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One-Pot Sequential Multistep Transformation of α,β-Unsaturated Trifluoromethyl Ketones: Facile Synthesis of Trifluoromethylated 2-Pyridones

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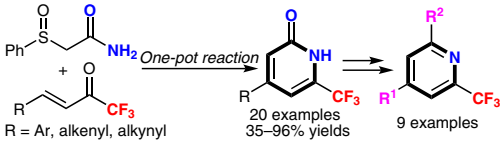

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Abstract A one-pot transformation of α,β-unsaturated trifluoromethyl ketones with 2-(phenylsulfinyl)acetamide to give trifluoromethylated 2-pyridones is realized. The reaction proceeds under mild conditions and involves multiple steps in an expeditious and controlled sequence to provide efficient access to a broad range of trifluoromethylated 2-pyridones in moderate to high yields. Moreover, further synthetic manipulations permit the routine synthesis of a diverse array of trifluoromethylated pyridines with good efficiency.

Key words trifluoromethyl group, pyridones, trifluoromethylpyridines, one-pot synthesis, multistep reaction

The 2-pyridone moiety is a unique type of structural motif present in numerous biologically active natural products, pharmaceuticals, ligands, and biomaterials.[1–4] Moreover, 2-pyridones have also been used as important building blocks for the preparation of a wide range of useful hetarene derivatives, such as pyridines.[5] On the other hand, the introduction of trifluoromethyl group (CF_3) into organic molecules has a significant impact on their physical and chemical properties, including their metabolic stability, solubility, and lipophilicity.[6] As such, the efficient synthesis of CF_3-functionalized heterocycles has been a longstanding goal within the organic-synthesis community.[7] More importantly, trifluoromethylated 2-pyridones and 2-(trifluoromethyl)pyridines have emerged as core units in an increasing number of valuable drugs and agrochemicals (Figure 1).

In this context, although the preparation of trifluoromethylated 2-pyridones has been described in several seminal studies,[8] implementing efficient and practical approaches to access these appealing compounds remains a significant challenge. Notably, Zhang and co-workers

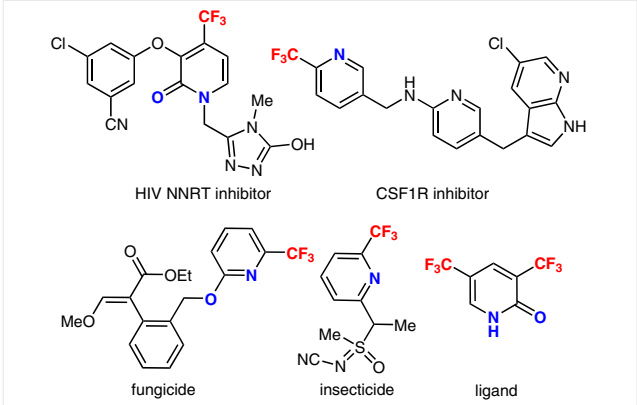
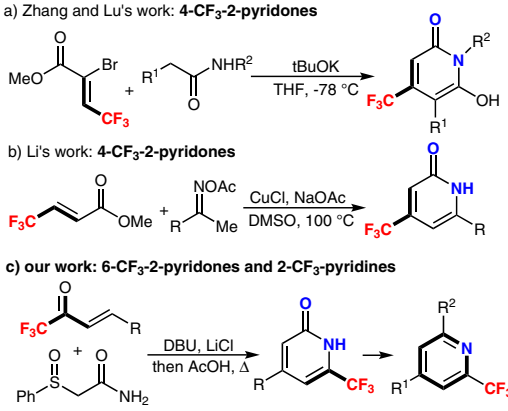


Figure 1 Trifluoromethylated 2-pyridone and 2-(trifluoromethyl)pyridine moieties found in bioactive molecules and ligands

reported a cycloaddition reaction between methyl (2*Z*)-2-bromo-4,4,4-trifluorobut-2-enoate and 2-tosylacetamides in the presence of potassium *tert*-butoxide to give a series of 4-(trifluoromethyl)-2-pyridones in moderate to good yields [Scheme 1(a)].[9] Li's group recently developed a copper-catalyzed [3 + 3] annulation of oxime acetates with trifluoromethylated acrylate that delivered a range of 4-(trifluoromethyl)-2-pyridones with good efficiency and selectivity [Scheme 1(b)].[10] Despite these remarkable advances, existing drawbacks such as cryogenic reaction temperatures, the use of transition metals or sensitive bases, and a limited substrate scope are continuing challenges to be overcome. In particular, a general and efficient approach for the construction of 6-(trifluoromethyl)-2-pyridones is surprisingly unprecedented.[11] In this regard, we anticipated that the employment of α,β-unsaturated trifluoromethyl ketones as key building blocks to react with appropriate nucleophilic partners might offer convenient access to 6-(trifluoromethyl)-2-pyridones. Here, we report our investigations on the

development of a one-pot protocol to generate CF_3-functionalized 2-pyridones under mild conditions [Scheme 1(c)]. Moreover, the wide synthetic utility of this method was further demonstrated by routine syntheses of a diverse array of CF_3-functionalized pyridines.

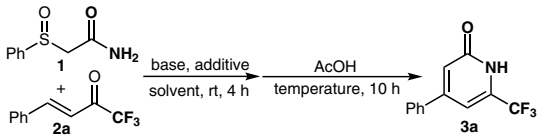


Scheme 1 Synthesis of trifluoromethylated 2-pyridones from various CF_3-containing building blocks

Inspired by the elegant work of the Fukuyama group,[12] we chose 2-(phenylsulfinyl)acetamide (**1**) as the nucleophilic partner to react with the α,β-unsaturated trifluoromethyl ketone **2a** (Table 1). At the outset, we screened a series of organic bases (DIPEA, DABCO, DMAP, and DBU) for their ability to facilitate the 1,4-addition step (Table 1, entries 1–4), and DBU turned out to be the best promoter.

In contrast to the previous study (in which the reaction was conducted at 50 °C), this process proceeded smoothly at room temperature, presumably due to the strongly electron-withdrawing nature of the trifluoromethyl group. Subsequently, acetic acid was added to the reaction system to trigger further reaction steps, leading to the formation of 4-phenyl-6-(trifluoromethyl)pyridin-2(1*H*)-one (**3a**) in a one-pot manner. To our great delight, in the presence of DBU and lithium chloride in acetonitrile, the desired product **3a** was obtained in 80% isolated yield (Table 1, entry 4). Encouraged by this result, we examined the effects of varying the amounts of DBU, LiCl, and AcOH (entries 5–7), revealing that the amount of AcOH could be dramatically reduced by half (entry 7). Remarkably, the reaction still proceeded in the absence of LiCl, giving **3a** in comparable yield (entry 8). The use of KCl or LiI also proved feasible, giving **3a** in practical yields (entries 9 and 10). Note that these results are again surprisingly different from those of a previous study,[13] highlighting the unique reactivity of trifluoromethylated compounds in comparison to their nonfluorinated counterparts. In addition, the effects of the reaction temperature and a series of solvents were also probed, but no improvement was observed (entries 11–15). Taken together, the optimal reaction conditions were established as

Table 1 Optimization of the Reaction Conditions[a]



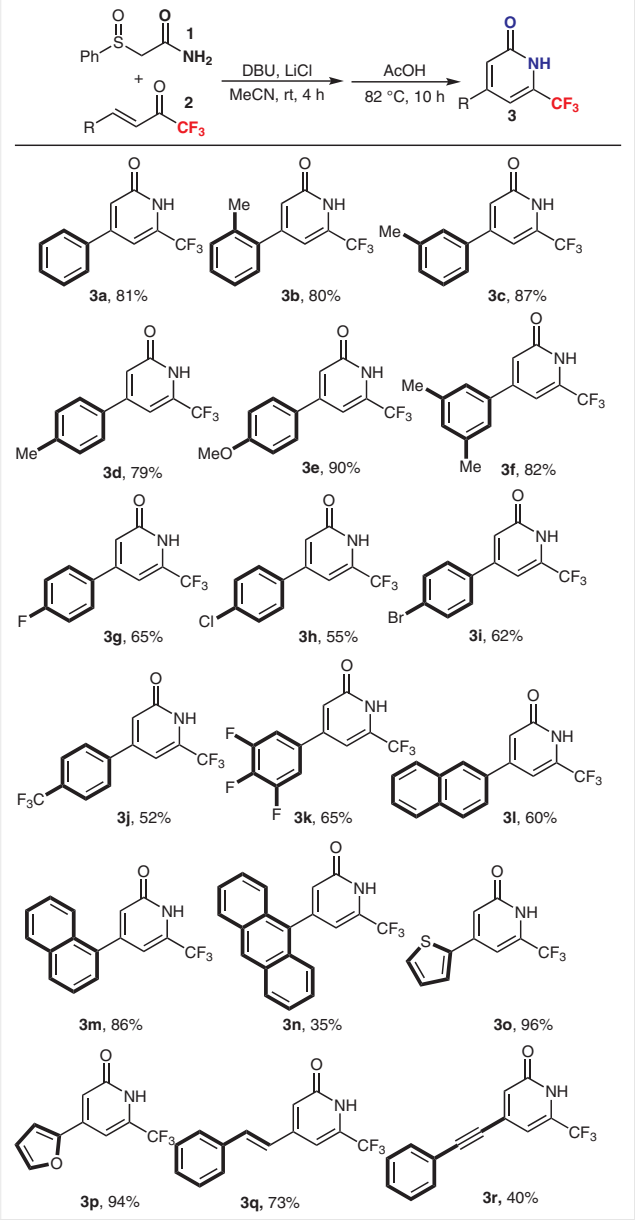
Entry	Base	Additive	Solvent	Temp (°C)	Yield[b] (%)
1	DIPEA	LiCl	MeCN	82	45
2	DABCO	LiCl	MeCN	82	3
3	DMAP	LiCl	MeCN	82	25
4	DBU	LiCl	MeCN	82	80
5[c]	DBU	LiCl	MeCN	82	38
6[d]	DBU	LiCl	MeCN	82	76
7[e]	DBU	LiCl	MeCN	82	81
8	DBU	–	MeCN	82	66
9	DBU	KCl	MeCN	82	58
10	DBU	LiI	MeCN	82	47
11[e]	DBU	LiCl	MeCN	65	23
12[e]	DBU	LiCl	toluene	82	45
13[e]	DBU	LiCl	DCE	82	60
14[e]	DBU	LiCl	THF	82	nr[f]
15[e]	DBU	LiCl	EtOAc	82	10

[a] Reaction conditions: **1** (0.4 mmol, 2.0 equiv), **2a** (0.2 mmol, 1.0 equiv), base (0.6 mmol, 3.0 equiv), additive (0.6 mmol, 3.0 equiv), solvent (3 mL), stirring, r.t., 4 h; then, AcOH (2 mmol, 10 equiv), indicated temperature, 10 h (unless otherwise noted).
[b] Yield of the isolated product.
[c] DBU (2.0 equiv) was employed.
[d] LiCl (2.0 equiv) was employed.
[e] AcOH (5.0 equiv) was employed.
[f] nr = no reaction.

follows: α,β-unsaturated trifluoromethyl ketone **2a** was treated with 2-(phenylsulfinyl)acetamide **1** in the presence of DBU and LiCl in MeCN at room temperature for four hours, then acetic acid was added and the mixture was refluxed for ten hours to give the desired trifluoromethylated pyridone **3a** in a one-pot operation (entry 7).

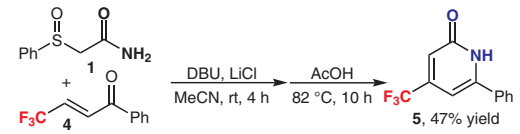
With the optimized reaction conditions in hand,[14] we set out to investigate the substrate scope with a range of α,β-unsaturated trifluoromethyl ketones (Scheme 2). The one-pot protocol proved to be pleasingly effective for substrates bearing electron-donating groups on the phenyl ring, as exemplified by the formation of products **3b–f** in high yields. Importantly, substitution patterns such as *ortho*, *para*, and *meta* had little influence on the reaction performance (products **3b–d**). To our delight, halogens, the trifluoromethyl group, and polyfluorinated substrates were also compatible with this reaction, permitting the generation of the corresponding 2-pyridones **3g–k** in practical yields. Moreover, trifluoromethyl ketones containing other types of aromatic ring, including 2-naphthyl, 1-naphthyl, 9-anthryl, 2-thienyl, and 2-furyl, also smoothly participated

in this transformation, giving the corresponding products **3l–p** in yields as high as 96% (**3o**). Remarkably, the broad scope of this reaction is further demonstrated by its the tolerance of (2-phenylethenyl)- and (2-phenylethynyl)-derived trifluoromethyl ketones under identical reaction conditions (products **3q** and **3r**). However, when alkyl-derived substrates were subjected to this reaction protocol, no formation of the target 2-pyridone was observed.



Scheme 2 Substrate scope for the synthesis of 6-(trifluoromethyl)-2-pyridones

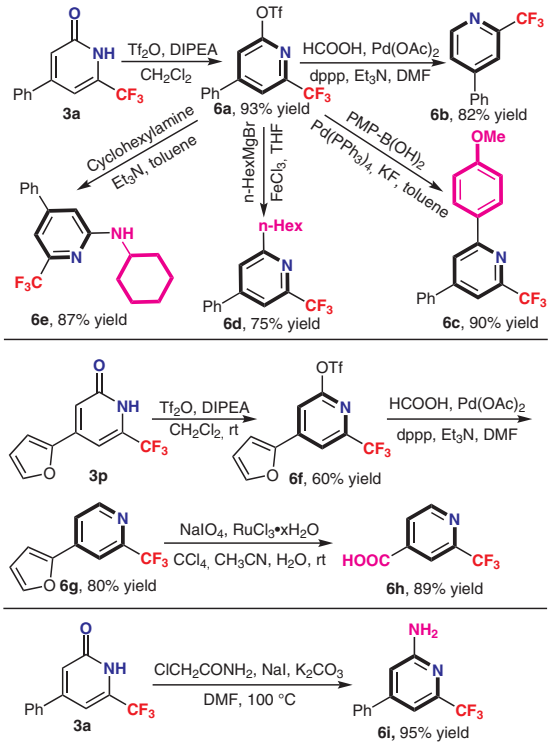
These encouraging results prompted us to explore the preparation of 4-(trifluoromethyl)-2-pyridones by means of this approach. To this end, the β-trifluoroethyl enone **4** was treated with 2-(phenylsulfinyl)acetamide (**1**) under the same one-pot reaction conditions (Scheme 3). Pleasingly, the corresponding 4-(trifluoromethyl)-2-pyridone **5** was obtained in 47% yield, highlighting the practicability of the current method.



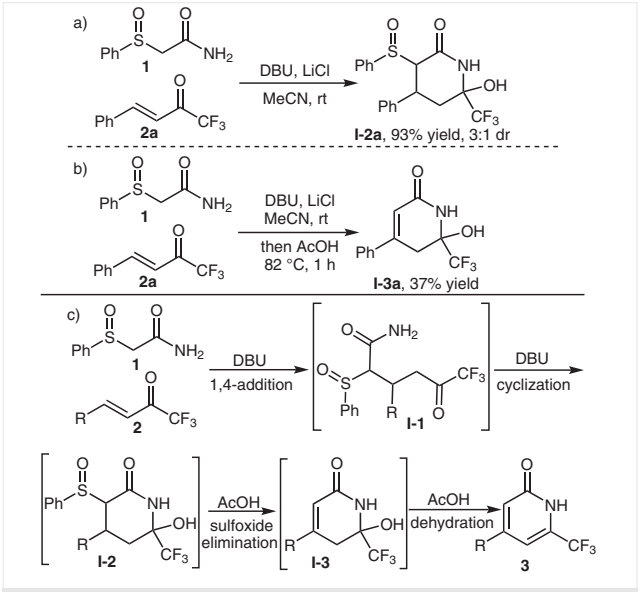
Scheme 3 Synthesis of a 4-trifluoromethyl-2-pyridone

To demonstrate the synthetic utility of our newly developed protocol, we next investigated further synthetic transformations of the 2-pyridone products. First, a gram-scale preparation of the 6-trifluoromethyl-2-pyridone **3a** was performed, and resulted in a slightly higher yield (85%), thereby providing additional proof of the robustness of this reaction. Subsequent O-triflation provided 4-phenyl-6-(trifluoromethyl)pyridin-2-yl triflate (**6a**) in excellent yield (Scheme 4),[15] thereby providing a range of opportunities for the generation of diverse CF_3-containing pyridines. For example, palladium-catalyzed detriflation proceeded smoothly to give 4-phenyl-2-(trifluoromethyl)pyridine (**6b**) in 82% yield.[16] Furthermore, the triflate **6a** is also compatible with classic cross-coupling methodologies, as exemplified by the formation of **6c** and **6d** in satisfactory yields through Suzuki coupling and iron-catalyzed sp^2–sp^3 coupling, respectively.[17] Moreover, the S_NAr reaction of **6a** with cyclohexylamine readily gave the biologically valuable compound **6e** in high yield.[18] Importantly, 2-(trifluoromethyl)isonicotinic acid (**6h**) was smoothly synthesized in good overall yield in three steps from the 4-furyl-2-pyridone **3p** (Scheme 4, middle). Finally, 4-phenyl-6-(trifluoromethyl)pyridin-2-amine (**6i**) was obtained in excellent yield by employing commercially available 2-chloroacetamide as an amine source (Scheme 4, bottom).[19] Note that CF_3-containing pyridines are core units found in many pharmaceutical targets and agrochemicals.[5a,20] Smith's group recently reported an elegant isothiourea-mediated one-pot synthesis of 4-trifluoromethylated pyridines from trifluoromethyl α,β-unsaturated ketimines.[21] Our synthetic protocol permits the routine synthesis of a diverse array of 2-trifluoromethyl-functionalized pyridines with good efficiency, thereby paving a way to further investigations in the synthesis of related functional molecules and their biological study.

To elucidate the mechanistic pathway of our multistep transformation, control experiments were carefully performed. As shown in Scheme 5(a), when the reaction was interrupted before the addition of acetic acid, the cyclized product **I-2a** was isolated in 93% yield. This solid result reveals that DBU is probably not only responsible for the 1,4-addition step, but also plays a critical role in promoting the



Scheme 4 Transformation of 6-(trifluoromethyl)-2-pyridones into various CF_3-functionalized pyridines



Scheme 5 Control experiments and proposed process

cyclization process. Moreover, when the reaction was stopped one hour after the addition of acetic acid, the intermediate **I-3a** was obtained and fully characterized [Scheme 5(b)].[22] This experiment suggests that the sulfoxide elimination occurs before the dehydration event. Based on these results, a proposed process is outlined in Scheme 5(c). Initially, 2-(phenylsulfinyl)acetamide **1** and the α,β-unsaturated trifluoromethyl ketone **2** undergo 1,4-addition in the presence of DBU; this is followed by a cyclization step to give intermediate **I-2**. Subsequently, sulfoxide elimination proceeds when acetic acid is added to the reaction sequence, generating intermediate **I-3**. At this stage, the dehydration is likely to occur expeditiously to provide the final product.

In conclusion, we have developed an efficient and practical transformation of α,β-unsaturated trifluoromethyl ketones with 2-(phenylsulfinyl)acetamide in a one-pot manner. This protocol permits the facile preparation of a broad range of CF_3-functionalized 2-pyridones and a diverse array of CF_3-functionalized pyridines in pleasing yields under mild conditions. Considering the high biological importance of CF_3-containing 2-pyridones and pyridines, this method holds the promise of finding applications in syntheses of potential pharmaceuticals and agrochemicals.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612077.

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(14) **6-(Trifluoromethyl)-2-pyridones 3a–r; General Procedure**
DBU (0.6 mmol, 89.7 μL) and the appropriate α,β-unsaturated trifluoromethyl ketone **2** (0.2 mmol, 1.0 equiv) were added to a mixture of 2-(phenylsulfinyl)acetamide (**1**; 0.4 mmol, 73.3 mg) and LiCl (0.6 mmol, 25.4 mg) in MeCN (4 mL) at r.t., and the mixture was stirred at r.t. for 4 h. When the trifluoromethyl ketone **2** was completely consumed (TLC), AcOH (1 mmol, 57.2 μL) was added, and the resulting mixture was refluxed for 10 h, then cooled to r.t. The reaction was then quenched with sat. aq $NaHCO_3$ and extracted with 10% MeOH–$CHCl_3$ (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, CH_2Cl_2–MeOH (80:1)].
4-Phenyl-6-(trifluoromethyl)pyridin-2(1*H*)-one (3a)
White solid; yield: 77.5 mg (81.0%); mp 198.4–200.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.83 (s, 1 H), 7.86–7.81 (m, 2 H), 7.61 (s, 1 H), 7.51 (dd, *J* = 5.8, 4.6 Hz, 3 H), 7.21 (s, 1 H). ^{19}F NMR (376 MHz, DMSO-d_6): δ = –66.65 (s). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.9, 152.2, 144.8 (q, J_{C-F} = 34.6 Hz), 136.2, 129.8, 129.2, 127.1, 121.5 (q, J_{C-F} = 272.4 Hz), 110.8, 110.3.
4-(2-Tolyl)-6-(trifluoromethyl)pyridin-2(1*H*)-one (3b)
White solid; yield: 81.0 mg (80.0%); mp 98.7–99.9 °C. IR (neat): 1666, 1632, 1550, 1444, 1403, 1348, 1174, 1133, 965, 945, 840 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.85 (s, 1 H), 7.27 (d, *J* = 25.6 Hz, 5 H), 6.86 (s, 1 H), 2.23 (s, 3 H). ^{19}F NMR (377 MHz, DMSO-d_6): δ = –66.78 (s). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.4 (s), 153.8 (s), 144.1 (q, J_{C-F} = 33.82 Hz), 137.8 (s), 134.7 (s), 130.7 (s), 129.0 (s), 128.8 (s), 126.2 (s), 121.5 (q, J_{C-F} = 272.33 Hz), 113.9 (s), 113.0 (s), 19.8 (s). HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{11}F_3NO$: 254.0789; found: 254.0793.

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