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Convenient one-pot synthesis of fluorinated DHPs derivatives and their further transformations

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ABSTRACT

One-pot four-component reactions of aromatic aldehyde, Meldrum's acid, ethyl-4,4,4-trifluoro-1,3-dioxobutanoate, and ammonium acetate afford ethyl 2-hydroxy-6-oxo-4-aryl-2-(trifluoromethyl)piperidine-3-carboxylate in good yields. The one-pot four-component process consists of an initial Michael addition, and a subsequent intramolecular cyclization. The effect of solvents on the reaction efficiency and yield is briefly investigated. The structure of product is further confirmed by XRD analysis. Meanwhile, the further transformation of hemi-aminal moiety to the corresponding dehydrated product is also achieved under the mild reaction conditions. The possible mechanism for the formation of product is presented.

Fluorine-containing compounds have attracted much interest since the introduction of fluorine atoms or fluoroalkyl moieties to an organic compound can bring about remarkable changes in the physical, chemical, and biological properties.[1–3] For example, the introduction of fluorine atoms or fluoroalkyl groups (particularly the CF_3 group) to molecules constitutes a classical and systematic modification of biological properties used in medicinal chemistry for the design of new drugs.[4] Consequently, more and more fluoroalkylated molecules have recently been found to be applied in the pharmaceutical fields.[5]

On the other hand, it is well known that the dihydropyridine (DHP) heterocyclic ring is a part of the fundamental skeleton of important classes of drugs.[6,7] For example, 1,4-dihydropyridines (1,4-DHPs) are the most important calcium channel modulators.[8] In fact, it is well established that slight structural modification on the DHP ring may bring about remarkable changes in pharmacological effect.[9] Due to these observations, fluoroalkylated DHP ring should be valuable building blocks to construct medicinally relevant complex structures.

To further explore the potentials of such kind of strategy for fluoroalkylated heterocyclic synthesis, we have recently started systematic studies on the synthesis of fluorine-containing compounds based on trifluoromethyl-1,3-dicarbonyl compound, a versatile fluorine-containing building block.[10] Herein, we wish to report a one-pot, four-component reaction to synthesize the 1,4-DHPs derivatives, together with their further dehydration reactions to the corresponding dehydrated 1,4-DHPs derivatives.

In our initial study, the one-pot four-component reaction was conducted by stirring the mixture of equivmolecular of corresponding aromatic aldehyde **1a**, Meldrum's acid **2**, ethyl-4,4,4-trifluoro-1,3-dioxobutanoate **3**, and ammonium acetate **4** in ethanol at room temperature for 2 h, however, no desired product **5a** was detected. Subsequently, the mixture was heated to reflux and stirred for 4 h, TLC showed that a new compound, which turned out to be the desired product, was formed and general workup afforded the product **5a** in 21% yield.

To optimize this reaction conditions, the same reaction was carried out in various solvents. The reaction results are summarized in Table 1. It was found that the reactions gave the product **5a** in relatively low yields in the solvents of ethanol, methanol, acetone, acetonitrile, and CH_2Cl_2 (Table 1, entries 1–5). Moreover, it was observed that the solvent effect played an important role in the transformation, and the reaction yield could be enhanced to 54% when AcOH was employed as the solvent (Table 1, entry 6). Prolonged reaction time (6 h) slightly increased the yield up to 61% (Table 1, entry 7).

The amount of ammonium acetate was the next considered factor. As shown in Table 1, the reactions gave the best yield when 1.2 equiv of NH_4OAc was used (Table 1, entry 9). When the amount of NH_4OAc was further increased to 2.0 equiv, the yield did not improve significantly (Table 1, entry 11). It should be noted that the reaction exclusively gave the *N*-heterocyclic compound **5a**, and no corresponding *O*-heterocyclic compound was obtained even though the reaction was carried out in the presence of 0.3 equiv of NH_4OAc (Table 1, entry 8).

With the optimal results in hand as shown in Table 1, entry 9, we investigated the scope and limitation of this one-pot, four-com-

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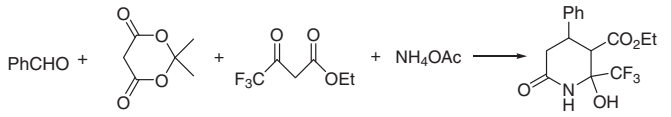
Table 1
Reaction of ethyl-4,4,4-trifluoro-1,3-dioxobutanoate **3** with benzaldehydes **1**, Meldrum's **2**, and NH_4OAc **4** under various conditions[a]



1a 2 3 4 5a

Entry	Solvent	NH_4OAc[a] (equiv)	Time (h)	Yield[b] (%)
1	EtOH	1.0	4	21
2	MeOH	1.0	4	20
3	MeCN	1.0	4	24
4	CH_3COCH_3	1.0	4	19
5	CH_2Cl_2	1.0	4	17
6	AcOH	1.0	4	54
7	AcOH	1.0	6	61
8	AcOH	0.3	6	26
9	AcOH	1.2	6	67
10	AcOH	1.5	6	65
11	AcOH	2.0	6	67

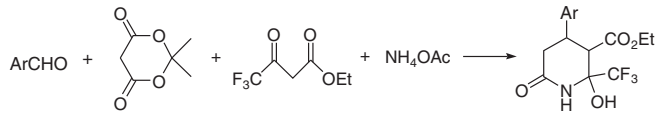
[a] All reactions were carried out at the reflux temperature with the NH_4OAc.
[b] Isolated yields.

ponent reaction with a variety of aromatic aldehydes, and the corresponding products **5** were generally obtained in moderate to good yields and the reaction results are summarized in Table 2.

On one hand, the aryldehydes bearing either electron-donating or electron-withdrawing group have slightly influenced the efficiency of the reaction. The substrates with electron-donating groups resulted in lower yield (Table 2, entries 12 and 13), while the substrates with electron-withdrawing groups (Table 2, entries 1–10) afforded the corresponding products in higher yield. On the other hand, the substituents located at *para*, *ortho*, or *meta* positions of aryldehydes have not shown much effect on the formation of products (Table 2, entries 7–9).

The structures of products 5 were fully confirmed by ^1H NMR, ^{19}F NMR, IR spectroscopy, mass spectrometry, and elemental analysis. For instance, the ^1H NMR spectrum of **5** exhibited a characteristic ABX system corresponding to the three protons of the heterocyclic ring, H4, H5a, and H5b. Usually H4 exhibited a dd peak in ABX system. However, in our cases, the H4 appeared as a ddd peak nearly at δ 3.6 ppm due to this characteristic dd peak was further coupled with H3 with J_{H-H} = 12.5 Hz. The coupling constant further revealed that the trans configuration of the two vicinal hydrogen atoms, H3 and H4, respectively. The chemical shift of CF_3 group in ^{19}F NMR was a singlet peak nearly at δ −84.4 ppm (s, 3F), which indicated that the CF_3 group was bonded to a quaternary carbon atom. Furthermore, the structure of product **5l** was confirmed by XRD analysis (Fig. 1).[13]

Table 2
Synthesis of **5**[11,12] under the optimal condition[a]



1 2 3 4 5

Entry	R	Product	Yield[b] (%)
1	Ph	**5a**	67
2	4-$O_2NC_6H_4$	**5b**	73
3	2-$O_2NC_6H_4$	**5c**	71
4	2,4-$(NO_2)_2C_6H_3$	**5d**	63
5	4-ClC_6H_4	**5e**	69
6	2-ClC_6H_4	**5f**	74
7	4-BrC_6H_4	**5g**	70
8	2-BrC_6H_4	**5h**	67
9	3-BrC_6H_4	**5i**	65
10	4-CNC_6H_4	**5j**	68
11	2-CNC_6H_4	**5k**	64
12	4-MeC_6H_4	**5l**	63
13	4-$MeOC_6H_4$	**5m**	61

[a] All reactions were carried out at the reflux temperature with the 1.2 equiv of NH_4OAc in the solvent of AcOH.
[b] Isolated yields.

From the results described above, a possible mechanism for the formation of compounds **5** was proposed in Scheme 1. It was conceivable that the initial event was the formation of **A** from aryldehyde **1** and Meldrum's acid **2** via Knoevenagel condensation, which underwent Michael addition with ethyl-4,4,4-trifluoro-1,3-dioxobutanoate **3** to produce the intermediate **B**. Intermediate **B** reacted with the ammonia, by losing one molecular acetone, to give ketene **C**, and then underwent intramolecular cyclization and decarboxylation to produce **5**. It was worth mentioning that the cyclic products must be formed by *N*-attack of intermediate **C**, other than by *O*-attack to afford the corresponding *O*-heterocyclic compounds.

Finally, we studied dehydration of compounds **5**. It should be indicated that the hemi-aminal moiety in **5** is stable, which resists dehydration under the present reaction conditions due to the strong electron-withdrawing effect of trifluoromethyl group on the six-membered ring.[14] However, it was found that water was smoothly eliminated from compounds **5** and the corresponding dehydrated 1,4-DHP derivatives were obtained in good yields in the presence of an excess of TsOH in refluxing $CHCl_3$ (Table 3). It was noted that when compared with the non-fluorinated substrates, most β-ketoester compounds studied resulted in the formation of the corresponding dehydrated products directly.[15]

In summary, we have shown that the one-pot four-component reaction provides a simple and convenient approach to ethyl 2-hydroxy-6-oxo-4-aryl-2-(trifluoromethyl)piperidine-3-carboxylate and ethyl 6-oxo-4-aryl-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate from readily available starting materials by dehydration of hemi-aminal moiety under mild conditions, which may be considered as useful CF_3-containing substrates for the synthesis of a wide variety of heterocyclic compounds with potential

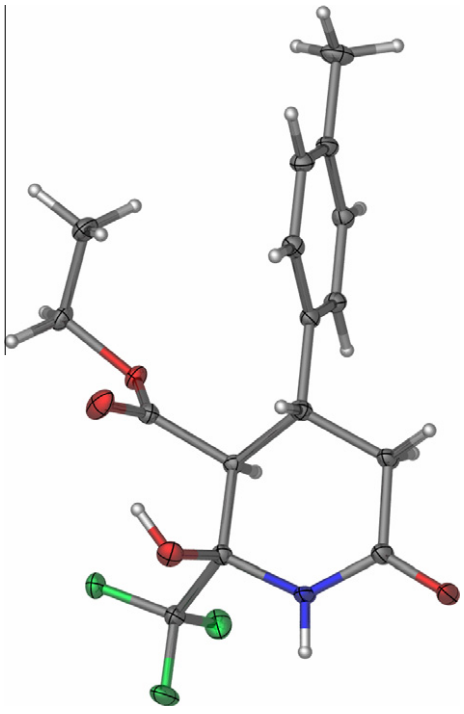
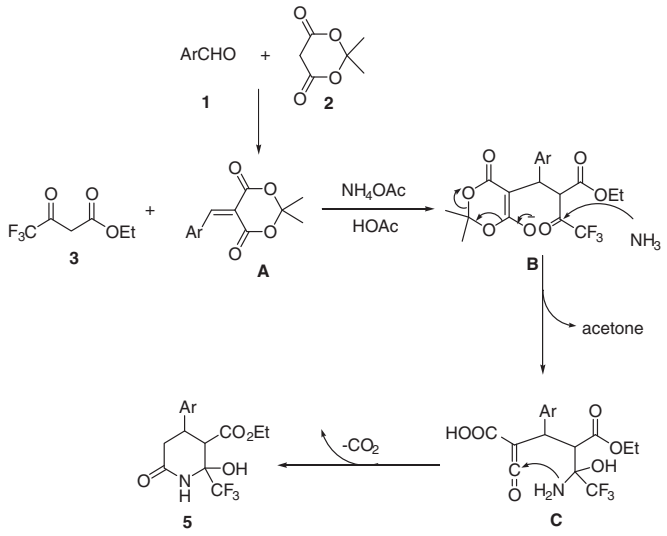
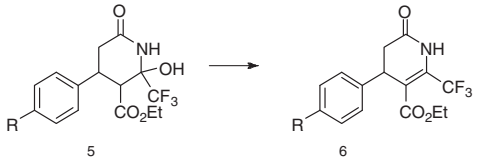


Figure 1. Crystal structure of compound **5l**.



Scheme 1. A possible mechanism for formation of **5**.

Table 3
Dehydration reaction of **5** to compound **6**[16,17]



Entry	R	Product	Time (h)	Yield[b] (%)
1	H	**6a**	5	81
2	4-O_2N	**6b**	3	89
3	2-Cl	**6c**	3	85

[a]Reaction conditions: **5** (0.5 mmol), *p*-TsOH (1.5 mmol, 3 equiv), solvent: $CHCl_3$ (8 ml), refluxing.
[b] Isolated yields.

biological activity. Further studies on the synthetic application of this method are now in progress.

Acknowledgments

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11. *Typical experimental procedure for synthesis of* **5a**: A mixture of ethyl-4,4,4-trifluoro-1,3-dioxobutanoate **3** (1.0 mmol, 184.0 mg), corresponding aromatic aldehyde **1a** (1.0 mmol, 106.0 mg), Meldrum's acid **2** (1.0 mmol, 144.0 mg), and ammonium acetate **4** (1.2 mmol, 94.0 mg) in acetic acid (8.0 mL) was heated at 118 °C for 6 h. After the evaporation of AcOH under reduced pressure, saturated aqueous $NaHCO_3$ solution and EtOAc were added. The two layers were separated and the aqueous layer was further extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel using petroleum ether/ethyl acetate, 10:1(v/v) as eluent to give the pure product **5a** 221.0 mg, 67% yield.
12. *Spectroscopic data for products* **5**: Compound **5a**: White solid; mp: 169–170 °C; IR (KBr) ν_{max}: 3448, 3212, 3110, 2983, 1734, 1691, 1496, 1377, 1201, 1028, 769, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.77 (t, J = 7.0 Hz, 3H), 2.71 (dd, J_1 = 18.0 Hz, J_2 = 12.5 Hz, 1H), 2.82 (dd, J_1 = 18.0 Hz, J_2 = 5.0 Hz, 1H), 3.18 (d, J = 12.5 Hz, 1H), 3.62 (ddd, $J_1 = J_2$ = 12.5 Hz, J_3 = 5.0 Hz, 1H), 3.81 (q, J = 7.0 Hz, 2H), 6.08 (s, 1H), 6.39 (s, 1H), 7.22–7.24 (m, 2H), 7.29–7.37 (m, 3H). ^{19}F NMR (470 MHz, $CDCl_3$): δ = −84.38 (s, 3F, CF_3); MS (ESI) m/z: 332 $[M+H]^+$; Anal. Calcd for $C_{15}H_{16}F_3NO_4$: C, 54.38; H, 4.87; N, 4.23. Found: C, 54.13; H, 4.87; N, 4.13.
13. CCDC-765386 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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16. *Typical experimental procedure for preparation of* **6a**: A solution of compounds **5** (0.5 mmol, 165.5 mg) and *p*-TsOH (1.5 mmol, 3.0 equiv, 285.0 mg) in $CHCl_3$ (8.0 mL) was refluxed (62 °C) for indicated hours until completion of the reaction (monitored by TLC). The solvent was removed by rotavapor and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate 8:1 (v/v) as eluent to afford the pure product **6a** 253.0 mg, 81% yield.
17. *Spectroscopic data for products* **6**: Compound **6a**: White solid; mp: 145–146 °C; IR (KBr) ν_{max}: 3224, 3135, 2993, 1720, 1689, 1598, 1484, 1368, 1217, 1013, 786, 772, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.0 Hz, 3H), 2.80 (dd, J_1 = 17.0 Hz, J_2 = 4.5 Hz, 1H), 2.96 (dd, J_1 = 17.0 Hz, J_2 = 7.5 Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 4.22–4.26 (m, 1H), 7.19–7.21 (m, 2H), 7.26–7.29 (m, 1H), 7.31–7.34 (m, 2H), 7.74 (s, 1H). ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.27 (s, 3F, CF_3); MS (ESI) m/z: 336 $[M+Na]^+$; Anal. Calcd for $C_{15}H_{14}F_3NO_3$: C, 57.51; H, 4.50; N, 4.47. Found: C, 57.72; H, 4.49; N, 4.36.