, J = 7.2 Hz, 3-$CO_2CH_2CH_3$), 1.09 (3H, t, J = 7.2 Hz, 5-$CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 167.9 (*C*=O), 167.8 (*C*=O), 155.3 (*C*-6), 154.5 (*C*-2), 142.9 (*C*-4), 141.5 (Ph-*C*), 131.7 (Ph-*C*), 131.3 (Ph-*C*), 129.8 (Ph-*C*), 128.8 (Ph-*C*), 127.3 (*C*-5), 126.9 (*C*-3), 122.3 (Ph-*C*), 61.7 (–OCH_2CH_3), 61.6 (–OCH_2CH_3), 23.0 (6-CH_3), 16.8 (4-CH_3), 14.1 (–OCH_2CH_3), 13.6 (–OCH_2CH_3); HRMS: calc. for $C_{19}H_{20}NO_4Br$ (M^+): 405.0576, found: 405.0575.

Dimethyl 2-(4-methylphenyl)-4,6-dimethylpyridine-3,5-dicarboxylate (3l). Yield 75%; light-yellow crystal; mp: 83.6–85.3 °C; δ_H (400 MHz, $CDCl_3$): 7.49 (2H, d, J = 8.0 Hz, Ph*H*), 7.24 (2H, d, J = 8.4 Hz, Ph*H*), 3.98 (3H, s, 3-CO_2CH_3), 3.68 (3H, s, 5-CO_2CH_3), 2.63 (3H, s, 6-CH_3), 2.40 (3H, s, CH_3Ph), 2.35 (3H, s, 4-CH_3); δ_C (100 MHz, $CDCl_3$): 169.1 (*C*=O), 168.8 (*C*=O), 156.3 (*C*-6), 155.5 (*C*-2), 142.3 (*C*-4), 138.9 (Ph-*C*), 136.6 (Ph-*C*), 129.2 (Ph-*C*), 128.1 (Ph-*C*), 127.9 (*C*-3), 126.8 (*C*-5), 52.5 (–OCH_3), 52.4 (–OCH_3), 23.2 (6-CH_3), 21.3 (Ph-CH_3), 17.0 (4-CH_3); HRMS: calc. for $C_{18}H_{19}NO_4$ (M^+): 313.1314, found: 313.1315.

Diethyl 2-(4-fluorophenyl)-4,6-dimethylpyridine-3,5-dicarboxylate (3m). Yield 71%; colorless oil; δ_H (400 MHz, $CDCl_3$): 7.60–7.56 (2H, m, Ph*H*), 7.14–7.10 (2H, m, Ph*H*), 4.47 (2H, q, J = 7.2 Hz, 3-$CO_2CH_2CH_3$), 4.15 (2H, q, J = 7.2 Hz, 5-$CO_2CH_2CH_3$), 2.63 (3H, s, 6-CH_3), 2.37 (3H, s, 4-CH_3), 1.43 (3H, t, J = 7.2 Hz, 3-$CO_2CH_2CH_3$), 1.07 (3H, t, J = 7.2 Hz, 5-$CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 168.2 (*C*=O), 168.1 (*C*=O), 164.5 (*C*-6), 162.0 (*C*-F), 155.2 (*C*-2), 142.9 (*C*-4), 135.7 (Ph-*C*), 130.2 (Ph-*C*), 128.5 (*C*-3), 127.2 (*C*-5), 115.3 (Ph-*C*), 61.7 (–OCH_2CH_3), 61.5 (–OCH_2CH_3), 23.0 (6-CH_3), 16.8 (4-CH_3), 14.1 (–OCH_2CH_3), 13.6 (–OCH_2CH_3); HRMS: calc. for $C_{19}H_{20}NO_4F$ (M^+): 345.1376, found: 345.1375.

Dimethyl 2-(4-chlorophenyl)-4,6-dimethylpyridine-3,5-dicarboxylate (3n). Yield 76%; light-yellow crystal; mp: 81.9–90.2°C; δ_H (400 MHz, $CDCl_3$): 7.55 (2H, d, J = 8.4 Hz, Ph*H*), 7.42 (2H, d, J = 8.4 Hz, Ph*H*), 4.00 (3H, s, 3-CO_2CH_3), 3.69 (3H, s, 5-CO_2CH_3), 2.66 (3H, s, 6-CH_3), 2.37 (3H, s, 4-CH_3); δ_C (100 MHz, $CDCl_3$): 168.7 (*C*=O), 168.6 (*C*=O), 155.7 (*C*-6), 155.0 (*C*-2), 143.3 (*C*-4), 137.9 (Ph-*C*), 135.2 (Ph-*C*), 129.6 (Ph-*C*), 128.7 (Ph-*C*), 128.4 (*C*-3), 126.9 (*C*-5), 52.6 (–OCH_3), 52.5 (–OCH_3), 23.1 (6-CH_3), 17.1 (4-CH_3); HRMS: calc. for $C_{17}H_{16}NO_4Cl$ (M^+): 333.0768, found: 333.0764.

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