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Journal of Fluorine Chemistry 128 (2007) 952–957
JOURNAL OF FLUORINE CHEMISTRY
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Regioselective synthesis of 6-trifluoromethyl-1,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran derivatives

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Received 12 January 2007; received in revised form 4 April 2007; accepted 4 April 2007
Available online 8 April 2007

Abstract

A facile two-step procedure for the synthesis of 6-(trifluoromethyl)-1,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran derivatives (**4**) from the reaction of 4-arylidene-3-methyl-1-phenyl-5-pyrazolones (**1**) with ethyl trifluoroacetoacetate (**2**), a versatile fluorinated building-block, was presented. Furthermore, to increase the efficiency of this reaction, the more convenient one-pot three-component process was also developed with a slightly lower yield. Treatment of **4** with P_2O_5, conc. H_2SO_4, $POCl_3$/Py or *p*-TsOH under the drastic conditions did not afford the corresponding dehydrated products.

Keywords: Ammonium acetate; Ethyl trifluoroacetoacetate; 4-Arylidene-3-methyl-1-phenyl-5-pyrazolones; 3-Methyl-1-phenyl-5-pyrazolone

1. Introduction

The introduction of a trifluoromethyl group into an organic compound can bring about remarkable changes in the physical, chemical and biological properties [1–3]. Thus, trifluoromethyl-substituted compounds are becoming increasingly important for the development of new agrochemicals and medicines. In recent years, the synthesis of fluorinated *O*-heterocyclic or *N*-heterocyclic compounds have draw much attention [4–6]. The β-ketoesters are well established as synthetic intermediates in heterocyclic chemistry [7]. The literature has reported a series of CF_3-substituted pyridines, pyrazoles and pyrans and their derivatives, which were prepared from the reactions of trifluoromethyl-1, 3-dicarbonyl compounds as fluorine-containing building-blocks [8–10]. For example, our group have reported the synthesis of a series of trifluoromethyl-containing pyrazole derivatives [9,11].

Evans and co-workers have reported the preparation of 2*H*,4*H*-dihydropyrazolo[3,4-*b*]pyrans from the reaction of 4-piperidines, 5-pyrazolones and malononitrile [12]. And we have previously reported the synthesis of 2-trifluoromethyl-3,4-dihydro-2*H*-pyran derivatives by the reaction of ethyl trifluoroacetoacetate with arylidenemalononitrile (Scheme 1) [13].

Owning to numerous advantages associated with ethyl trifluoroacetoacetate as fluorinated building-block and in continuation of our work, we focused our attention on the reaction of ethyl trifluoroacetoacetate with another α,β-unsaturated carbonyl compounds. In this paper, we wish to report the preparation of 6-(trifluoromethyl)-1,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran derivatives (**4**) in the presence of ammonium acetate in good to excellent yields.

2. Results and discussion

Initially, we tried the reaction of ethyl trifluoroacetoacetate (**2**) with 4-benzylidene-3-methyl-1-phenyl-5-pyrazolones (**1a**), obtained from the condensation of benzaldehyde with 3-methyl-1-phenyl-5-pyrazolone, in the presence of triethylamine (0.5 equiv.) in ethanol. The reaction was carried out under the different conditions such as by varying the reaction temperature from room temperature to refluxing, however, the major product was not obtained. Then, we investigated the reaction using secondary amine, piperidine (0.5 equiv.) and a

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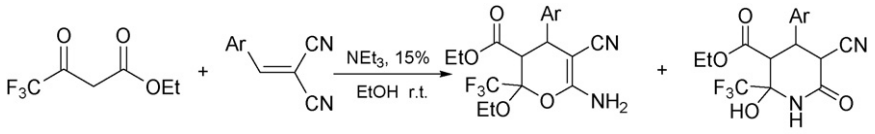
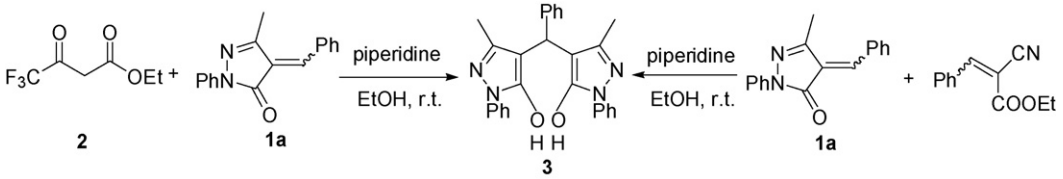
doi:10.1016/j.jfluchem.2007.04.004



Scheme 1.



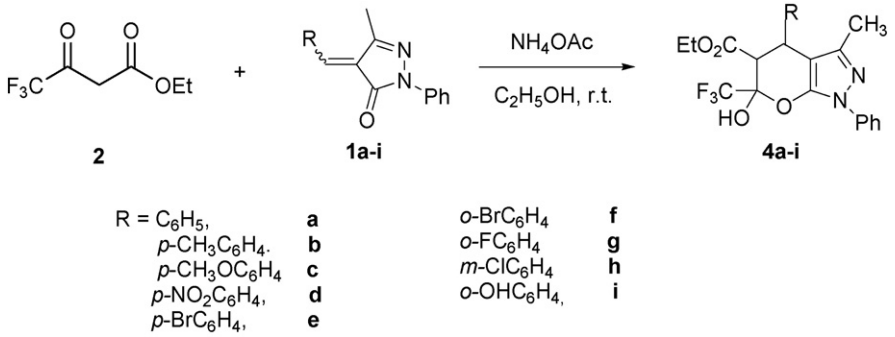
Scheme 2.

major solid product was isolated by chromatography column in low yield (34%). To our surprise, the ^{19}F NMR spectra clearly showed that no fluorine atom attached to the solid product. On the basis of ^{1}H NMR spectra data and IR analysis, the product was identified as 5,5′-dimethyl-2,2′-diphenyl-1,2,1′,2′-tetrahydro-4,4′-phenylmethanediyl-bis-pyrazol-3-one (**3**), other than the expected fluorinated products (Scheme 2). The obtained product (**3**) was the same as the previous reported product [14], despite the different starting materials were applied to the reaction (Scheme 2). The result revealed that, to some extent, the basicity of piperidine was too strong to be involved in the reaction, leading to the cleavage of carbon–carbon double bond, in other words, the occurrence of retro-knoevenagel condensation of 4-arylidene-3-methyl-1-phenyl-5-pyrazolone in the presence of a trace amount of water. Subsequently, the newly generated 3-methyl-1-phenyl-5-pyrazolone reacted with the substrate **1a** to afford the **3**.

More recently, ammonium acetate has been used widely as a base or a catalyst in Biginelli reactions [15,16], Hantsch reactions [17] and other reactions [18,19]. With this aim in view, we applied the ammonium acetate to this reaction. Treatment of 3-methyl-1-phenyl-4-phenylidene-5-pyrazolone (**1a**) with 1 equiv. of ammonium acetate followed by **2** in ethanol at room temperature for 2 h gave the corresponding 1,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran **4a** exclusively in 70% yield. Spectroscopic analysis supported the structure assignment. For instance, the ^{1}H NMR spectrum of **4a** in $CDCl_3$ consisted of eight peaks: 7.73–7.23 (m, 10H, ArH), 5.93 (s, 1H, OH), 4.25 (d, J = 11.1 Hz, 1H, CH), 4.06–3.98 (q, J = 7.2 Hz, 2H, CH_2), 3.11 (d, J = 11.1 Hz, 1H, CH), 1.64 (s, 3H, CH_3), 0.96 (t, J = 7.2 Hz, 3H, CH_3), which were corresponding to 10 aromatic protons, 1 hydroxy proton, 2 six-membered ring protons, 1 ethoxy group (CH_3CH_2O) and 1 methyl group. The structure of **4a** is clearly assigned as *trans* by the analysis of the vicinal coupling constant of the two methine protons (J = 11.7 Hz) and by the analogy with earlier reported paper [20,21]. In its ^{19}F NMR spectrum, the chemical shift of CF_3 group of **4a** was a singlet peak at δ −83.60 ppm, which indicated it was bonded the sp^3 saturated carbon atom. The MS spectrum of **4a** showed a weak molecular ion peak at *m*/*z* 447 (M^+, 1.68%), and the base peak as well as the rest of strong peaks was at *m*/*z* 77 ($C_6H_5^+$, 100%), 261 ([M-1-CF_3COCH_2-CO_2Et]$^+$, 91.25%), 69 (CF_3^+, 56.97%), respectively. Meanwhile, the typical and strong absorption at 3537 cm^{-1} in IR spectrum also confirmed the existence of OH group in **4a**.

4-Arylidene-3-methyl-1-phenyl-5-pyrazolones (**1b–i**) bearing a variety of functional groups also gave the corresponding pyran derivatives **4** in good to excellent yields (Scheme 3; Table 1). It should be noted that, in some cases, the products were complexed with one molecular ethanol or water, based on the evidence revealed by ^{1}H NMR and microanalysis (Scheme 4; Fig. 1).

Furthermore, in attempt to enhance the efficiency of this reaction, we investigated the development of a stoichiometric one-pot three-component process, in which the enone **1** could be generated in situ from the corresponding aldehydes and 3-methyl-1-phenyl-5-pyrazolone (Scheme 5). To the ethanol solution of 3-methyl-1-phenyl-5-pyrazolone was added



Scheme 3.

Table 1
Synthesis of 6-(trifluoromethyl)-1,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran derivatives[a]

Entry	**1** R	Reaction time (h)	Product yield[b] (%)
1	**1a** C_6H_5	2	70
2	**1b** *p*-$CH_3C_4H_6$	2	88
3	**1c** *p*-$CH_3OC_4H_6$	4	60
4	**1d** *p*-$NO_2C_6H_4$	1	91
5	**1e** *p*-BrC_6H_4	1	90
6	**1f** *o*-BrC_6H_4	1	65
7	**1g** *o*-FC_6H_4	1	81
8	**1h** *m*-ClC_6H_4	1	79
9	**1i** *o*-HOC_6H_4	2	100
10	**1j** furan-2-yl	4	–[b]
11	**1k** iso-C_3H_7	8	–[b]

In order to definitely determine the structure of this series of compound, **4c** was further confirmed by the single crystal X-ray crystallographic study. The molecular structure of **4c** is shown in Fig. 1. Some selected bond lengths and angles are listed in Table 2.

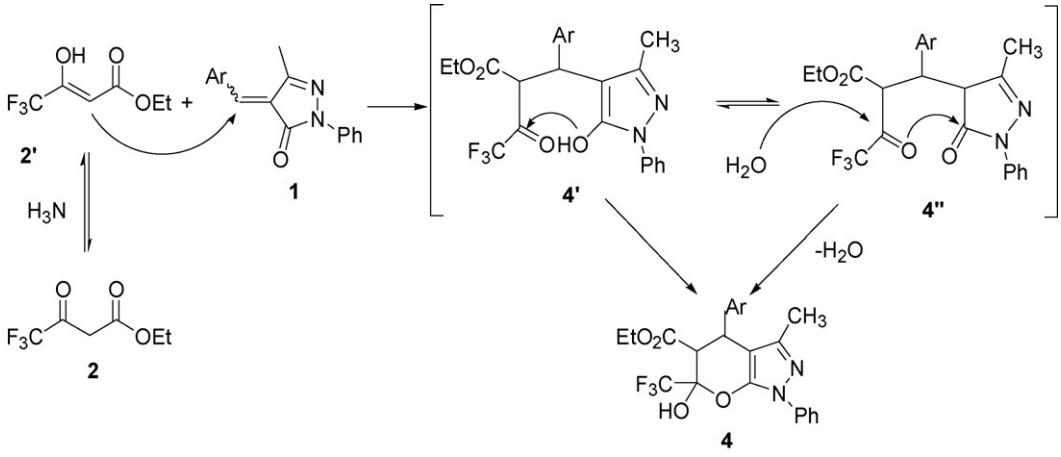
[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), ammonium acetate (1 mmol) and ethanol (5 mL) as solvent at room temperature;.

[b] No reaction occurred.

benzaldehyde followed by **2** and ammonium acetate, the resultant mixture was stirred at room temperature for 2 h, general workup afforded **4a** in 60% yield (Table 2).

However, our attempts to prepare the dehydrated product according to the procedure for the synthesis of trifluoromethyl-substituted pyrazole derivatives failed [9], demonstrating an unusual stability of this fused heterocyclics. Compared with the α-hydroxytetrahydropyridine, which smoothly eliminated water to form the corresponding 1,4-dihydropyridines [22a,22b], the product **4** was unaffected by either conc. H_2SO_4, P_2O_5 in $CHCl_3$ or $POCl_3$/Py, *p*-TsOH in boiling toluene. The result was consistent with Martins' reported work that the dehydration reaction was an elimination reaction where the stability of its activated complex depended on the participation of electron pair of neighbor heteroatom present in the heterocyclic ring. The more difficult dehydration of compounds **4** compared to α-hydroxytetrahydropyridine was caused by the weaker electron-donating strength of the oxygen atom in the pyran ring than that of the nitrogen atom in the pyridine ring [22c].

In conclusion, we have developed a convenient reaction for the synthesis of compounds (**4a–i**) from readily available starting ethyl trifluoroacetoacetate and enones with a variety of functional groups under the mild reaction condition. To increase the efficiency of this reaction, the one-pot three-component



Scheme 4.

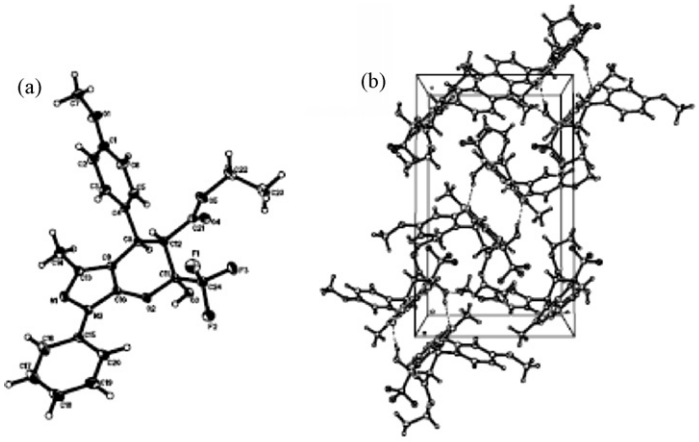
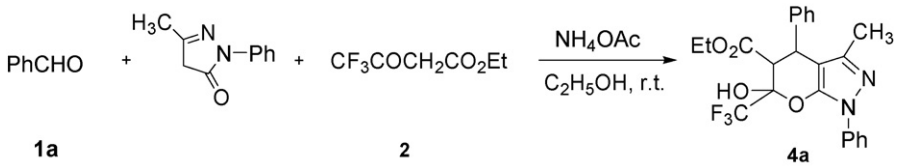


Fig. 1. (a) Crystal structure of compound **4c** and (b) packing map of molecular **4c** on the basis of this finding, a plausible reaction mechanism is shown in Scheme 4.



Scheme 5.

Table 2
Selected bond length and bond angle of compound **4c**

Bond length (Å)		Bond angle (°)	
C(4)–C(8)	1.515 (5)	O(3)–C(11)–C(24)	105.8 (3)
C(8)–C(9)	1.502 (5)	O(2)–C(11)–C(12)	109.6 (3)
C(8)–C(12)	1.546 (5)	C(10)–C(9)–C(13)	103.9 (3)
C(9)–C(10)	1.360 (5)	C(9)–C(10)–N(2)	110.3 (3)
C(9)–C(13)	1.401 (5)	C(4)–C(8)–C(12)	111.8 (3)
C(10)–O(2)	1.360 (4)	C(9)–C(8)–C(4)	113.8 (3)
C(10)–N(2)	1.362 (4)	C(21)–C(12)–C(11)	112.8 (3)
C(11)–O(2)	1.448 (4)	C(11)–C(12)–C(8)	109.4 (3)
C(11)–C(24)	1.529 (5)	C(10)–O(2)–C(11)	113.1 (2)
C(11)–C(12)	1.540 (5)	C(10)–N(2)–C(15)	131.9 (3)

process was also developed, in which the enone was generated in situ from aldehyde and 3-methyl-1-phenyl-5-pyrazolone.

3. Experimental

Melting points were measured in Melt-Temp apparatus and were uncorrected. ^{1}H and ^{19}F NMR spectra were recorded in $CDCl_3$ on a 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. Low resolution mass spectrum was obtained using the either electron impact ionization technique (70 eV) or electro-spray ionization mass spectra (ESIMS), respectively. Elemental analyses were performed by this Institute. X-ray diffraction crystal structure analysis was obtained on a Bruker P4 instrument. Compounds **1a–i** were prepared according to the literature methods [23].

The crystal data of **4c**: $C_{24}H_{23}F_3N_2O_5$, FW = 476.44, temperature 273(2)(K), monoclinic, *P*2(1)/c, wavelength 0.71073 Å, $a = 13.443(5)$ Å, $\alpha = 90^\circ$, $b = 10.169(4)$ Å, $\beta = 94.817(5)^\circ$, $c = 16.940(7)$ Å, $\gamma = 90^\circ$, $V = 2307.5(16)$ Å^3, $Z = 4$, $D_c = 1.371$ mg/m^3, absorption coefficient 0.112 mm^{-1}, $F(0\,0\,0) = 992$, $2.3^\circ < \theta < 25.00^\circ$, reflections collected 11,322, absorption correction expirical, transmission $0.9672_{max} - 0.9565_{min}$, final *R* indices $R_1 = 0.0787$, $wR_2 = 0.2122$.

3.1. Reactions between enones (*1*) and ethyl trifluoroacetoacetate (*2*) to produce 6-(trifluoromethyl)-1,4,5,6-tetrahydropyrazolo[3,4-b]pyrans (*4*) typical procedure

A mixture of enone (**1a**; 264 mg, 1 mmol), ethyl trifluoroacetoacetate (**2**; 184 mg, 1 mmol) and ammonium acetate (77 mg, 1 mmol) in ethanol (5 mL) was stirred at room temperature for 2 h. The reaction mixture was diluted with ethyl acetate (3 × 20 mL), washed with H_2O, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over silica gel, eluted with hexane/ethyl acetate (5/1) to give **4a** as a sole product.

3.2. One-pot reaction

A mixture of ethyl trifluoroacetoacetate (**2**; 184 mg, 1 mmol), benzaldehyde (106 mg, 1 mmol), 3-methyl-1-phenyl-5-pyrazolone (174 mg, 1 mmol) and ammonium acetate (77 mg, 1 mmol) in ethanol (5 mL) was stirred at room temperature for 2 h. The reaction mixture was diluted with ethyl acetate (3 × 20 mL), washed with H_2O, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over silica gel, eluted with hexane/ethyl acetate (5/1) to give **4a** as a sole product.

3.2.1. 1,4-Diphenyl-5-ethoxylcarbonyl-6-hydroxy-3-methyl-6-(trifluoromethyl)-1,4,5,6 -tetrahydropyrazolo[3,4-b]pyran (*4a*)

White solid; mp: 88–90 °C; FT-IR υ_{max} (KBr, cm^{-1}): 3537, 2982, 2937, 1745, 1601, 1522, 1497, 1194, 1010, 754, 703; ^{1}H NMR δ ($CDCl_3$): 7.73–7.23 (m, 10H, ArH), 5.93 (s, 1 H, OH), 4.25 (d, $J = 11.1$ Hz, 1 H, CH), 4.06–3.98 (q, $J = 7.2$ Hz, 2H, CH_2), 3.11 (d, $J = 11.1$ Hz, 1H, CH), 1.64 (s, 3H, CH_3), 0.96 (t, $J = 7.2$ Hz, 3H, CH_3) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −83.60 (s, 3F, CF_3) ppm; MS (70 eV, EI) *m/z* (%): 447 ([M+1]$^+$, 1.68), 261 ([M-1-$CF_3COCH_2CO_2Et$]$^+$, 91.24), 77 ($C_6H_5^+$, 100), 69 (CF_3^+, 56.97); anal. calcd. for $C_{23}H_{21}F_3N_2O_4{\cdot}H_2O$: C, 59.48; H, 4.96; N, 6.03; found: C, 59.48; H, 4.97; N, 5.88%.

3.2.2. 5-Ethoxylcarbonyl-6-hydroxy-3-methyl-1-phenyl-4-tolyl-6-(trifluoromethyl)-1,4,5, 6-tetrahydropyrazolo[3,4-b]pyran (*4b*)

White solid; mp: 100–102 °C; FT-IR υ_{max} (KBr, cm^{-1}): 3755, 2982, 2927, 1746, 1601, 1518, 1497, 1196, 1009, 756, 691; ^{1}H NMR δ ($CDCl_3$): 7.75–7.13 (m, 9H, ArH), 5.68 (s, 1H, OH), 4.22 (d, $J = 11.1$ Hz, 1H, CH), 4.06–4.03 (q, $J = 7.2$ Hz, 2H, CH_2), 3.14 (d, $J = 11.1$ Hz, 1H, CH), 1.68 (s, 3H, CH_3), 0.99 (t, $J = 7.2$ Hz, 3H, CH_3) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: –83.69 (s, 3F) ppm; MS (ESI): 461 (M^++H); anal. calcd. for $C_{24}H_{23}F_3N_2O_4$: C, 62.61; H, 5.00; N, 6.09; found: C, 62.67; H, 5.07; N, 5.95%.

3.2.3. 5-Ethoxylcarbonyl-6-hydroxy-3-methyl-4-(4-methoxylphenyl)-1-phenyl-6-(trifluoro methyl)-1,4,5,6-tetrahydropyrazolo[3,4-b]pyran (*4c*)

White solid; mp: 93–96 °C; FT-IR υ_{max} (KBr, cm^{-1}): 3753, 2982, 2929, 1744, 1686, 1601, 1514, 1459, 1341, 1250, 1188,

756, 692; ^{1}H NMR δ ($CDCl_3$): 7.73–6.86 (m, 9H, ArH), 5.78 (s, 1H, OH), 4.21 (d, J = 11.4 Hz, 1H, CH), 4.08–4.01 (q, J = 7.2 Hz, 2H, CH_2), 3.82 (S, 3H, OCH_3), 3.07 (d, J = 11.4 Hz, 1H, CH), 1.67 (s, 3H, CH_3), 1.00 (t, J = 7.2 Hz, 3H, CH_3) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −83.67 (s, 3F) ppm; MS (ESI): 477 (M^++H); anal. calcd. for $C_{24}H_{23}F_3N_2O_5$: C, 60.50; H, 4.83; N, 5.88; found: C, 60.51; H, 4.88; N, 5.73%.

*3.2.4. 5-Ethoxylcarbonyl-6-hydroxy-3-methyl-4-(4-nitrophenyl)-1-phenyl-6-(trifluorome-thyl)-1,4,5,6-tetrahydropyrazolo[3,4-b]pyran (**4d**)*

White solid; mp: 99–101 °C; FT-IR υ_{max} (KBr, cm^{-1}): 3753, 2372, 2346, 1743, 1599, 1523, 1348, 1194, 1009, 758, 693; ^{1}H NMR δ ($CDCl_3$): 8.25–7.26 (m, 9H, ArH), 6.08 (s, 1H, OH), 4.42 (d, J = 11.1 Hz, 1H, CH), 4.09–4.01 (q, J = 7.2 Hz, 2H, CH_2), 3.74–3.67 (q, J = 7.2 Hz, 2H, CH_3CH_2OH), 3.08 (d, J = 11.1 Hz, 1H, CH), 1.62 (s, 3H, CH_3), 1.22 (t, J = 7.2 Hz, 3H, CH_3CH_2OH), 1.01 (t, J = 7.2 Hz, 3H, CH_3) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: –83.32 (s, 3F, CF_3) ppm; MS (ESI): 492 (M^+); anal. calcd. for $C_{23}H_{20}F_3N_3O_6{\cdot}CH_3CH_2OH$: C, 55.66; H, 4.82; N, 7.79; found: C, 55.89; H, 4.85; N, 7.73%.

*3.2.5. 4-(4-Bromophenyl)-5-ethoxylcarbonyl-6-hydroxy-3-methyl-1-phenyl-6-(trifluorom-ethyl)-1,4,5,6-tetrahydropyrazolo[3,4-b]pyran (**4e**)*

White solid; mp: 105–109 °C; FT-IR υ_{max} (KBr, cm^{-1}): 3651, 2982, 2374, 1745, 1702, 1601, 1522, 1235, 1199, 1072, 1011, 757, 692; ^{1}H NMR δ ($CDCl_3$): 7.73–7.13 (m, 9H, ArH), 5.63 (s, 1H, OH), 4.24 (d, J = 10.2 Hz, 1H, CH), 4.08–4.04 (q, J = 7.2 Hz, 2H, CH_2), 3.06 (d, J = 10.2 Hz, 1H, CH), 1.68 (s, 3H, CH_3), 1.03 (t, J = 7.2 Hz, 3H, CH_3) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −83.60 (s, 3F, CF_3) ppm; MS (ESI): 525 (M^+); anal. calcd. for $C_{23}H_{20}BrF_3N_2O_4$: C, 52.57; H, 3.81; N, 5.33; found: C, 52.54; H, 3.86; N, 5.06%.

*3.2.6. 4-(2-Bromophenyl)-5-ethoxylcarbonyl-6-hydroxy-3-methyl-1-phenyl-6-(trifluorom-ethyl)-1,4,5,6-tetrahydropyrazolo[3,4-b]pyran (**4f**)*

White solid; mp: 101–103 °C; FT-IR υ_{max} (KBr, cm^{-1}): 2988, 2965, 2358, 2339, 1749, 1601, 1532, 1499, 1211, 1172, 1018, 904, 755, 687; ^{1}H NMR δ ($CDCl_3$): 7.74–7.18 (m, 9H, ArH), 6.14 (s, 1H, OH), 5.03 (d, J = 11.1 Hz, 1H, CH), 4.15–4.08 (q, J = 7.2 Hz, 2H, CH_2), 3.15 (d, J = 11.1Hz, 1H, CH), 1.64 (s, 3H, CH_3), 1.01 (t, J = 7.2 Hz, 3H, CH_3) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −83.59 (s, 3F, CF_3) ppm; MS (70eV, EI) *m/z* (%): 342/340 ([M-$CF_3COCH_2CO_2Et$]$^+$, 7.24/6.93), 262 ([M-Br-$CF_3COCH_2CO_2Et$]$^+$, 20.41), 261 ([M-1-Br-$CF_3COCH_2CO_2Et$]$^+$, 100), 185 ([$CF_3COCH_2CO_2Et$ + 1]$^+$, 8.44), 69 (CF_3^+, 59.46); anal. calcd. for $C_{23}H_{20}BrF_3N_2O_4{\cdot}H_2O$: H_2O: C, 50.83; H, 4.05; N, 5.16; found: C, 51.03; H, 3.89; N, 5.16%.

*3.2.7. 5-Ethoxylcarbonyl-4-(2-fluorophenyl)-6-hydroxy-3-methyl-1-phenyl-6-(trifluorom-ethyl)-1,4,5,6-tetrahydropyrazolo[3,4-b]pyran (**4g**)*

White solid; mp: 84–86 °C; FT-IR υ_{max} (KBr, cm^{-1}): 3749, 2983, 1746, 1601, 1522, 1494, 1456, 1190, 1164, 1008, 756, 691; ^{1}H NMR δ ($CDCl_3$): 7.79–7.06 (m, 9H, ArH), 6.01 (s, 1H, OH), 4.68 (d, J = 11.7 Hz, 1H, CH), 4.13–4.02 (q, J = 7.2 Hz, 2H, CH_2), 3.23 (d, J = 11.7 Hz, 1H, CH), 1.65 (s, 3H, CH_3), 1.00 (t, J = 7.2 Hz, 3H, CH_3) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −83.62 (s, 3F, CF_3), −119.61 (s, 1F, ArF) ppm; MS (ESI): 465 (M^++H); anal. calcd. for $C_{23}H_{20}F_4N_2O_4{\cdot}H_2O$: C, 57.26; H, 4.56; N, 5.81; found: C, 57.38; H, 4.51; N, 5.56%.

*3.2.8. 4-(2-Chlorophenyl) 5-ethoxylcarbonyl-6-hydroxy-3-methyl-1-phenyl-6-(trifluoro-methyl)-1,4,5,6-tetrahydropyrazolo[3,4-b]pyran (**4h**)*

White solid; mp: 91–92 °C; FT-IR υ_{max} (KBr, cm^{-1}): 3336, 3066, 2983, 1744, 1715, 1599, 1522, 1498, 1195, 1164, 1076, 1009, 757, 691; ^{1}H NMR δ ($CDCl_3$): 7.78–7.12 (m, 9H, ArH), 5.96 (s, 1H, OH), 4.23 (d, J = 11.7 Hz, 1H, CH), 4.10–4.03 (q, J = 7.2 Hz, 2H, CH_2), 3.06 (d, J = 11.7 Hz, 1H, CH), 1.67 (s, 3H, CH_3), 1.02 (t, J = 7.2 Hz, 3H, CH_3) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −83.51 (s, 3F, CF_3) ppm; MS (ESI): 481 (M^++H); anal. calcd. for $C_{23}H_{20}ClF_3N_2O_4{\cdot}H_2O$: C, 55.37; H, 4.41; N, 5.62; found: C, 55.22; H, 4.62; N, 5.54%.

*3.2.9. 5-Ethoxylcarbonyl-6-hydroxy-4-(2-hydroxylphenyl)-3-methyl-1-phenyl-6-(trifluo-romethyl)-1,4,5,6-tetrahydropyrazolo[3,4-b]pyran (**4i**)*

White solid; mp: 136–138 °C; FT-IR υ_{max} (KBr, cm^{-1}): 3426, 2974, 2362, 2334, 1716, 1622, 1583, 1487, 1231, 1186, 1088, 1023, 990, 758; ^{1}H NMR δ ($CDCl_3$): 7.47–6.91 (m, 9H, ArH), 5.38 (s, 1H, OH), 4.39 (d, J = 11.7 Hz, 1H, CH), 4.15–4.12 (q, J = 7.2 Hz, 2H, CH_2), 3.07 (d, J = 11.7 Hz, 1H, CH), 1.62 (s, 3H, CH_3), 1.05 (t, J = 7.2 Hz, 3H, CH_3) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −84.16 (s, 3F, CF_3) ppm; MS (70eV, EI) *m/z* (%): 462 (M^+, 3.09), 371 ([M-C_7H_7]$^+$, 4.52), 278 ([M-$CF_3COCH_2CO_2Et$]$^+$, 100), 277 ([M-1-$CF_3COCH_2CO_2Et$]$^+$, 51.03), 77 ($C_6H_5^+$, 24.78), 69 (CF_3^+, 24.66); anal. calcd. for $C_{23}H_{21}F_3N_2O_5$: C, 59.74; H, 4.55; N, 6.06; found: C, 59.71; H, 4.56; N, 5.71%.

Acknowledgement

This work is supported by the National Science Foundation of China (Nos. 20672072, 20532040).

References

[1] R.E. Bank, Organofluorine Chemistry: Principles and Commercial Application, Plenum and Elsevier, New York, 1994.
[2] R.E. Filler, Organic Chemistry in Medicinal Chemistry and Biochemical Applications, Plenum and Elsevier, Amsterdam, 1993.
[3] R. Ling, M. Yoshida, P.S. Mariano, J. Org. Chem. 61 (1996) 4439–4449.
[4] I. Katsuyama, S. Ogawa, Y. Yamaguchi, K. Funabiki, M. Matsui, H. Muramatsu, K. Shibata, Synthesis (1997) 1321–1324.
[5] H. Amii, T. Kobayashi, H. Terasawa, K. Uneyama, Org. Lett. 3 (2001) 3103–3105.
[6] C.H. Xing, S.Z. Zhu, J. Org. Chem. 69 (2004) 6486–6488.
[7] R.S. Atkinson, E. Barker, P.J. Edwards, G.A. Thomson, J. Chem. Soc. Perkin Trans. 112 (1995) 1533–1543.
[8] A. Loupy, A. Petit, D.B. Delpon, J. Fluorine Chem. 75 (1995) 215–216.
[9] L.P. Song, S.Z. Zhu, J. Fluorine Chem. 111 (2001) 201–205.

[10] M. Marull, M. Schlosser, Eur. J. Org. Chem. 8 (2003) 1576–1588.
[11] L.P. Song, Q.L. Chu, S.Z. Zhu, J. Fluorine Chem. 107 (2001) 107–112.
[12] A.M. Shestopalov, Y.M. Emeliyanova, A.A. Shestopalov, L.A. Rodinovskaya, Z.I. Niazimbetova, D.G. Evans, Org. Lett. 4 (2002) 423–425.
[13] X.F. Li, L.P. Song, C.H. Xing, J.W. Zhao, S.Z. Zhu, Tetrahedron 62 (2006) 2255–2263.
[14] H.S. Ammida Nagwa, A. Giath, Asian J. Chem. 15 (2) (2003) 616–620.
[15] J.S. Yadav, S.P. Kumar, G. Kondaji, R.S. Rao, K. Nagaiah, Chem. Lett. 33 (2004) 1168–1169.
[16] J. Mabry, B. Ganem, Tetrahedron Lett. 47 (2006) 55–56.
[17] J.H. Lee, Tetrahedron Lett. 46 (2005) 7329–7330.
[18] S. Mitsumori, H.L. Zhang, P.H. Cheong, K.N. Houk, F. Tanaka, C.F. Barbas, J. Am. Chem. Soc. 128 (2006) 1040–1041.
[19] R. Sakamoto, M. Ryoto, S. Kume, H. Sampei, M. Sugimoto, H. Nishihara, Chem. Commun. 9 (2005) 1214–1217.
[20] C.P. Chuang, An-I. Tsai, Synthesis 4 (2006) 675–699.
[21] R. Antonioletti, S. Malancona, P. Bovicelli, Tetrahedron 58 (2002) 8825–8831.
[22] (a) I. Katsuyama, K. Funabiki, M. Matsui, H. Muramatsu, K. Shibata, Tetrahedron Lett. 37 (24) (1996) 4177–4178;
(b) V.G. Nenajdenko, S.V. Druzhinin, E.S. Balenkova, J. Fluorine Chem. 127 (2006) 865–873;
(c) M.A.P. Martins, W. Cunico, S. Brondani, R.L. Peres, N. Zimmermann, F.A. Rosa, G.F. Fiss, N. Zanatta, H.G. Bonacorso, Synthesis 9 (2006) 1485–1493.
[23] N.E. Seyhan, A.D. Adams, E.J. Gess, K.S. Ragone, B.J. Kober, M.B. Lampert, P. Umrigar, D.C. Lankin, G.W. Griffin, J. Chem. Soc. Perkin Trans. 1 (1983) 325–331.