Journal of Fluorine Chemistry 181 (2016) 1–6

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

Fenton reagent-catalyzed trifluoromethylation of enamines of 3-oxocarboxylates with CF_3I

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ARTICLE INFO

Article history:
Received 5 October 2015
Received in revised form 20 October 2015
Accepted 23 October 2015
Available online 9 November 2015

Keywords:
Trifluoromethylation
Fenton reagent
3-Oxo-2-(trifluoromethyl)carboxylates
(2,2,2-Trifluoroethyl)ketones

ABSTRACT

The trifluoromethylation of enamines of ethyl 3-oxocarboxylates catalyzed by Fenton reagent with CF_3I was investigated. Trifluoromethylation followed by acid hydrolysis provided 3-oxo-2-(trifluoromethyl)-carboxylates in 64–94% yields, which were greater than those obtained by the trifluoromethylation of 3-oxocarboxylates as reported previously. Enamines trifluoromethylated at the 2-position were isolated as intermediates. Hydrolysis and successive decarboxylation of the obtained 3-oxo-2-(trifluoromethyl)-carboxylates under acidic conditions provided (2,2,2-trifluoroethyl)ketones in satisfactory yields.

1. Introduction

Recently, we reported that Fenton reagent composed of $FeSO_4$ or Cp_2Fe and aqueous H_2O_2 catalyzes the trifluoromethylation of olefinic C–H bonds in nucleobases and aromatic compounds by generating trifluoromethyl radicals from CF_3I in DMSO [1,2]. Based on the observed reactivity and regioselectivity, the trifluoromethylation was concluded to proceed in a manner similar to the electrophilic substitution of aromatic compounds. Furthermore, the methylene carbon between the two carbonyl groups in 3-oxocarboxylates was trifluoromethylated by CF_3I in the presence of Fenton reagent catalyst, giving 3-oxo-2-(trifluoromethyl)carboxylates in 40–73% yield [3].

In solutions, 3-oxocarboxylates exist in equilibrium between the enol and keto forms (Scheme 1). When the trifluoromethylation of ethyl 3-oxo-2-methylbutanoate (whose enol form has no H at the C2 position) was attempted under the same conditions as those of the trifluoromethylation of ethyl 3-oxocarboxylates [3], ethyl 3-oxo-2-methylbutanoate was completely recovered, indicating that the enol form was more reactive than the keto form and that trifluoromethylation of 3-oxocarboxylates chiefly occurs the C=C double bond in the enol form. However, peaks corresponding to the enol form were not observed in the ^1H NMR of the reaction solutions [3]. These results confirmed that the unsatisfactory yields of 3-oxo-2-(trifluoromethyl)carboxylates were due to the low concentration of the more reactive enol form than keto form.

3-Oxo-2-(trifluoromethyl)carboxylates produced by the trifluoromethylation of 3-oxocarboxylates at the C2 carbon provided 5-fluoropyrazole-4-carboxylates *via* cyclization with hydrazines [3], indicating that 3-oxo-2-(trifluoromethyl)carboxylates may serve as building blocks for fluorinated heterocyclic compounds. In addition, it is well known that 3-oxocarboxylic acids or their esters provide corresponding the methylketones through acid hydroxylation and base decarboxylation [4]. Thus, they can potentially furnish (2,2,2-trifluoroethyl)ketones, which have garnered significant attention as precursors in the synthesis of various medicines [5], drug candidates [6] and potential intermediates [7]. This motivated us to develop a protocol that would result in improve yields of 3-oxo-2-(trifluoromethyl)carboxylates.

The bond between C2 and C3 in the enamines of 3-oxocarboxylates is a fixed C=C double bond, similar to the enol form of 3-oxocarboxylates (Scheme 1). Therefore, these enamines should exhibit greater reactivity than 3-oxocarboxylates in the present trifluoromethylation.

Herein, we report that 3-oxo-2-(trifluoromethyl)carboxylates can be obtained in high yields by the trifluoromethylation of the

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http://dx.doi.org/10.1016/j.jfluchem.2015.10.013
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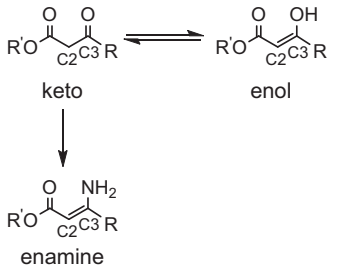


Scheme 1. Keto–enol equilibrium of 3-oxocarboxylates.

corresponding enamines, followed by hydrolysis in the presence of an acid. In addition, acid-catalyzed hydrolysis and decarboxylation by an acid of these products readily provided the (2,2,2-trifluoroethyl)ketones in excellent yields.

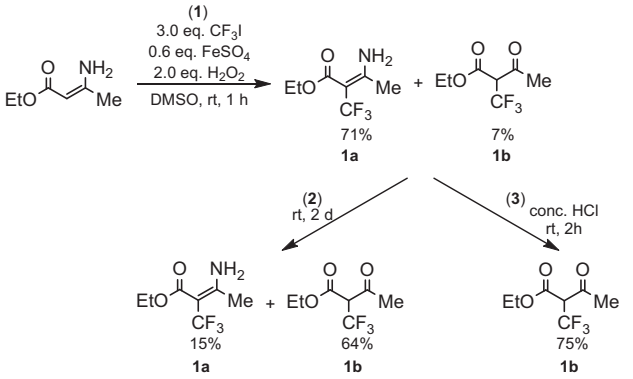
2. Results and discussion

2.1. Trifluoromethylation of enamines

Trifluoromethylation is carried out using an aqueous solution of H_2O_2. Therefore, the stability of enamines of 3-oxocarboxylates under acidic conditions was examined. A mixture of ethyl 3-amino-2-butenoate, the enamine synthesized form ethyl 3-oxobutanoate, and 2.0 equivalents of H_2O_2 in DMSO were stirred for 18 h at room temperature; the enamine was completely recovered. Thus, ethyl 3-amino-2-butenoate was not hydrolyzed to ethyl 3-oxobutanoate and the C=C double bond remained intact.

Scheme 2 depicted the results of the trifluoromethylation of ethyl 3-amino-2-butenoate. After trifluoromethylation of the enamine (path (**1**)), the ^{19}F NMR spectrum indicated the formation of two products, their corresponding peaks appeared at −48.6 ppm and −63.8 ppm, and the yields calculated using an internal standard were 71% and 7%, respectively, giving a total yield of 78%. The latter peak was assigned to the desired product, ethyl 3-oxo-2-(trifluoromethyl)butanoate (**1b**), by comparison to the reported ^{19}F NMR chemical shift and coupling constant (d, J_{FH} = 9.0 Hz) [3].

After two days at room temperature, the yield of product **1a** decreased to 15% while the yield of **1b** increased to 64% (path (**2**)). Thus, the total yield of path (2) was 79%, which was essentially the same as the total yield recorded for path (**1**) (78%). Furthermore, the peak corresponding to **1a** in the ^{19}F NMR spectrum completely disappeared upon addition of conc. HCl, increasing the yield of **1b** from 7% to 75% (path (**3**)). This yield (75%) was also virtually the same as the total yield of **1a** and **1b** observed in path (**1**). Product **1b** was isolated in 64% yield after path (**3**) and its ^1H, ^{13}C and ^{19}F NMR data completely matched with those of ethyl 3-oxo-2-(trifluoromethyl)butanoate [3].



Scheme 2. Trifluoromethylation of ethyl 3-amino-2-butenoate.

These results strongly indicated that **1a** was the intermediate in the formation of **1b** from the enamine. Therefore, we attempted to isolate **1a** from the reaction mixture. Half the amount of $FeSO_4$ and a shorter reaction time (0.5 h) (as compared to that used in path (**1**)) provided only **1a** in a low yield. ^1H, ^{13}C and ^{19}F NMR revealed that **1a** is ethyl 3-amino-2-(trifluoromethyl)-2-butenoate, which was converted to **1b** (79% yield) upon addition of conc. HCl. Therefore, trifluoromethylation of the enamine to **1a** and conversion of **1a** to **1b** occurred successively due to the acidity of H_2O_2 in path (**1**). Furthermore, an extended reaction time (path (**2**)) and the addition of HCl (path (**3**)) facilitated the conversion of **1a** to **1b**. The conversion in path (**2**) contradicts the results of the H_2O_2 stability experiment described above, suggesting that $FeSO_4$ and/or the presence of the trifluoromethyl group facilitated the conversion.

As expected, the total ^{19}F NMR yield of **1a** and **1b** (78%) was around twice the reported ^{19}F NMR yield obtained in the trifluoromethylation of ethyl 3-oxobutanoate (43%) [3]. This was undoubtedly due to the exclusive existence of the reactive C=C bond in the enamine.

In the trifluoromethylation of 3-oxocarboxylates [3], $FeSO_4$ was more effective than Cp_2Fe which provided the higher yield with some substrates such as 2,6-dichloroaniline, 3-hydroxypyridine and pyrazole [2]. Similarly, the trifluoromethylation of the enamine with Cp_2Fe afforded a lower yield of **1b**, 41% ^{19}F NMR yield, than $FeSO_4$.

Next the trifluoromethylation of various enamines of 3-oxocarboxylates was examined. The substrates were synthesized from the corresponding ethyl 3-oxocarboxylates *via* reaction with $AcONH_4$ [8]. Trifluoromethylation of the obtained enamines proceeded readily and the successive HCl-catalyzed hydrolysis gave the desired ethyl 3-oxo-2-(trifluoromethyl)carboxylates in satisfactory yields (Table 1).

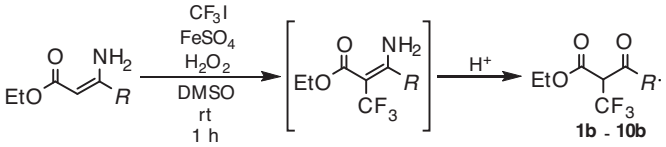
The yields for entries 2–5 (66–94%) were greater than the yields obtained in the previous report, 32–63% [3]. This could also be explained by the higher reactivity of the enamines than the 3-oxocarboxylates.

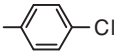
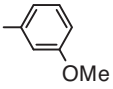
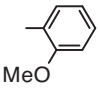
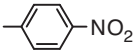
As with **1a** in Scheme 1, the intermediates were isolated from the enamine substrates shown in Table 1. Notably, ethyl 3-amino-3-phenyl-2-(trifluoromethyl)-2-propenoate (**4a**) was obtained in an excellent yield (93%) from 3-amino-3-phenyl-2-propenoate (Scheme 3). Hydrolysis of isolated intermediate **4a** with conc. HCl proceeded smoothly to give **4b** in an excellent yield.

2.2. Decarboxylation of (trifluoromethyl)enamines

Finally, we attempted to synthesize (2,2,2-trifluoroethyl)ketones from ethyl 3-oxo-2-(trifluoromethyl)carboxylates. The synthesis of methylketones from 3-oxocarboxylic acids or their esters is performed with an acid for hydroxylation and a base for decarboxylation [4]. If the same procedure was applied to 3-oxo-2-(trifluoromethyl)carboxylates, (2,2,2-trifluoroethyl)ketones could likely be readily obtained. However, several reports have suggested that the use of a base is unsuitable for the synthesis of (α-trifluoromethyl)ketones from α-trifluoromethyl carbonyls. For example, Ishihara and co-workers reported that the addition of a base in the form of lithium enolates to α-trifluoromethyl carbonyls afforded α,β-unsaturated-β,β-difluoro ketones through defluorination [7c]. To avoid defluorination by a base, Shibata and co-workers developed the palladium-catalyzed decarboxylative allylation of allyl α-trifluoromethyl-β-keto esters [9]. Therefore, we examined the stability of 3-oxo-2-(trifluoromethyl)carboxylates under basic conditions using **4b**. Following the addition of 3.0 mL of 2.0 mol/L NaOH aqueous solution to **4b** in MeOH

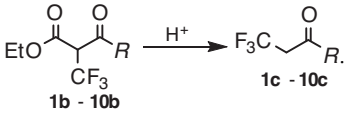
Table 1
Trifluoromethylation[a] and hydrolysis[b] of various enamines to 3-oxo-2-(trifluoromethyl)carboxylates

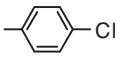
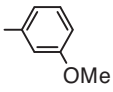
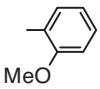
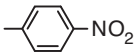


Entry	-*R*	Yield/%[c]
1	-Me (**1b**)	64
2	-^{i}Pr (**2b**)	66
3	-^{n}Bu (**3b**)	76
4	-Ph (**4b**)	94
5	-tolyl (**5b**)	90
6		92
7		82
8		80
9		86
10		85

[a] Enamines: 2.0 mmol, CF_3I: 6.0 mmol, $FeSO_4$: 0.6 mmol, H_2O_2: 4.0 mmol, DMSO: 10 mL.
[b] Conc. HCl: 2.0 mL, rt, 2 h.
[c] Isolated yield.

Table 2
Synthesis of (2,2,2-trifluoroethyl)ketones *via* decarboxylation of 3-oxo-2-(trifluoromethyl)carboxylates.[a]



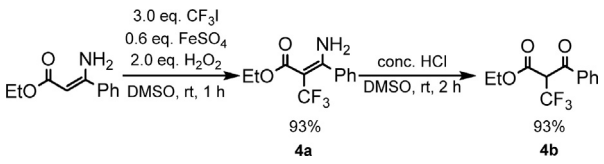
Entry	-*R*	Yield/%[b]
1	-Me (**1b**)	74[c]
2	-^{i}Pr (**2b**)	83[c]
3	-^{n}Bu (**3b**)	87[c]
4	-Ph (**4b**)	88
5	-tolyl (**5b**)	75
6		81
7		62
8		87
9		86
10		88

[a] **1b**–**10b**: 0.18–2.0 mmol, conc. HCl: 2.9–3.0 mL, AcOH: 2.0–3.0 mL, 100 °C, 4–8 h.
[b] Isolated yield.
[c] ^{19}F NMR yield.

(0.833 mol/L, 6.0 mL) and stirring for 2 h at room temperature, peaks of **4b**, desired product (phenyl(2,2,2-trifluoroethyl)ketone, **4c**) and any other organofluorine compounds were not observed in the ^{19}F NMR spectrum at all. This indicated that defluorination of **4b** by a base caused the decomposition of primary product of (β,β-difluorovinyl)phenylketone to 3-oxo-3-phenylpropionic acid [10]. Owing to the instability under basic conditions, we investigated the use of an acid in the synthesis of (2,2,2-trifluoroethyl)ketones. Screening of acids and other reaction conditions revealed that decarboxylation proceeded smoothly upon heating at 100 °C for 4–8 h in the presence of AcOH and conc. HCl. As shown in Table 2, satisfactory yields of the (2,2,2-trifluoroethyl)ketones were obtained from the corresponding 3-oxo-2-(trifluoromethyl)carboxylates listed in Table 1 under the optimized conditions.

The one-pot synthesis of **4c** was examined using ethyl 3-amino-3-phenyl-2-propenoate (**4a**). Conc. HCl and AcOH were added directly to the reaction mixture, immediately after the trifluoromethylation of the enamine. However, the yield of **4c** was poor (28%), suggesting that DMSO was an unsuitable solvent for the decarboxylation.

In the reaction with ethyl 3-amino-4,4,4-trifluoro-2-butenoate, trifluoromethylated enamine **11a** was obtained in 63% isolated

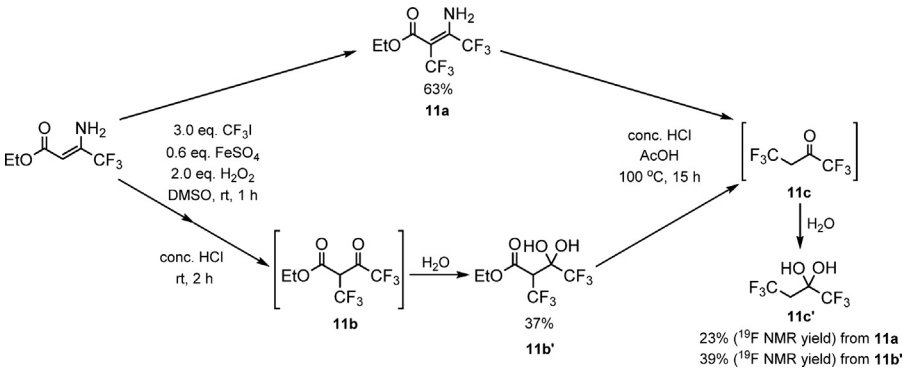


Scheme 3. Trifluoromethylation of ethyl 3-amino-3-phenyl-2-propenoate.

yield in a similar manner to those shown in Scheme 2 and Table 1. However, the hydrolysis of **11a** did not result in ethyl 4,4,4-trifluoro-3-oxo-2-(trifluoromethyl)butanoate **11b**, but yielded ethyl 4,4,4-trifluoro-3,3-dihydroxy-2-(trifluoromethyl)butanoate **11b′**. Moreover, decarboxylation of **11a** or **11b′** did not afford 1,1,1,4,4,4-hexafluoro-2-butanone **11c**, but generated 1,1,1,4,4,4-hexafluoro-2,2-butanediol **11c′** (Scheme 4). It is well known that the addition of H_2O to (perfluoroalkyl)ketones provides *gem*-diols [11]. The trifluoromethyl groups in **11b** and **11c** are directly bound to the carbonyl carbons. Therefore, H_2O present in the reagents used in the trifluoromethylation and decarboxylation, *i.e.*, aqueous H_2O_2 and conc. HCl, caused the hydration of **11b** and **11c** to the *gem*-diols.

To date, a number of routes towards α-trifluoromethyl ketones, including (2,2,2-trifluoroethyl)ketones, using various trifluoromethylating reagents have been reported [12]. Among them, two radical mechanisms and an ionic mechanism have been reported for the synthesis of (2,2,2-trifluoroethyl)ketones using CF_3I. With regard to the radical mechanisms, a trifluoromethyl radical is generated *via* a photoredox reaction, either with a Ru catalyst [13] or Et_3B at −78 °C [14], which adds to silyl enol ethers or lithium enolates, respectively. The ionic mechanism proceeds *via* the oxidative addition of CF_3I to Rh(I) [15]; the generated trifluoromethyl anion furnishes (2,2,2-trifluoroethyl)ketones upon reaction with α,β-unsaturated ketones. Because Fenton reagent is inexpensive and the reaction conditions are very mild, the present method is a promising candidate for the practical synthesis of (2,2,2-trifluoroethyl)ketones with CF_3I.

On the other hand, it is very difficult to synthesize α-trifluoromethyl ketones (1-substituted-(2,2,2-trifluoroethyl)ketones) using this method. Thus, 3-oxocarboxylates that possess



Scheme 4. Trifluoromethylation of ethyl 3-amino-4,4,4-trifluoro-2-butenoate and decarboxylation of trifluoromethylated products (**11a** and **11b**).

a trifluoromethyl group and another functional group such as an alkyl moiety at the C2 position must be obtained. However, it is impossible to obtain such 3-oxocarboxylates from enamines, because the C2 position of an enamine must be substituted by a functional group (Scheme 1); therefore, we could not introduce a trifluoromethyl group at the C2 position. In addition, we were unable to obtain C2-substituted 3-oxo-2-(trifluoromethyl)carboxylates from the C2-substituted keto form of 3-oxocarboxylates *via* the direct trifluoromethylation using Fenton reagent.

3. Conclusion

In conclusion, we demonstrated an efficient route towards 3-oxo-2-(trifluoromethyl)carboxylates which are viable precursors to synthetically important fluorinated compounds, by employing enamines of 3-oxocarboxylates as substrates. The obtained 3-oxo-2-(trifluoromethyl)carboxylates were readily converted to (2,2,2-trifluoroethyl)ketones *via* decarboxylation in the presence of an acid. The use of 3-oxo-2-(trifluoromethyl)carboxylates, 3-amino-2-(trifluoromethyl)propenoates and (2,2,2-trifluoroethyl)ketones as building blocks for fluorinated compounds is currently under investigation in our laboratory.

4. Experimental

4.1. General techniques

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ or $(CD_3)_2SO$ on a Bruker DRX-500 (^{13}C 125 MHz) and DRX-250 (^{1}H 250 MHz, ^{19}F 235 MHz) using tetramethylsilane as an internal reference for ^{1}H and ^{13}C NMR, and fluorotrichloromethane as an external reference for ^{19}F NMR. The chemical shifts are expressed in ppm (δ). The multiplicities are indicated by brs (broad singlet), d (doublet), t (triplet), q (quartet), quint (quintet) and m (multiplet). The ^{19}F NMR yields were calculated using 2,2,2-trifluoroethanol as an internal standard. IR, high-resolution mass spectroscopy (HR–MS) and melting point (Mp) were measured using a HORIBA FT-720, a JMS-T100LP AccTOF LC-plus 4G and a METLLER TOLEDO MP70 Melting Point System, respectively. IR spectra were obtained in reflective mode. All the commercially available reagents were used as received without purification.

4.2. Reaction procedures

4.2.1. Synthesis of 3-amino-2-propenoates

The synthesis of ethyl 3-amino-3-phenyl-2-propenoate is described below as a representative example. 3.0 g of MS3A was placed in a reaction vessel under an argon atmosphere. Then, 40 mL of EtOH and 4.81 g (25 mmol) of ethyl 3-phenylpropionate were added, and the mixture was stirred for 2 days at 80 °C. After the reaction was completed, MS3A was removed by filtration and the resulting solution was concentrated in *vacuo*. After H_2O was added to the obtained crude mixture, the product was extracted with ethyl acetate (70 mL × 3). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Filtration of Na_2SO_4 followed by silica gel column chromatography (eluent hexane/ethyl acetate = 8/1 v/v) provided ethyl 3-amino-3-phenyl-2-propenoate as a pale yellow oil in 81% yield (3.88 g).

4.2.2. Synthesis of 3-oxo-2-(trifluoromethyl)carboxylates ***1b–10b***

The synthesis of ethyl 3-oxo-3-phenyl-2-(trifluoromethyl)propionate (**4b**) is described below as a representative example. 382 mg (2.0 mmol) of ethyl 3-amino-3-phenyl-2-propenoate, 2.0 mL of CF_3I 3.0 mol/L DMSO solution (CF_3I 6.0 mmol), 0.6 mL of $FeSO_4$ 1.0 mol/L aqueous solution ($FeSO_4$ 0.60 mmol) and 8.0 mL of DMSO were placed in a reaction vessel under an argon atmosphere. Then, 0.4 mL of a 30% aqueous solution of H_2O_2 (H_2O_2 4.0 mmol) was added to the reaction mixture dropwise at a rate of 0.040 mL/min for 10 min at room temperature. The mixture was stirred for 1 h. Subsequently, 2.0 mL of conc. HCl was added and the mixture was stirred for 2 h. H_2O was added to the obtained mixture and the product was extracted into diethyl ether (70 mL × 3). The organic layer was washed with aqueous $Na_2S_2O_3$ and then brine, and dried over anhydrous Na_2SO_4. Filtration of Na_2SO_4 followed by silica gel column chromatography (eluent hexane/ethyl acetate = 4/1 v/v) provided ethyl 3-oxo-3-phenyl-2-(trifluoromethyl)propionate **4b** as a colourless oil in 94% yield (489 mg).

4.2.3. Synthesis of trifluoromethylated enamines ***1a*** and ***4a***

The synthesis of ethyl 3-amino-3-phenyl-2-(trifluoromethyl)-2-propenoate (**4a**) is described below as a representative example. 382 mg (2.0 mmol) of ethyl 3-amino-3-phenyl-2-propenoate, 2.0 mL of CF_3I 3.0 mol/L DMSO solution (CF_3I 6.0 mmol), 0.6 mL of $FeSO_4$ 1.0 mol/L aqueous solution ($FeSO_4$ 0.6 mmol) and 8 mL of DMSO were placed in a reaction vessel under an argon atmosphere. Then, 0.4 mL of a 30% aqueous solution H_2O_2 (H_2O_2 0.4 mmol) was added to this reaction mixture dropwise at a rate of 0.040 mL/min for 10 min at room temperature. The mixture was stirred for 0.5 h. Aqueous Na_2SO_3 was added to the obtained mixture and the product was extracted into diethyl ether (70 mL × 3). Then, the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Filtration of Na_2SO_4 followed by silica gel column chromatography (eluent hexane/ethyl acetate = 4/1 v/v) provided ethyl 3-amino-3-phenyl-2-(trifluoromethyl)-2-propenoate **4a** as a pale yellow solid in 93% yield (480 mg).

4a (259 mg, 1.0 mmol) was converted to **4b** using 1.0 mL of conc. HCl in DMSO (5.0 mL) at room temperature for 2 h in 93% yield (243 mg).

*4.2.4. Synthesis of (2,2,2-trifluoroethyl)ketones **1c–10c***

The synthesis of phenyl(2,2,2-trifluoroethyl)ketone (**4c**) is described below as a representative example. 520 mg (2.0 mmol) of **4b** was placed in a reaction vessel under an argon atmosphere. Then, 2.0 mL of acetic acid and 2.0 mL of conc. HCl were successively added, and the resulting mixture was stirred for 8 h at 100 °C. After the reaction, H_2O was added to the obtained mixture and the product was extracted into diethyl ether (70 mL × 3). Then, the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Filtration of Na_2SO_4 followed by silica gel column chromatography (eluent hexane/ethyl acetate = 8/1 v/v) provided phenyl(2,2,2-trifluoroethyl)ketone **4c** as a pale yellow solid in 88% yield (331 mg).

4.3. Characterization of products

Following 11 compounds are new and Mp (in the case of solid), NMR (^{1}H, ^{13}C and ^{19}F), IR and HR–MS data of them are shown below. The other compounds are known and the characterization data of ^{1}H, ^{13}C and ^{19}F NMR agreed with the reported data.

*4.3.1. Ethyl 3-amino-2-(trifluoromethyl)-2-butenoate (**1a**)*

White solid. Mp °C 36.4–37.7 °C ^{1}H NMR (DMSO-d_6) δ 1.17 (t, J = 7.1 Hz, 3H), 2.11 (q, J_{HF} = 3.2 Hz, 2H), 4.09 (q, J = 7.1 Hz, 2H), 8.07 (brs, 1H), 9.12 (brs, 1H). ^{13}C NMR (DMSO-d_6) δ 14.4, 21.3 (q, J_{CF} = 4.6 Hz), 59.1, 85.0 (q, J_{CF} = 31.9 Hz), 127.1 (q, J_{CF} = 268.3 Hz), 165.3, 167.2. ^{19}F NMR (DMSO-d_6) δ −48.6 (q, J_{FH} = 3.2 Hz). IR (neat) 3392, 1628, 1508, 1321, 1261, 1086, 1055, 1011, 951, 796, 731 cm^{-1}. HR–MS: calcd for $C_7H_{11}NO_2F_3$ (M+H): 198.0736; found: 198.0772.

*4.3.2. Ethyl 3-amino-3-phenyl-2-(trifluoromethyl)-2-propenoate (**4a**)*

Pale yellow solid. Mp 61.0–62.5 °C. ^{1}H NMR (DMSO-d_6) δ 1.22 (t, J = 7.1 Hz, 3H), 4.17 (q, J = 7.1 Hz, 2H), 7.31–7.37 (m, 2H), 7.41–7.50 (m, 3H), 8.10 (brs, 1H), 9.13 (brs, 1H). ^{13}C NMR (DMSO-d_6) δ 14.4, 59.6, 85.8 (q, J_{CF} = 31.4 Hz), 126.0 (q, J_{CF} = 268.5 Hz), 127.3 (q, J_{CF} = 1.2 Hz), 128.3, 129.8, 137.1, 160.0 (q, J_{CF} = 1.8 Hz), 167.3. ^{19}F NMR (DMSO-d_6) δ −47.6. IR (neat) 3392, 1597, 1520, 1487, 1282, 1090, 1038, 889, 781, 702 cm^{-1}. HR–MS: calcd for $C_{12}H_{13}NO_2F_3$ (M+H): 260.0893; found: 260.0882.

*4.3.3. Ethyl 3-amino-4,4,4-trifluoro-2-(trifluoromethyl)-2-butenoate (**11a**)*

colorless oil. ^{1}H NMR (DMSO-d_6) δ 1.21 (t, J = 7.1 Hz, 3H), 4.21 (q, J = 7.1 Hz, 2H), 9.06 (brs, 2H). ^{13}C NMR (DMSO-d_6) δ 14.0, 60.9, 87.2 (q, J_{CF} = 35.0 Hz), 120.0 (q, J_{CF} = 279.0 Hz), 124.1 (q, J_{CF} = 268.2 Hz), 150.6 (q, J_{CF} = 34.9 Hz), 166.8. ^{19}F NMR (DMSO-d_6) δ −52.3 (q, J_{FF} = 15.4 Hz, 3F), −64.3 (q, J_{FF} = 15.4 Hz, 3F). IR (neat) 1682, 1620, 1269, 1165, 1111, 1036, 897, 796, 733, 679 cm^{-1}. HR–MS: calcd for $C_7H_8NO_2F_6$ (M+H): 252.0459; found: 252.0488.

*4.3.4. Ethyl 3-oxo-2-(trifuoromethyl)heptanoate (**4b**)*

Pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 7.3 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 1.19–1.30 (m, 2H), 1.43–1.52 (m, 2H), 2.62–2.69 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 5.36 (q, J_{HF} = 9.0 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 13.6, 13.7, 21.4, 24.8, 42.4, 60.1 (q, J_{CF} = 25.7 Hz), 62.4, 122.6 (q, J_{CF} = 279.6 Hz), 162.7 (q, J_{CF} = 3.0 Hz), 197.7. ^{19}F NMR (DMSO-d_6) δ −63.4 (d, J_{FH} = 9.0 Hz). IR (neat) 1755, 1730, 1468, 1373, 1346, 1252, 1161, 1113, 1024, 843, 688 cm^{-1}. HR–MS: calcd for $C_{10}H_{16}O_3F_3$ (M+H): 241.1046; found: 241.1071.

*4.3.5. Ethyl 3-[3-(trifluoromethyl)phenyl]-2-(trifluoromethyl) propanoate (**7b**)*

Pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 1.07 (t, J = 7.1 Hz, 3H), 4.12–4.22 (m, 2H), 6.50 (q, J_{HF} = 8.4 Hz, 1H), 7.83–7.90 (m, 1H), 8.11–8.16 (m, 1H), 8.31–8.37 (m, 1H), 8.38–8.43 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 13.6, 56.3 (q, J_{CF} = 26.0 Hz), 62.7, 122.9 (q, J_{CF} = 280.0 Hz), 123.8 (q, J_{CF} = 272.6 Hz), 125.7 (q, J_{CF} = 3.8 Hz), 130.2 (q, J_{CF} = 32.6 Hz), 130.7, 131.2 (q, J_{CF} = 3.5 Hz), 132.9, 136.0 (q, J_{CF} = 1.0 Hz), 162.6 (q, J_{CF} = 2.9 Hz), 187.6. ^{19}F NMR (DMSO-d_6) δ −61.4 (s, 3F), −63.1 (t, J_{FH} = 8.4 Hz, 3F). IR (neat) 1751, 1705, 1614, 1331, 1234, 1124, 1074, 1024, 810, 692, 652 cm^{-1}. HR–MS: calcd for $C_{13}H_9O_3F_6$ (M–H): 327.0461; found: 327.0503.

*4.3.6. Ethyl 3-(3-methoxyphenyl)-2-(trifluoromethyl)propanoate (**8b**)*

Colorless oil. ^{1}H NMR (DMSO-d_6) δ 1.09 (t, J = 7.1 Hz, 3H), 3.83 (s, 3H), 4.17 (t, J = 7.1 Hz, 2H), 6.33 (q, J_{HF} = 8.6 Hz, 1H), 7.29–7.34 (m, 1H), 7.48–7.58 (m, 2H), 7.64–7.69 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 13.8, 55.7, 56.1 (q, J_{CF} = 25.8 Hz), 62.5, 113.6, 121.2, 121.7, 122.9 (q, J_{CF} = 280.0 Hz), 130.5, 136.6, 159.9, 163.0 (q, J_{CF} = 2.9 Hz), 188.2. ^{19}F NMR (DMSO-d_6) δ −63.1 (d, J_{FH} = 8.6 Hz). IR (neat) 1747, 1695, 1599, 1431, 1344, 1255, 1225, 1151, 1109, 1022, 787, 683 cm^{-1}. HR–MS: calcd for $C_{13}H_{14}O_3F_3$ (M+H): 291.0839; found: 291.0853.

*4.3.7. Ethyl 3-(2-methoxyphenyl)-2-(trifluoromethyl)propanoate (**9b**)*

Pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 1.13 (t, J = 7.1 Hz, 3H), 3.86 (s, 3H), 4.13–4.23 (m, 2H), 5.66 (q, J_{HF} = 8.9 Hz, 1H), 7.06–7.12 (m, 1H), 7.20–7.25 (m, 1H), 7.62–7.68 (m, 1H), 7.73–7.77 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 13.8, 55.9, 60.5 (q, J_{CF} = 24.7 Hz), 62.3, 113.0, 121.0, 123.1 (q, J_{CF} = 280.7 Hz), 125.0 (q, J_{CF} = 0.9 Hz), 130.5, 136.0, 159.0, 163.0 (q, J_{CF} = 2.9 Hz), 187.2. ^{19}F NMR (DMSO-d_6) δ −62.8 (d, J_{FH} = 8.9 Hz). IR (neat) 1743, 1685, 1599, 1485, 1298, 1227, 1159, 1103, 1020, 868, 760, 619 cm^{-1}. HR–MS: calcd for $C_{13}H_{14}O_3F_3$ (M+H): 291.0839; found: 291.0853.

*4.3.8. Ethyl 3-(4-nitrophenyl)-2-(trifluoromethyl)propanoate (**10b**)*

Pale yellow solid. Mp 39.1–41.7 °C. ^{1}H NMR (DMSO-d_6) δ 1.08 (t, J = 7.1 Hz, 3H), 4.14–4.21 (m, 2H), 6.46 (q, J_{HF} = 8.4 Hz, 1H), 8.29 (d, J = 9.0 Hz, 2H), 8.41 (d, J = 9.0 Hz, 2H). ^{13}C NMR (DMSO-d_6) δ 13.7, 56.7 (q, J_{CF} = 26.1 Hz), 62.9, 122.8 (q, J_{CF} = 280.1 Hz), 124.4, 130.5, 139.7, 151.0, 162.5 (q, J_{CF} = 2.8 Hz), 187.8. ^{19}F NMR (DMSO-d_6) δ −63.0 (d, J_{FH} = 8.4 Hz). IR (neat) 1724, 1709, 1531, 1346, 1240, 1155, 1124, 1005, 849, 685 cm^{-1}. HR–MS: calcd for $C_{12}H_9NO_5F_3$ (M+H): 304.0438; found: 304.0479.

*4.3.9. Ethyl 4,4,4-trifluoro-3,3-dihydroxy-2-(trifluoromethyl)butanoate (**11b′**)*

Colorless oil. ^{1}H NMR (DMSO-d_6) δ 1.19 (t, J = 7.1 Hz, 3H), 3.85 (q, J_{HF} = 8.7 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 7.79 (brs, 2H). ^{13}C NMR (DMSO-d_6) δ 13.9, 54.9 (q, J_{CF} = 26.2 Hz), 61.8, 92.2 (qq, J_{CF} = 1.1, 33.0 Hz), 122.7 (q, J_{CF} = 289.9 Hz), 123.3 (q, J_{CF} = 280.3 Hz), 163.4 (q, J_{CF} = 3.2 Hz). ^{19}F NMR (DMSO-d_6) δ −61.0 (m, 3F), −82.5 (q, J_{FF} = 4.1 Hz, 3F). IR (neat) 1726, 1338, 1169, 1074, 1018, 897, 868, 719 cm^{-1}. HR–MS: calcd for $C_7H_7O_4F_3$ (M–H): 269.0254; found: 269.0254.

*4.3.10. (2,2,2-trifluoroethyl)[3-(trifluoromethyl)phenyl]ketone (**7c**)*

White solid. Mp 44.6–45.8 °C. ^{1}H NMR (DMSO-d_6) δ 4.53 (q, J_{HF} = 10.8 Hz, 2H), 7.78–7.85 (m, 1H), 8.04–8.10 (m, 1H), 8.24–8.30 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 42.1 (q, J_{CF} = 26.9 Hz), 123.9 (q, J_{CF} = 272.6 Hz), 125.0 (q, J_{CF} = 3.8 Hz), 125.1 (q, J_{CF} = 276.2 Hz), 129.8 (q, J_{CF} = 32.5 Hz), 130.4, 130.5 (q, J_{CF} = 3.6 Hz), 132.4, 136.5 (q, J_{CF} = 1.9 Hz), 190.5 (q, J_{CF} = 2.7 Hz). ^{19}F NMR (DMSO-d_6) δ −61.1 (t, J_{FH} = 10.8 Hz, 3F), −61.2 (s, 3F). IR (neat) 1707, 1371, 1329, 1275,

1207, 1124, 1101, 930, 804, 692, 621 cm^{-1}. HR–MS: calcd for $C_{10}H_5OF_6$ (M–H): 255.0245; found: 255.0235.

4.3.11. 1,1,1,4,4,4-Hexafluoro-2,2-butanediol (**11c'**)

Colorless oil. ^1H NMR (DMSO-d_6) δ 2.69 (q, J_{HF} = 11.0 Hz, 2H), 7.38 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 39.3 (q, J_{CF} = 27.6 Hz), 91.2 (qq, J_{CF} = 2.9, 32.3 Hz), 123.6 (q, J_{CF} = 289.0 Hz), 125.4 (q, J_{CF} = 276.8 Hz). ^{19}F NMR (DMSO-d_6) δ −59.0 (m, 3F), −84.4 (q, J_{FH} = 3.4 Hz, 3F). IR (neat) 1265, 1182, 1147, 1080, 991 cm^{-1}. HR–MS: calcd for $C_4H_3O_2F_6$ (M–H): 197.0037; found: 197.0016.

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