Tetrahedron 66 (2010) 913–917

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Iodine-promoted imino-Diels–Alder reaction of fluorinated imine with enol ether: synthesis of 2-perfluorophenyl tetrahydroquinoline derivatives

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ARTICLE INFO

Article history:
Received 21 September 2009
Received in revised form 18 November 2009
Accepted 24 November 2009
Available online 2 December 2009

Keywords:
Hetero-Diels–Alder reaction
Imine
Iodine catalyst
Fluorinated tetrahydroquinoline
Synthesis

ABSTRACT

Iodine was used to catalyze the hetero-Diels–Alder reaction of pentafluorobenzylidineaniline (C_6F_5CH=NAr **1**) with enol ethers to afford the corresponding tetrahydroquinolines derivatives as a mixture of *cis*/*trans* stereoisomers in moderate yields. These products could also be prepared by one-pot, three-component reaction of pentafluorophenylaldehyde, anilines, and enol ethers under the same reaction condition. Mild and neutral reaction conditions, facile experimental procedure, and low price of iodine should make this method attractive for practical synthesis of many fluorinated tetrahydroquinoline derivatives.

1. Introduction

Hetero-Diels–Alder reaction is one of the most powerful synthetic routes for constructing oxygen or nitrogen-containing six-membered heterocycles.[1–4,19,20] Tetrahydroquinoline derivatives are an important class of compounds in the field of pharmaceuticals and exhibit a wide spectrum of biological activities.[5–7] In addition, pyranoquinoline derivatives have been found to possess a vast range of pharmacological activities. The imino-Diels–Alder reaction provides an easy access to pyrano- and furoquinolines. The reaction can be catalyzed by many kinds of catalysts, such as Lewis acids BF_3OEt, $TiCl_4$, $AlCl_3$, $LiBF_4$,[4,8–10] and salen-Al.[11] Recently, metal triflate, such as $Yb(OTf)_3$, $Sc(OTf)_3$, etc., were found to be effective for this transformation.[12–14] However, many Lewis acids are deactivated or sometimes decomposed by nitrogen-containing reactants. Even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are required, because the acids are trapped by nitrogen of both reactants and products.[1,2] Recently Crousse et al. reported that fluorinated alcohol, such as $(CF_3)_2CHOH$, CF_3CH_2OH could promote the reaction.[15]

To the best of our knowledge, Diels–Alder reaction of fluorinated imines C_6F_5CH=NAr with enol ethers have never been reported. In this paper, we describe a novel and efficient procedure for the synthesis of the 2-pentafluorophenyl tetrahydroquinoline derivates using a catalytic amount of iodine in trifluoroethanol under neutral conditions.

2. Results and discussion

In the initial experiment *N*-pentafluorobenziliden aniline C_6F_5CH=C_6H_5 **1a** was chosen as the substrate to react with 3,4-dihydro-2*H*-pyran (DHP) **2** in THF.[16] After stirring at room temperature for 24 h, no reaction occurred. The reaction mixture was then refluxed for 12 h, leading to the decomposition of nearly 35% of **1a** according to TLC and ^1H and ^{19}F NMR analysis. Other solvents, such as CH_3CN and CH_2Cl_2 were also tried for this reaction, however no expected cycloaddition reaction took place, and **1a** was recovered. When the reaction was carried out in more polar solvent CF_3CH_2OH, after stirring for 48 h at room temperature (as monitored by TLC), the desired cycloadduct pyrano-2-pentafluorophenyl tetrahydroquinolines were obtained in 46% yield as a mixture of *cis* and *trans* isomers (**3a** and **4a**), which could be easily separated and purified by column chromatograph on silicagel using petroleum ether–ethyl acetate (20:1) as the eluent (Scheme 1).

The structural assignment of *cis*- and *trans*-isomers were done on the basis of the coupling constant[17] between protons H_2 and H_3 because value of $J_{(H2,H3)}$ for *cis*-isomer **3a** (4.8 Hz), which is significantly smaller than that for *trans*-isomer **4a** (11.4 Hz).

When a catalytic amount of I_2 (5% mol) was added into the reaction mixture, the reaction was finished in 24 h and gave 54% of product

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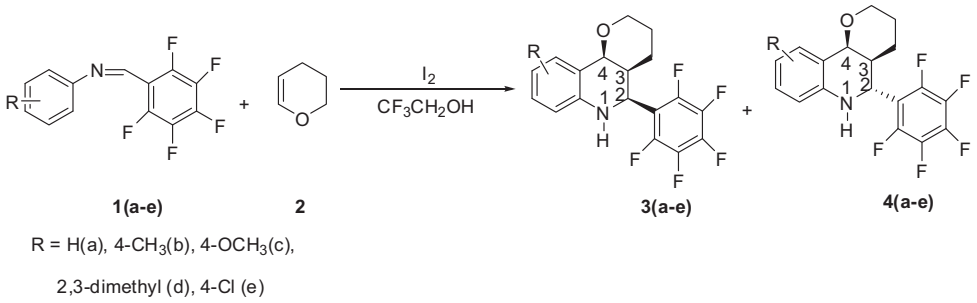
doi:10.1016/j.tet.2009.11.092



Scheme 1. The reaction of fluorinated imines with DHP **2**.

(Table 1, entry 6). Further increase of the amount of I_2 to 15 mol % could accelerate the reaction efficiently and improve the yield to 63% (Table 1, entry 7). As mentioned above this reaction did not occur in CH_2Cl_2; however, in the presence of 15 mol % of I_2, **1a** reacted with DHP **2** or 2,3-dihydrofuran (DHF) **5** gave only the *cis* product **3a** and **6a** in 24% and 22% yields, respectively, while no corresponding *trans* products **4a** and **7a** were isolated (Table 1, entries 9 and 10).

Table 1
Reaction Results of 1a with DHP (**2**) or DHF(**5**) under different reaction conditions

Entry	Solvent	Cat.	Temp(°C)	Time (h)	Enol ether[a]	Product and yield[b](%)
1	THF	No	rt	24	**2**	N.R.
2	THF	No	80	12	**2**	N.R.[c]
3	CH_3CN	No	rt	24	**5**	N.R.
4	$CHCl_2$	No	rt	24	**5**	N.R.
5	CF_3CH_2OH	No	rt	48	**2**	**3a** (27); **4a** (20)
6	CF_3CH_2OH	I_2 (5%)	rt	24	**2**	**3a** (24); **4a** (30)
7	CF_3CH_2OH	I_2 (15%)	rt	12	**2**	**3a** (33); **4a** (30)
8	CF_3CH_2OH	I_2 (15%)	rt	12	**5**	**6a** (21); **7a** (22)
9	CH_2Cl_2	I_2 (15%)	rt	12	**5**	**3a** (24)[d]
10	CH_2Cl_2	I_2 (15%)	rt	12	**2**	**6a** (22)[d]

[a] Mole ratio of **1a**/**2** (or **5**) is 1:2.
[b] Isolated yield calcd based on **1a**.
[c] 35% of **1a** was decomposed.
[d] No *trans*-isomer product **4a** (or **6a**) was isolated.

It is clear that the iodine promoted this reaction, acting as a Lewis acid that can coordinate to the nitrogen atom of the polar C=N bond (Scheme 2). More polar solvent (such as CF_3CH_2OH) increased the coordination ability of the iodine, therefore leading to better yields of the products.

Table 2
I_2 catalyzed synthesis of 2-pentafluorophenyl tetrahedroquinoline derivatives[a]

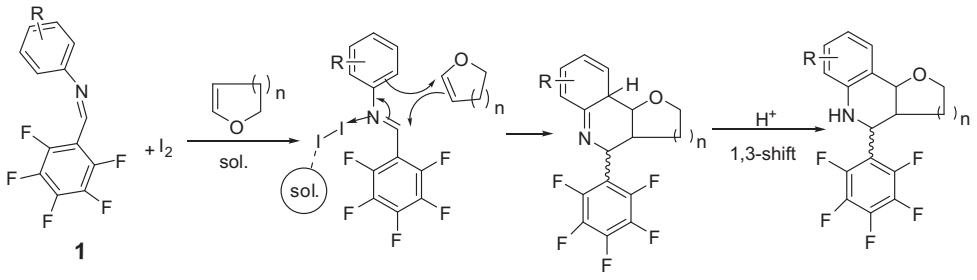
Entry	Imines	Enol ether **2** or **5**	Products and yield(%)	*cis*/*trans*
1	**1a**	**2**	**3a** (33); **4a** (30)	52:48
2	**1a**	**5**	**6a** (22); **7a** (22)	50:50
3	**1b**	**2**	**3b** (27); **4b** (21)	57:43
4	**1b**	**5**	**6b** (25); **7b** (20)	55:45
5	**1c**	**2**	**3c** (13); **4c** (52)	20:80
6	**1c**	**5**	**6c** (11); **7c** (56)	17:83
7	**1d**	**2**	**3d** (28); **4d** (23)	55:45
8	**1d**	**5**	**6d** (24); **7d** (18)	57:43
9	**1e**	**2**	**3e** (23); **4e** (20)	53:47
10	**1e**	**5**	**6e** (24); **7e** (21)	53:47

[a] Reaction was carried out in the presence of 15-mol % I_2, CF_3CH_2OH (25 mL) as solvent at room temperature for 12 h.

All the new products are fully characterized by IR, ^1H NMR, ^{19}F NMR, MS and elemental analysis. For compound *trans*-**4b**,the structure was further confirmed by an X-ray crystal diffraction analysis (Fig. 1).[18]

The effect of the electronic properties of the substituted phenyl ring in imine **1** upon the yield and stereoselectivity of the products remain unclear. Four imines **1a** (R=H), **1b** (R=4-CH_3), **1d** (R=2,3-dimethyl), and **1e** (R=4-Cl) gave the *cis*-isomer products (*cis*/*trans* ratios around 1.1–1.3:1) but imine **1c** (R=OCH_3) gave *trans*-isomer **4c** and **7c** as the major product (the *trans*/*cis* ratios are 4.0:1 and 4.8:1, respectively).

One-pot, three-component synthesis of the target products from pentafluorophenylaldehyde, anilines, and dihydropyran in the presence of I_2 (15 mol %) was also studied. The reaction was carried out in CF_3CH_2OH by stirring for 14 h at room temperature, the expected products **3** and **4** were obtained, respectively. (Scheme 4).

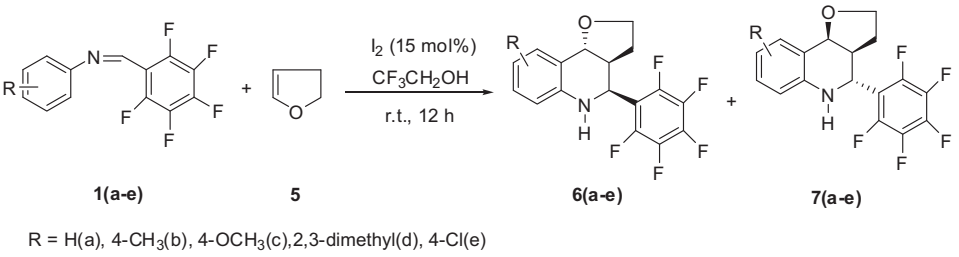


Scheme 2. Proposed mechanism for imino-Diels–Alder reaction catalyzed by iodine.

Under the optimum reaction conditions (Table 1, entry 7) a variety of fluorinated imines (**1a**–**1e**) was treated with two electron-rich olefines [(DHP) **2** and 2,3-Dihydrofuran (DHF) **5**] affording the corresponding 2-pentafluorophenyl substituted tetrahydroqunoline in 43–67% yields. These results are summarized in Table 2 (Scheme 3).

3. Conclusion

In conclusion, we have prepared a series of 2-pentafluorophenyl pyrano [3,2-*c*] and furo [3,2-*c*]-tetrahydroquinolines by the reaction of pentafluorobenzylidiene aniline with DHP or DHF using I_2 as the catalyst in CF_3CH_2OH at room temperature. Under similar conditions,



Scheme 3. The reaction of fluorinated imines **1** with DHF **5**.

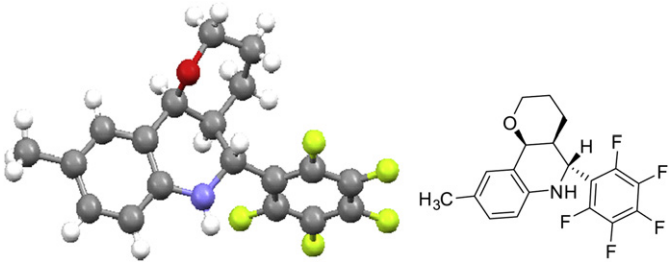


Figure 1. X-ray crystal diffraction analysis of compound **4b**.

one-pot, three-component reaction of pentafluorobenzaldehyde, anilines, and an enol ether afforded the same products. The neutral and mild reaction conditions, coupled with facile experimental procedure, made this method attractive for practical preparation of fluorine-containing tetrahydroquinoline derivatives.

4. Experimental

4.1. General

Melting points are measured on a Temp-Melt. apparatus and are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker AM-300 instruments with Me_4Si and $CFCl_3$ as the internal and external standards, respectively. FTIR spectra were obtained with a Nicolet AV-360 spectrophotometer. Low resolution mass spectra (LRMS) or high resolution mass spectra (HRMS) were obtained on a Finnigan GC–MS 4021 or a Finnigan MAT-8430 instrument using the electron impact ionization technique (70 eV1), respectively. Elemental analyses were performed by this institute. Single crystal X-ray structure analysis was performed on a Bruker P4 instrument.

4.2. General procedure for synthesis of tetrahydroquinoline

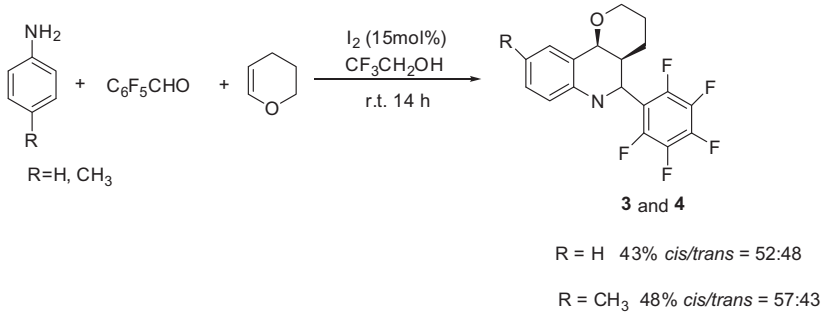
2,3-Dihydropyran (DHP) **2** (168 mg, 2 mmol) was dropped into a solution of imine **1a** (271 mg, 1 mmol), and iodine (38 mg, 0.15 mmol) in CF_3CH_2OH (25 mL) at room temperature for 12 h, removing CF_3CH_2OH using a rotary evaporator, and then the residue was dissolved in CH_2Cl_2. The solution was washed with 5% aqueous $Na_2S_2O_3$ (10 mL), brine (10 mL) and dried over $MgSO_4$. After evaporation of solvent under vacuum, the crude product was purified by flash column chromatography (petroleum ether:ethyl acetate, 20:1, v/v) to provide pyrano derivatives **3a** and **4a**.

*4.2.1. Compound **3a**.* White solid; mp 157–159 °C; IR (KBr, film): 3326, 2959, 1655, 1607, 1502, 1007, 753 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.38 (d, 1H, J=8.4 Hz, Ph), 7.04–7.09 (m, 1H, Ph), 6.75–6.81 (m, 1H, Ph), 6.51–6.57 (m, 1H, Ph), 5.20 (d, 1H, J=4.8 Hz, NCH), 5.05 (d, 1H, J=2.4 Hz, OCH), 3.52–3.57 (m, 1H, OCH_2), 3.33–3.91 (m, 1H, OCH_2), 2.11–2.22 (m, 1H, CH), 1.38–1.57 (m, 4H, $2CH_2$); ^{19}F NMR ($CDCl_3$): δ=−138.84 (d, 2F, J=16.9 Hz), −154.09 (m, 1F, J=14.1 Hz), −160.81 (d, 2F, J=8.5 Hz); MS (m/z, %): 355 (M^+, 61.75); 311 ($M^+-OCH_2CH_2$, 12.15), 296 ($M^+-OCH_2CH_2CH_2$, 100), 130 ($M^+-OCH_2CH_2CH_2-C_6F_5$, 46.48), 77 ($C_6H_5^+$, 15.22); Anal. Cacld for $C_{18}H_{14}F_5NO$ (%): C, 60.85; H, 3.97; N, 3.94. Found: C, 60.84; H, 4.30; N, 3.68.

*4.2.2. Compound **4a**.* White solid; mp 47–49 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.13 (d, 1H, J=7.5 Hz, Ph), 7.00–7.05 (m, 1H, Ph), 6.62–6.71 (m, 1H, Ph), 6.42–6.50 (m, 1H, Ph), 5.22 (d, 1H, J=11.4 Hz, NCH), 4.33 (d, 1H, J=2.7 Hz, OCH), 4.02 (m, 2H, OCH_2), 2.44 (d, J=11.4 Hz, 1H, CH), 1.72–1.77 (m, 2H, CH_2), 1.41–1.30 (m, 2H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−141.3 (2F, J=16.7 Hz), −154.9 (1F, 1F, J=14.3 Hz), −161.9 (2F, J=8.6 Hz).

*4.2.3. Compound **3b**.* White solid; mp131–134 °C; IR (KBr, film): 3347, 2940, 2856, 1626, 1524, 1500, 1259, 961 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.99 (s, 1H, ArH), 6.86 (d, 1H, J=8.1 Hz, ArH), 6.46 (d, 1H, J=8.1 Hz, ArH), 5.25 (d, 1H, J=12 Hz, NCH), 4.33 (d, 1H, J=2.1 Hz, OCH), 4.01–4.12 (m, 1H, OCH_2), 3.62–3.75 (m, 1H, OCH_2), 2.40–2.52 (m, 1H, CH), 2.18 (s, 3H, CH_3), 1.64–1.80 (m, 2H, CH_2), 1.18–1.43 (m, 2H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−140.21 to −140.24 (2F), −153.40 to −153.44 (1F), −160.59 to −160.62 (2F); MS (m/z, %): 369 (M^+, 32.80); 202 ($M^+-C_6F_5$, 3.76), 77 ($C_6H_5^+$, 8.10); Anal. Cacld for $C_{19}H_{16}F_5NO$ (%): C, 61.79; H, 4.37; N, 3.79. Found: C, 61.82; H, 4.43; N, 3.58.

*4.2.4. Compound **4b**.* ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.16 (s, 1H, ArH), 6.88 (d, 1H, J=8.4 Hz, ArH), 6.49 (d, 1H, J=8.4 Hz, ArH), 5.20 (d, 1H,



Scheme 4. One-pot, three-component synthesis of the 2-perfluorophenyl tetrahydroquinolines.

J=5.1 Hz, NCH), 4.84 (s, OCH), 3.61–3.74 (m, 1H, OCH_2), 3.29–3.42 (m, 1H, OCH_2), 2.04–2.18 (m, 1H, CH), 2.12 (s, 3H, CH_3), 1.64–1.78 (m, 2H, CH_2), 1.25–1.35 (m, 2H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−138.81 to −138.85 (2F), −153.98 to −154.02 (1F), −160.92 to −160.97 (2F).

4.2.4.1. X-ray data. $C_{19}H_{16}F_5NO$: FW=369.33; temperature 298 (K); Monoclinic, P2 (1)/c;wavelength 0.71 Å; a=8.7332 (13) Å, b=9.4049 (14) Å, c=20.384 (3) Å, α=90.00°, β=101.871 (2)°, γ=90.00°; V=1638.4 (4) Å^3; Z=4.

4.2.5. Compound ***3c***. White solid; mp 162–163 °C; IR (KBr, film): 3326, 2956, 2897, 1655, 1527, 1495, 1006, 805 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.94 (s, 1H, ArH), 6.66 (s, 1H, ArH), 6.51(s, 1H, ArH), 5.16 (d, J=5.7 Hz, 1H, NCH), 4.95 (d, J=2.1 Hz, 1H, OCH), 3.69 (s, 3H, OCH_3), 3.49–3.60 (m, 1H, OCH_2), 3.31–3.40 (m, 1H, OCH_2), 2.07–3.21 (m, 1H, CH), 1.40–1.57 (m, 4H, 2CH_2); ^{19}F NMR ($CDCl_3$): δ=−139.90 to −139.91 (2F), −155.51 to −155.52 (1F), −162.00 to −162.01 (2F); MS (m/z, %): 386 (M^++1, 22.55), 385 (M^+, 100.00), 354 (M^+−OCH_3, 14.18), 327 (M^+−$OCH_2CH_2CH_2$, 14.08), 160 (M^+−$OCH_2CH_2CH_2$–C_6F_5, 37.75), 77 ($C_6H_5^+$, 7.61); Anal. Cacld for $C_{19}H_{16}F_5NO_2$ (%): C, 59.22; H, 4.19; N, 3.64. Found: C, 59.06; H, 4.39; N, 3.51.

4.2.6. Compound ***4c***. Mp 57–58 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.73 (s, 1H, Ar), 6.72 (d, J=8.4 Hz, 1H, Ar), 6.48 (d, J=8.4 Hz, 1H, Ar), 5.20 (d, J=11.4 Hz, 1H, NCH), 4.33 (s, 1H, OCH), 4.01–4.13 (m, 1H, OCH_2), 3.74 (s, 3H, OCH_3), 3.57–3.68 (m, 1H, OCH_2), 2.39–2.51 (m, 1H, CH), 1.64–1.78 (m, 2H, CH_2), 1.27–1.44 (m, 2H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−141.30 to −141.31 (2F), −154.80 to −154.81 (1F), −161.82 to −161.83 (2F).

4.2.7. Compound ***3d***. White solid; mp °C; IR (KBr, film): 3386, 2918, 1655, 1606, 1501, 1473, 999, 960; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.15 (d, 1H, J=8.1 Hz, ArH), 6.65 (d, 1H, J=8.1 Hz, ArH), 5.22 (d, 1H, J=5.7 Hz, NCH), 5.06 (d, 1H, J=1.8 Hz, OCH), 3.47–3.61 (m, 1H, OCH_2), 3.31–3.45 (m, 1H, OCH_2), 2.70–2.82 (m, 1H, CH), 2.40 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.28–1.81 (m, 4H, 2CH_2); ^{19}F NMR ($CDCl_3$): δ=−140.00 to −140.01 (2F), −153.73 to −153.74 (1F), −160.92 to −160.93 (2F); MS (m/z, %): 384 (M^++1, 21.40), 383 (M^+, 84.80), 324 (M^+−$OCH_2CH_2CH_2$, 100.00), 216 (M^+−C_6F_5, 13.99), 158 (M^+−$OCH_2CH_2CH_2$–C_6F_5, 51.75), 91 ($C_6H_5CH_3$, 15.25), 77 ($C_6H_5^+$, 14.97); HRMS Calcd for $C_{20}H_{18}F_5NO$: 383.1309. Found: 383.1315.

4.2.8. Compound ***4d***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.05 (d, 1H, J=7.2 Hz, ArH), 6.66 (d, 1H, J=7.2 Hz, ArH), 5.39 (d, 1H, J=12.0 Hz, NCH), 4.43 (d, 1H, J=2.4 Hz, OCH), 4.03–4.22 (m, 1H, OCH_2), 3.66–3.82 (m, 1H, OCH_2), 2.41–3.57 (m, 1H, CH), 2.28 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.83–1.90 (m, 2H, CH_2), 1.53–1.36 (m, 2H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−140.53 to −140.54 (2F), −155.10 to −155.11 (1F), −161.90 to −161.91 (2F).

4.2.9. Compound ***3e***. White solid; mp154–156 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.17 (s, 1H, ArH), 6.99 (d, 1H, J=8.1 Hz, ArH), 6.44 (d, 1H, J=8.1 Hz, ArH), 5.22 (d, 1H, J=11.7 Hz, NCH), 4.32 (d, 1H, J=2.4 Hz, OCH), 3.91–4.13 (m, 1H, OCH_2), 3.51–3.65 (m, 1H, OCH_2), 2.33–2.45 (m, 1H, CH), 1.45–1.79 (m, 2H, CH_2), 1.25–1.37 (m, 2H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−140.70 to −140.71 (2F), −153.64 to −153.65 (1F), −160.88 to −160.89 (2F); 13C NMR (CDCl3): δ = 114.3–136.1 (m), 142.2, 130.7, 129.5, 123.1, 122.4, 116.2, 73.9, 68.9, 45.9, 34.9, 24.5, 21.4; MS (m/z, %): 391 (M^++2, 35.00) 389 (M^+, 100.00), 333 (M^+−$OCH_2CH_2CH_2$, 9.01), 224 (M^+−C_6F_5, 5.24), 167 (M^+−$OCH_2CH_2CH_2$–C_6F_5, 8.45), 91 ($C_6H_5CH_3$, 44.55), 77 ($C_6H_5^+$, 6.91); HRMS Calcd for $C_{18}H_{13}ClF_5NO$: 389.0606. Found: 389.0609.

4.2.10. Compound ***4e***. Mp 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.15 (s, 1H, ArH), 6.97 (d, 1H, J=8.4 Hz, ArH), 6.47 (d, 1H, J=8.4 Hz, ArH), 5.11 (d, 1H, J=4.2 Hz, NCH), 4.99 (d, 1H, J=3.0 Hz, OCH), 3.55–3.74 (m, 1H, OCH_2), 3.21–3.41 (m, 1H, OCH_2), 2.02–2.17 (m, 1H, CH), 1.61–1.83 (m, 2H, CH_2), 1.18–1.32 (m, 2H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−139.26 to −139.27 (2F), −154.12 to −154.13 (1F), −160.88 to −160.89 (2F).

4.2.11. Compound ***6a***. White solid; mp159–161 °C; IR (KBr, film): 3325, 2836, 1655, 1614, 1504, 1125, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.63 (d, 1H, J=8.1 Hz, Ph), 7.35–7.40 (m, 1H, Ph), 7.06–7.11 (m, 1H, Ph), 6.91 (d, 1H, J=8.1 Hz, Ph); 4.86 (d, 1H, J=5.1 Hz, NCH), 4.61 (d, 1H, J=11.4 Hz, OCH), 4.25–4.31 (m, 1H, OCH_2), 4.06–4.10 (m, 1H, OCH_2), 3.08–3.10 (m, 1H, CH), 2.37–2.44 (m, 1H, CH_2), 1.75–1.81 (m, 1H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−139.64 to −139.69 (2F), −153.08 to −153.23 (1F), −160.67 to −160.86 (2F); MS (m/z, %): 341 (M^+, 36.39); 296 (M^+−OCH_2CH_2, 100.00), 130 (M^+−OCH_2CH_2–C_6F_5, 34.36), 77 ($C_6H_5^+$, 16.46); Anal. Cacld for $C_{17}H_{12}F_5NO$ (%): C, 59.83; H, 3.54; N, 4.10. Found: C, 59.78; H, 3.66; N, 4.00.

4.2.12. Compound ***7a***. Mp 174–175 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.29 (d, 1H, J=7.8 Hz, Ph), 7.04 (m, 1H, Ph), 6.79 (m, 1H, Ph), 6.56 (d, 1H, J=7.5 Hz, Ph), 5.20 (d, 1H, J=7.8 Hz, NCH), 4.61 (d, 1H, J=3.3 Hz, OCH), 3.73–3.77 (m, 2H, OCH_2), 2.74–2.80 (m, 1H, CH), 2.18–2.23 (m, 1H, CH_2), 1.60–1.67 (m, 1H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−140.27 to −140.60 (2F), −155.18–155.24 (1F), −161.74 to −161.81 (2F).

4.2.13. Compound ***6b***. White solid; mp 161–163 °C; IR (KBr, film): 3322, 2861, 1622, 1510, 1270, 974, 813 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.19 (s, 1H, ArH), 6.92 (d, 1H, J=8.1 Hz, ArH), 6.58 (d, 1H, J=8.1 Hz, ArH); 4.56 (d, 1H, J=5.4 Hz, NCH), 4.30 (d, 1H, J=11.1 Hz, OCH), 3.95–4.02 (m, 1H, OCH_2), 3.71–3.84 (m, 1H, OCH_2), 2.79–2.87 (m, 1H, CH), 2.19 (s, 3H, CH_3), 2.01–2.13 (m, 1H, CH_2), 1.39–1.46 (m, 1H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−139.21 to −139.27 (2F), −152.61 to −153.69 (1F), −160.29 to −160.34 (2F); MS (m/z, %): 355 (M^+, 70.65), 310 (M^+−OCH_2CH_2, 100.00), 188 (M^+−C_6F_5, 9.11), 144 (M^+−OCH_2CH_2–C_6F_5, 21.47), 77 ($C_6H_5^+$, 7.72); HRMS Calcd for $C_{18}H_{14}F_5NO$: 355.0996. Found: 355.09 98.

4.2.14. Compound ***7b***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.18 (s, 1H, ArH), 6.88 (d, 1H, J=8.1 Hz, ArH), 6.54 (d, 1H, J=8.1 Hz, ArH); 4.56 (d, 1H, J=10.8 Hz, NCH), 4.30 (d, 1H, J=3.0 Hz, OCH), 3.79–3.91 (m, 2H, OCH_2), 2.72–2.89 (m, 1H, CH), 2.21 (s, 3H, CH_3), 1.69–1.81 (m, 1H, CH_2), 1.37–1.49 (m, 1H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−139.41 to −139.47 (2F), −154.31 to −154.37 (1F), −160.89 to −160.93 (2F).

4.2.15. Compound ***6c***. White solid; mp130–131 °C; IR (KBr, film): 3364, 2945, 2835, 1655, 1523, 1501, 1260, 976 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.24 (s, 1H, ArH), 7.04 (d, 1H, J=8.7 Hz, ArH), 6.91 (d, 1H, J=9.0 Hz, ArH), 4.90 (d, 1H, J=5.1 Hz, NCH), 4.59 (d, 1H, J=11.4 Hz, OCH), 4.30–4.41 (m, 1H, OCH_2), 4.00–4.16 (m, 1H, OCH_2), 4.04 (s, 3H, OCH_3), 3.09–3.17 (m, 1H, CH), 2.39–2.51 (m, 1H, CH_2), 1.79–1.93 (m, 1H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−139.70 to −139.75 (2F), −153.42 to −153.44 (1F), −160.82 to −160.83 (2F); MS (m/z, %): 371 (M^+, 18.50), 370 (M^+−1, 100.00), 326 (M^+−OCH_2CH_2, 71.75), 160 (M^+−OCH_2CH_2–C_6F_5, 6.89), 77 ($C_6H_5^+$, 3.49); Anal. Cacld for $C_{18}H_{14}F_5NO_2$ (%): C, 58.23; H, 3.80; N, 3.77. Found: C, 58.09; H, 3.52; N, 3.70.

4.2.16. Compound ***7c***. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.24 (s, 1H, ArH), 7.04 (d, 1H, J=8.7 Hz, ArH), 6.91 (d, 1H, J=9.0 Hz, ArH), 4.90 (d, 1H, J=5.1 Hz, NCH), 4.59 (d, 1H, J=11.4 Hz, OCH), 4.29–4.38 (m, 1H, OCH_2), 3.99–4.15 (m, 1H, OCH_2), 4.04 (s, 3H, OCH_3), 3.07–3.21 (m, 1H, CH), 2.39–2.47 (m, 1H, CH_2), 1.76–1.93 (m, 1H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−139.70 to −139.72 (2F), −153.41 to −153.42 (1F), −160.82 to −160.83 (2F).

4.2.17. Compound ***6d***. White solid; mp 143–145 °C; IR (KBr, film): 3397, 2962, 2351, 1742, 1612, 1504, 972, 799 cm^{-1}; ^{1}H NMR

(300 MHz, $CDCl_3$): δ=7.13 (d, 1H, J=7.8 Hz, ArH), 6.65 (d, 1H, J=7.8 Hz, ArH), 4.55 (d, 1H, J=5.1 Hz, NCH), 4.33 (d, 1H, J=11.1 Hz, OCH), 3.90–4.11 (m, 1H, OCH_2), 3.67–3.79 (m, 1H, OCH_2), 2.65–2.78 (m, 1H, CH), 2.24 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.01–2.14 (m, 1H, CH_2), 1.38–1.47 (m, 1H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−140.01 to −140.03 (2F), −153.71 to −153.72 (1F), −160.92 to −160.93 (2F); MS (m/z, %): 370 (M^++1, 10.41); 369(M^+, 57.28), 324 ($M^+-OCH_2CH_2$, 100.00), 202 ($M^+-C_6F_5$, 6.94), 158 ($M^+-OCH_2CH_2-C_6F_5$, 25.56), 91 ($C_6H_5CH_3$, 20.25), 77 ($C_6H_5^+$, 15.71); HRMS Calcd for $C_{19}H_{16}F_5NO$: 369.1152. Found: 369.1150.

4.2.18. 4.2.18Compound ***7d***. ^1H NMR (300 MHz, $CDCl_3$): δ=6.53 (d, 1H, J=7.8 Hz, ArH), 6.32 (d, 1H, J=7.8 Hz, ArH), 5.22 (s, 1H, NCH), 4.64 (d, 1H, J=11.4 Hz, OCH), 3.71–3.92 (m, 2H, OCH_2), 2.76–2.89 (m, 1H, CH), 2.20 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.87–1.97 (m, 1H, CH_2), 1.37–1.49 (m, 1H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−144.6.01 to −144.62 (2F), −154.93 to −154.94 (1F), −161.60 to −161.61 (2F).

4.2.19. Compound ***6e***. White solid; mp °C; ^1H NMR (300 MHz, $CDCl_3$): δ=7.30 (s, 1H, ArH), 7.03 (d, 1H, J=9.0 Hz, ArH), 6.58 (d, 1H, J=9.0 Hz, ArH), 4.51 (d, 1H, J=5.1 Hz, NCH), 4.25 (d, 1H, J=11.4 Hz, OCH), 3.81–3.95 (m, 1H, OCH_2), 3.67–6.76 (m, 1H, OCH_2), 2.69–2.76 (m, 1H, CH), 2.24 (m, 1H, CH); ^{19}F NMR ($CDCl_3$): δ=−140.10 to −140.11 (2F), −153.42 to −153.43 (1F), −161.26 to −161.27 (2F); MS (m/z, %): 377 (M^++2, 24.21); 375 (M^+, 64.18),332 (M^++2OCH_2CH_2, 43.22),330 ($M^+-OCH_2CH_2$, 100.00), 208 ($M^+-C_6F_5$, 10.32), 164 ($M^+-OCH_2CH_2-C_6F_5$, 20.55), 91 ($C_6H_5CH_3$, 10.73), 77 ($C_6H_5^+$,3.06); HRMS Calcd for $C_{17}H_{11}ClF_5NO$: 375.0449. Found: 275.0456.

4.2.20. Compound ***7e***. ^1H NMR (300 MHz, $CDCl_3$): δ=7.23 (s, 1H, ArH), 6.96 (d, 1H, J=8.4 Hz, ArH), 6.58 (d, 1H, J=8.4 Hz, ArH), 5.10 (d, 1H, J=7.8 Hz, NCH), 5.01 (d, 1H, J=2.4 Hz, OCH), 3.63–3.85 (m, 2H, OCH_2), 2.61–2.83 (m, 1H, CH), 1.97–2.14 (m, 1H, CH_2), 1.21–1.37 (m, 1H, CH_2); ^{19}F NMR ($CDCl_3$): δ=−140.40 to −140.41 (2F), −154.60 to −154.61 (1F), −161.43 to −161.44 (2F).

Acknowledgements

This work supported by the National Natural Science Foundation of China (NNSFC) (Nos. 20532040) and Science and Technology Commission of Shanghai Municipality (08JC1409900).

References and notes

1. Weinreb, S. M. In *Plain Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 401–449.
2. Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: San Diego, 1987; Chapters 2 and 9.
3. Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1.
4. Yadav, J. S.; Reddy, B. V. S.; Madhuri, C. R.; Sabitha, G. *Synthesis* **2001**, *7*, 1065.
5. Yamada, N.; Kadowaki, S.; Takahashi, K.; Umezu, K. *Biochem. Pharmacol.* **1992**, *44*, 1211.
6. Faber, K.; Stueckler, H.; Kappe, T. *Heterocycl. Chem.* **1984**, *21*, 1177.
7. Johnson, J. V.; Rauckman, S.; Baccanari, P. D.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942.
8. Babu, G.; Perumal, P. T. *Tetrahedron Lett.* **1998**, *39*, 3225.
9. Crousse, B.; Begue, J. P.; Delpon, D. B. *Tetrahedron Lett.* **1998**, *39*, 5765.
10. Ma, Y.; Qian, C.; Xie, M.; Sun, J. *J. Org. Chem.* **1999**, *64*, 6462.
11. Magesh, C. T.; Makesh, S. V.; Perumal, P. T. *Bioorg. Med. Chem. Lett.* **2004**, 2035.
12. Hadden, M.; Stevenson, P. J. *Tetrahedron Lett.* **1999**, *40*, 1215.
13. Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. *Chem. Rev.* **2002**, *102*, 2227.
14. Sundararajan, G.; Prabagaran, N.; Varghese, B. *Org. Lett.* **2001**, *3*, 1973.
15. Spanedda, M. V.; Crousse, B.; Begue, J. P.; Delpon, D. B. *Tetrahedron Lett.* **2003**, *44*, 217.
16. Zhu, S. Z.; Zhu, S. F.; Jin, G. F.; Li, Z. T. *Tetrahedron Lett.* **2005**, *46*, 2713.
17. Semwal, A.; Nayak, S. K. *Synth. Commun.* **2006**, 227.
18. CCDC 744033 contains the supplementary crystallographic data of compound **4b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.
19. Wang, Y. G.; Lin, X. F.; Cui, S. L. *Synlett* **2004**, 1175.
20. Lin, X. F.; Cui, S. l; Wang, Y. G. *Tetrahedron Lett.* **2006**, 4509.