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Study on the reactions of ethyl 4,4,4-trifluoro-3-oxobutanoate with arylidenemalononitriles

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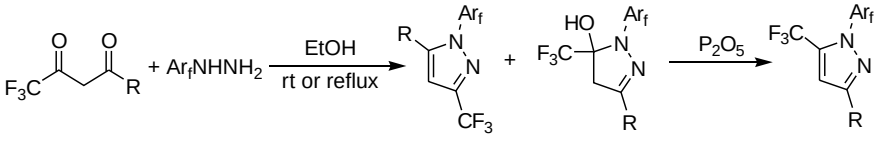
Abstract—In the presence of a catalytic amount of NEt_3, ethyl 4,4,4-trifluoro-3-oxobutanoate **1** reacted readily with arylidenemalononitriles **2** in ethanol at room temperature. It gave two products 2-trifluoromethyl-3,4-dihydro-2*H*-pyran derivatives **3** and 2-(trifluoromethyl)piperidine derivatives **4**, the ratio of **3** and **4** was depended on the substrates **2** and reaction solvents. Reflux of the ethanol solution of **4** with a catalytic amount of NEt_3 afforded 2-trifluoromethyl-1,4,5,6-tetrahydropyridine derivatives **5** in moderate to good yields. The structures of new compounds **3**, **4** and **5** were determined by spectral methods, microanalysis and X-ray diffraction analysis. A possible reaction mechanism for the formation of **3**, **4** and **5** was presented.

1. Introduction

It is well known that 1,3-dicarbonyl compounds reacted with the α,β-unsaturated carbonyl compounds or acrylonitrile derivatives through Michael addition reaction,[1] some adducts could further proceed intramolecular condensation to give cyclic compounds.[2] Furthermore, the selective incorporation of a fluorine atom or fluoroalkyl group into aromatic or heterocyclic system frequently confers biological or physical properties to such molecules.[3] The reactions of fluorinated-1,3-dicarbonyl compounds as fluorine-containing building blocks have been studied extensively.[4,5] For example, our group have reported the reaction of trifluoromethyl-1,3-diketone with per(poly)-fluorophenylhydrazines.[5]



However, to the best of our knowledge, the reactions of trifluoromethyl-containing 1,3-dicarbonyl compounds with arylidenemalononitriles have not been reported. In this paper, we wish to describe our recent study on the reactions of ethyl 4,4,4-trifluoro-3-oxobutanoate **1** with arylidenemalononitriles **2**.

2. Results and discussion

2.1. Reaction of 4,4,4-trifluoro-3-oxobutanoate 1 with arylidenemalononitriles 2

Firstly, the reaction of ethyl 4,4,4-trifluoro-3-oxobutanoate **1** with benzylidenemalononitrile **2a** was investigated as a model reaction. To a solution of **2a** (3 mmol) in ethanol (10 ml, AR, 99.7%) was added an equimolecular amount of ethyl 4,4,4-trifluoro-3-oxobutanoate **1** and a catalytic amount of NEt_3 (0.5 mmol). After stirring of the mixture for 6 h at room temperature, the TLC analysis showed that the starting materials disappeared and two new compounds formed. After removal of the solvent under reduced pressure, the residue was separated and purified by column chromatography on silica gel using petroleum ether–ethyl acetate (4/1, v/v) as the eluent, compound **3a** was first isolated as a white solid in 59% yield and the more polar product **4a** was obtained later in 32% yield (scheme 1).

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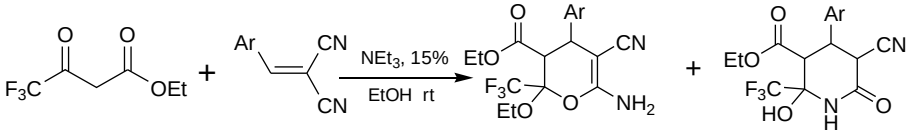


1 2 3 4

Ar=

2a	Ph	2f	*p*-FC_6H_4
2b	*p*-$MeOC_6H_4$	2g	*p*-$O_2NC_6H_4$
2c	*p*-HOC_6H_4	2h	Furan-2-yl
2d	*p*-MeC_6H_4	2i	α-Naphthyl
2e	*p*-ClC_6H_4		

Scheme 1.

The structures of **3a** and **4a** were determined by spectral methods and elemental analysis. The ^{1}H NMR spectrum of **3a** in $CDCl_3$ consisted of eight peaks; they were at δ 0.99 (t, J=7.2 Hz, 3H), 3.88 (q, J=7.2 Hz, 2H), 1.32 (t, J=7.2 Hz, 3H), 3.95 (q, J=7.2 Hz, 2H), 2.94 (d, J=11.7 Hz, 1H), 4.13 (d, J=11.7 Hz, 1H), 4.66 (br, s, 2H), and 7.25–7.34 (m, 5H), corresponding to two ethoxyl groups(CH_3CH_2O), two six-membered ring protons, $CONH_2$ and five aromatic protons. The coupling constant of the vicinal six-membered ring protons in **3a** was 11.7 Hz, which indicated a trans confirmation of the vicinal hydrogen atoms.[6] In its ^{19}F NMR spectrum, the chemical shift of CF_3 group of **3a** was a singlet peak at δ −77.33, which indicated it was bonded to the sp^3 saturated carbon atom. The MS spectrum of **3a** had a strong molecular ion peak at m/z 384 (M^+, 39.7%), and the base peak was at m/z 171 (M^+−EtO–CO_2Et–CF_3–CN, 100%). Meanwhile, the typical and strong absorptions at 3422 and 2203 cm^{-1} in IR spectrum confirmed the existence of NH_2 and CN groups in **3a**. The compound **4a** had eight peaks in its ^{1}H NMR spectrum, they were at δ 0.78 (t, J=7.2 Hz, 3H), 3.28 (dd, J=9, 3 Hz, 1H), 3.86 (q, J=7.2 Hz, 2H), 3.86 (d, J=9 Hz, 1H), 3.87 (d, J=3 Hz, 1H), 6.0 (br, s, 1H), 6.59 (br, s, 1H) and 7.26–7.44 (m, 5H). The ^{19}F NMR spectrum of **4a** was a singlet peak at δ −84.39. Compound **4a** had a weak molecular ion peak at m/z 356 (M^+, 3.68%) and the base peak was at m/z 239 (M^+−H_2O–CO_2Et–CN, 100%). The strong absorptions at 3257, 2273, 1735 and 1690 cm^{-1} in IR were corresponding to OH, NH, CN, CO_2Et and $CONH_2$ groups, respectively. Under the same reaction condition, other arylidenemalononitriles such as **2b–i** reacted with ethyl 4,4,4-trifluoro-3-oxobutanoate **1** to afford the similar reaction products. All the reaction results were summarized in Table 1.

Table 1. Reaction of $CF_3COCH_2CO_2Et$ **1** and arylidenemalononitriles **2**[a]

Entry	Ar in **2**	Time (h)	Yields (%)[b]			
			Product **3** and **4**			
1	**2a** C_6H_5	6	**3a**	59	**4a**	32
2	**2b** *p*-$MeOC_6H_4$	48	**3b**	16	**4b**	62
3	**2c** *p*-HOC_6H_4	72	**3c**	27	**4c**	35
4	**2d** *p*-MeC_6H_4	24	**3d**	20	**4d**	71
5	**2e** *p*-ClC_6H_4	6	**3e**	51	**4e**	32
6	**2f** *p*-FC_6H_4	6	**3f**	80	**4f**	Trace[c]
7	**2g** *p*-$NO_2C_6H_4$	6	**3g**	20	**4g**	60
8	**2h** Furan-2-yl-	50	**3h**	70	**4h**	Trace[c]
9	**2i** α-Naphthyl-	50	**3i**	80	**4i**	Trace[c]

[a] Reaction conditions: **1** (3 mmol), **2** (3 mmol), NEt_3 (0.5 mmol), ethanol (10 ml, AR 99.7%), room temperature.
[b] Isolated yields.
[c] Not isolated.

The steric structures of **3d** and **4d** were further determined by the single crystal X-ray crystallographic study. It was

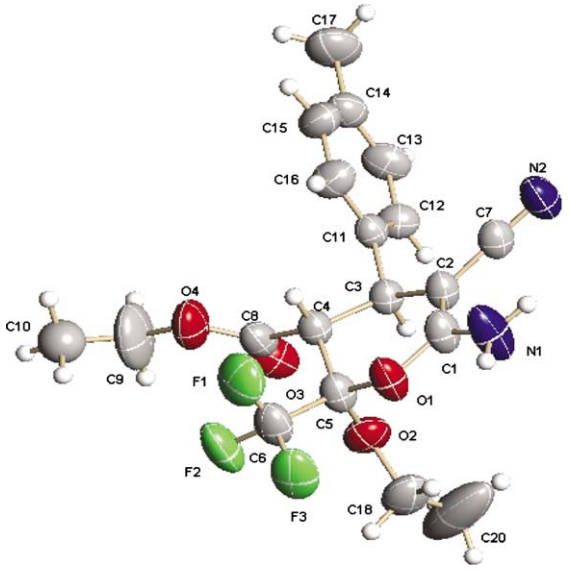


Figure 1. The ORTEP view of **3d**.

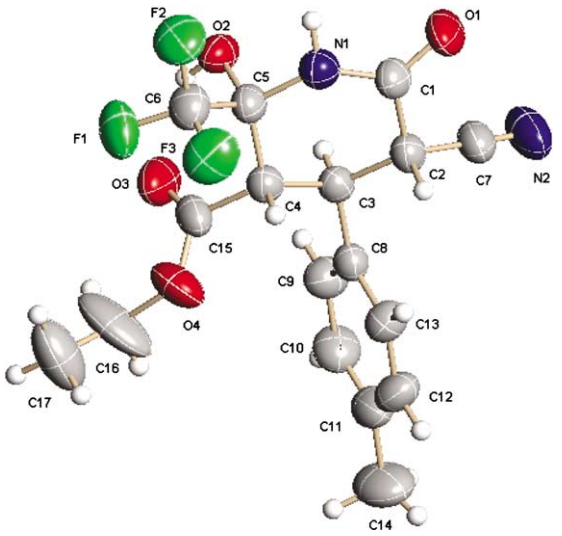
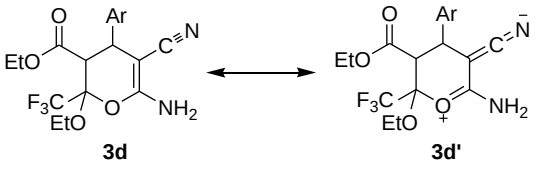


Figure 2. The ORTEP view of **4d**.

Table 2. Selected bond lengths (Å), bond angles (°) of **3d**, **4d** and **5d**

3d		4d		5d	
		Bond lengths			
O(1)–C(1)	1.361(4)	O(1)–C(1)	1.202.(2)	O(1)–C(1)	1.220(2)
O(1)–C(5)	1.422(3)	O(2)–C(5)	1.405(2)	O(2)–C(7)	1.207(3)
O(2)–C(5)	1.361(4)	N(1)–C(1)	1.350(2)	O(3)–C(8)	1.193(3)
N(1)–C(1)	1.324(4)	N(1)–C(5)	1.428(2)	N(1)–C(1)	1.356(3)
N(2)–C(7)	1.146(4)	N(2)–C(7)	1.131(2)	N(1)–C(5)	1.403(3)
C(1)–C(2)	1.347(4)	C(1)–C(2)	1.522(3)	C(1)–C(2)	1.513(3)
C(2)–C(3)	1.509(4)	C(2)–C(3)	1.528(3)	C(2)–C(3)	1.533(3)
C(2)–C(7)	1.404(4)	C(2)–C(7)	1.459(3)	C(2)–C(7)	1.541(3)
C(3)–C(4)	1.541(4)	C(3)–C(4)	1.538(3)	C(3)–C(4)	1.508(3)
C(4)–C(5)	1.535(4)	C(4)–C(5)	1.529(3)	C(4)–C(5)	1.335(3)
		Bond angles			
N(1)–C(1)–C(2)	127.2(3)	O(1)–C(1)–N(1)	122.45(18)	O(1)–C(1)–N(1)	122.0(2)
N(1)–C(1)–O(1)	110.2(3)	O(1)–C(1)–C(2)	121.44(17)	O(1)–C(1)–C(2)	122.5(2)
C(2)–C(1)–O(1)	122.6(3)	N(1)–C(1)–C(2)	116.00(17)	N(1)–C(1)–C(2)	115.4(2)
C(1)–C(2)–C(7)	117.9(3)	C(7)–C(2)–C(1)	108.40(16)	C(5)–C(4)–C(8)	125.9(2)
C(1)–C(2)–C(3)	122.0(3)	C(7)–C(2)–C(3)	111.64(16)	C(5)–C(4)–C(3)	120.1(2)
C(7)– C(2)–C(3)	120.2(3)	C(1)–C(2)–C(3)	114.88(15)	C(8)–C(4)–C(3)	113.93(19)
O(1)–C(5)–C(4)	110.8(3)	C(2)–C(3)–C(4)	107.78(15)	C(4)–C(5)–N(1)	121.3(2)
C(1)–O(1)–C(5)	118.7(2)	C(1)–N(1)–C(5)	125.40(16)	C(4)–C(5)–C(6)	126.3(2)
N(2)–C(7)–C(2)	178.9(3)	N(2)–C(7)–C(2)	179.0(3)	N(1)–C(5)–C(6)	112.42(19)

unambiguous to observe the trans relationship between the vicinal six-membered ring protons in compound **3d** and **4d** (Figs. 1 and 2). The selected bond lengths and bond angles of **3d** and **4d** were listed in Table 2. The bond lengths of O(1)–C(1), C(1)–C(2), C(2)–C(7), and N(2)–C(7) in **3d** was 1.361(4), 1.347(4), 1.404(4), and 1.146(4) Å, respectively, indicating that compounds **3** consisted of a conjugated system in O(1)–C(1)–C(2)–C(7)–N(2) as shown in Scheme 2.



Scheme 2.

2.2. Solvent effect on the reaction of 1 with 2

According to the structures of **3** and **4**, it was clear that the solvent EtOH and H_2O participated in the reaction. To investigate the solvent effects, this reaction was carried out in several different solvent systems; all the results were summarized in Table 3.

In absolute ethanol (entry 2, Table 3), the reaction of **1** with **2a** completed within 7 h and gave **3a** exclusively in 85% yield. Using methanol (AR, 99.5%) as the solvent, the similar product **3a′** was obtained in a yield of 80% accompanying with a small amount of **4a** (10%) (entry 9, Table 3). In aqueous ethanol ($C_2H_5OH/H_2O=2:1$), the reaction of **1** with **2a** completed within 3 h and gave **4a** as a major product (80%) accompanying with a 10% yield of **3a** (entry 3, Table 3). Meanwhile, when the reaction of **1** with **2a** was carried out in water, it required 48 h to finish the reaction, because of the poor solubility of the starting materials in water, and it afforded **4a** (90%) as the exclusive product. In unpurified solvent of CH_3CN (AR) or CH_2Cl_2 (AR), the product **4a** was isolated in 60 and 55%, respectively, without formation of **3a**. However, in absolute

Table 3. Reaction of $CF_3COCH_2CO_2Et$ **1** and **2a** in different solvents[a]

Entry	Solvent	Time (h)	Product yields (%)[b]	
			3a	**4a**
1	EtOH[c]	6	59	32
2	EtOH[d]	7	85	0
3	EtOH–H_2O(2/1)	3	10	80
4	H_2O	48	0	90
5	CH_3CN[d]	6	No reaction	No reaction
6	CH_3CN[c]	4	0	60
7	CH_2Cl_2[d]	6	No reaction	No reaction
8	CH_2Cl_2[c]	4	0	55
9	CH_3OH[c]	7	80(**3a′**)[e]	10
10	CH_3OH[d]	8	85	0

[a] Reaction conditions: **1** (3 mmol), **2** (3 mmol), NEt_3 (0.5 mmol), room temperature.
[b] Isolated yields.
[c] AR and without purification.
[d] Absolute solvent.
[e] Structure of **3a′**.

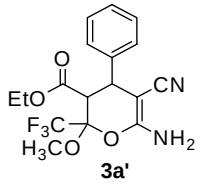
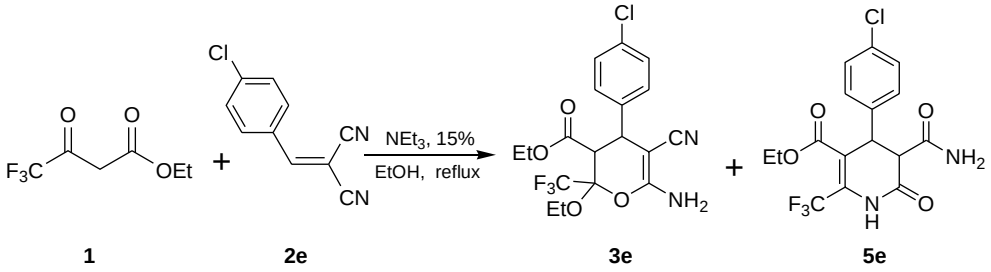


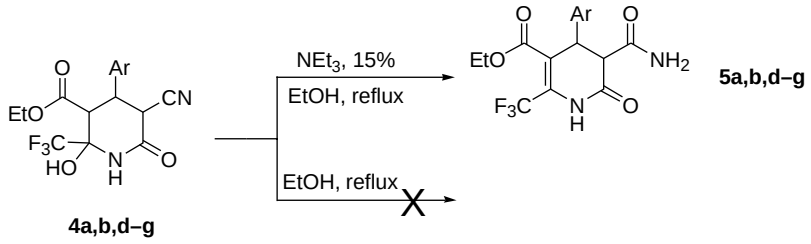
Table 4. Reaction of $CF_3COCH_2CO_2Et$ **1** with **2** in EtOH–H_2O (2/1, v/v)[a]

Entry	Ar in **2**	Time (h)	Yields (%)[b]	
			3	**4**
1	**2a** C_6H_5–	3	**3a** 10	**4a** 80
2	**2b** *p*-$MeOC_4H_5$–	5	**3b** 5	**4b** 78
3	**2d** *p*-MeC_4H_5–	4.5	**3d** 5	**4d** 63
4	**2e** *p*-ClC_4H_5–	3	**3e** 7	**4e** 69
5	**2f** *p*-FC_4H_5–	4	**3f** 8	**4f** 75
6	**2g** *p*-$NO_2C_4H_5$–	3	**3g** 5	**4g** 75
7	**2h** 2-Furanyl–	5	Trace	—[c]
8	**2i** α-Naphthyl–	6	Trace	—[c]

[a] Reaction conditions: **1** (3 mmol), **2** (3 mmol), NEt_3 (0.5 mmol), room temperature.
[b] Isolated yields.
[c] Decomposed on the workup.



Scheme 3.



Scheme 4.

CH_3CN or CH_2Cl_2, no reaction occurred (entries 5 and 7, Table 3).

When the reaction was carried out in aqueous ethanol ($C_2H_5OH/H_2O=2:1$), the reaction time was dramatically reduced comparing to that required in ethanol (Table 1). Under this condition, compounds **4a**–**b**,**d**–**g** were isolated as the major products. Unfortunately, the **4h** and **4i** were not isolated because the products decomposed and gave a complex mixture during the work-up. All the results were listed in Table 4.

It should be noted that the primary Michael addition products could not be obtained under the investigated reaction conditions, because they readily undergo the consecutive and irreversible reaction. This phenomenon should be attributed to the strong electronic withdrawing nature of CF_3, leading to the carbonyl group was much more easily to be attacked by the nucleophiles such as ethanol or water.

As shown in Table 1, it was found that reactions of arylidenemalononitriles **2b**–**d** (entries 2–4, Table 1), which have an electronic donating group on the para position of the phenyl group with ethyl 4,4,4-trifluoro-3-oxobutanoate **1** required longer reaction time comparing to other arylidenemalononitriles such as **2a** and **2e**,**f**,**g** (entries 5–7, Table 1), which bear an electronic withdrawing group on the para position of phenyl group. This result was similar to the kinetic studies on the Michael reaction of arylidenemalononitriles.[7] The reaction of **1** with **2f**, **2h** and **2i** (entries 6, 8, and 9, Table 1) afforded **3f**, **3h**, and **3i** in 80, 70, and 80% yields, respectively, but the corresponding **4f**, **4h**, and **4i** were not isolated. The electronic effect of substituted group (in Table 1) affecting the ratio of products **3** and **4** could not be explained at this stage.

2.3. Transformation of 4 to 5

The above results prompted us to further study the temperature effect on this reaction. A mixture of the reaction of **1** (3 mmol) and an equimolecular amount of 2-(4-chlorobenzylidene)malononitrile **2e** with a catalytic amount of Et_3N (0.5 mmol) was refluxed in ethanol (10 ml, AR 99.7%). After stirring for 6 h, TLC analysis showed the reaction was completed and a new compound formed in addition to the expected product **3e**, but no **4e** was detected by TLC. A new compound ethyl 5-carbamoyl-4-(4-chlorophenyl)-6-oxo-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate **5e** was isolated in 20% yield along with **3e** in 50% isolated yield (Scheme 3). It could be speculated that under the reflux condition, compound **4e** could be transformed into compound **5e**.

Thus, a series of transformation of **4** to **5** was investigated. As expected, reflux of the solution of **4a** (2 mmol) in 8 ml ethanol (AR 99.7%) with NEt_3 (0.3 mmol) afforded **5a** in 69% yield. In the absence of a catalytic amount of NEt_3, no reaction occurred. Under the same reaction conditions, a series of new compounds **5b**,**d**–**g** was also obtained (Scheme 4). The reaction results were listed in Table 5.

Table 5. Transformation of **4** to **5** in EtOH in the presence of NEt_3[a]

Entry	4	Time (h)	Product 5	Yield (%)[b]
1	**4a**	4	**5a**	69
2	**4b**	4	**5b**	53
3	**4d**	4	**5d**	66
4	**4e**	4	**5e**	80
5	**4f**	4	**5f**	65
6	**4g**	4	**5g**	50

[a] Reaction condition: **4** (2 mmol), NEt_3 (0.3 mmol), refluxed in ethanol (8 ml AR, 99.7%).
[b] Isolated yields.

All the new compounds **5** were fully characterized. For example, the ^1H NMR spectrum of **5a** in $CDCl_3$ showed eight peaks: they were at δ 1.19 (t, $J=7.2$ Hz, 3H), 3.61 (d, $J=3$ Hz, 1H), 4.17 (q, $J=7.2$ Hz, 2H), 4.91 (s, 1H), 5.49 (br, s, 1H), 6.19 (br, s, 1H), 7.2–7.37 (m, 5H,), 7.52 (br, s, 1H). It was noteworthy that the signals of two protons attached to nitrogen atom of amide group showed two

different chemical shifts at δ 5.49 and 6.19, respectively. In its ^{19}F NMR spectrum, the chemical shift of CF_3 group in **5a** was a singlet peak at δ −64.27, indicating that it was bonded to the unsaturated sp^2 carbon atom. The MS spectrum of **5a** showed its weak molecular ion peak at *m/z* 356 (M^+, 1.98%) and the base peak at 312 (M^+-CONH_2, 100%). Meanwhile, in the IR spectrum of **5a**, no absorption peaks in the range of 2000–2400 cm^{-1}, indicating that there was no cyano group in **5a**. Furthermore, the steric structure of **5d** was further confirmed by single crystal X-ray diffraction analysis (Fig. 3). The selected bond lengths and bond angles of **5d** were also listed in Table 2. The crystal data and structure refinement parameters of **3d**, **4d** and **5d** were listed in Table 6.

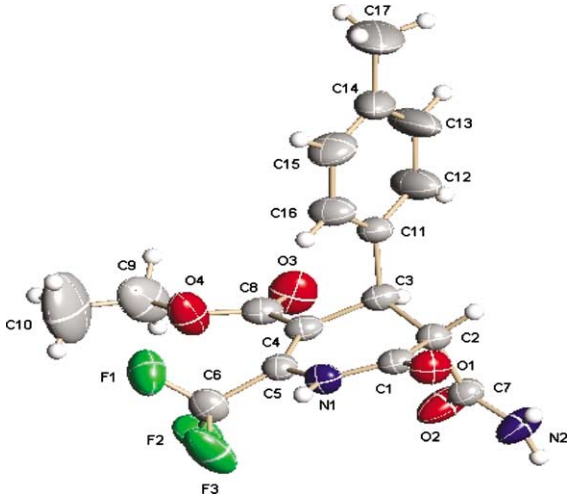
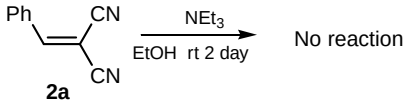


Figure 3. The ORTEP view of **5d**.

2.4. Mechanism

According to the structure of **3**, which has the ethoxyl group at the 2-position of the ring, while **4** had a lactam unit, it was clear that the ethanol and water participated in the reaction processes, respectively. To determine how the cyano group hydrolyzed during the reaction, a solution of **2a** in ethanol with a catalytic amount of NEt_3 was carried out. After stirring for 2 days at room temperature, TLC analysis showed that no reaction occurred and the starting material **2a** remained (Scheme 5), which indicated that the cyano group hydrolyzed after the formation of intermediate **A**. Moreover, to this reaction, a catalytic amount of Et_3N was necessary, otherwise the reaction did not occur even with prolonged reaction time.

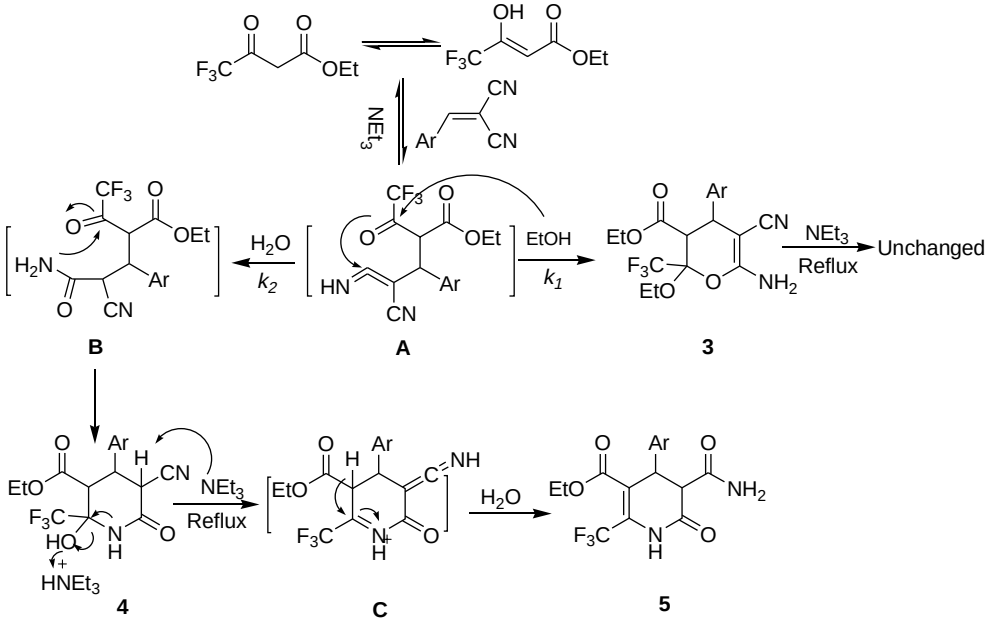


Scheme 5.

Based on these results above, a possible mechanism for the formation of **3**, **4** and **5** was illustrated in Scheme 6. Firstly, the Michael adduct intermediate **A** was formed by Michael addition reaction, and then the solvent ethanol attacked trifluoroacetyl group of the intermediate **A**, followed by the intramolecular attack to the enimine to form the six-membered ring product **3**. Alternatively, the intermediate **A** could be hydrolyzed by water to form **B**, then through intramolecular condensation yielding the cyclic product **4**. At refluxed temperature, **4** could be transformed into **5** by losing a water molecule, and followed by the hydrolysis of the cyano group. However, it should be noted that in the absence of a catalytic amount of NEt_3, **5** could not be

Table 6. The crystal data of **3d**, **4d** and **5d**

	3d	**4d**	**5d**
CCDC	28,4791	28,4792	28,4793
Empirial formula	$C_{19}H_{21}F_3N_2O_4$	$C_{17}H_{17}F_3N_2O_4$	$C_{17}H_{17}F_3N_2O_4$
*F*w	398.38	370.33	370.33
Temp (K)	293(2)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073	0.71073
Cryst syst	Triclinic	Monoclinic	Monoclinic
Space group	*P*−1	*P*2(1)/*c*	*C*2/*c*
Unit cell dimens			
a (Å)	8.3233(10)	8.3300(9)	20.197(2)
b (Å)	9.5566(12)	10.4557(11)	11.6217(14)
c (Å)	13.1239(16)	20.118(2)	15.4193(18)
α (°)	76.801(2)	90	90
β (°)	80.048(2)	91.672(2)	94.328(2)
γ (°)	88.410(2)	90	90
Volume ($Å^3$)	1001.0(2)	1751.4(3)	3609.0(7)
Z	2	4	8
Calcd density (Mg/m^3)	1.322	1.404	1.363
Absorp coeff (mm^{-1})	0.111	0.121	0.117
F(000)	416	768	1536
Cryst size (mm)	0.516×0.427×0.368	0.506×0.427×0.218	0.505×0.332×0.070
θ Range for data collection (°)	1.62–26.00	2.03–27.00	2.02–27.00
Goodness-of-fit on F^2	1.055	1.002	0.839
Final *R* indices	*R*1=0.0793	*R*1=0.0519	*R*1=0.0523
[$I>2\sigma$ (*I*)]	*wR*2=0.2410	*wR*2=0.1396	*wR*2=0.1151
R indices (all data)	*R*1=0.0982	*R*1=0.0796	*R*1=0.1083
	*wR*2=0.2601	*wR*2=0.1532	*wR*2=0.1321
Largest diff peak and hole (e $Å^{-3}$)	0.748 and −0.451	0.285 and −0.250	0.222 and −0.182



Scheme 6.

obtained under the refluxed condition. This should be partly attributed to the active proton of the vicinal cyano group in compound **4**, which could assist the hydrolysis by the intermediate **C** as depicted in scheme 6. In contrast, the cyano group in compound **3** was much more stable than that in compound **4**, it resisted to hydrolysis and remained unchanged under the refluxed condition, this was partly because there existed a conjugated system in compound **3** as mentioned above, partly because there was no active proton at the vicinal position of cyano group in compound **3**. Furthermore, in the aqueous EtOH, the reaction could complete within a shorter time (Table 4), which manifested that the rate constant k_2 for the formation of **4** from intermediate **A** should be larger than the rate constant k_1 for the formation of **3**.

3. Conclusions

In summary, the reaction of $CF_3COCH_2CO_2Et$ **1** with arylidenemalononitriles **2** under NEt_3 catalysis was studied in detail. Different reaction conditions gave different results. In ethanol (AR, 99.7%) the reaction gave two products 2-trifluoromethyl-3,4-dihydro-2*H*-pyrans derivatives **3** and 2-(trifluoromethyl)piperidine derivatives **4**. When it was carried out in aqueous ethanol ($C_2H_5OH/H_2O=2:1$), **4** became the major product. In absolute ethanol, **3** was the exclusive product. In CH_3CN or CH_2Cl_2 (AR) the reaction only afforded **4**, whereas in absolute CH_3CN or CH_2Cl_2, no reaction occurred. Reflux of **4** with the catalysis of NEt_3 in ethanol afforded 2-trifluoromethyl-1,4,5,6-tetrahydropyridines derivatives **5**. Further chemical transformation of above compounds now is under investigation.

4. Experimental

Melting points were measured in Melt-Temp apparatus and were uncorrected. ^1H and ^{19}F NMR spectra were recorded in $CDCl_3$ (unless mentioned in text) Bruker AM-300 instruments with Me_4Si and $CFCl_3$ (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Lower resolution mass spectrum were obtained on Finnigan GC–MS 4021 using the electron impact ionization technique (70 ev). High-resolution mass spectra (HRMS) were obtained on Ionspec 4.7 T FTMS using MALDI/DHB. Elemental analyses were performed by this Institute. X-ray diffraction crystal structure analysis was obtained on Bruker P4 instrument.

4.1. General procedure for the reaction of ethyl 4,4,4-trifluoro-3-oxobutanoate 1 with arylidenemalononitriles 2a in ethanol

To a 50 ml round bottle flask containing **2a** (462 mg, 3 mmol) was added 10 ml ethanol, and then ethyl 4,4,4-trifluoro-3-oxobutanoate **1** (552 mg, 3 mmol) and NEt_3 (0.5 mmol) were added under stirring at room temperature. The mixture was continuously stirred at room temperature. After 6 h, the TLC analysis showed the reaction was finished. The solvent was evaporated and the residue was chromatographed on a silica column using petroleum ether–ethyl acetate (4/1, v/v) as eluent to afford the **3a** (512 mg, 59%) and **4a** (299 mg, 32%), respectively. The two solid products were recrystallized from petroleum ether/ethyl acetate to give the pure compounds.

4.1.1. Ethyl 6-amino-5-cyano-2-ethoxy-4-phenyl-2-trifluoromethyl-3,4-dihydro-2*H*-pyran-3-carboxylate 3a. White solid; mp 154–156 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, $J=7.2$ Hz, 3H), 1.32 (t, $J=7.2$ Hz, 3H), 2.94 (d, $J=11.7$ Hz, 1H), 3.88 (q, $J=7.2$ Hz, 2H), 3.95 (q, $J=7.2$ Hz, 2H), 4.13 (d, $J=11.7$ Hz, 1H), 4.66 (br, s, 2H), 7.25–7.36 (m, 5H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −77.33 (s, 3F); IR (KBr) υ_{max} 3422, 3330, 3285, 2992, 2203, 1735, 1670, 1615 cm^{-1}; MS (70 eV, EI) *m*/*z* (%) 385 (MH^+, 8.02), 384 (M^+, 39.70), 355 (M^+-Et, 5.74), 338

(M^+ −EtOH, 8.24), 309 (M^+ −Et–EtOH, 6.88), 265 (M^+ −CO_2Et–EtOH, 65.83), 292 (M^+ −2EtOH, 10.33), 223 (M^+ −2EtOH–CF_3, 4.95), 171 (M^+ −EtO–CO_2Et–CF_3–CN, 100), 69 (CF_3^+, 14.65). Anal. Calcd for $C_{18}H_{19}F_3N_2O_4$: C, 56.25%; H, 4.95%; N, 7.29%. Found: C, 56.14%; H, 5.16%; N, 7.23%.

4.1.2. Ethyl 5-cyano-2-hydroxy-6-oxo-4-phenyl-2-(trifluoromethyl)piperidine-3-carboxylate 4a. White solid; mp 163–166 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J=7.2 Hz, 3H), 3.28 (dd, J=9, 3 Hz, 1H), 3.86 (q, J=7.2 Hz, 2H), 3.86 (d, J=9 Hz, 1H), 3.87 (d, J=3 Hz, 1H), 6.0 (br, s, 1H), 6.59 (br, s, 1H), 7.26–7.44 (m, 5H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −84.39 (s, 3F); IR (KBr) υ_{max} 3257, 3138, 2989, 2273, 1735, 1690 cm^{-1}; MS (70 eV, EI) *m/z* (%): 356 (M^+, 3.68), 265 (M^+ −H_2O–CO_2Et, 67.70), 239 (M^+ −H_2O–CO_2Et–CN, 100), 69 (CF_3^+, 11.70). Anal. Calcd for $C_{16}H_{15}F_3N_2O_4$: C, 53.93%; H, 4.21%; N, 7.87%. Found: C, 53.98%; H, 4.22%; N, 7.84%.

4.1.3. Ethyl 6-amino-5-cyano-2-methoxy-4-phenyl-2-trifluoromethyl-3,4-dihydro-2*H*-pyran-3-carboxylate 3a′ (reaction in methanol). White solid; mp 153–155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, J=7.2 Hz, 3H), 2.95 (d, J=11.4 Hz, 1H), 3.60 (s, 3H), 3.95 (q, J=7.2 Hz, 2H), 4.10 (d, J=11.4 Hz, 1H), 4.72 (br, s, 2H), 7.23–7.35 (m, 5H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −76.99 (s, 3F); IR (KBr) υ_{max} 3439, 3336, 2963, 2199, 1732, 1673, 1605, 1465 cm^{-1}; MS (70 eV, EI) *m/z* (%) 370 (M^+, 28.40), 338 (M^+ −CH_3OH, 2.85), 265 (M^+ −CO_2Et–CH_3OH, 78.11), 171 (M^+ −CH_3O–CO_2Et–CF_3–CN, 100), 69 (CF_3^+, 6.52). Anal. Calcd for $C_{17}H_{17}F_3N_2O_4$: C, 55.14%; H, 4.59%; N, 7.57%. Found: C, 54.90%; H, 4.64%; N, 7.52%.

4.1.4. Ethyl 6-amino-5-cyano-2-ethoxy-4-(4-methoxyphenyl)-2-trifluoromethyl-3,4-dihydro-2*H*-pyran-3-carboxylate 3b. White solid; mp 168–169 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.01 (t, J=7.2 Hz, 3H), 1.29 (t, J=7.2 Hz, 3H), 2.89 (d, J=11.7 Hz, 1H), 3.77 (s, 3H), 3.86 (q, J=7.2 Hz, 2H), 3.95 (q, J=7.2 Hz, 2H), 4.07 (d, J=11.7 Hz, 1H), 4.68 (br, s, 2H), 6.84 (d, J_{AB}=8.7 Hz, 2H), 7.16 (d, J_{AB}=8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −77.37 (s, 3F); IR (KBr) υ_{max} 3438, 3348, 3186, 2992, 2193, 1736, 1647, 1601, 1517 cm^{-1}; MS (70 eV, EI) *m/z* (%) 415 (MH^+, 3.03), 414 (M^+, 13.24); 385 (M^+ −Et, 1.42), 368 (M^+ −EtOH, 2.82), 295 (M^+ −CO_2Et–EtOH, 31.00), 202 (M^+ +1–EtO–CO_2Et–CF_3–CN, 100), 69 (CF_3^+, 2.81). Anal. Calcd for $C_{19}H_{21}F_3N_2O_5$: C, 55.07%; H, 5.07%; N, 6.76%. Found: C, 55.07%; H, 5.20%; N, 6.72%.

4.1.5. Ethyl 5-cyano-2-hydroxy-4-(4-methoxyphenyl)-6-oxo-2-(trifluoromethyl)-piperidine-3-carboxylate 4b. White solid; mp 162–164 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J=7.2 Hz, 3H), 3.24 (dd, J=7.2, 4.8 Hz, 1H), 3.82 (s, 3H), 3.80 (J=4.8 Hz, 1H), 3.81 (J=7.2 Hz, 1H), 3.90 (q, J=7.2 Hz, 2H) 5.98 (br, s, 1H), 6.71 (br, s, 1H), 6.92 (d, J_{AB}=8.4 Hz, 2H), 7.20 (d, J_{AB}=8.4 Hz, 2H); ^{19}F NMR δ ($CDCl_3$, 282 MHz) −84.36 (s, 3F); IR (KBr) υ_{max} 3554, 3459, 3325, 3071, 2261, 1733, 1689, 1613, 1518 cm^{-1}; MS (70 eV, EI) *m/z* (%): 386 (M^+, 17.58), 359 (M^+ −HCN, 8.93), 295 (M^+ −H_2O–CO_2Et, 100), 269 (M^+ −H_2O–CO_2Et–CN, 48.92), 69 (CF_3^+, 5.75); HRMS for $C_{17}H_{17}F_3N_2O_5Na^{+1}$ Calcd: 409.0982. Found: 409.0999.

4.1.6. Ethyl 6-amino-5-cyano-2-ethoxy-4-(4-hydroxyphenyl)-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-3-carboxylate 3c. White solid; mp 188–191 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (t, J=7.2 Hz, 3H), 1.30 (t, J=7.2 Hz, 3H), 2.92 (d, J=11.7 Hz, 1H), 3.88 (q, J=6.9 Hz, 2H), 3.97 (q, J=7.2 Hz, 2H), 4.07 (d, J=11.7 Hz, 1H), 4.66 (br, s, 2H), 5.88 (s, 1H), 6.72 (d, J_{AB}=8.4 Hz, 2H), 7.09 (d, J_{AB}=8.7 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.36 (s, 3F); IR (KBr) υ_{max} 3421, 3333, 3290, 2203, 1730, 1665, 1600 cm^{-1}; MS (*m/z*, %): 401 (MH^+, 3.64), 400 (M^+, 16.08), 371 (M^+ −Et, 2.14), 354 (M^+ −EtOH, 4.50), 281 (M^+ − CO_2Et–EtOH, 46.23), 188 (M^+ +1−EtO–CO_2Et–CF_3–CN, 100), 69 (CF_3^+, 5.91). Anal. Calcd for $C_{18}H_{19}F_3N_2O_5$: C, 54.00%; H, 4.75%; N, 7.00%. Found: C, 53.96%; H, 4.85%; N, 7.06%.

4.1.7. Ethyl 5-cyano-2-hydroxy-4-(4-hydroxyphenyl)-6-oxo-2-(trifluoromethyl)-piperidine-3-carboxylate 4c. White solid; mp 215–217 °C; ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 0.87 (t, J=7.2 Hz, 3H), 3.64 (d, J=12.3 Hz, 1H), 3.83–3.95 (m, 3H), 4.48 (d, J=12.3 Hz, 1H), 6.56 (br, s, 1H), 6.83–6.88 (m, 2H), 7.32–7.36 (m, 2H), 8.42 (br, s, 1H), 8.56 (br, s, 1H); ^{19}F NMR (CD_3COCD_3, 282 MHz) δ −83.63 (s, 3F); IR (KBr) υ_{max} 3563, 3531, 3481, 3298, 2976, 2258, 1732, 1703, 1615, 1599, 1520 cm^{-1}; MS (70 eV, EI) *m/z* (%): 372 (M^+, 9.54), 327 (M^+ −EtO, 7.53), 281 (M^+ −H_2O–CO_2Et, 100), 255 (M^+ −H_2O–CO_2Et–CN, 45.43), 69 (CF_3^+, 20.31). Anal. Calcd for $C_{16}H_{15}F_3N_2O_5$: C, 51.61%; H, 4.03%; N, 7.53%, Found: C, 51.67%; H, 4.02%; N, 7.52%.

4.1.8. Ethyl 6-amino-5-cyano-2-ethoxy-4-*p*-tolyl-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-3-carboxylate 3d. White solid; mp 179–181 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02 (t, J=7.2 Hz, 3H), 1.30 (t, J=7.2 Hz, 3H), 2.32 (s, 3H), 2.92 (d, J=11.7 Hz, 1H), 3.87 (q, J=7.2 Hz, 2H), 3.96 (q, J=7.2 Hz, 2H), 4.09 (d, J=11.7 Hz, 1H), 4.64 (br, s, 2H), 7.13 (m, 4H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −77.34 (s, 3F); IR (KBr) υ_{max} 3449, 3273, 3222, 3182, 2987, 2197, 1740, 1647, 1599, 1518 cm^{-1}; MS (70 eV, EI) *m/z* (%) 399 (MH^+, 4.86), 398 (M^+, 21.07), 369 (M^+ −Et, 2.55), 352 (M^+ −EtOH, 4.15), 323 (M^+ −Et–EtOH, 3.77), 306 (M^+ −2EtOH, 8.88), 279 (M^+ −CO_2Et–EtOH, 60.60), 185 (M^+ −EtO–CO_2Et–CF_3–CN, 100), 69 (CF_3^+, 6.63). Anal. Calcd for $C_{19}H_{21}F_3N_2O_4$: C, 57.29%; H, 5.28%; N, 7.04%. Found: C, 57.46%; H, 5.53%, N, 7.01%.

4.1.9. Ethyl 5-cyano-2-hydroxy-6-oxo-4-*p*-tolyl-2-(trifluoromethyl)-piperidine-3-carboxylate 4d. White solid; mp 147–149 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.8 (t, J=7.2 Hz, 3H), 2.35 (s, 3H), 3.27 (d, J=10.8 Hz, 1H), 3.85 (q, J=7.2 Hz, 2H), 3.78–3.91 (m, 2H), 6.03 (br, s, 1H), 6.87 (br, s, 1H), 7.15–7.26 (m, 4H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −84.30 (s, 3F); IR (KBr) υ_{max} 3273, 3187, 2900, 2257, 1728, 1516, 1477 cm^{-1}; MS (70 eV, EI) *m/z* (%): 370 (M^+, 2.30), 279 (M^+ −H_2O–CO_2Et, 41.34), 253 (M^+ −H_2O–CO_2Et–CN, 50.00), 69 (CF_3^+, 34.60). Anal. Calcd for $C_{17}H_{17}F_3N_2O_4$: C, 55.14%; H, 4.59%; N, 7.57%. Found: C, 55.24%; H, 4.81%; N, 7.60%.

4.1.10. Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-ethoxy-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-3-carboxylate 3e. White solid; mp 138–140 °C; ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 1.03 (t, J=7.2 Hz, 3H), 1.30 (t, J=7.2 Hz, 3H), 2.88 (d, J=11.7 Hz, 1H), 4.12 (d, J=11.7 Hz, 1H), 3.87 (q, J=7.2 Hz, 2H), 3.96 (q, J=7.2 Hz, 2H), 4.66 (br, s, 2H), 7.18–7.32 (m, 4H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −77.20 ppm; IR (KBr) υ_{max} 3421, 3329, 2988, 2189, 1749, 1655, 1598, 1492 cm^{-1}; MS (70 eV, EI) *m/z* (%) 420/418 (M^+, 8.97/25.14), 374/372 (M^+ −EtOH, 5.20/10.31), 345/343 (M^+ −Et–EtOH, 3.44/5.93), 328/326 (M^+ −2EtOH, 6.53/7.30), 301/299 (M^+ −CO_2Et–EtOH, 34.92/76.23), 207/205 (M^+ −EtO–CO_2Et–CF_3–CN, 100/84.31), 69 (CF_3^+, 14.84); HRMS for $C_{18}H_{18}ClF_3N_2O_4Na^{+1}$ Calcd: 441.0799. Found: 441.0819.

4.1.11. Ethyl 4-(4-chlorophenyl)-5-cyano-2-hydroxy-6-oxo-2-(trifluoromethyl)-piperidine-3-carboxylate 4e. White solid; mp 146–148 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J=7.2 Hz, 3H), 3.25 (d, J=10.8 Hz, 1H), 3.82–3.86 (m, 2H), 3.90 (q, J=7.2 Hz, 2H), 5.91 (br, s, 1H), 6.52 (br, s, 1H), 7.23–7.43 (m, 4H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −84.36 (s, 3F); IR (KBr) υ_{max} 3268 (br), 3182, 2900, 2258, 1708, 1590, 1492 cm^{-1}; MS (70 eV, EI) *m/z* (%): 392/390 (M^+, 2.15/6.20), 301/299 (M^+ −H_2O–CO_2Et, 30.72/80.20), 275/273 (M^+ −H_2O–CO_2Et–CN, 40.17/100), 69 (CF_3^+, 11.13). Anal. Calcd for $C_{16}H_{14}ClF_3N_2O_4$: C, 49.17%; H, 3.59%; N, 7.17%. Found: C, 49.15%; H, 3.59%; N, 7.27%.

4.1.12. Ethyl 6-amino-5-cyano-2-ethoxy-4-(4-fluorophenyl)-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-3-carboxylate 3f. White solid; mp 123–128 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.01 (t, J=7.2 Hz, 3H), 1.29 (t, J=6.9 Hz, 3H), 2.87 (d, J=12.0 Hz, 1H), 3.89 (q, J=6.9 Hz, 2H), 3.96 (q, J=7.2 Hz, 2H), 4.12 (d, J=12.0 Hz, 1H), 4.78 (br, s, 2H), 6.98–7.04 (m, 2H, Ar–H), 7.21–7.26 (m, 2H, Ar–H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −77.29 (s, 3F), −114.4 (m, 1F); IR (KBr) υ_{max} 3489, 3332, 2195, 1748, 1738, 4660, 1608, 1596, 1346 cm^{-1}; MS (70 eV, EI) *m/z* (%) 403 (MH^+, 6.92), 402 (M^+, 24.19), 373 (M^+ −Et, 4.59), 356 (M^+ −EtOH, 10.15), 283 (M^+ − CO_2Et–EtOH, 76.42), 189 (M^+ −EtO–CO_2Et–CF_3–CN, 100), 69 (CF_3^+, 8.78). Anal. Calcd for $C_{18}H_{18}F_4N_2O_4$: C, 53.73%; H, 4.48%; N, 6.97%. Found: C, 53.75%; H, 4.56%; N, 6.93%.

4.1.13. Ethyl 5-cyano-4-(4-fluorophenyl)-2-hydroxy-6-oxo-2-(trifluoromethyl)-piperidine-3-carboxylate 4f. White solid; mp 147–150 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J=7.2 Hz, 3H), 3.25 (d, J=10.8 Hz, 1H), 3.78–3.95 (m, 4H), 5.92 (br, s, 1H), 6.50 (br, s, 1H), 7.11–7.32 (m, 4H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −84.56 (s, 3F), −111.4 (m, 1F); IR (KBr) υ_{max} 3309, 3292, 3243, 1734, 1689, 1516, 1379 cm^{-1}; MS (70 eV, EI) *m/z* (%): 374 (M^+, 3.15), 283 (M^+ −H_2O–CO_2Et, 77.32), 257 (M^+ −H_2O–CO_2Et–CN, 100), 69 (CF_3^+, 18.23). Anal. Calcd for $C_{16}H_{14}F_4N_2O_4$: C, 51.34%; H, 3.74%; N, 7.49%. Found: C, 50.95%; H, 3.93%; N, 7.47%.

4.1.14. Ethyl 6-amino-5-cyano-2-ethoxy-4-(4-nitrophenyl)-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-3-carboxylate 3g. White solid; mp 72–74 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (t, J=7.2 Hz, 3H), 1.32 (t, J=7.2 Hz, 3H), 2.92 (d, J=11.7 Hz), 3.89 (q, J=7.2 Hz, 2H), 3.96 (q, J=7.2 Hz, 2H), 4.40 (d, J=11.7 Hz, 1H), 4.74 (br, s, 2H), 7.46–7.51 (m, 2H), 8.20–8.23 (m, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −77.17 (s, 3F), IR (KBr) υ_{max} 3453, 3329, 2987, 2199, 1741, 1654, 1524, 1350 cm^{-1}; MS (70 eV, EI) *m/z* (%) 431 (M^++2, 4.50), 400 (M^+ −Et, 3.11), 383 (M^+ −EtOH, 6.59), 310 (M^+ −CO_2Et–EtOH, 29.34), 69 (CF_3^+, 16.49). Anal. Calcd for $C_{18}H_{18}F_3N_3O_6$: C, 50.35%; H, 4.20%; N, 9.79%. Found: C, 50.46%; H, 4.14%; N, 9.85%.

4.1.15. Ethyl 5-cyano-2-hydroxy-4-(4-nitrophenyl)-6-oxo-2-(trifluoromethyl)-piperidine-3-carboxylate 4g. White solid; mp 174–175 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J=7.2 Hz, 3H), 3.36 (d, J=12 Hz, 1H), 3.84–4.07 (m, 4H), 5.78 (br, s, 1H), 6.62 (br, s, 1H), 7.53 (d, J_{AB}=8.4 Hz, 2H), 8.31 (d, J_{AB}=8.4 Hz, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −84.41 (s, 3F); IR (KBr) υ_{max} 3545, 3484, 3291, 2270, 1729, 1702, 1640, 1609, 1523 cm^{-1}; MS (70 eV, EI) *m/z* (%): 310 (M^+ −H_2O–CO_2Et, 25.47), 284 (M^+ −H_2O–CO_2Et–CN, 100), 69 (CF_3^+, 6.89); HRMS for $C_{16}H_{14}F_3N_3O_6Na^{+1}$ Calcd: 424.0727. Found: 424.0743.

4.1.16. Ethyl 6-amino-5-cyano-2-ethoxy-4-(furan-2-yl)-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-3-carboxylate 3h. White solid; mp 178–179 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.11 (t, J=7.2 Hz, 3H), 1.28 (t, J=7.2 Hz, 3H), 3.18 (d, J=11.7 Hz, 1H), 3.85 (q, J=7.2 Hz, 2H), 4.06 (q, J=7.2 Hz, 2H), 4.30 (d, J=11.7 Hz, 1H), 4.59 (br, s, 2H), 6.28–6.31 (m, 1H), 7.24–7.27 (m, 1H), 7.35–7.37 (m, 1H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −77.32 (s, 3F); IR (KBr) υ_{max} 3415, 3333, 2198, 1736, 1663, 1616, 1376 cm^{-1}; MS (70 eV, EI) *m/z* (%) 374 (M^+, 100), 345 (M^+ −Et, 12.28), 328 (M^+ −EtOH, 67.46), 255 (M^+ −CO_2Et–EtOH, 95.93), 69 (CF_3^+, 22.10). Anal. Calcd for $C_{16}H_{17}F_3N_2O_5$: C, 51.34%; H, 4.55%; N, 7.49%. Found: C, 51.53%; H, 4.86%; N, 7.48%.

4.1.17. Ethyl 6-amino-5-cyano-2-ethoxy-4-(naphthalen-1-yl)-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-3-carboxylate 3i. White solid; mp 198–199 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73 (t, J=7.2 Hz, 3H), 1.39 (t, J=7.1 Hz, 3H), 3.20 (d, J=11.7 Hz, 1H), 3.69 (q, J=7.2 Hz, 2H), 3.95 (q, J=7.2 Hz, 2H), 4.64 (br, s, 2H), 5.16 (d, J=11.7 Hz), 7.33–7.58 (m, 4H), 7.77–8.00 (m, 2H), 8.26 (d, J=8.4 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −76.9 (s, 3F); IR (KBr) υ_{max} 3419, 3321, 3194, 2203, 1741, 1655, 1606, 1375 cm^{-1}; MS (70 eV, EI) *m/z* (%): 435 (M^++1, 74.52), 434 (M^+, 3.16), 405 (M^+ −Et, 4.56), 315 (M^+ − CO_2Et–EtOH, 76.83), 233 (M^+ −EtO–CO_2Et–CF_3–CN, 29.41), 69 (CF_3^+, 21.88). Anal. Calcd for $C_{22}H_{21}F_3N_2O_4$: C, 60.83%; H, 4.84%; N, 6.45%. Found: C, 61.05%; H, 4.85%; N, 6.27%.

4.2. General procedures for the transformation of 4 to 5

To the solution of **4a** (2 mmol in 8 ml ethanol) was added NEt_3 (0.3 mmol) under stirring, and then the mixture was heated to reflux. After 6 h, the TLC analysis showed the reaction was completed. After removal of the solvent under reduced pressure the residue was purified by column chromatography on silica gel using petroleum and ethyl acetate (6/4, v/v) as eluent. Recrystallization from petroleum and ethyl acetate gave the pure **5a**.

4.2.1. Ethyl 5-carbamoyl-6-oxo-4-phenyl-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate 5a. White solid; mp 160–163 °C; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J=7.2 Hz, 3H), 3.61 (d, J=3 Hz, 1H), 4.17 (q, J=7.2 Hz,

2H), 4.91 (s, 1H), 5.49 (br, s, 1H), 6.19 (br, s, 1H), 7.2–7.37 (m, 5H), 7.52 (br, s, 1H); ^{19}F NMR δ −64.27 (s, 3F); IR (KBr) ν_{max} 3444, 3232, 3169, 1701, 1680, 1305, 1159 cm^{-1}; MS (70 eV, EI) *m/z* (%): 356 (M^+, 1.98), 312 (M^+-CONH_2, 100), 69 (CF_3, 7.23), 44 ($CONH_2^+$, 53.82). Anal. Calcd for $C_{16}H_{15}F_3N_2O_4$: C, 53.93%; H, 4.21%; N, 7.87%. Found: C, 53.87%; H, 4.38%; N, 7.85%.

4.2.2. Ethyl 5-carbamoyl-4-(4-methoxyphenyl)-6-oxo-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate 5b. White solid; mp 151–153 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J=7.2 Hz, 3H), 3.58 (d, J=3.6 Hz, 1H), 3.78 (s, 3H) 4.16 (q, J=7.2 Hz, 3H), 4.83 (s, 1H), 5.51 (br, s, 1H), 6.18 (br, s, 1H), 6.85 (d, J_{AB}=8.4 Hz, 2H), 7.27 (d, J_{AB}=8.4 Hz, 2H), 7.54 (br, s, 1H); ^{19}F NMR δ −62.95 (s, 3F); IR (KBr) ν_{max} 3403, 3170, 2943, 1682, 1611, 1512, 1307, 1180 cm^{-1}; MS (70 eV, EI) *m/z* (%): 386 (M^+, 2.21), 342 (M^+-CONH_2, 100), 69 (CF_3, 7.46), 44 ($CONH_2^+$, 44.48). Anal. Calcd for $C_{17}H_{17}F_3N_2O_5$: C, 52.85%; H, 4.40%; N, 7.25%. Found: C, 52.95%; H, 4.49%; N, 7.34%.

4.2.3. Ethyl 5-carbamoyl-6-oxo-4-*p*-tolyl-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate 5d. White solid; mp 155–158 °C; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J=7.2 Hz, 3H), 2.31 (s, 3H), 3.58 (d, J=2.7 Hz, 1H), 4.15 (q, J=7.2 Hz, 2H), 4.83 (s, H), 5.76 (br, s, 1H), 6.22 (br, s, 1H), 7.07–7.14 (m, 4H), 7.98 (br, s, 1H); ^{19}F NMR δ −64.32 (s, 3F); IR (KBr) ν_{max} 3446, 3048, 3232, 3146, 1701, 1637, 1607, 1307, 1165 cm^{-1}; MS (70 eV, EI) *m/z* (%): 370 (M^+, 0.52), 326 (M^+-CONH_2, 100), 69 (CF_3, 1.55), 44 ($CONH_2^+$, 4.32). Anal. Calcd for $C_{17}H_{17}F_3N_2O_4$: C, 55.14%; H, 4.59%; N, 7.57%. Found: 55.08%; H, 4.56%; N, 7.70%.

4.2.4. Ethyl 5-carbamoyl-4-(4-chlorophenyl)-6-oxo-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate 5e. White solid; mp 176–178 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J=7.2 Hz, 3H), 3.56 (d, J=3 Hz, 1H), 4.17 (q, J=7.2 Hz, 2H), 4.89 (s, 1H), 5.52 (br, 1H), 6.19 (br, s, 1H), 7.14–7.17 (m, 2H), 7.27–7.51 (m, 2H), 7.75 (br, s, 1H); ^{19}F NMR δ −64.30 (s, 3F); IR (KBr) ν_{max} 3446, 3228, 3139, 2952, 1701, 1603, 1493, 1372, 1303, 1165 cm^{-1}; MS (70 eV, EI) *m/z* (%): 390 (M^+, 0.71), 348/346 (M^+-CONH_2, 37.11/100), 69 (CF_3, 4.88), 44 ($CONH_2^+$, 10.35). Anal. Calcd for $C_{16}H_{14}ClF_3N_2O_4$: C, 49.17%; H, 3.59%; N, 7.17%. Found: 49.10%; H, 3.74%; N, 7.17%.

4.2.5. Ethyl 5-carbamoyl-4-(4-fluorophenyl)-6-oxo-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate. 5f. White solid; mp 137–139 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J=7.2 Hz, 3H), 3.57 (d, J=3.3 Hz, 1H), 4.16 (q, J=7.2 Hz, 2H), 4.90 (s, 1H), 5.55 (br, s, 1H), 6.20 (br, s, 1H), 6.96–7.07 (m, 2H), 7.18–7.28 (m, 2H), 7.51 (br, s, 1H); ^{19}F NMR δ −64.36 (s, 3F), −114.23 (m, 1F); IR (KBr) ν_{max} 3444, 1697 (br), 1606, 1373, 1305, 1163 cm^{-1}; MS (70 eV, EI) *m/z* (%): 374 (M^+, 0.50), 330 (M^+-CONH_2, 100), 69 (CF_3, 2.85), 44 ($CONH_2^+$, 5.85); HRMS for $C_{16}H_{14}F_4N_2O_4Na^{+1}$ Calcd: 397.0781. Found: 397.0794.

4.2.6. Ethyl 5-carbamoyl-4-(4-nitrophenyl)-6-oxo-2-(trifluoromethyl)-1,4,5,6-tetrahydropyridine-3-carboxylate 5g. White solid; mp 190–195 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J=7.2 Hz, 3H), 3.59 (d, J=3 Hz, 1H), 4.18 (q, J=7.2 Hz, 2H), 5.05 (s, 1H), 5.50 (br, 1H), 6.24 (br, s, 1H), 7.41–7.43 (m, 2H), 7.48 (br, s, 1H), 8.21–8.24 (m, 2H); ^{19}F NMR δ −64.22 (s, 3F), IR (KBr) ν_{max} 3408, 3217, 3119, 1716, 1678, 1624, 1599, 1519, 1353, 1305 cm^{-1}; MS (70 eV, EI) *m/z* (%): 401 (M^+, 0.59), 357 (M^+-44, 100), 69 (CF_3, 4.28), 44 ($CONH_2^+$, 13.25). Anal. Calcd for $C_{16}H_{14}F_3N_3O_6$: C, 47.88%; H, 3.49%; N, 10.47%. Found: 47.92%; H, 3.43%; N, 10.58%.

4.3. X-ray crystal structure data of compounds 3d, 4d and 5d

Intensity data were collected at 293(2) K on Bruker P4 diffractometer with graphite monochromator and Mo Kα radiation (λ=0.71073 Å). The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically, hydrogen atoms were included but not refined. The final cycle of full matrix least-squares refinement was based on $F2$, respectively. All calculations were performed using SHELXS-97 and SHELXL-97 programs. X-ray data for compounds **3d**, **4d** and **5d** are listed in Table 6.

Crystallographic data have been deposited to the Cambridge Crystallographic Data Center, CCDC 284791 for **3d**, 284792 for **4d** and 284793 for **5d**. Copies of the information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.ac.uk), upon request.

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