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Three-component synthesis of novel trifluoromethyl-containing tetrahydropyran derivatives

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ABSTRACT

L-Proline-catalyzed reaction of ethyl 4,4,4-trifluoroacetoacetate, cinnamaldehyde and anilines provide a novel method for preparation of ethyl-6-(arylamino)-2-hydroxy-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate derivatives in good yields. The reaction was conducted by initial Michael addition, followed by intra-molecular cyclization under mild conditions. The structure of a typical ethyl-2-hydroxy-4-phenyl-6-(*m*-tolylamino)-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (**4h**) was confirmed by XRD analysis. A plausible mechanism is presented.

1. Introduction

In a multicomponent reactions (MCRs), several bonds are formed in one step and most of the atoms contribute to the newly formed product [1]. MCRs offer many advantages over traditional approaches. These include: few reaction steps, good overall yield, environmental friendliness, resource effective, and simple operation [2]. Tietze has referred to the number of bonds, which are formed in one sequence as the bond-forming efficiency (BFE, or bond-forming economy) [3]. Thus superb MCRs must also display high BFE. In brief, MCRs have attracted considerable interest owing to their exceptional synthetic efficiency.

Recently, the catalytic property of L-proline was observed to have broad activity in aldol- [4–6], Mannich- [7–9], Michael- [10,11], Diels-Alder- [12–14], α-amination reactions and Knoevenagel reactions [15,16].

Functionalized tetrahydropyrans (THP) are the central component in a large number of biologically active natural products [17–19]. Generally, tetrahydropyran derivatives are synthesized by Prins cyclization using an acid catalyst [20–23]. Alternatively they can be formed by hetero-Diels-Alder cyclization [24–26]. In addition it has also been reported that this reaction can be catalyzed by indium halides as Lewis acid [27,28]. While considerable effort has been devoted to syntheses of these heterocycles, much investigation is still needed to develop more general and practical methods for this transformation. Thus, in this study we used organocatalysts in a one-pot reaction of cinnamaldehyde, anilines and ethyl 4,4,4-trifluoroacetoacetate. This reaction successfully generated a series of ethyl-6-(arylamino)-2-hydroxy-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate derivatives (Scheme 1).

2. Results and discussion

In the absence of catalyst, the reaction was very inefficient and only gave traces of the desired product even with a prolonged reaction time (18 h). Similarly when the organic bases Et_3N and pieperidine were respectively used as catalysts, similar results were obtained. Finally when L-proline (10 mol%) was used as catalyst, with stirring at room temperature for 4 h, the reaction proceeded smoothly (TLC) where **4** were obtained in good yield (Table 1), without formations of byproduct **5** (Scheme 1). The catalytic activities of other amino acids such as L-tyrosine, DL-alanine and DL-2-phenylglycine were also examined; however, the reaction results were not satisfied under the same reaction conditions (entries 4–6, Table 1).

Next, the influence of solvent on these MCRs was briefly studied. The reactions were carried out in different solvents at room temperature catalyzed by L-proline (10 mol%). As shown in Table 1, the reaction gave moderate yields in solvents of low polarity as dichloromethane. However, the reaction gave much better yields in more polar solvents such as ethyl acetate and ethanol. It should be noted that the reaction gave the lowest yield in water due to the solubility of the starting materials.

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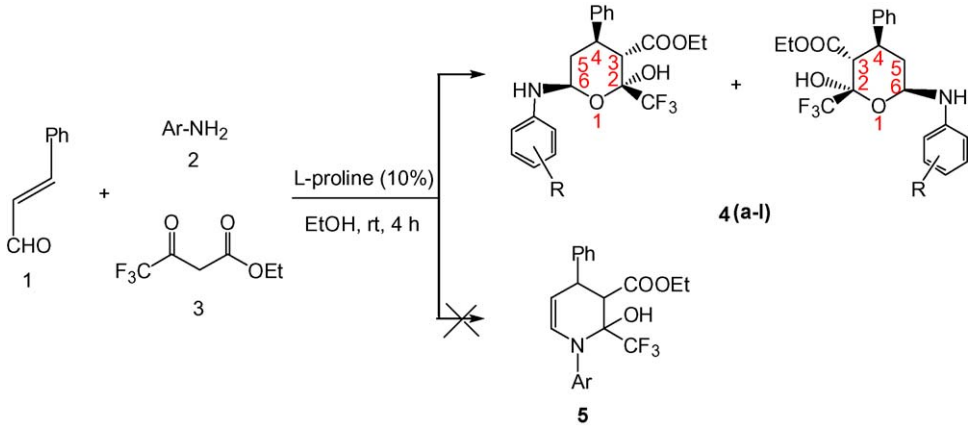


Scheme 1.

The efficiency of this three-component reaction was investigated under optimal reaction conditions. We carried out the reactions with a variety of anilines. The reaction results are summarized in Table 2. Most of reactions proceeded smoothly at room temperature, and the appropriate expected products were obtained in moderate to good yields.

As shown in Table 2, it was clear that the product yield was influenced by both electronic and steric effects of the substituting group of various anilines. First, for the anilines bearing electron-donating group, the product yields were high (entries 3–5; Table 2); on the other hand, the anilines bearing electron-withdrawing group displayed low product yield (entry 9; Table 2). Secondly, the anilines possessing *ortho* positions substituents gave product yields that were lower than those aniline containing *para* or *meta* positioned substituents (entries 2 and 7; 3, 8 and 12; Table 2).

It should be noted that when *o*-nitroaniline, *o*-chloro-*p*-nitroaniline, *o*-phenylenediamine, α-naphthylamine, benzylamine and *n*-butylamine were used, the reactions were unsuccessful and the desired products were not obtained.

The structures of compounds **4** were confirmed by ^{1}H NMR, ^{19}F NMR, MS, IR spectroscopies and elemental analysis. The specific rotation values showed that the products **4** were racemic mixtures. In addition, the structure of **4h** was determined by X-ray crystallographic study (Fig. 1).

The crystal study indicated that the tetrahydropyran ring adopted a chair conformation, the absolute configurations of these two isomers were (2S, 3R, 4S, 6R) and (2R, 3S, 4R, 6S), respectively. It was also clear that the bulky substituting groups occupy equatorial bond positions, resulting in antiperiplannar formation of more stable molecules. Trifluoromethyl group occupied the *trans* position with ethoxylcarbonyl groups due to the intramolecular H-bond which formed between the protons attached to

Table 1
Screening of the catalysts and solvents for this MCRs[a].

Entry	Catalyst	Solvent	Time (h)	Yield of **4** (%)[b]
1	No	EtOH	18	Trace
2	Et_3N	EtOH	12	Trace
3	Pieperidine	EtOH	12	Trace
4	L-Tyrosine	EtOH	4	20
5	DL-Alanine	EtOH	4	24
6	DL-Phenylglycine	EtOH	4	23
7	L-Proline	EtOH	4	88
8	L-Proline[c]	CH_2Cl_2	4	63
9	L-Proline[c]	AcOEt	4	75
10	L-Proline[c]	H_2O	4	40
11	L-Proline[c]	EtOH	4	80

[a] Reaction conditions: *m*-toluidine (1 mmol), cinnamaldehyde (1 mmol), ethyl 4,4,4-trifluoroacetoacetate (1 mmol), solvent (1 mL), catalyst (10 mol%), rt.
[b] Isolated yield.
[c] 4-Chloro-phenylamine (1 mmol) was used as reaction substrate.

Table 2
Synthesis of ethyl-6-(arylamino)-2-hydroxy-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate[a].

Entry	R	Product	Yield of **4** (%)[b]
1	H	**4a**	76
2	4-Cl	**4b**	80
3	2-CH_3	**4c**	79
4	2-OCH_3	**4d**	85
5	4-OCH_2CH_3	**4e**	79
6	3-Br	**4f**	77
7	2-Cl	**4g**	78
8	3-CH_3	**4h**	88
9	3-NO_2	**4i**	72
10	2,4-CH_3	**4j**	73
11	2,5-CH_3	**4k**	75
12	4-CH_3	**4l**	83

[a] Reaction conditions: aniline (1 mmol); cinnamaldehyde (1 mmol); ethyl 4,4,4-trifluoroacetoacetate (1 mmol); L-proline (10 mol%); EtOH (1 mL); rt.
[b] Isolated yield.

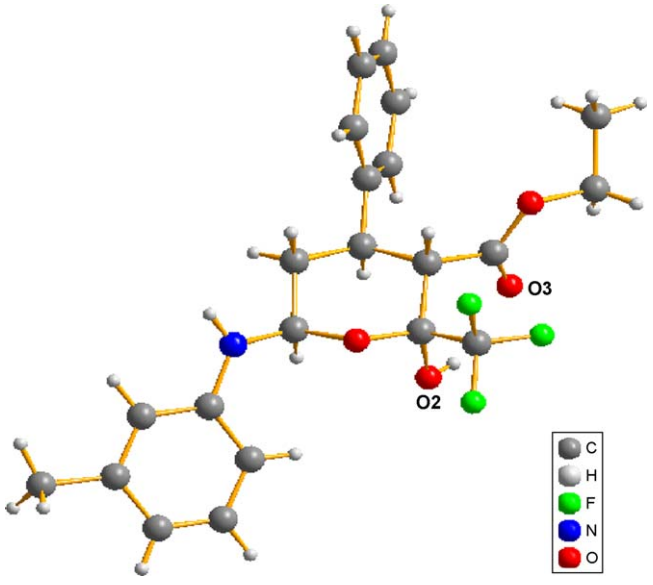
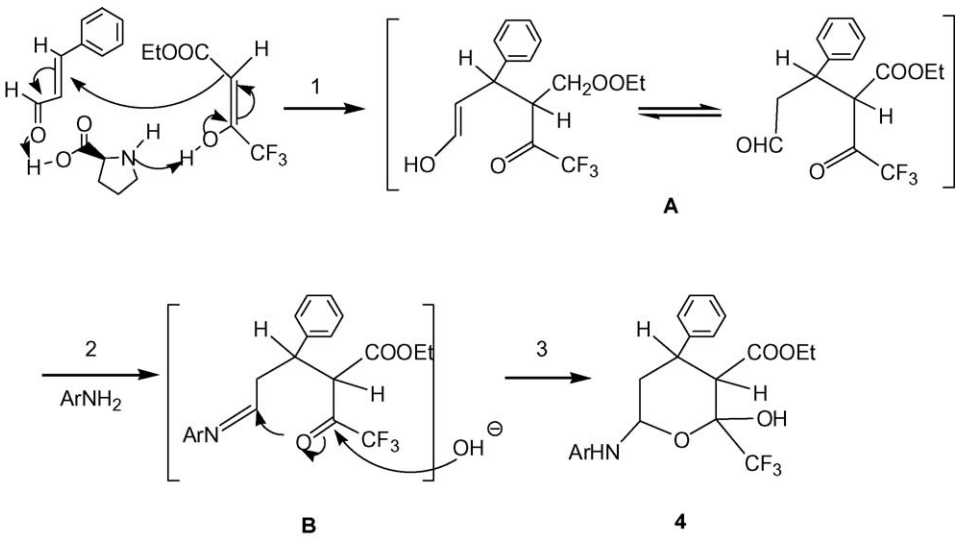


Fig. 1. X-ray crystal structure of **4h**.



Scheme 2. A plausible mechanism of coupling of aniline, cinnamaldehyde and ethyl 4,4,4-trifluoroacetoacetate.

oxygen O2 of hydroxyl group and the oxygen O3 of carbonyl group (D (O3. . .H2A) = 2.07 Å; ∠(O2–H2A. . .O3) = 144.80°).

In ^{19}F NMR, the chemical shift of CF_3 group in all products was a singlet peak nearly at δ: −85.3 to −85.4 ppm (s, 3F), is indicated that the CF_3 group resided next to the saturated sp^3 carbon atom. In addition, the signal of OH group was not visible in ^{1}H NMR except for **4i**, **4j** and **4l**.

Menendez and co-workers reported the use of aromatic amines, cinnamaldehyde, and ethyl acetoacetate along with cerium ammonium nitrate (CAN) (catalyst) to synthesize 1,4-dihydropyridines derivatives in 2007 [29]. Similarly, Kumar and Maurya reported a comparable reaction catalyzed by L-proline under solvent free conditions in 2008 [30]. These reactions employed classic Hantzsch synthetic methods. However, in our case we exclusively obtained tetrahydropyran derivatives. The difference was attributed to the electronic nature of trifluoromethyl group. More specifically, the carbonyl group was readily attacked by hydroxyl group to give the corresponding ketone hydrate (nucleophilic oxygen atom intermediate). This intermediate then in turn could attack the carbon atom of imine group to exclusively produce the corresponding tetrahydropyran derivatives, without formation of 4-H-dihydro-pyridine moiety.

A plausible mechanism of this three-component reaction is outlined as follows (Scheme 2). Firstly, cinnamaldehyde reacted with ethyl 4,4,4-trifluoroacetoacetate via Michael reaction to form the intermediate A, catalyzed by L-proline through step 1 as an acid/base catalyst; the imine intermediate B is formed though step 2; thereafter the carbonyl group is hydrolyzed by water to form the nucleophilic oxygen atom intermediate and finally intra-molecular cyclization yields the expected product though step 3. The isolated products we obtained were racemic mixtures.

3. Conclusion

In summary, we have developed a new and efficient organo-catalyzed one-pot, three-component reaction protocol for the synthesis of a series of 6-arylamino-2-trifluoromethyl-tetrahydropyran derivatives. The reaction is performed under mild conditions via coupling of anilines, cinnamaldehyde and ethyl 4,4,4-trifluoroacetoacetate. The advantages of this method include: accessible starting materials, simple experimental procedure, an inexpensive and non-toxic catalyst, and high product yield.

4. Experimental

4.1. General

Melting points were measured with digital melting point apparatus (WRS-1B, Shanghai Precision & Scientific Instrument Co. Ltd.) and were uncorrected. ^{1}H NMR and ^{19}F NMR spectra were acquired in $CDCl_3$ on Bruker AM-500 instruments with Me_4Si and $CFCl_3$ as the internal standards, respectively. FT-IR spectra were obtained with a Nicolet AVATAR-370 spectrophotometer. An Agilent Technologies 5975 inert Mass Selective Detector was used to acquire mass spectra. Elemental analyses were performed using a Vario ELIII Analyzer. X-ray crystal structure data were collected on a Bruck SMART CCD area-detector diffractometer using graphite monochromatized Mo Kα radiation (λ = 0.71073 Å) at 296(2) K.

4.2. Typical experimental procedure for the synthesis of ethyl-6-(arylamino)-2-hydroxy-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (**4a**–**4l**)

To a mixture of cinnamaldehyde (2.0 mmol), anilines (2.0 mmol), and ethyl 4,4,4-trifluoro-acetoacetate (2.0 mmol) in EtOH (1 mL), 0.20 mmol of L-proline as catalyst was added and stirred at room temperature for 4 h. EtOH was evaporated and the reaction mixture was then poured into saturated brine (15 mL) and extracted with ethyl acetate (15 mL × 3). The organic layer was dried over anhydrous magnesium sulfate and evaporated to dryness. A crude solid was obtained. The pure product was obtained through crystallization from ethyl acetate/petroleum ether (V_{EA}/V_{PE} = 1/8).

4.2.1. Ethyl-2-hydroxy-4-phenyl-6-(phenylamino)-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (**4a**)

White solid, mp: 136–138 °C. Yield: 76%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 0.80 (t, 3H, J = 7.0 Hz, CH_3); 1.95 (ddd, 1H, J = 12.5, 12.5, 10.5. Hz, C^5H); 2.20 (ddd, 1H, J = 12.5, 3.5, 2.0 Hz, C^5H); 2.98 (d, 1H, J = 12.5 Hz, C^3H); 3.46 (ddd, 1H, J = 12.5, 12.5, 3.5 Hz, C^4H); 3.85–3.89 (m, 2H, OCH_2); 5.69 (dd, 1H, J = 10.5, 2.0 Hz, C^6H); 5.84 (s, 1H, NH); 6.84–7.36 (m, 10H, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −85.3 (s, 3F). IR (KBr, cm^{-1}): 3385, 1695, 1607, 1513, 1472, 1450, 1201, 757, 696. MS (*m/z*, %): 409 (M^+, 28), 206 (PhC_3HNHPh^+, 100), 139 ($CF_3COCH_2CO^+$, 14), 115 ($EtOCOCH_2CO^+$, 25), 104

(PhCH = CH_2^+, 35), 69 (CF^+, 13). Anal. Calcd for: $C_{21}H_{22}F_3NO_4$ (%): C, 61.66; H, 5.42; N, 3.42. Found: C, 61.56; H, 5.45; N, 3.26.

4.2.2. Ethyl-6-(4-chloro-phenylamino)-2-hydroxy-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (**4b**)

White solid, mp: 118–120 °C. Yield: 80%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 0.79 (t, 3H, J = 7.0 Hz, CH_3); 1.92 (ddd, 1H, J = 12.5, 12.5, 10.5 Hz, C^5H); 2.18 (ddd, 1H, J = 12.5, 3.5, 2.0 Hz, C^5H); 2.97 (d, 1H, J = 12.5 Hz, C^3H); 3.45 (ddd, 1H, J = 12.5, 12.5, 3.5 Hz, C^4H); 3.85–3.90 (m, 2H, OCH_2); 5.62 (dd, 1H, J = 10.5, 2.0 Hz, C^6H); 5.86 (s, 1H, NH); 6.76–7.36 (m, 9H, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −85.4 (s, 3F). IR (KBr, cm^{-1}): 3437, 1709, 1603, 1589, 1516, 1478, 1197, 760, 699. MS (m/z, %): 443 (M^+, 9), 220 ($C_9H_7O_3F_3^+$, 100), 139 ($CF_3COCH_2CO^+$, 13), 115 ($EtOCOCH_2CO^+$, 15), 104 (PhCH = CH_2^+, 40), 69 (CF3$^+$, 9). Anal. Calcd for: $C_{21}H_{21}ClF_3NO_4$ (%): C, 56.83; H, 4.77; N, 3.16. Found: C, 56.64; H, 4.95; N, 3.28.

4.2.3. Ethyl-2-hydroxy-4-phenyl-6-(o-tolylamino)-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (**4c**)

White solid, mp: 125–127 °C. Yield: 79%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 0.81 (t, 3H, J = 7.0 Hz, CH_3); 2.01 (ddd, 1H, J = 12.5, 12.5, 10.5 Hz, C^5H); 2.15 (s, 3H, Ar-CH_3); 2.18 (ddd, 1H, J = 12.5, 3.5, 2.0 Hz, C^5H); 3.00 (d, 1H, J = 12.5 Hz, C^3H); 3.45 (ddd, 1H, J = 12.5, 12.5, 3.5 Hz, C^4H); 3.85–3.90 (m, 2H, OCH_2); 5.71 (dd, 1H, J = 10.5, 2.0 Hz, C^6H); 5.84 (s, 1H, NH); 6.76–7.36 (m, 9H, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −85.3 (s, 3F). IR (KBr, cm^{-1}): 3437, 1709, 1603, 1589, 1516, 1455, 1198, 760, 699. MS (m/z, %): 423 (M^+, 19), 220 ($C_9H_7O_3F_3^+$, 78), 139 ($CF_3COCH_2CO^+$, 34), 115 ($EtOCOCH_2CO^+$, 51), 104 (PhCH = CH_2^+, 100), 69 (CF_3^+, 33). Anal. Calcd for (%): $C_{22}H_{24}F_3NO_4$: C, 62.40; H, 5.71; N, 3.31. Found: C, 62.15; H, 5.82; N, 3.17.

4.2.4. Ethyl-2-hydroxy-6-(2-methoxy-phenylamino)-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (**4d**)

Yellow solid, mp: 129–131 °C. Yield: 85%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 0.80 (t, 3H, J = 7.0 Hz, CH_3); 2.03 (ddd, 1H, J = 12.5, 12.5, 10.5 Hz, C^5H); 2.22 (ddd, 1H, J = 12.5, 3.5, 2.0 Hz, C^5H); 2.98 (d, 1H, J = 12.5 Hz, C^3H); 3.45 (ddd, 1H, J = 12.5, 12.5, 3.5 Hz, C^4H); 3.82 (s, 1H, OCH_3); 3.85–3.90 (m, 2H, OCH_2); 5.70 (dd, 1H, J = 10.5, 2.0 Hz, C^6H); 5.83 (s, 1H, NH); 6.79–7.35 (m, 9H, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −85.3 (s, 3F). IR (KBr, cm^{-1}): 3431, 1694, 1604, 1521, 1478, 1459, 1202, 738. MS (m/z, %): 439 (M^+, 50), 220 ($C_9H_7O_3F_3^+$, 77), 139 ($CF_3COCH_2CO^+$, 50), 123 ($CH_3OPhNH_2^+$, 100), 115 ($EtOCOCH_2CO^+$, 75), 104 (PhCH = CH_2^+, 68), 69 (CF_3^+, 49). Anal. Calcd for: $C_{22}H_{24}F_3NO_5$ (%): C, 60.13; H, 5.51; N, 3.19. Found: C, 60.36; H, 5.56; N, 3.02.

4.2.5. Ethyl-6-(4-ethoxy-phenylamino)-2-hydroxy-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (**4e**)

White solid, mp: 106–108 °C. Yield: 79%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 0.80 (t, 3H, J = 7.5 Hz, CH_3); 1.37 (t, 3H, J = 7.0 Hz, CH_3); 1.90 (ddd, 1H, J = 12.5, 12.5, 10.5 Hz, C^5H); 2.18 (ddd, 1H, J = 12.5, 3.5, 2.0 Hz, C^5H); 2.97 (d, 1H, J = 12.5 Hz, C^3H); 3.44 (ddd, 1H, J = 12.5, 12.5, 3.5 Hz, C^4H); 3.85–3.90 (m, 2H, OCH_2); 3.95–3.99 (m, 2H, Ar-OCH_2); 5.70 (dd, 1H, J = 10.5, 2.0 Hz, C^6H); 5.81 (s, 1H, NH); 6.80–7.35 (m, 9H, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −85.3 (s, 3F). IR (KBr, cm^{-1}): 3381, 1701, 1606, 1515, 1474, 1200, 820, 759. MS (m/z, %): 453 (M^+, 51), 250 ($EtOPhNHC_3HPh^+$, 33), 220 ($C_9H_7O_3F_3^+$, 49), 139 ($CF_3COCH_2CO^+$, 46), 104 (PhCH = CH_2^+, 61), 69 (CF_3^+, 58). Anal. Calcd for: $C_{23}H_{26}F_3NO_5$ (%): C, 60.92; H, 5.78; N, 3.09. Found: C, 61.06; H, 5.79; N, 2.97.

4.2.6. Ethyl-6-(3-bromo-phenylamino)-2-hydroxy-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (**4f**)

Yellow solid, mp: 113–115 °C. Yield: 77%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 0.80 (t, 3H, J = 7.0 Hz, CH_3); 1.93 (ddd, 1H, J = 12.5, 12.5, 10.5 Hz, C^5H); 2.18 (ddd, 1H, J = 12.5, 3.5, 2.5 Hz, C^5H); 2.98 (d, 1H, J = 12.5 Hz, C^3H); 3.45 (ddd, 1H, J = 12.5, 12.5, 3.5 Hz, C^4H); 3.84–3.91 (m, 2H, OCH_2); 5.63 (dd, 1H, J = 10.5, 2.0 Hz, C^6H); 5.85 (s, 1H, NH); 6.79–7.36 (m, 9H, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −85.4 (s, 3F). IR (KBr, cm^{-1}): 3445, 1705, 1598, 1504, 1482, 1459, 1193, 767, 703. MS (m/z, %): 487/489 (M^+, 10/10), 284/286 ($BrPhNHC_3HPh^+$, 31/25), 220 ($C_9H_7O_3F_3^+$, 30), 139 ($CF_3COCH_2CO^+$, 58), 115 ($EtOCOCH_2CO^+$, 100), 104 (PhCH = CH_2^+, 67), 69 (CF_3^+, 49). Anal. Calcd for: $C_{21}H_{21}BrF_3NO_4$ (%): C, 51.65; H, 4.33; N, 2.87. Found: C, 52.03; H, 4.46; N, 2.59.

4.2.7. Ethyl-6-(2-chloro-phenylamino)-2-hydroxy-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (**4g**)

White solid, mp: 126–128 °C. Yield: 78%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 0.81 (t, 3H, J = 7.0 Hz, CH_3); 2.04 (ddd, 1H, J = 12.5, 12.5, 10.5 Hz, C^5H); 2.25 (ddd, 1H, J = 12.5, 3.5, 2.0 Hz, C^5H); 3.01 (d, 1H, J = 12.5 Hz, C^3H); 3.47 (ddd, 1H, J = 12.5, 12.5, 3.5 Hz, C^4H); 3.86–3.90 (m, 2H, OCH_2); 5.68 (dd, 1H, J = 10.5, 2.0 Hz, C^6H); 5.88 (s, 1H, NH); 6.75–7.36 (m, 9H, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −85.4 (s, 3F). IR (KBr, cm^{-1}): 3416, 1696, 1602, 1520, 1445, 1469, 1200, 744, 696. MS (m/z, %): 443 (M^+, 21), 240/242 ($ClPhNHC_3HPh^+$, 52/22), 220 ($C_9H_7O_3F_3^+$, 30), 139 ($CF_3COCH_2CO^+$, 24), 127/129 ($ClPhNH_2^+$, 100/34), 115 ($EtOCOCH_2CO^+$, 29), 104 (PhCH = CH_2^+, 46), 69 (CF_3^+, 30). Anal. Calcd for: $C_{21}H_{21}ClF_3NO_4$ (%): C, 56.83; H, 4.77; N, 3.16. Found: C, 56.60; H, 4.82; N, 2.86.

4.2.8. Ethyl-2-hydroxy-4-phenyl-6-(m-tolylamino)-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (**4h**)

White solid, mp: 117–119 °C. Yield: 88%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 0.80 (t, 3H, J = 7.0 Hz, CH_3); 1.93 (ddd, 1H, J = 12.5, 12.5, 10.5 Hz, C^5H); 2.29 (s, 3H, Ar-CH_3); 2.17 (ddd, 1H, J = 12.5, 3.5, 2.0 Hz, C^5H); 2.97 (d, 1H, J = 12.5 Hz, C^3H); 3.45 (ddd, 1H, J = 12.5, 12.5, 3.5 Hz, C^4H); 3.84–3.90 (m, 2H, OCH_2); 5.68 (dd, 1H, J = 10.5, 2.0 Hz, C^6H); 5.82 (s, 1H, NH); 6.64–7.36 (m, 9H, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −85.3 (s, 3F). IR (KBr, cm^{-1}): 3421, 1710, 1608, 1523, 1491, 1458, 1187, 773. MS (m/z, %): 423 (M^+, 26), 220 ($C_9H_9O_3F_3^+$, 100), 139 ($CF_3COCH_2CO^+$, 48), 115 ($EtOCOCH_2CO^+$, 73), 104 (PhCH = CH_2^+, 69), 69 (CF_3^+, 54). Anal. Calcd for: $C_{22}H_{24}F_3NO_4$ (%): C, 62.40; H, 5.71; N, 3.31. Found: C, 62.55; H, 5.70; N, 3.11.

4.2.9. Ethyl-2-hydroxy-6-(3-nitro-phenylamino)-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (**4i**)

Yellow solid, mp: 134–136 °C. Yield: 72%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 0.80 (t, 3H, J = 7.0 Hz, CH_3); 1.98 (ddd, 1H, J = 12.5, 12.5, 10.5 Hz, C^5H); 2.23 (ddd, 1H, J = 12.5, 3.5, 2.0 Hz, C^5H); 2.99 (d, 1H, J = 12.5 Hz, C^3H); 3.48 (ddd, 1H, J = 12.5, 12.5, 3.5 Hz, C^4H); 3.86–3.90 (m, 2H, OCH_2); 4.65 (d, 1H, J = 9.5 Hz, OH); 5.71 (dd, 1H, J = 10.5, 2.0 Hz, C^6H); 5.91 (s, 1H, NH); 7.18–7.69 (m, 9H, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −85.3 (s, 3F). IR (KBr, cm^{-1}): 3427, 1699, 1623, 1589, 1530, 1439, 1196, 764, 737. MS (m/z, %): 453 (M^+, 4), 250 ($O_2NPhNC_3HPh^+$, 6), 220 ($C_9H_7O_3F_3^+$, 24), 139 ($CF_3COCH_2CO^+$, 39), 127 (PhC_3N^+, 100), 115 ($EtOCOCH_2CO^+$, 54), 104 (PhCH = CH_2^+, 61), 69 (CF_3^+, 34). Anal. Calcd for: $C_{21}H_{21}F_3N_2O_6$ (%): C, 55.51; H, 4.66; N, 6.16. Found: C, 55.73; H, 4.82; N, 5.89.

4.2.10. Ethyl-6-(2,4-dimethyl-phenylamino)-2-hydroxy-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (**4j**)

Yellow solid, mp: 105–107 °C. Yield: 73%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 0.80 (t, 3H, J = 7.0 Hz, CH_3); 1.98 (ddd, 1H, J = 12.5, 12.5, 10.5 Hz, C^5H); 2.15 (s, 3H, Ar-CH_3); 2.25 (s, 3H, Ar-CH_3); 2.21 (ddd, 1H, J = 12.5, 3.5 2.0 Hz, C^5H); 2.97 (d, 1H, J = 12.5 Hz, C^3H); 3.45 (ddd, 1H, J = 12.5, 12.5, 3.5 Hz, C^4H); 3.84–3.90 (m, 2H, OCH_2); 4.00 (bs, 1H, OH); 5.67 (dd, 1H, J = 10.5, 2.0 Hz, C^6H); 5.83 (s, 1H, NH); 6.88–7.36 (m, 8H, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −85.3 (s, 3F). IR (KBr, cm^{-1}): 3432, 1706, 1618, 1518, 1452, 1183, 814, 760. MS (m/z, %): 437 (M^+, 53), 234 [$(CH_3)_2PhNHC_3HPh^+$, 80], 220

($C_9H_7O_3F_3^+$, 41), 139 ($CF_3COCH_2CO^+$, 42), 121 [$(CH_3)_2PhNH_2^+$, 100], 115 ($EtOCOCH_2CO^+$, 55), 104 ($PhCH=CH_2^+$, 53), 69 (CF_3^+, 33). Anal. Calcd for: $C_{23}H_{26}F_3NO_4$ (%): C, 63.15; H, 5.99; N, 3.20. Found: C, 62.99; H, 5.95; N, 2.91.

4.2.11. Ethyl-6-(2,5-dimethyl-phenylamino)-2-hydroxy-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (4k)

White solid, mp: 118–120 °C. Yield: 75%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 0.80 (t, 3H, J = 7.0 Hz, CH_3); 1.98 (ddd, 1H, J = 12.5, 12.5 10.5 Hz, C^5H); 2.11 (s, 3H, Ar-CH_3); 2.33 (s, 3H, Ar-CH_3); 2.23 (ddd, 1H, J = 12.5, 3.5 2.0 Hz, C^5H); 2.98 (d, 1H, J = 12.5 Hz, C^3H); 3.47 (ddd, 1H, J = 12.5, 12.5, 3.5 Hz, C^4H); 3.84–3.90 (m, 2H, OCH_2); 5.69 (dd, 1H, J = 10.5, 2.0 Hz, C^6H); 5.82 (s, 1H, NH); 6.60–7.36 (m, 8H, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −85.3 (s, 3F). IR (KBr, cm^{-1}): 3435, 1710, 1616, 1585, 1528, 1495, 1196, 760, 699. MS (m/z, %): 437 (M^+, 27), 234 [$(CH_3)_2PhNHC_3HPh^+$, 100], 220 ($C_9H_7O_3F_3^+$, 33), 139 ($CF_3COCH_2CO^+$, 42), 121 [$(CH_3)_2PhNH_2^+$, 97], 115 ($EtOCOCH_2CO^+$, 58), 104 ($PhCH=CH_2^+$, 52), 69 (CF_3^+, 34). Anal. Calcd for: $C_{23}H_{26}F_3NO_4$ (%): C, 63.15; H, 5.99; N, 3.20. Found: C, 62.89; H, 5.99; N, 2.93.

4.2.12. Ethyl-2-hydroxy-4-phenyl-6-(p-tolylamino)-2-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (4l)

Yellow solid, mp: 104–106 °C. Yield: 83%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 0.83 (t, 3H, J = 7.0 Hz, CH_3); 1.94 (ddd, 1H, J = 12.5, 12.5, 10.5 Hz, C^5H); 2.29 (s, 3H, Ar-CH_3); 2.23 (ddd, 1H, J = 12.5, 3.5 2.0 Hz, C^5H); 2.99 (d, 1H, J = 12.5 Hz, C^3H); 3.48 (ddd, 1H, J = 12.5, 12.5, 3.5 Hz, C^4H); 3.87–3.92 (m, 2H, OCH_2); 4.26 (s, 1H, OH); 5.69 (dd, 1H, J = 10.5, 2.0 Hz, C^6H); 5.85 (s, 1H, NH); 6.79–7.37 (m, 9H, ArH). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −85.3 (s, 3F). IR (KBr, cm^{-1}): 3379, 1693, 1618, 1587, 1522, 1495, 1202, 811, 698. MS (m/z, %): 423 (M^+, 34), 220 ($C_9H_9O_3F_3^+$, 100), 139 ($CF_3COCH_2CO^+$, 31), 115 (($EtOCOCH_2CO^+$, 56), 104 ($PhCH=CH_2^+$, 42), 69 (CF_3^+, 36). Anal. Calcd for: $C_{22}H_{24}F_3NO_4$ (%): C, 62.40; H, 5.71; N, 3.31. Found: C, 62.65; H, 5.71; N, 3.01.

4.3. X-ray crystal structure data of compounds 4h

CCDC 703269 contains the supplementary crystallographic data for this paper. These results can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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