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K_2CO_3-assisted one-pot sequential synthesis of 2-trifluoromethyl-6-difluoromethylpyridine-3,5-dicarboxylates under solvent-free conditions

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ABSTRACT

A novel synthesis of 2-trifluoromethyl-6-difluoromethylpyridine-3,5-dicarboxylates by three-component reaction of ethyl trifluoroacetoacetate, aldehydes, and ammonium acetate in the presence of K_2CO_3 under solvent-free conditions via sequential Hantzsch reaction/dehydration/dehydrofluorination in a one-pot process was described.

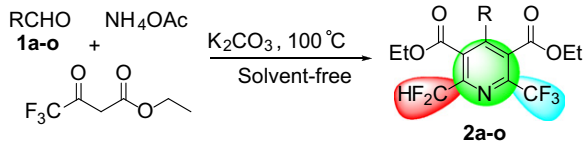
Trifluoromethylated pyridines have been widely used in medicinal and agricultural chemistry.[1] For example, Enpiroline, a trifluoromethyl-containing 4-pyridinemethanol phosphate, has been discovered as a promising antimalarial compound.[2] Fluazinam, an N-phenylpyridinamine compound, is a highly active fungicide with broad spectrum.[3] In recent years, the introduction of difluoromethyl group (–CF_2H) into biologically active compounds has attracted much interest due to its unique physiological properties.[4] Compared to the trifluoromethylated compounds, most difluoromethylated derivatives can serve as hydrogen bond donors and provide further opportunity for interaction with biological molecules.[5] Thiazopyr, a pyridine derivative with both trifluoromethyl and difluoromethyl groups, has been registered as a new pre-emergence selective herbicide for the control of various annual grasses and broadleaf weeds.[6]

The most straightforward method to introduce difluoromethyl group into molecules involves the reaction of the corresponding carbonyl compounds with fluorinating reagents such as diethylaminosulfur trifluoride (DAST), Deoxofluor™, and *N*,*N*-diethyl-α,α-difluoro-(*m*-methylbenzyl) amine (DFMBA).[7–9] However, there has been little research on the nucleophilic fluorination reaction of pyridine aldehydes or ketones. Although the dehydrofluorination of trifluoromethyl-substituted dihydropyridines has been reported as an alternate route for the synthesis of difluoromethyl-substituted pyridines, the procedures were associated with several shortcomings, including the addition of dehydrating agents and strong organic bases, the use of toxic organic solvents, the long reaction time, and the tedious work-up procedures.[10] Therefore, it is highly desirable to develop a practical and mild method for the synthesis of difluoromethyl-containing pyridines.

Nowadays, much attention has been given to the reactions under solvent-free conditions for economic and environmental reasons. Furthermore, solvent-free reactions not only represent a clean, simple, efficient, and safe procedure with noticeable increases in reactivity and selectivity but also sometimes lead to a significant change in the course of a reaction and afford totally different products.[11,12]

Herein, we would like to describe an unexpected K_2CO_3-catalyzed sequential cyclization/dehydration/dehydrofluorination/aromatization for the synthesis of 2-trifluoromethyl-6-difluoromethylpyridine-3,5-dicarboxylate via a one-pot three-component condensations of aldehydes, ethyl trifluoroacetoacetate, and ammonium acetate under solvent-free conditions (Scheme 1).

According to the literature, trifluoromethyl-substituted 1,4-dihydropyridines can be prepared by the dehydration of the diethyl 2,6-dihydroxy-2,6-bis(trifluoromethyl)piperidine-3,5-dicarboxylates (**III**, Scheme 3), which are obtained by the Hantzsch reaction of ethyl trifluoroacetoacetate.[13] Up till now, several dehydration agents such as phosphorus oxychloride-pyridine, sulfuric acid, and phosphorus oxychloride-pyridine adsorbed on silica gel have been developed and used for their dehydration.[14–16] Recently, we planned to synthesize a series of trifluoromethyl-substituted 1,4-dihydropyridines for the purpose of screening the bioactive compounds. However, when the Hantzsch reaction of ethyl trifluoroacetoacetate, benzaldehyde, and ammonium acetate was carried out without a solvent, an unprecedented dehydration product was obtained with the loss of one mole of water, diethyl 2-hydroxy-2,



Scheme 1. Synthesis of 2-trifluoromethyl-6-difluoromethylpyridine-3,5-dicarboxylates **2a–o**.

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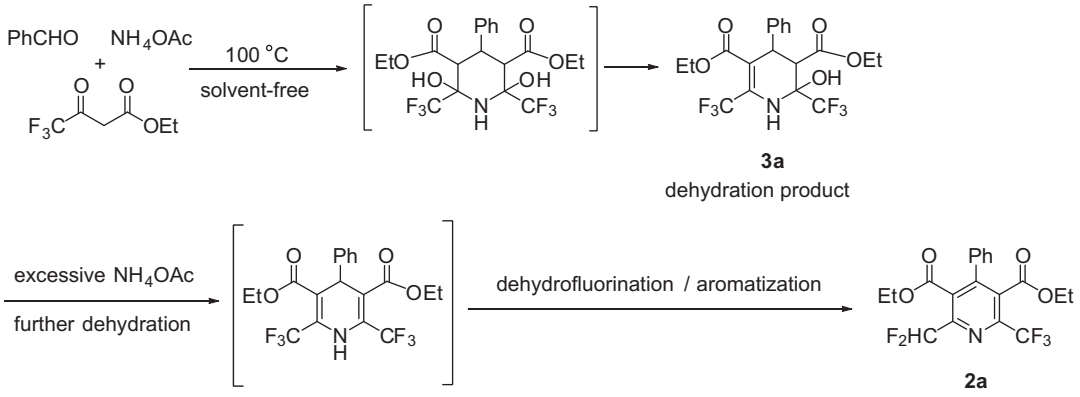
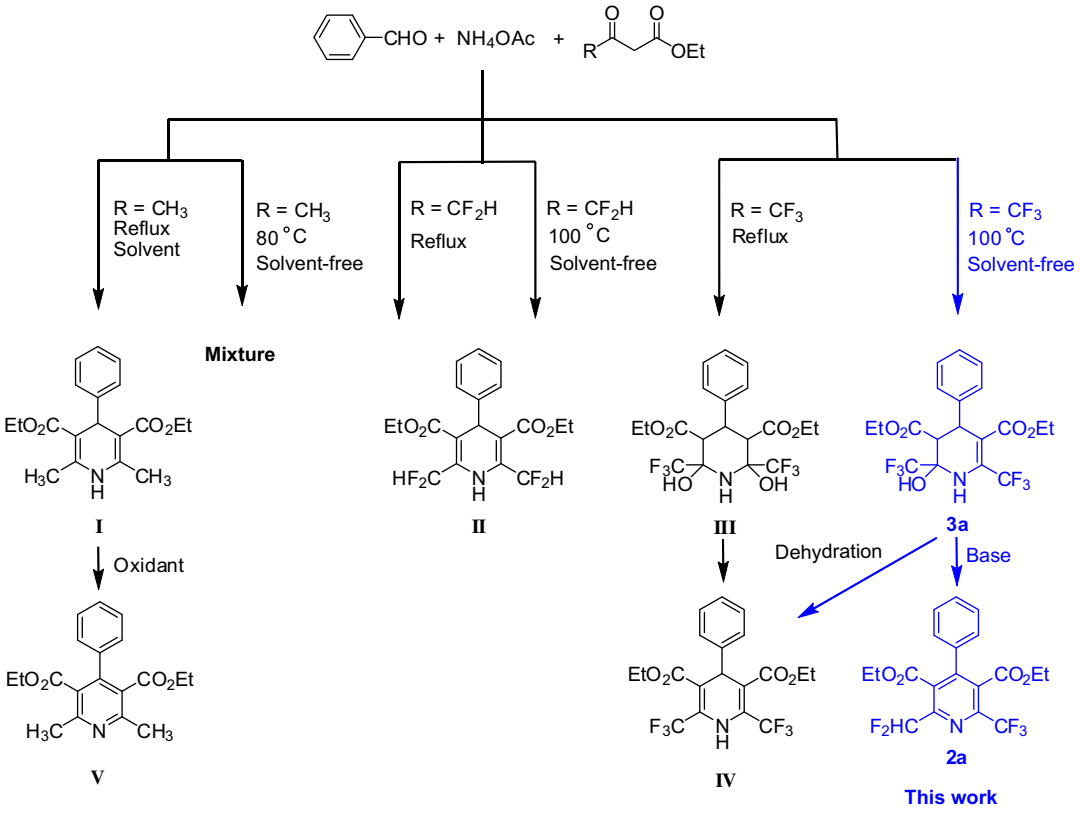


Scheme 2. Model reaction for the synthesis of **2a**.



Scheme 3. The comparison of reaction conditions and products among the different 1,3-dicarbonyl substrates for the Hantzsch reaction.

6-bis(trifluoromethyl)-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate **3a** was isolated as the main product. Furthermore, an increase in the amount of NH_4OAc resulted in the loss of another one mole of water, and then the dehydrofluorination took place to generate the aromatic product, diethyl 2-difluoromethyl-4-phenyl-6-trifluoromethylpyridine-3,5-dicarboxylate **2a** (Scheme 2). It was unusual that both dehydration and dehydrofluorination proceeded smoothly under such a mild condition to give trifluoromethyl- and difluoromethyl-substituted pyridine in a one-pot process. Encouraged by this result, benzaldehyde, ethyl trifluoroacetoacetate, and ammonium acetate were selected as representative reactants for further optimization of the reaction conditions.

Initially, attempts to improve the yield of **2a** by increasing the amount of NH_4OAc were unsuccessful. As NH_4OAc might not be the appropriate base for the HF elimination, we turned our attention to search for a more suitable base. Several bases were screened and the results are shown in Table 1. The yield was significantly

Table 1
Effect of several bases on the synthesis of compound **2a**

Entry	Base (equiv)	Time (h)	Yield of **2a**[a]
1	None	24	—[b]
2	CH_3COONH_4 (3.0)	5	43
3	Pyridine (1.0)	24	Trace[c]
4	DBU (1.0)	2	75
5	DMAP (1.0)	2.5	76
6	K_2CO_3 (1.0)	2	77
7	NaOH	17	37

[a] Yields were based on GC analysis.
[b] Compound **3a** was obtained as the main product in 54% yield.
[c] Compound **3a** was obtained as the main product in 52% yield.

Table 2
Effect of temperature on the one-pot reaction under solvent-free conditions

Entry	Temperature (°C)	Time (h)	Yield of **2a**[a]
1	90	18	59
2	100	2.5	77
3	120	1	69

[a] Yields were based on GC analysis.

Table 3
Synthesis of 2-trifluoromethyl-6-difluoromethylpyridine-3,5-dicarboxylate **2a–o** under solvent-free conditions

Compd	R	Yield[a]
2a	C_6H_5	77
2b	4-$CH_3C_6H_4$	58
2c	4-$OCF_3C_6H_4$	67
2d	4-$OCH_3C_6H_4$	74
2e	4-CNC_6H_4	93
2f	4-FC_6H_4	72
2g	3-BrC_6H_4	53
2h	3-(6-Cl-pyridinyl)	92
2i	3-CH_3-thienyl-2-	73
2j	Thienyl-3-	75
2k	4-ClC_6H_4	66
2l	3-Pyridinyl	78
2m	4-BrC_6H_4	86
2n	Furan-2-	29
2o	$CH_3CH_2CH_2$	25

[a] Yields were based on GC analysis.

affected by the base. When the model reaction was performed in the absence of base, no further dehydration and dehydrofluorination reactions occurred and **3a** was obtained as the main product. Among the various bases tested, 1,5-diazabicyclo[4.3.0]non-5-ene (DBU), 4-dimethylaminopyridine (DMAP), and K_2CO_3 gave good yield of **2a**. Long reaction time was needed and only low yield of **2a** was obtained when NaOH was used as base. Considering K_2CO_3 as an easily available, economical, and toxicologically harmless base, we selected it as base to perform this one-pot sequential synthesis of 2-difluoromethyl-6-trifluoromethylpyridine-3,5-dicarboxylate.

The reaction was also conducted in various solvents, but all the reactions were found to proceed slower, and the yields were much lower, than the reactions performed under solvent-free conditions.

The effects of the temperature on the reaction were examined under solvent-free conditions in the presence of K_2CO_3. As shown in Table 2, the reaction proceeded smoothly at 100 °C, yielding the expected product in 76% yield. However, increasing or decreasing the temperature would lead to a decrease in yield.

Under these optimized reaction conditions, we investigated the generality and scope of the one-pot three-component reaction (Table 3). In all cases of substituted benzaldehydes, the reaction could afford 2-trifluoromethyl-6-difluoromethylpyridine-3,5-dicarboxylate **2a–o** in good yields.[17–19] The electron-withdrawing substituents on the aromatic ring seemed to be favorable for the reaction. Heterocyclic aromatic aldehydes, except furan aldehyde, were good substrates as well. Whereas, when aliphatic aldehydes were used, the products were obtained in low yields.

As indicated above, quite different results of Hantzsch reaction of ethyl trifluoroacetoacetate have been obtained under solvent-free conditions. Therefore, it was of interest for us to compare the reaction conditions and products of Hantzsch reaction of other 1,3-dicarbonyl substrates (Scheme 3). In the case of ethyl acetoacetate, the classic Hantzsch reaction proceeded efficiently in solvent at reflux and the corresponding product, 1,4-dihydropyridine (**I**), could be further oxidized to (**V**). The reaction proceeded in a different way when it was conducted under solvent-free conditions and a mixture of 1,4- and 1,2-dihydropyridine was observed.[12a] The reaction of ethyl difluoroacetoacetate with benzaldehyde and ammonium acetate yielded 1,4-DHP (**II**) products in good yield under both refluxing and solvent-free conditions.[20] When ethyl trifluoroacetoacetate served as the substrate, dehydration process was promoted in the absence of dehydrating agents under solvent-free conditions affording tetrahydropyridine **3a** instead of product (**III**), which was obtained as the main product in refluxing solvent. Compound **3a** could either be further dehydrated to 1,4-DHP (**IV**) by using a dehydration agent such as sulfuric acid or aromatized to product **2a** in the presence of base under solvent-free conditions.

In conclusion, an efficient, solvent-free K_2CO_3-assisted method has been developed for the synthesis of 2-trifluoromethyl-6-difluoromethylpyridine-3,5-dicarboxylates. The fluorine-containing pyridines were obtained by the reaction of trifluoromethyl acetoacetate with aldehydes, ammonium acetate via dehydration, dehydrofluorination, and aromatization under mild conditions without additional dehydration reagent and oxidant.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.041.

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17. *Experimental*: All chemicals were purchased commercially and used without further purification. Melting points were measured in 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. The ^{19}F NMR was measured with external CF_3CO_2H as the standard. Gas chromatography (GC) was recorded on HP 6890 Plus GC instrument and high-resolution mass spectra (HRMS) were recorded under electron impact conditions using a MicroMass GCT CA 055 instrument.
18. *General procedure for the synthesis of substituted pyridines* **2a**–**o**: The mixture of aldehyde **1** (2 mmol), ethyl trifluoroacetoacetate (4 mmol), ammonium acetate (2 mmol), and K_2CO_3 (2 mmol) was stirred at 100 °C until the reaction was completed (monitored by TLC). Ethyl acetate (5 mL) was added and the solution was washed with satd aq NaCl solution 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.
19. *Typical data for representative compound*: Diethyl 2-difluoromethyl-4-phenyl-6-trifluoromethylpyridine-3,5-dicarboxylate (**2a**): Light yellow viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.49–7.29 (5H, m, Ph*H*), 6.84 (1H, t, $^{1}J_{HF}$ = 54.2 Hz, C*H*F_2), 4.09 (4H, q, J = 7.2 Hz, 2 × $CO_2CH_2CH_3$), 1.01 (3H, t, J = 7.6 Hz, $CO_2CH_2CH_3$), 0.98 (3H, t, J = 7.2 Hz, $CO_2CH_2CH_3$) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.1, 163.8, 149.8, 148.9 (t, $^{2}J_{CF}$ = 26.0 Hz), 143.9 (q, $^{2}J_{CF}$ = 35.8 Hz), 133.2, 131.4, 130.7, 129.7, 128.4, 128.3, 120.5 (q, $^{1}J_{CF}$ = 274.3 Hz), 112.7 (t, $^{1}J_{CF}$ = 242.5 Hz), 62.6, 62.5, 13.4 ppm; ^{19}F NMR ($CDCl_3$, 376 MHz): δ = −64.9 (3F, s, –CF_3), −115.7 (2F, d, J_{HF} = 54.3 Hz, –CHF_2) ppm; HRMS: calcd for $C_{19}H_{16}NO_4F_5$ (M^+): 417.0999, found: 417.0995.
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