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Facile one-pot three-component reaction to synthesize trifluoromethylated cyclopenta[*b*]pyran derivatives and their further transformation

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ABSTRACT

A series of trifluoromethylated cyclopenta[*b*]pyran derivatives were synthesized efficiently from 1,3-cyclopentanedione, arylaldehydes, and ethyl 4,4,4-trifluoro-3-oxobutanoate via one-pot multi-component reaction catalyzed by NH_4OAc. This one-pot multi-component process comprises an initial Michael addition and a subsequent intramolecular cyclization reaction. The effect of catalysts and solvents on the reaction efficiency and the yield were investigated. The structure of product **4f** was further confirmed by XRD analysis. Meanwhile, further transformation of hemi-ketal moiety to the corresponding dehydrated product is also studied. In addition, a possible mechanism of this reaction is proposed herein.

Multicomponent reactions (MCRs) have proved to be one of the most powerful and efficient methods for the preparation of bioactive heterocyclic compounds because of its atom economy, simple experimentation, and high yields of the products.[1] MCRs, such as the Biginelli,[2] Passerini,[3] Ugi,[4] and Hantzsch, provide a wide variety of methods to synthesize important heterocycles.[5] Hence, such reactions have constituted increasingly valuable approaches for preparing products with complex structure and libraries in recent years.[6]

Fluorine-containing heterocycles are widely recognized as important organic molecules showing interesting biological activities with potential for applications in the medicinal and agricultural fields.[7] Introduction of trifluoromethyl groups into heterocycles can bring about remarkable changes in the physical, chemical, and biological properties.[8] Thus, trifluoromethyl-substituted heterocycles are becoming increasingly important for the development of new agrochemicals and medicines. The reactions of trifluoromethyl-1,3-dicarbonyl compounds, as fluorine-containing building blocks, have been investigated extensively,[9] and are well established as synthetic intermediates in heterocyclic chemistry.[10] In recent years, the synthesis of fluorinated *O*-heterocyclic or *N*-heterocyclic compounds have received much attention.[11] With this aim, we reported the synthesis of a variety of trifluoromethyl containing heterocycles based on the fluorinated building block strategy.

4*H*-Pyran moiety is a constituent of many natural products, showing important biological and pharmacological activities.[12] Due to their important use in organic synthesis, the synthetic methodology for cyclopenta[*b*]pyrans have been studied for many years.[13] Recently, Tu et al. presented a methodology to synthesize a series of 4-aryl-cyclopenta[*b*]pyran derivatives from aromatic aldehyde, 1,3-cyclopentanedione and malononitrile or ethyl cyanoacetate via multi-component reaction under solvent-free and catalyst-free conditions.[14] The cyclopenta[*b*]pyrans could also be constructed by ruthenium/TFA-catalyzed coupling of activated secondary propargylic alcohols with cyclic 1,3-diones.[15] However, the synthesis of the corresponding trifluoromethylated cyclopenta[*b*]pyrans is scarcely documented or not investigated thoroughly in the literature. In addition, in order to evaluate the potential applications of MCRs in the field of organofluorine chemistry and to continue our ongoing study on the synthesis of fluorine-containing heterocyclic compounds via MCRs based on the trifluoromethyl-1,3-dicarbonyl compounds, a versatile fluorine-containing building block, herein, we wish to report a one-pot, three-component reaction to synthesize the ethyl 4-aryl-2-hydroxy-5-oxo-2-(trifluoromethyl)-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-3-carboxylate derivatives, and their further dehydration reaction.

Initially, we carried out the one-pot, three-component reaction of benzaldehyde **1a**, 1,3-cyclopentanedione **2,** and ethyl 4,4,4-trifluoro-3-oxobutanoate **3** as model reaction. To a solution of **1a** (1 mmol), **2** (1 mmol), and **3** (1 mmol) in ethanol (15.0 mL) was added a catalytic amount of Et_3N (25 mol %). The mixture was then

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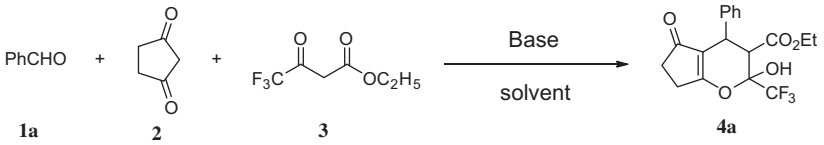
Table 1
Optimization of the one-pot reaction under various conditions[a]

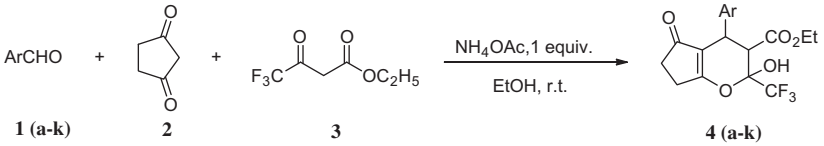


1a 2 3 4a

Entry	Base/equiv	Solvent	Time/T	Yield of **4a**[b] (%)
1	—[c]	EtOH	24/rt	Trace
2	Et_3N/0.25	EtOH	24/rt	Trace
3	Et_3N/0.25	EtOH	8/reflux	35
4	Piperidine/0.25	EtOH	24/rt	26
5	Piperidine/0.25	EtOH	24/reflux	31
6	NH_4OAc/1.00	EtOH	8/rt	67
7	NH_4OAc/1.00	EtOH	24/reflux	59
8	NH_4OAc/0.50	EtOH	8/rt	54
9	NH_4OAc/2.00	EtOH	8/rt	64
10	Pyridine/0.25	EtOH	24/rt	Trace
11	DABCO/0.25	EtOH	24/reflux	20
12	NH_4OAc/1.00	MeOH	8/rt	57
13	NH_4OAc/1.00	THF	24/rt	27
14	NH_4OAc/1.00	CH_2Cl_2	24/rt	40
15	NH_4OAc/1.00	CH_3CN	24/rt	18
16	NH_4OAc/1.00	DME	24/rt	Trace

[a] Reaction and conditions: **1a** (1 mmol), **2** (1 mmol), **3** (1 mmol), solvent:15 mL.
[b] Isolated yield.
[c] Without catalyst.

Table 2
One-pot synthesis of product **4**[a,17,18]



1 (a-k) 2 3 4 (a-k)

Entry	Ar	Time/h	Product	Yield[b] (%)
1	C_6H_5	8	**4a**	67
2	*p*-FC_6H_4	8	**4b**	77
3	*p*-ClC_6H_4	8	**4c**	64
4	*p*-BrC_6H_4	8	**4d**	62
5	*p*-$O_2NC_6H_4$	8	**4e**	63
6	*p*-NCC_6H_4	8	**4f**	56
7	*p*-$CH_3C_6H_4$	8	**4g**	59
8	*m*-ClC_6H_4	8	**4h**	66
9	*m*-BrC_6H_4	8	**4i**	60
10	*m*-$O_2NC_6H_4$	8	**4j**	61
11	*p*-$CH_3OC_6H_4$	24	**4k**	24
12	*o*-ClC_6H_4	24	—	—
13	2,4-$Cl_2C_6H_4$	24	—	—

[a] Reaction and conditions: aryldehyde **1**(**a**–**k**) (1.5 mmol), 1,3-cyclopentanedione **2** (1.5 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate **3** (1.5 mmol), NH_4OAc (1.0 equiv.), EtOH (15.0 mL), room temperature.
[b] Isolated yield.

stirred at room temperature for 24 h, however, this reaction failed to occur and the starting materials were recovered. Hence, the mixture was heated to reflux, after stirring for 8 h, TLC analysis showed that the reaction did not proceed efficiently. General work-up afforded the product **4a** only in 35% yield as a white solid (entry 3, Table 1).

Based on the above results, the reaction conditions were optimized to improve the yield by changing bases and solvents. The effects of a variety of organic bases and the amount on the reaction efficiency and yield were first screened. As shown in Table 1, when the reaction was performed in the absence of base, no product was obtained (entry 1, Table 1). It was observed that the reaction took much longer time to give **4a** in 26% yield when piperidine was utilized as catalyst (entry 4, Table 1). Other organic bases such as DABCO and Pyridine used in place of Et_3N resulted in lower yields of **4a** (entries 10–11, Table 1). Surprisingly, the yield was improved significantly when 1 equiv of NH_4OAc was used (entry 6, Table 1). It should be indicated that the reaction exclusively gave the *O*-heterocycles **4a**, and no corresponding *N*-heterocycles were detected even though the reaction was carried out in the presence of excess of NH_4OAc (entry 9, Table 1). The above reaction results indicated that NH_4OAc, served as soft brønsted acid, played a unique role in the one-pot, three-component reaction, other than a reactant.[16]

With the optimal results in hand as shown in Table 1, entry 6, we investigated the scope and limitation of this one-pot, three-component reaction. A variety of aromatic aldehydes with

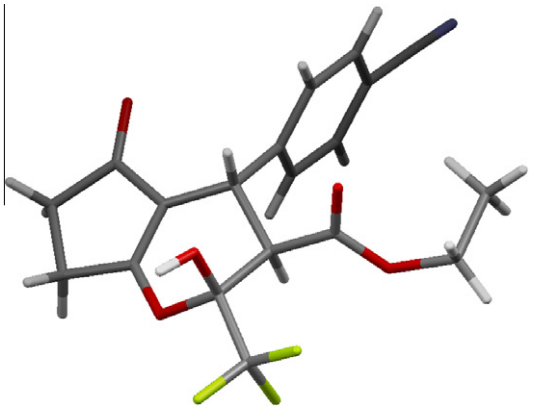
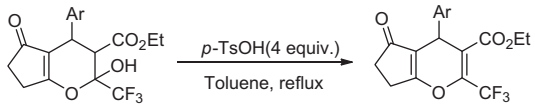


Figure 1. X-Ray crystal structure of compound **4f**.

Table 3
Reaction results of dehydration of **4**[a,b,20,21]



4 5

Entry	Ar	Time/h	Product	Yield[b] (%)
4a	C_6H_5	12	**5a**	70
4c	*p*-ClC_6H_4	12	**5b**	72
4g	*m*-ClC_6H_4	12	**5c**	71

[a] Reaction and conditions: **4** (1.0 mmol), *p*-TsOH (4.0 mmol, 4.0 equiv), solvent: toluene (15.0 mL), reflux.
[b] Isolated yields.

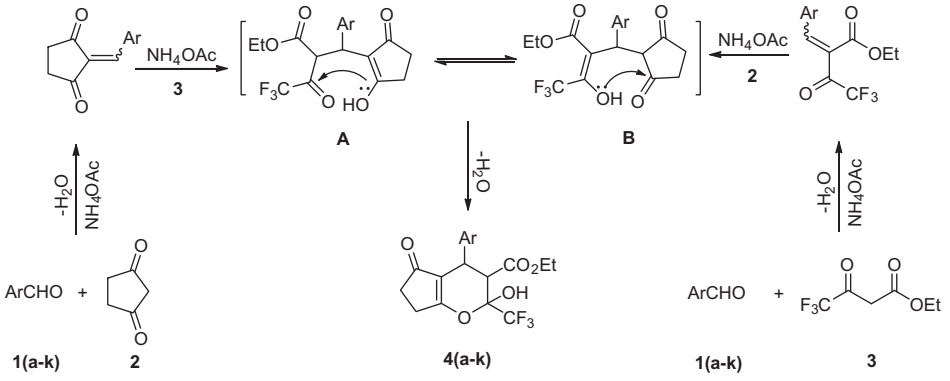
electron-withdrawing or electron-donating groups were employed as substrates and the reactions afforded the corresponding products in moderate to good yields. As shown in Table 2, it was clear that the product yield was influenced by both electronic and steric effects of the substituting groups on the aromatic aldehydes. The aromatic aldehydes with strong electron-donating groups afforded lower yield of the corresponding products with prolonged time (entry 11, Table 2). Furthermore, the effect of steric hindrance on the aromatic aldehydes was noticeable. The substituents located at the *para* or *meta* positions of aromatic aldehydes have not shown much effect on the formation of products (entries 3 and 8, Table 2). But *ortho*-substituted aromatic aldehydes such as 2-chloro-benzaldehyde gave no expected product. TLC analysis showed that the starting material remained unreacted. Similarly, steric hindered aromatic aldehydes such as 2,4-dichloro-benzaldehyde, gave no expected product either. The above results showed that the reactivity of substrates significantly depended on both the electronic and the steric effects of the substituents.

The structures of compounds **4(a–k)** were fully confirmed by ^{1}H NMR, ^{19}F NMR, MS, IR spectroscopies, and elemental analysis. For instance, the characteristic features of the ^{1}H NMR in $CDCl_3$ spectra of **4a** were the appearance of doublets at δ 3.92 and 2.94 ppm with J_{H-H} = 11.5 Hz for 3-H and 4-H protons, respectively, indicating a *trans* configuration of the vicinal two hydrogen atoms. The stereochemistry of **4** was attributed to that the intra-molecular cyclization would be an energetically favorable process, affording more stable '*trans*' configuration of **4**. The chemical shift of CF_3 group in ^{19}F NMR was a singlet peak at δ −83.65 ppm (s, 3F), which indicated that the CF_3 group was bonded to a quaternary carbon atom. The structure of compound **4f** was further confirmed by single crystal X-ray analysis to support our speculation on structures of these products (Fig. 1).[19]

Based on the above results, a possible mechanism for the formation of **4**(**a**–**k**) was illustrated in Scheme 1. First, an intermediate **A** or **B** was formed via initial Knoevenagel condensation reaction followed by Michael addition reaction catalyzed by NH_4OAc, which then underwent intramolecular cyclization reaction to afford the compounds **4(a–k)** exclusively.

Finally, we studied the dehydration of compounds **4**. It should be indicated that the hemi-ketal moiety in compounds **4** is stable. Due to the strong electron-withdrawing effect of trifluoromethyl group on the six-membered ring, compounds **4** resist dehydration under the present reaction conditions. It was found that water was smoothly eliminated from compounds **4** and the corresponding dehydrated derivatives **5** were obtained in good yields by the treatment of an excess of *p*-TsOH in refluxing toluene. The reaction results were listed in Table 3. The structure identity of compounds **5** was fully supported by spectral and microanalysis data.

In summary, we have shown that the one-pot three-component reaction provides a facile and convenient approach to synthesize the ethyl 4-aryl-2-hydroxy-5-oxo-2-(trifluoromethyl)-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-3-carboxylate derivatives from readily available starting materials. The soft brønsted acid, NH_4OAc, plays a unique role in this one-pot, three-component reaction. Meanwhile, the dehydration of hemi-ketal moiety to ethyl 4-aryl-5-oxo-2-(trifluoromethyl)-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carboxylate derivatives were also achieved. These new compounds may be considered as useful CF_3-containing substrates for the synthesis of a variety of heterocyclic compounds with potential biological activity.



Scheme 1. Plausible mechanism for formation of **4**(**a**–**k**).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.023.

References and notes

1. (a) Chebanov, V. A.; Muravyova, E. A.; Desenko, S. M.; Musatov, V. I.; Knyazeva, I. V.; Shishkina, S. V.; Shishkin, O. V.; Kappe, C. O. *J. Comb. Chem.* **2006**, *8*, 427–434; (b) Dondoni, A.; Massi, A.; Sabbatini, S.; Bertolasi, V. *J. Org. Chem.* **2002**, *67*, 6979–6994.
2. (a) Nilsson, B. L.; Overman, L. E. *J. Org. Chem.* **2006**, *71*, 7706–7714; (b) Vugts, D. J.; Koningstein, M. M.; Schmitz, R. F.; de Kanter, F. J.; Groen, M. B.; Orru, R. V. *Chem.-Eur. J.* **2006**, *12*, 7178–7189.
3. Xu, L. W.; Xia, C. G.; Li, L. *J. Org. Chem.* **2004**, *69*, 8482–8484.
4. Fewell, S. W.; Smith, C. M.; Lyon, M. A.; Dumitrescu, T. P.; Wipf, P.; Day, B. W.; Brodsky, J. L. *J. Biol. Chem.* **2004**, *279*, 51131–51140.
5. (a) Chebanov, V. A.; Saraev, V. E.; Desenko, S. M.; Chernenko, V. N.; Shishkina, S. V.; Shishkin, O. V.; Kobzar, K. M.; Kappe, C. O. *Org. Lett.* **2007**, *9*, 1691–1694; (b) De Silva, R. A.; Santra, S.; Andreana, P. R. *Org. Lett.* **2008**, *10*, 4541–4544; (c) Glasnov, T. N.; Stadlbauer, W.; Kappe, C. O. *J. Org. Chem.* **2005**, *70*, 3864–3870; (d) Evans, C. G.; Gestwicki, J. E. *Org. Lett.* **2009**, *11*, 2957–2959.
6. (a) Okandeji, B. O.; Gordon, J. R.; Sello, J. K. *J. Org. Chem.* **2008**, *73*, 5595–5597; (b) Isaacson, J.; Loo, M.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1461–1463; (c) Pirali, T.; Callipari, G.; Ercolano, E.; Genazzani, A. A.; Giovenzana, G. B.; Tron, G. C. *Org. Lett.* **2008**, *10*, 4199–4202; (d) Scheffelaar, R.; Paravidino, M.; Muilwijk, D.; Lutz, M.; Spek, A. L.; Ruijter, E. *Org. Lett.* **2009**, *11*, 125–128; (e) Berlozecki, S.; Szymanski, W.; Ostaszewski, R. *Tetrahedron* **2008**, *64*, 9780–9783; (f) Ilyin, A.; Kysil, V.; Krasavin, M.; Kurashvili, I.; Ivachtchenko, A. V. *J. Org. Chem.* **2006**, *71*, 9544–9547; (g) Bonnaterre, F.; Bois-Choussy, M.; Zhu, J. P. *Org. Lett.* **2006**, *8*, 4351–4354; (h) Casabona, D.; Cativiela, C. *Tetrahedron* **2006**, *62*, 10000–10004.
7. (a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123–3197; (b) Frezza, M.; Balestrino, D.; Soule' re, L.; Reverchon, S.; Queneau, Y.; Forestier, C.; Doutheau, A. *Eur. J. Org. Chem.* **2006**, 4731–4736; (c) Leroux, F.; Lefebvre, O.; Schlosser, M. *Eur. J. Org. Chem.* **2006**, 3147–3151; (d) Buscemi, S.; Pace, A.; Piccionello, A.; Macaluso, G.; Vivona, N. *J. Org. Chem.* **2005**, *70*, 3288–3291; (e) Filler, R.; Banks, R. E. *Organofluorine Chemicals and Their Industrial Applications*; Ellis Horwood: Chichester, UK, 1979.
8. (a) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Tokyo: Kodansha & Elsevier Biomedical, 1982; (b) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Organofluorine Compounds in Medical Chemistry and Boimedical Application*; Elsevier: Amsterdam, 1993; (c) Prabhakaran, J.; Underwood, M. D.; Parsey, R. V.; Arango, V.; Majo, V. J.; Simpson, N. R.; Heertum, R. V.; Mann, J. J.; Kumar, J. S. D. *Bioorg. Med. Chem.* **2007**, *15*, 1802–1807.
9. (a) Yi, H.; Song, L. P.; Wang, W.; Liu, J. N.; Zhu, S. Z.; Deng, H. M.; Shao, M. *Chem. Commun.* **2010**, *46*, 6941–6943; (b) Wang, P. Y.; Song, L. P.; Yi, H.; Zhang, M.; Deng, H. M.; Shao, M. *Tetrahedron Lett.* **2010**, *51*, 3975–3977; (c) Song, L. P.; Li, X. F.; Xing, C. H.; Li, D. M.; Zhu, S. Z.; Deng, H. M.; Shao, M. *Synlett* **2010**, 830–834; (d) Dai, B. F.; Song, L. P.; Wang, P. Y.; Yi, H.; Jin, G. F.; Zhu, S. Z.; Shao, M. *Synlett* **2009**, 1842–1846; (e) Song, S. D.; Song, L. P.; Dai, B. F.; Yi, H.; Jin, G. F.; Zhu, S. Z.; Shao, M. *Tetrahedron* **2008**, *64*, 5728–5735; (f) Li, D. M.; Song, L. P.; Li, X. F.; Xing, C. H.; Peng, W. M.; Zhu, S. Z. *Eur. J. Org. Chem.* **2007**, 3520–3525; (g) Li, D. M.; Song, L. P.; Song, S. D.; Zhu, S. Z. *J. Fluorine Chem.* **2007**, *128*, 952–957; (h) Li, X. F.; Song, L. P.; Xing, C. H.; Zhao, J. W.; Zhu, S. Z. *Tetrahedron* **2006**, *62*, 2255–2263.
10. Atkinson, R. S.; Barker, E.; Edwards, P. J.; Thomson, G. A. *J. Chem. Soc. Perkin Trans. 1* **1995**, 1533–1543.
11. (a) Katsuyama, I.; Ogawa, S.; Yamaguchi, Y.; Funabiki, K.; Matsui, M.; Muramatsu, H.; Shibata, K. *Synthesis* **1997**, 1321–1324; (b) Amii, H.; Kobayashi, T.; Terasawa, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 3103–3105; (c) Xing, C. H.; Zhu, S. Z. *J. Org. Chem.* **2004**, *69*, 6486–6488.
12. (a) Uckun, F. M.; Chen, M.; Vassilev, A. O.; Huang, H.; Jan, S. T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 541–545; (b) Gonzalez, R.; Martin, N.; Seoane, C.; Marco, J. L.; Albert, A.; Cano, F. H. *Tetrahedron Lett.* **1992**, *33*, 3809–3812.
13. (a) Li, J. J.; Tang, W. Y.; Lu, L. M.; Su, W. K. *Tetrahedron Lett.* **2008**, *49*, 7117–7120; (b) Kumar, A.; Sharma, S.; Maurya, R. A.; Sarkar, J. *J. Comb. Chem.* **2010**, *12*, 20–24.
14. Yao, C. S.; Jiang, B.; Li, T. J.; Qin, B. B.; Feng, X. d.; Zhang, H. H.; Wang, C. H.; Tu, S. J. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 599–601.
15. Cadierno, V.; Díez, J.; Gimeno, J.; Nebra, N. *J. Org. Chem.* **2008**, *73*, 5852–5858.
16. Bala, B. D.; Balamurugan, K.; Perumal, S. *Tetrahedron Lett.* **2011**, *52*, 4562–4566.
17. *Typical experimental procedure for synthesis of* **4a**: To a mixture of benzaldehyde **1a** (159.0 mg, 1.5 mmol), 1,3-cyclopentanedione **2** (147.0 mg, 1.5 mmol), and ethyl 4,4,4-trifluoro-3-oxobutanoate **3** (276.0 mg, 1.5 mmol) in 15 mL EtOH was added 1.0 mmol of NH_4OAc as catalyst. The resultant mixture was stirred at room temperature for 8 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated and the residue was purified by column chromatography on a silica gel using petroleum ether/ethyl acetate (1:1, v/v) as eluent to afford the pure product **4a** 371.1 mg, 67% yield.
18. *Spectroscopic data for products* **4**: compound **4a**: White solid; mp: 192.6–193.1 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.98 (t, J = 7.0 Hz, 3H), 2.52 (t, J = 5.0 Hz, 2H), 2.71–2.85 (m, 2H), 2.94 (d, J = 11.5 Hz, 1H), 3.92 (dt, J_1 = 11.5 Hz, J_2 = 2.5 Hz, 1H), 4.04 (q, J = 7.0 Hz, 2H), 5.85 (s, 1H), 7.10–7.12 (m, 2H), 7.28–7.35 (m, 3H). ^{19}F NMR (470 MHz, $CDCl_3$): δ = −83.85 (s, 3F, CF_3); IR (KBr) ν_{max}: 3426, 3070, 2987, 2939, 2768, 2578, 1741, 1620, 1371, 1351, 1236, 1194, 1166, 1110, 1002, 964, 746, 703 cm^{-1}; MS (ESI) m/z: 371 $[M+H]^+$, 393 $[M+Na]^+$; Anal. Calcd for $C_{18}H_{17}F_3O_5$: C, 58.38; H, 4.63. Found: C, 58.51; H, 4.75.
19. CCDC 860234 contains the Supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.ac.uk/data_request/cif.
20. *Typical experimental procedure for synthesis of* **5c**: A mixture of **4c** (404.5 mg, 1.0 mmol) and *p*-TsOH (4.0 mmol) in 15 mL toluene was refluxed for 12 h until completion of the reaction (monitored by TLC). The mixture was cooled to room temperature. And then it was poured into water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated and the residue was purified by column chromatography on a silica gel using petroleum ether/ethyl acetate (4:1, v/v) as eluent to afford the pure product **5c** 274.5 mg, 71% yield.
21. *Spectroscopic data for products* **5**: Compound **5c**: White solid; mp: 77.3–78.3 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.07 (t, J = 7.0 Hz, 3H), 2.50–2.53 (m, 2H), 2.74–2.86 (m, 2H), 4.02–4.12 (m, 2H), 4.67 (s, 1H), 7.13–7.27 (m, 4H), ^{19}F NMR (470 MHz, $CDCl_3$): δ = −66.98 (s, 3F,); IR (KBr) ν_{max}: 3061, 2989, 2941, 1732, 1691, 1643, 1375, 1218, 1151, 1067, 1037, 947, 742, 698 cm^{-1}; MS (ESI) m/z: 387/389 $[M+H]^+$, 409/411 $[M+Na]^+$; Anal. Calcd for $C_{18}H_{14}ClF_3O_4$: C, 55.90; H, 3.65. Found: C, 55.97; H, 3.70.