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One-Pot Reactions for Modular Synthesis of Polysubstituted and Fused Pyridines

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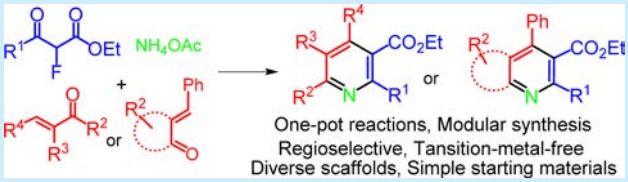
Supporting Information

ABSTRACT: A 2-fluoro-1,3-dicarbonyl-initiated one-pot Michael addition/[5 + 1] annulation/dehydrofluorinative aromatization reaction sequence is introduced for regioselective synthesis of di-, tri-, tetra-, and pentasubstituted pyridines as well as fused pyridines. This simple and modular synthesis is performed using readily available starting materials and under transition-metal catalyst-free conditions.



Pyridine is the top nitrogen heterocyclic system in medicinal chemicals.[1] Pyridine derivatives also play an important role in natural products,[2] agricultural chemicals,[3] functional polymers,[4] and ligands for catalysis.[5] Shown in Figure 1 are selected structures of pyridine-containing natural products and bioactive compounds.[6] Annulations and cycloadditions are two general approaches for making pyridine rings.[7] The annulation methods include [5 + 1],[8] [3 + 3] (Bohlmann–Rahtz),[9] [3 + 2 + 1] (Kröhnke and Bohlmann–Rahtz),[10] and [2 + 2 + 1 + 1] (Hantzsch and Chichibabin).[11] The cycloaddition methods include aza-[4 + 2] (Diels–Alder and inverse electron demand Diels–Alder)[12] and [2 + 2 + 2] cycloadditions.[13] Other methods such as electrocyclizations,[14] ring expansions,[15] radical reactions,[16] and multicomponent reactions[7b,17] have also been developed for making pyridines. However, many of these reactions have drawbacks of side reactions, need transition-metal catalysts, require special starting materials, and lack regioselectivity in the synthesis of polysubstituted pyridines. Other than ring forming reactions, the substitution reaction of pyridines is an alternative approach for pyridine derivatives,[7c,17] but they also have regioselectivity issues due to the electron-deficient nature of the pyridine ring.[18] Introduced in this paper is a [5 + 1] annulation-based approach for regioselective synthesis of polysubstituted pyridines by one-pot synthesis and under transition-metal catalyst-free conditions.

Organofluorine chemistry is an active research topic because introduction of fluorine atom(s) could have a significant effect on parent molecules' chemical, physical, and biological properties.[19] In addition, organofluorine compounds are also feasible synthons for substitution and dehydrofluorination reactions. The dehydrofluorinations have been utilized in converting CH–CF to C=C,[20] CHF–CF or CH–CF_2 to C=CF,[21,22] and related reactions.[23]

In our continuous efforts on the development of green synthetic methods,[24] we have reported a one-pot synthesis of fluorinated cyclohexenones **1** through sequential fluorination and Robinson annulation of 1,3-dicarbonyls.[25] We have extended

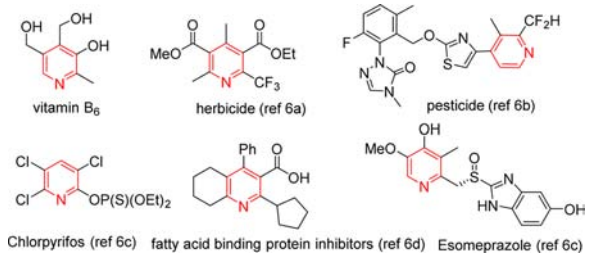
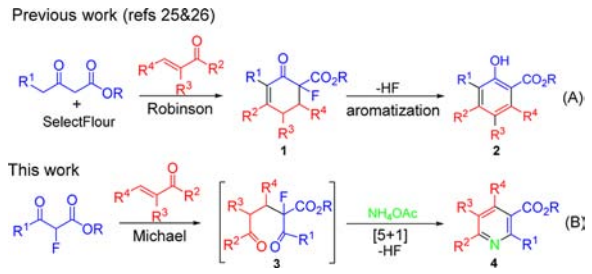


Figure 1. Representative bioactive pyridine derivatives.

Scheme 1. α-Fluor-1,3-dicarbonyls for Synthesis of Phenols and Pyridines



the method for making polysubstituted phenols **2** through dehydrofluorinative aromatization (Scheme 1A).[26] In connection with the challenge associated with the regioselective synthesis of heteroarenes, we designed a new one-pot synthesis including Michael addition of 2-fluoro-1,3-dicarbonyls followed by [5 + 1] annulation of 1,5-dicarbonyls **3** with NH_4OAc and *in situ* dehydrofluorinative aromatization for substituted pyridines **4** (Scheme 1B). We envisioned that it could be a straightforward and efficient process for assembling polysubstituted pyridines.

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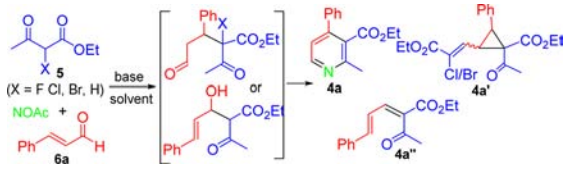
Our first attempt was to establish the one-pot synthesis protocol of using 0.2 mmol α-fluoro-β-ketoester **5a** with 1.0 equiv each of cinnamaldehyde **6a** and NH_4OAc as a model reaction (Table 1). It was found that the reaction of **5a** produced

Table 1. Screening of One-Pot Reactions of β-Ketoesters 5[a]



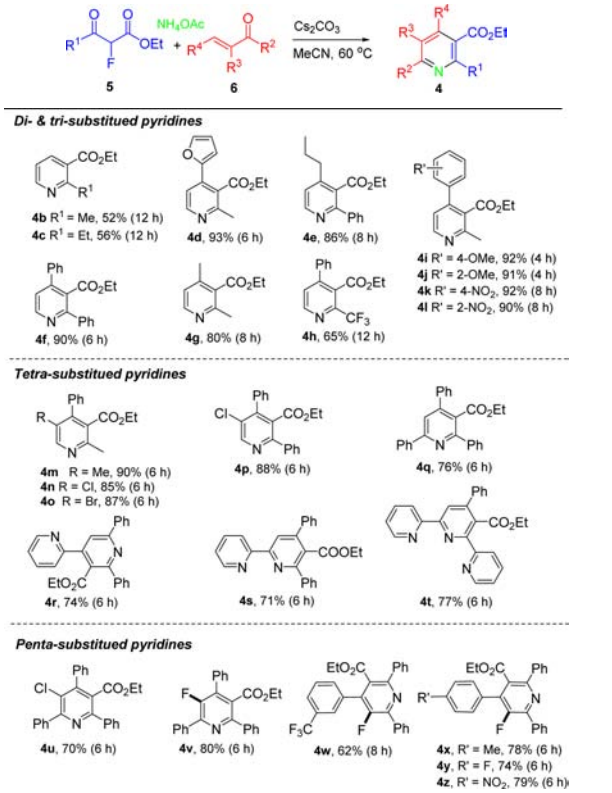
entry	X	base	solvent	temp (°C)	4a (%)	4a′ (%)	4a″ (%)
1	F	Cs_2CO_3	MeCN	25	41		
2	F	Cs_2CO_3	MeCN	40	63		
3	F	**Cs_2CO_3**	**MeCN**	**60**	**93**		
4	Cl	Cs_2CO_3	MeCN	25	<5	37	
5	Br	Cs_2CO_3	MeCN	25	<5	32	
6	Cl	KF	MeCN	25	26	26	
7	Cl	KF	MeCN	60	51	19	
8	H	Cs_2CO_3	MeCN	25	17		39
9	H	Cs_2CO_3	MeCN	60	29		43
10	F	Cs_2CO_3	DMF	60	37		
11	F	piperidine	EtOH	60	87		
12	F	piperidine	H_2O	60	<5		
13	F	$(NH_4)_2CO_3$	MeCN	60	41[b]		
14	F	Cs_2CO_3	MeCN	60	91[c]		

[a]Reaction condition: **5** (0.2 mmol), **6a** (0.2 mmol), NH_4OAc (0.4 mmol), MeCN (1 mL), 4 h, GC yield. [b]In the absence of NH_4OAc, $(NH_4)_2CO_3$ (0.2 mmol). [c]5 mmol scale-up, isolated yield.

product **4a** in 41% GC yield in MeCN at room temperature (entry 1). Increasing the reaction temperature to 60 °C resulted in **4a** in 93% yield (entry 3). Reactions using α-chloro-β-ketoester or α-bromo-β-ketoester to replace α-fluoro-β-ketoester gave cyclopropane derivatives **4a′** instead of **4a** as a major product because of Cl and Br are good leaving groups for nucleophilic substitution to form cyclopropanation (entries 4 and 5).[27,28] Using less basic KF to replace Cs_2CO_3 for the reaction of α-chloro-β-ketoester increased the yield of **4a** to 51% (entry 7). The possibility of F-exchange was eliminated since no α-fluoro-β-ketoester was detected by F-NMR and GC-MS from the mixture of heating α-chloro-β-ketoester with KF at 60 °C. The reaction of β-ketoester **5** (X = H) resulted in a small amount of **4a** (25 °C, 17%; 60 °C, 29%) after air oxidative aromatization, while the Knoevenagel adduct **4a″** was the major product under the basic reaction conditions for β-ketoester (entries 8 and 9).[10c] Results shown in Table 1 demonstrate that α-fluoro-β-ketoester **5a** is a better substrate than its analogues (X = Cl, Br, H). The fluorinated Michael addition intermediate blocks cyclopropanation to form **4a′**, avoids Knoevenagel adduct **4a″**, and allows [5 + 1] annulation with NH_4OAc to form a pyridine ring after dehydrofluorinative aromatization.[23b,26,29] After screening additional bases including piperidine and $(NH_4)_2CO_3$, as well as solvents such as DMF, EtOH, and water (entries 10−13), it was found that Cs_2CO_3 and MeCN make a good combination. A scaled-up reaction with 5 mmol of α-fluoro-β-ketoester produced product **4a** in 91% isolated yield (entry 14).

The reactions shown in Table 1 are good for the synthesis of 2,3,4-trisubstituted pyridine **4a**. We then focused our efforts on making different kinds of substituted pyridines and also exploring the generality of the one-pot synthesis (Table 2).[30] Thus, readily available α-fluoro-β-ketoesters **5**[31] bearing different R^1 were

Table 2. One-Pot Synthesis of Polysubstituted Pyridines 4[a]



[a]Reaction conditions: 1 equiv (0.2 mmol) each of **5**, **6**, and Cs_2CO_3, 2 equiv of NH_4OAc, in MeCN (1 mL); isolated yield.

reacted with a range of α,β-unsaturated aldehydes or α,β-unsaturated ketones **6** bearing electron-donating or -withdrawing groups (R^2−R^4). When aldehydes **6** (R^2, R^3, R^4 = H) were used as Michael acceptors for the reactions with β-ketoesters **5** and NH_4OAc, 2,3-disubstituted pyridines **4b,c** were obtained in 52% and 56% yield, respectively. When aldehydes **6** (R^2, R^3 = H) were used for the reactions, 2,3,4-trisubstituted pyridine **4d−l** were obtained in 65−93% yields. By further extending the reaction scope by using aldehydes **6** (R^2 = H), 2,3,4,5-tetrasubstituted pyridines **4m−p** were prepared in 85−90% yields. Using chalcones **6** as Michael acceptors, 2,3,4,6-tetrasubstituted pyridines **4q−t** were prepared in 71−76% yields.[32]

Pentasubstituted pyridines **4u−z** were also successfully synthesized in 62−80% yields by using R^3 and R^4 substituted ketones **6** as Michael acceptors (Table 2). The structure of product **4x** was supported by X-ray single crystal analysis. Worthy of note is that fully substituted pyridines **4v−z** with a fluorine atom at the 3- or 5-position are of significant interest in medicinal chemistry.[5c,33] Compared to the reported methods for 3-fluoropyridines by aromatic substitution[34] or annulation of complex building blocks under transition-metal catalysis,[33,35] our method uses readily available α-fluoro-α,β-unsaturated ketones[31] as Michael acceptors for the one-pot synthesis. It is much more practical and efficient than literature protocols and provides quick access to many unexplored 3- or 5-fluoropyridines for biological tests.

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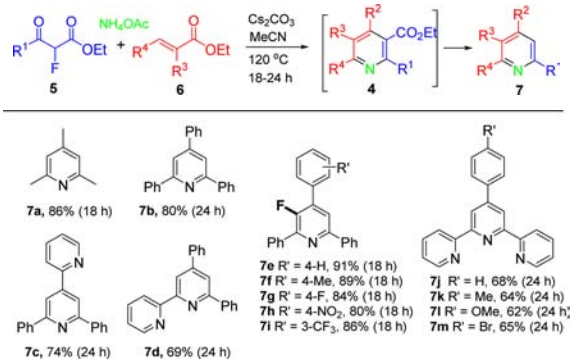
We also explored the decarboxylation of substituted pyridines **4** following our reported procedures for the synthesis of fluorinated cyclohexenones and phenols.[25,26] However, decarboxylation of pyridines, such as **4a** and **4m**, derived from α,β-unsaturated aldehydes **6**, only gave less than 10% products by GC analysis. To our delight, substituted pyridines derived from α,β-unsaturated ketones **6** could be readily decarboxylated by heating. The decarboxlylation process could be integrated as the last step of the one-pot synthesis by performing the reaction at 120 °C for 18−24 h. Symmetric 2,4,6-trisubstituted pyridines **7a** and **7b**, and tetrasubstituted pyridines **7e−i** were synthesized in greater than 80% yields (Table 3). By introducing a pyridine

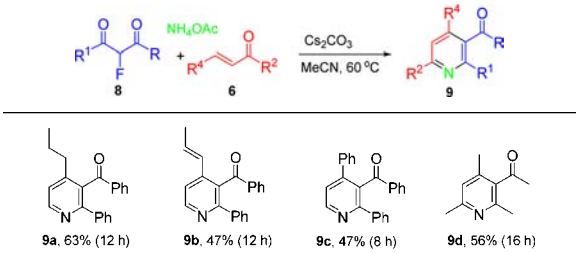
Table 3. One-Pot Synthesis of Decarboxylated Pyridines 7[a]



[a]Reaction conditions: 1 equiv (0.2 mmol) each of **5**, **6**, and Cs_2CO_3, and 2 equiv of NH_4OAc, in MeCN (1 mL); isolated yield.

moiety into α,β-unsaturated ketones **6**, bipyridines **7c** and **7d** were synthesized in good yields. Reactions of pyridine-bearing β-ketoesters **5** and α,β-unsaturated ketones **6** afforded highly valuable terpyridine ligands **7j−m** in greater than 60% yields. One-pot reactions of α-fluoro-1,3-diketones **8** with α,β-unsaturated ketones **6** afforded 2,3,4-trisubstituted pyridines **9a−d** bearing a benzoyl or an acetyl group at the 3-position in moderate yields (Table 4).

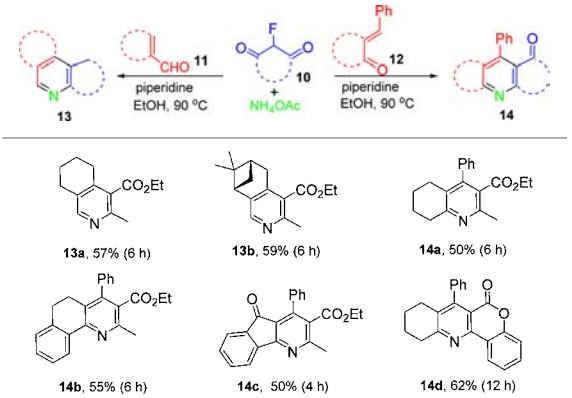
Table 4. One-Pot Synthesis of Pyridines 9[a]



[a]Reaction conditions: 1 equiv (0.2 mmol) each of **8**, **6**, and Cs_2CO_3, 2 equiv of NH_4OAc, in MeCN (1 mL); isolated yield.

The accomplishment of the one-pot synthesis for polysubstituted pyridines encouraged us to extend the reaction scope for making fused pyridines. After quick optimization of reaction conditions, piperidine was found to be a good base and EtOH a good solvent. Reactions of 2-fluoro-1,3-dicarbonyls **10** with cyclic aldehydes **11** or cyclic ketones **12** resulted in a series of pyridine-fused scaffolds such as tetrahydroisoquinolines **13a,b** and **14a**, dihydrobenzoquinoline **14b**, indenopyridinone **14c**, and tetrahydrochromenoquinolinone **14d** in 50−62% yields (Table 5).

Table 5. One-Pot Synthesis of Fused-Pyridines 13 and 14[a]



[a]Reaction conditions: 1 equiv (0.2 mmol) each of **10**, **11** (or **12**), and pyridine, 2 equiv of NH_4OAc, in EtOH (1 mL); isolated yield.

In summary, we have developed a 2-fluoro-1,3-dicarbonyl-initiated one-pot synthesis involving Michael addition/[5 + 1] annulation/dehydrofluorinative aromatization for regioselective and modular synthesis of a wide range of di-, tri-, tetra-, and pentasubstituted pyridines as well as fused pyridines. In addition to pot economy and a broad substrate scope, the new method has additional advantages of being a transition-metal catalyst-free synthesis and using readily available starting materials for the construction of diverse pyridine derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02883.

Experimental details and spectral data for all new compounds (PDF)

Crystallographic data for **4x** (CIF)

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Notes

The authors declare no competing financial interest.

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