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Syntheses of 2-(trifluoromethyl)-1,3-dicarbonyl compounds through direct trifluoromethylation with CF_3I and their application to fluorinated pyrazoles syntheses

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ABSTRACT

Direct trifluoromethylation of 1,3-dicarbonyl compounds with CF_3I in the presence of a Fenton reagent in dimethylsulfoxide was investigated. 1,3-Diketones, 3-oxocarboxylates and 3-oxocarboxamides were readily trifluoromethylated at the methylene carbon between two oxo groups. Cycloaddition of hydrazine derivatives to the obtained 2-(trifluoromethyl)-1,3-dicarbonyl compounds provided fluorinated pyrazoles. 4-(Trifluoromethyl)pyrazole derivatives were formed from 2-(trifluoromethyl)-1,3-diketones, while 3-oxo-2-(trifluoromethyl)carboxylates or carboxamides gave 5-fluoropyrazole-4-carboxylates or carboxamides, respectively, via 3-hydrazono-2-(trifluoromethyl)carboxylates or carboxamides as an intermediate.

1. Introduction

Pyrazole derivatives are important compounds in the area of medicines[1] and agrichemicals.[2] Fluorinated pyrazoles, in particular, frequently exhibit significant biological activity.[3] Therefore, efficient synthetic methods for these compounds have been in high demand. Among fluorinated pyrazoles, the derivatives having trifluoromethyl group at the 3- and/or 5-position are synthesized through the classical cycloaddition of hydrazine derivatives to 1,3-dicarboyl compounds that possess one or two (trifluoromethyl) carbonyl group at the 1- and/or 3-position.[4] In contrast, 2-(trifluoromethyl)-1,3-dicarbonyl compounds, in which a trifluoromethyl group is positioned between two oxo groups, have not thus far been used in the synthesis of pyrazole derivatives. This is presumably owing to unavailability of 2-(trifluoromethyl)-1,3-dicarbonyl compounds, since previously reported methods for the synthesis of 2-(trifluoromethyl)-1,3-dicarbonyl compounds require uncommon compounds as a starting material.[5] With regard to the methods using the more available and relatively simple starting material, direct trifluoromethylation of 1,3-dicarbonyl compounds has been reported for the synthesis of 2-(trifluoromethyl)-1,3-dicarbonyl compounds. So far, trifluoromethylation of the 2-position of 1,3-diphenylpropane-1,3-dione using (4-fluorophenyl)(3-nitorophenyl)trifluoromethylsulfonium salt[6] and electrochemical trifluoromethylation of various 1,3-dicarbonyl compounds with trifluoroacetic acid[7] have been reported. Nevertheless, these methods are unsuitable for general purposes owing to the need for expensive trifluoromethylating reagent or special apparatus.

Recently, we found that an electrophilic trifluoromethyl radical is generated from CF_3I by a Fenton reagent in dimethylsulfoxide (DMSO) and catalytic trifluoromethylation of various nucleobases[8] and five- or six-membered (hetero)aromatic compounds[9] can be achieved with this radical. The orientation of this trifluoromethylation was virtually explained by the general trend of electrophilic substitution, for example, the electron-rich 5-position of uracil is selectively trifluoromethylated.[8]

On the basis of the fact that the 2-position of 1,3-dicarbonyl compounds is electron-rich, we investigated direct trifluoromethylation of the 2-position of 1,3-diketones, 3-oxocaroboxylates, and 3-oxocarboxamides with CF_3I in the presence of the Fenton reagent in DMSO. Furthermore, we demonstrated 4-trifluoromethylpyrazole derivatives syntheses through cycloaddition of hydrazine derivatives to 2-(trifluoromethyl)-1,3-

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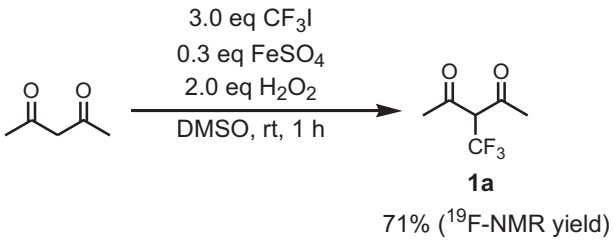
diketones. This study also revealed that 5-fluoropyrazole derivatives were obtained from 3-oxo-2-(trifluoromethyl)caroboxylates and 3-oxo-2-(trifluoromethyl)oxocaboxamides by cycloaddition of hydrazine derivatives via 3-hydrazono-2-(trifluoromethyl)carboxylates or carboxamides as an intermediate.

2. Results and discussion

2.1. Direct trifluoromethylation of various 1,3-dicarbonyl compounds

When a 30% H_2O_2 aqueous solution was added to a DMSO solution of pentane-2,4-dione, CF_3I, and an $FeSO_4$ aqueous solution followed by stirring for 1 h at room temperature, the formation of 3-(trifluoromethyl)pentane-2,4-dione (**1a**) was confirmed by ^{19}F NMR in 71% yield (Scheme 1).

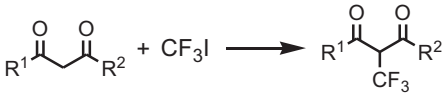


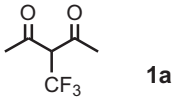
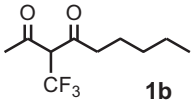
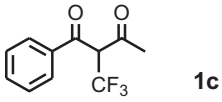
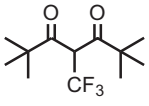
Scheme 1.

The screening of Fe(II) compounds and peroxides revealed that $FeSO_4$ and H_2O_2 aqueous solution exhibited the highest activity. Table 1 shows the results of trifluoromethylation of 1,3-diketones under the condition delineated in Scheme 1. All the substrates were trifluoromethylated at the position between two oxo groups. The highest yield was obtained with 3-(trifluoromethyl)pentane-2,4-dione (entry 1), suggesting that the yield is partly dependent on the bulkiness of R^1 and R^2 for 1,3-diketones as a substrate. In entry 3, a small amount of the product that was trifluoromethylated at the *para*-position of the phenyl ring in R^1 was detected (<5%).

Table 2 lists the results of trifluoromethylation of various ethyl 3-oxocarboxylates under the same conditions as Table 1. The corresponding 3-oxo-2-(trifluoromethyl)carboxylates were obtained though the yields were not satisfactory. Successive repetition of the trifluoromethylation increased the yield up to a satisfactory value as shown in entry 1 (43%→73%). In entry 3 (R^1=Ph), a small amount of the product in which the trifluoromethylation occurred at the *para*-position of R^1 was also detected (<5%).

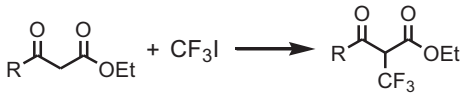
Table 1
Trifluoromethylation of 1,3-diketones with CF_3I in the presence of the Fenton reagent[a]

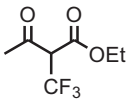
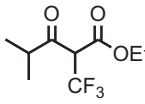
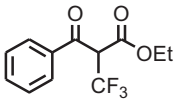
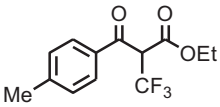
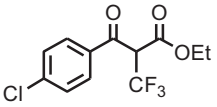


Entry	R^1	R^2	Product	Yield/%[b]
1	Me	Me	 **1a**	71 (42)
2	Me	Pentyl	 **1b**	51 (38)
3	Ph	Me	 **1c**	38 (32)
4	^{t}Bu	^{t}Bu	 **1d**	27 (25)

[a] Solvent DMSO, [1,3-diketones]=0.2 M. The used amount of $FeSO_4$, CF_3I, and H_2O_2 were 0.3 equiv, 3.0 equiv, and 2.0 equiv to a 1,3-diketone, respectively. All the reactions were carried out for 1 h at room temperature.
[b] ^{19}F NMR yield. The values in the parentheses are isolated yields.

Table 2
Trifluoromethylation of ethyl 3-oxocarboxylates with CF_3I in the presence of the Fenton reagent[a]



Entry	R	Product	Yield/%[b]
1	Me	 **2a**	43
2	^{i}Pr	 **2b**	73 (63)[c]
3	Ph	 **2c**	40 (32)
4	*p*-Tolyl	 **2d**	47 (33)
5	4-ClPh	 **2e**	60 (49)

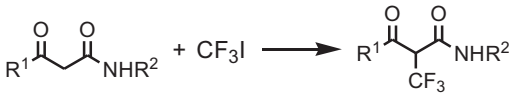
[a] The reaction conditions are same as those in Table 1.
[b] ^{19}F NMR yield. The values in the parentheses are isolated yields.
[c] The trifluoromethylation was successively carried out three times (see Experimental Section 4.2.2).

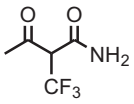
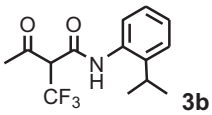
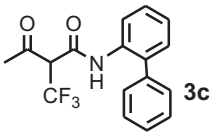
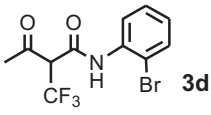
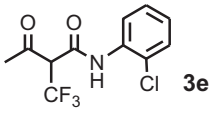
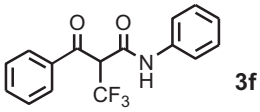
Furthermore, we examined trifluoromethylation of 3-oxocarboxiamides as shown in Table 3. The desired 3-oxo-2-(trifluoromethyl)carboxiamides were obtained in moderate yields under the same condition as Table 1.

The mechanism of trifluoromethylation is presumably the same as that of nucleobases and aromatic compounds.[8,9] Fig. 1 depicts the postulated mechanism where trifluoromethylation of pentane-2,4-dione is typified. The hypothetical steps involved in the trifluoromethylation are as follows; (i) Fe(II) reduces H_2O_2 to a hydroxyl radical, (ii) the hydroxyl radical is rapidly trapped by the DMSO solvent to form a radical adduct **A**, (iii) a methyl radical is generated from **A**, (iv) the reaction of CF_3I and the methyl radical releases a trifluoromethyl radical, (v) the trifluoromethyl radical adds to the 3-position of pentane-2,4-dione or 4-hydroxypent-3-ene-2-one, that is, the enol-form of pentane-2,4-dione to form a radical species **B**, and (vi) Fe(III) oxidizes **B** to **1a** and is reduced to Fe(II).

The substrates evaluated in Tables 1–3 ought to exist in tautomeric equilibrium between keto- and enol-forms. ^1H NMR in the DMSO-d_6 solution at room temperature revealed that keto/enol

Table 3
Trifluoromethylation of 3-oxobutyramide derivatives with CF_3I in the presence of the Fenton reagent[a]



Entry	R^1	R^2	Product	Yield/%[b]
1	Me	H	 **3a**	92 (75)
2	Me	4-^{i}PrPh	 **3b**	58 (52)
3[c]	Me	Biphenyl-2-yl	 **3c**	51 (44)
4	Me	4-BrPh	 **3d**	50 (42)
5	Me	4-ClPh	 **3e**	46 (39)
6	Ph	Ph	 **3f**	55 (45)

[a] The reaction conditions are same as those of Table 1.
[b] ^{19}F NMR yield. The values in the parentheses are isolated yields.
[c] The trifluoromethylation was successively carried out twice.

ratio was ca. 1:1 for pentane-2,4-dione, while ethyl 3-oxocarboxylate and 3-oxobutyramide were mainly in the keto-form. On the other hand, the trifluoromethylation of dimethyl or diethyl malonate, which exists only in the keto-form, did not afford trifluoromethylated products at all. This suggests that the trifluoromethylation proceeds chiefly with the enol-form of 1,3-dicarbonyl compounds in the step (v). However, the order of the yield of trifluoromethylated products is 3-oxobutyramide (entry 1 in Table 3) >pentane-2,4-dione (entry 1 in Table 1) >ethyl 3-oxocarboxylate (entry 1 in Table 2); this order does not agree with the amount of each enol-form estimated by ^1H NMR. Recently, Belova and co-workers reported the quantum chemical investigation of various 1,3-dicarbonyl compounds.[10] According to their report, the orders of the net charge of the carbon atom between two oxo groups are 3-oxobutyramide (−0.585) >pentane-2,4-dione (−0.579) >methyl 3-oxobutanoate (−0.575) in the keto-form and 3-oxobutyramide (−0.472) >pentane-2,4-dione (−0.471) >methyl 3-oxobutanoate (−0.468) in the enol-form. Taking into account the electrophilicity of the trifluoromethyl radical, it is reasonable that this trend in the electron density is exactly the same as the yields of the trifluoromethylated compounds. Therefore, whether reacting species be keto- or enol-form, the difference in the reactivity can be explained in the term of the electron density.

A trace amount of a trifluoromethylated enol-form as a product was detected only with **1a**, **1b**, and **2c** by ^{19}F NMR (δ=−51.3, −50.7, and −57.1 ppm, respectively), indicating that the keto-form is the main species in the tautomeric equilibrium of the products.

2.2. Cycloaddition of hydrazine derivatives to 2-(trifluoromethyl)-1,3-diketone

It is well-known that cycloaddition of hydrazine derivatives to 1,3-diketones readily proceeds to form 3,5-disubstituted pyrazoles.[11] The 2-(trifluoromethyl)-1,3-diketones obtained in Table 1 were thus expected to provide potentially biological active 3,5-disubstituted 4-(trifluoromethyl)pyrazoles[12] via this cycloaddition. As expected, 3,5-dimethyl-4-(trifluoromethyl)pyrazole derivatives were obtained in satisfactory yields by the cycloaddition of hydrazine derivatives to **1a** under a mild condition (Table 4).

Because **1a** is a symmetric 2-(trifluoromethyl)-1,3-diketone, the reactions in Table 4 necessarily generate a sole product. In contrast,

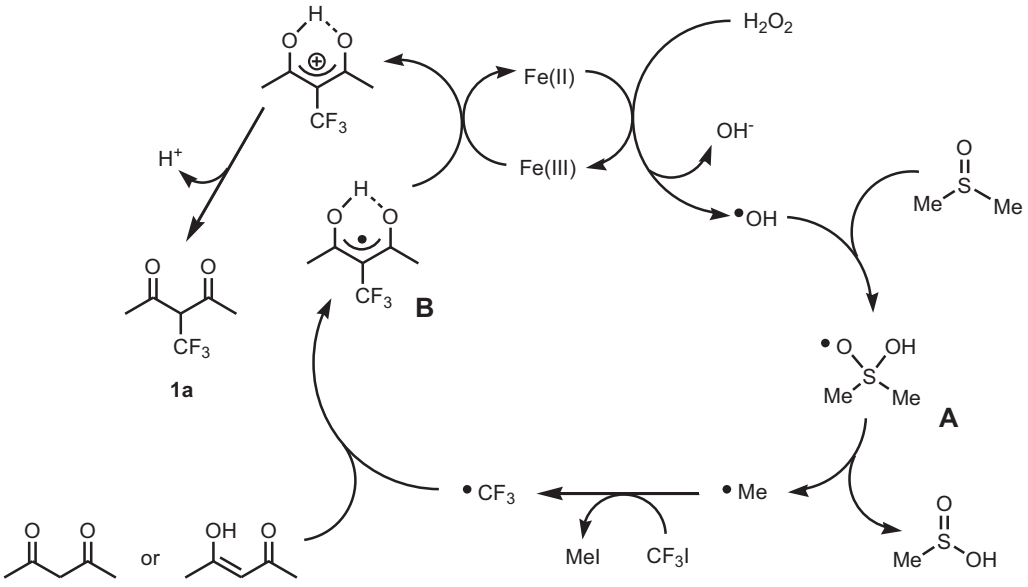
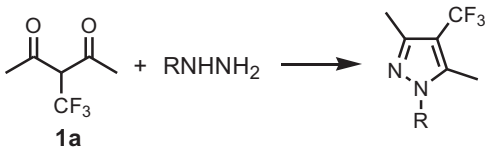
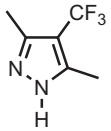
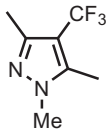
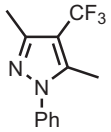


Fig. 1. Postulated mechanism of trifluoromethylation of pentane-2,4-dione.

Table 4
Cycloaddition of hydrazine derivatives to **1a**[a]

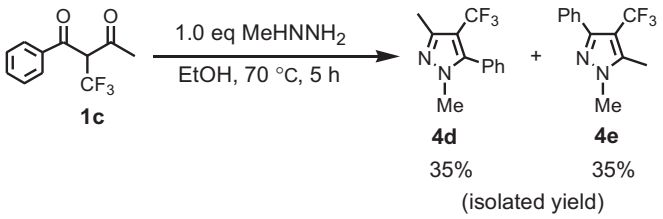


1a

Entry	R	Product	Isolated yield (%)
1[b]	H	 **4a**	94
2[c]	Me	 **4b**	76
3[d]	Ph	 **4c**	92

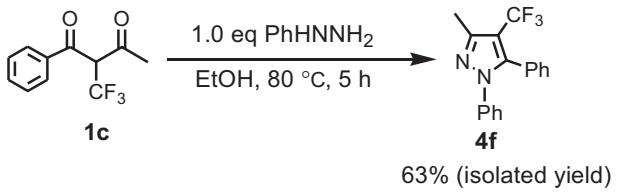
[a] [**1a**]=0.50–0.63 M, [hydrazine]/[**1a**]=1.0, EtOH 3–10 mL. All the reactions were carried out for 5 h.
[b] Reaction temperature was 60 °C.
[c] Reaction temperature was 70 °C.
[d] Reaction temperature was 80 °C.

two product isomers may be formed from asymmetric 2-(trifluoromethyl)-1,3-diketones. Indeed, the cycloaddition of methylhydrazine to 1-phenyl-2-(trifluoromethyl)butane-1,3-dione (**1c**) afforded a mixture of 1,3-dimethyl-5-phenyl-4-(trifluoromethyl) pyrazole (**4d**), and 1,5-dimethyl-3-phenyl-4-(trifluoromethyl)pyrazole (**4e**) in a 1:1 ratio (Scheme 2). The ^{1}H, ^{13}C, and ^{19}F NMR spectra of **4d** and **4e** were in agreement with those of the compounds that were synthesized by the trifluoromethylation of 1,3-dimethyl-5-phenylpyrazole and 1,5-dimethyl-3-phenylpyrazole, respectively, with CF_3I in the presence of the Femton reagent.[9]



Scheme 2.

In contrast to the formation of two isomers from **1c** and methylhydrazine, it is interesting that the cycloaddition of phenylhydrazine to **1c** produced 3-methyl-1,5-diphenyl-4-(trifluoromethyl)pyrazole (**4f**, Scheme 3) as a sole products; **4f** was identified in the same manner as **4d** and **4e**.



Scheme 3.

The nitrogen lone pair in hydrazine derivatives should selectively attack to the methylcarbonyl carbon in **1c**, which is less sterically hindered than the phenylcarbonyl.[13] In the cycloaddition of methylhydrazine to **1c** (Scheme 2), the nucleophilic attack of both sterically favored NH_2 and electronically favored NHMe will occur, resulting in the formation of the mixture of **4d** and **4e**. In contrast, **4f** was exclusively formed presumably owing to the fact that the sterically small NH_2 is more nucleophilic than NHPh. A similar selectivity as seen in Scheme 3 was observed in the cycloaddition of arylhydrazines to 4,4,4-trifluoro-1-arylbutane-1,3-diones to form 1,5-diaryl-3-(trifluoromethyl)pyrazoles.[4g]

Many synthetic methods for obtaining biologically active 4-(trifluoromethyl)pyrazole derivatives have been reported.[4h,12,14] We believe that the present method is more preferable than those methods because it offers the advantages of improved availability, cost, and handling of the reagents.

2.3. Cycloaddition of hydrazine derivatives to 3-oxo-2-(trifluoromethyl)carboxylates

Cycloaddition of hydrazine derivatives to 3-oxo-2-(trifluoromethyl)carboxylates was also examined. In the cycloaddition of methylhydrazine to ethyl 3-oxo-2-(trifluoromethyl)butanoate (**2a**), it was anticipated that 5-hydroxy-1,3-dimethyl-4-(trifluoromethyl)pyrazole would be formed on the basis of the precedence that 4-fluoro-5-hydroxy-1,3-dimethylpyrazole is formed from methylhydrazine and methyl 2-fluoro-3-oxobutanoate.[15] However, ^{1}H, ^{13}C, and ^{19}F NMR spectra indicated that the product actually obtained was ethyl 5-fluoro-1,3-dimethylpyrazole-4-carboxylate (**5a**). In order to determine the structure of **5a**, X-ray crystallography was attempted. However, the poor crystallinity of **5a** necessitated chemical conversion. Consecutive performing hydrolysis of **5a** with HCl/CH_3COOH, chlorination with oxalyl dichloride and amidation in an aqueous NH_3 solution successfully provided colorless and transparent plate-like crystal, which possessed crystallinity good enough for X-ray crystallography. The ORTEP diagram shown in Fig. 2 clearly revealed that this crystal was 5-fluoro-1,3-dimethylpyrazole-4-carboxamide (**7a**).

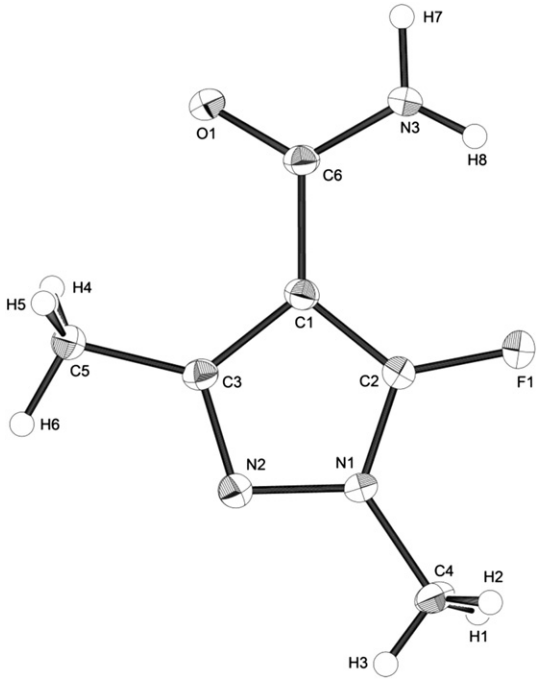
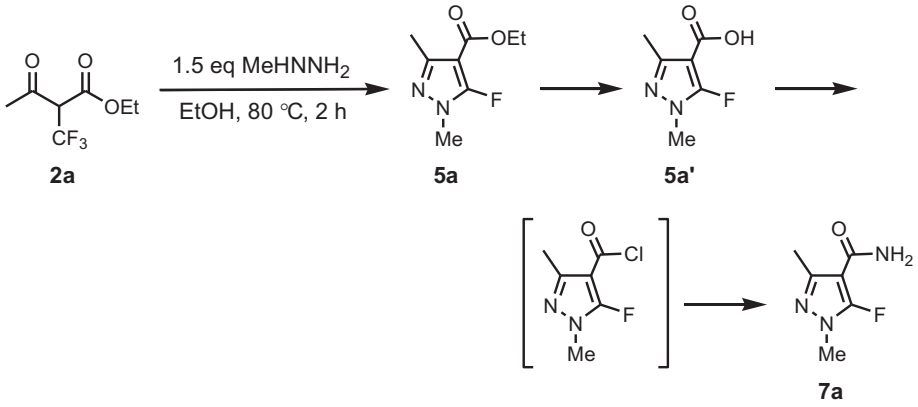


Fig. 2. The ORTEP diagram of **7a**.

Because the fluorine atom at the 5-position should have remained intact throughout the chemical conversion of **5a** to **7a** as illustrated in Scheme 4, we concluded that **5a** is the product of the cycloaddition of methylhydrazine to **2a**.



Scheme 4.

Table 5 lists the yields of various 1,3-disubstituted 5-fluoropyrazole-4-carboxylates obtained through cycloaddition of various hydrazine derivatives to **2a**–**e**.

The poor crystallinity of **5b**–**h** precluded X-ray structural evaluation. Nonetheless, the ^{19}F NMR data supported the formation of 1,3-disubstituted 5-fluoropyrazole-4-carboxylates. The ^{19}F NMR chemical shifts of the products fell within the range of −118.6 to −123.4 ppm, which is consistent with those of methyl 1-aryl-5-fluoropyrazole-4-carboxylates, from −118.8 to −123.3 ppm.[16]

Interestingly, the cycloaddition of phenylhydrazine to **2a** afforded not ethyl 5-fluoro-3-methyl-1-phenylpyrazole-4-carboxylate (**5i**) but ethyl 3-(phenylhydrazono)-2-(trifluoromethyl)butanoate (**6**) as shown in Scheme 5. Given that the addition of NEt_3 to the EtOH solution of isolated **6** smoothly provided ethyl 5-fluoro-3-methyl-1-phenylpyrazole-4-carboxylate (**5i**), **6** is considered to be an intermediate of this cycloaddition.

Scheme 6 illustrates the postulated mechanism for conversion of **6** to **5i**. NEt_3 abstracts the hydrogen atom at the 2-position of **6** to generate an anionic species **C**. In succession, **C** releases a fluoride anion from trifluoromethyl group to form ethyl 3-(phenylhydrazono)-2-(difluoromethylene)butanoate (**D**). Because the difluoromethylene carbon having two fluorine atoms in **D** should be more electropositive than the carbonyl carbon, the lone pair of the terminal nitrogen atom attacks the former olefinic carbon selectively, resulting in the formation of **5i**. A similar mechanism is proposed in the cycloaddition of methyl 3-methoxy-2-trifluoromethylacrylate and arylhydrazines to form methyl 1-aryl-5-fluoropyrazole-4-carboxylates.[16]

Ethyl 3-(arylhydrazono)-2-(trifluoromethyl)butanoates were also isolated from the reaction mixture of **2a** and the other arylhydrazines and were converted to the corresponding 1-aryl-5-fluoro-3-methylpyrazole-4-carboxylates by the addition of NEt_3 (Scheme 7).

Unfortunately, these 3-(arylhydrazono)-2-(trifluoromethyl)butanoates were not sufficiently stable for full characterization. With regard to **5j**–**l**, the ^{19}F and ^{13}C NMR data confirmed 1-aryl-5-fluoro-3-methylpyrazole-4-carboxylates structure.

Based on the results presented in Schemes 5 and 7, we attempted the one-pot synthesis of 1-aryl-5-fluoro-3-methylpyrazole-4-carboxylates starting from **2a** and arylhydrazines. This method involved the reaction of **2a** and an arylhydrazine performed in EtOH at 80 °C for 2 h (process A) followed by the addition of NEt_3 to the reaction mixture (process B). Table 6 shows that this one-pot synthesis gave the desired products in moderate yields.

On the basis of the results obtained from Schemes 5, 7 and those presented in Table 6, it can be concluded that 3-(arylhydrazono)-2-(trifluoromethyl)butanoates are the intermediates of the cycloaddition of arylhydrazines to **2a**. On the other hand, the cycloaddition of alkylhydrazine derivatives to **2a**–**e** (Table 5) afforded no 3-(alkylhydrazono)-2-(trifluoromethyl)butanoate, which is expected to be the intermediate for entries 1, 2, 6, 7, and 8 in Table 5.

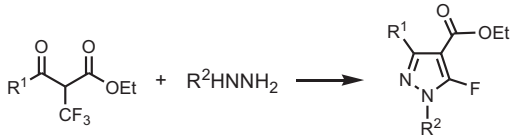
In general, the nucleophilicity of the lone pair of nitrogen in alkylhydrazono group is higher than that in arylhydrazono group. Consequently, 3-(alkylhydrazono)-2-(trifluoromethyl)butanoate should convert quickly to 5-fluoropyrazole-4-carboxylates, resulting in non-detection of an intermediate. Indeed, even when the reactions in entries 1 and 6 in Table 5 were carried out with lower ratio of [hydrazine]/[butanoate] (=1.0), no 3-(alkylhydrazono)-2-(trifluoromethyl)butanoate intermediate was formed and only the decline of the yields of 5-fluoropyrazole-4-carboxylates was observed (**5a** 57% and **5f** 70%). This suggests that the nucleophilic attack of the lone pair of the terminal nitrogen in the alkylhydrazono group is very fast. In addition to nucleophilicity, the basicity of the hydrazine derivatives and intermediates should also be taken into account. The stronger basicity of alkylhydrazines and 3-(alkylhydrazono)-2-(trifluoromethyl)butanoates than the corresponding each aryl derivatives should facilitate the abstraction of the hydrogen atom at the 2-position of a 3-oxo-2-(trifluoromethyl)carboxylate.

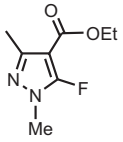
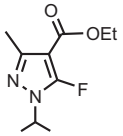
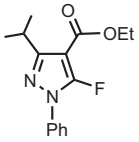
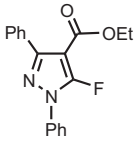
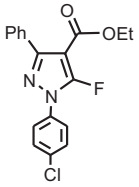
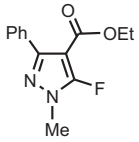
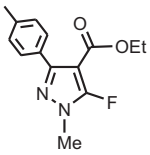
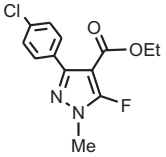
In order to detect a 3-(alkylhydrazono)-2-(trifluoromethyl) butanoate intermediate, the cycloaddition of isopropylhydrazine to **2a** (entry 2 in Table 5) was carried out under milder conditions than those employed in Table 5, as shown in Scheme 8. Under the outlined conditions, both of ethyl 3-(isopropylhydrazono)-2-(trifluoromethyl)butanoate and **5b** were observed using ^{19}F NMR. At longer reaction times, 3-(isopropylhydrazono)-2-(trifluoromethyl) butanoate disappeared and only **5b** was detected. In this way, the intermediate of this cycloaddition was successfully detected.

The yield of **5b** after the consumption of the intermediate was smaller than the total amount of the intermediate and **5b** after 1 h reaction, 69%. Because this intermediate decomposed within a few days at 5 °C after the isolation probably due to the basicity itself, the disappearance of this intermediate is derived from the decomposition during the reaction.

Nevertheless, the non-detection of 3-phenyl and 3-isopropyl-3-(arylhydrazono)-2-(trifluoromethyl)butanoates that are the anticipated intermediates in entries 3–5 in Table 5 has not been clarified yet. In a similar manner to entries 1 and 6 in Table 5, only the decline of the yield (**5d** 38%) were observed with the lower ratio of [hydrazine]/[butanoate] (=1.0) in entry 4 in Table 5. Instability derived from the repulsion between the phenyl or isopropyl group and an aryl group may facilitate the nucleophilic attack and/or the abstraction of the hydrogen atom at the 2-position.

Table 5
Cycloaddition of hydrazine derivatives to 3-oxo-2-(trifluoromethyl)carboxylates[a]



Entry	R^1	R^2	Product	Isolated yield/%
1	Me (**2a**)	Me	 **5a**	78
2	Me (**2a**)	^{i}Pr	 **5b**	41
3	^{i}Pr (**2b**)	Ph	 **5c**	57
4	Ph (**2c**)	Ph	 **5d**	70
5[b]	Ph (**2c**)	4-ClPh	 **5e**	58
6	Ph (**2c**)	Me	 **5f**	88
7	*p*-Tolyl (**2d**)	Me	 **5g**	60
8	4-ClPh (**2e**)	Me	 **5h**	74

[a] [3-Oxo-2-(trifluoromethyl)carboxylate]=0.17–0.20 mM, [hydrazine]/[3-oxo-2-(trifluoromethyl)carboxylate]=1.5–2.0, EtOH 3–5 mL. All the reactions were carried out at 80 °C for 2 h.

[b] Since 4-chlorophenylhydrazine was supplied as a HCl salt, its EtOH solution including the same equivalent of NEt_3 was used.

The cycloaddition of hydrazine derivatives to 2-(trifluoromethyl)-1,3-diketones afforded no 5-fluoropyrazole derivatives as described in Section 2.2. This indicates that the carbonyl carbon in a 2-trifluoromethyl-1,3-diketone is remarkably reactive to the nucleophilic attack of the lone pair of nitrogen in the hydrazine derivatives. This difference in the reactivity between 3-oxo-2-(trifluoromethyl)carboxylates and 2-(trifluoromethyl)-1,3-diketones is reasonable from the general trend of their reactivity. In addition, the electron-withdrawing nature of the trifluoromethyl group may also contribute to the high reactivity of the 2-(trifluoromethyl)-1,3-diketones.

It is known that the cycloaddition of arylhydrazines to methyl 3-methoxy-2-trifluoromethylacrylate forms methyl 1-aryl-5-fluoropyrazole-4-carboxylate.[16] Since the 2-position of 3-oxopropionates or malonates was not trifluoromethylated by the Fenton reagent, 1-aryl-5-fluoropyrazole-4-carboxylates could not be synthesized using the current method. Nevertheless, our method can be utilized as a supplement to the reported method for 5-fluoropyrazole-4-carboxylates synthesis.

2.4. Cycloaddition of hydrazine derivatives to 3-oxo-2-(trifluoromethyl)propinonamides

In the same manner as described in Section 2.3, cycloaddition of hydrazine derivatives to 3-oxopropinonamides provided 1,3-disubstituted 5-fluoro-4-carboxamides. Table 7 lists the results of the cycloaddition of methyl or phenylhydrazine to **3a**–**d** and **f**.

As a matter of course, the ORTEP diagram of **7a** obtained in entry 1 in Table 7 agreed with **7a** synthesized from **5a** in Scheme 4. With regard to the other products, the ^{19}F NMR chemical shifts were consistent with the formation of 1-aryl-5-fluoro-3-methylpyrazole-4-carboxamides.

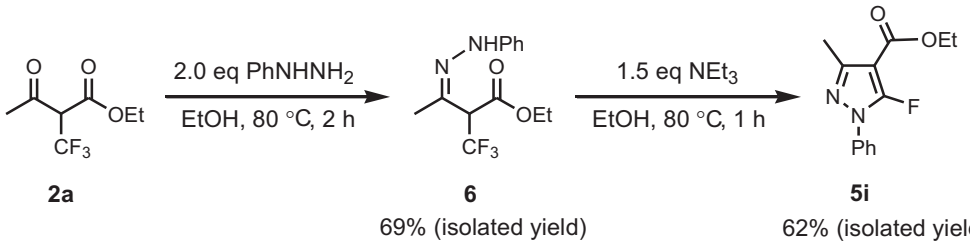
The addition of NEt_3 was necessary for the cycloaddition of phenylhydrazine to 3-oxo-2-(trifluoromethyl)butyramide derivatives as well as the cycloaddition of arylhydrazines to 3-oxo-2-(trifluoromethyl)butanoates. Table 8 summarizes the results of the one-pot synthesis of 5-fluoro-3-methyl-1-phenylpyrazole-4-carboxiamides from **3a**–**c**, **e** performed in a similar manner as that in Table 6.

The desired products were obtained in satisfactory yields. The ^{19}F NMR chemical shifts of the products also indicate that the 5-position of each compound was fluorinated.

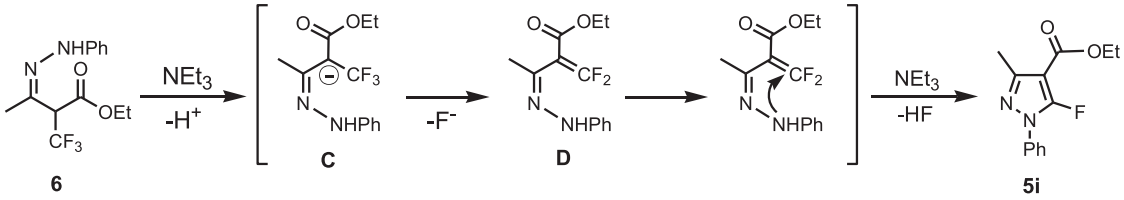
3-(Phenylhydrazono)-2-(trifluoromethyl)butyramide (**8**) was isolated from the reaction mixture of **3a** and phenylhydrazine in 75% isolated yield after process A. Furthermore, we confirmed that **8** was converted into **7g** by the addition of NEt_3 or K_2CO_3 in EtOH (Scheme 9).

In the reactions of phenylhydrazine and **3b**, **3c**, **3e**, we also isolated the corresponding 3-(arylhydrazono)-2-(trifluoromethyl) butyramides in 40–71% yields, respectively, though various spectra data were not obtained due to their instability. Since 1-aryl-5-fluoro-3-methylpyrazole-4-carboxamides were formed from isolated these compounds in the presence of NEt_3 (Scheme 10), a similar reaction as proposed in Scheme 5 can be applied here. Because carbonyl carbons of amides are generally unreactive in the nucleophilic attack, that mechanism is within reason.

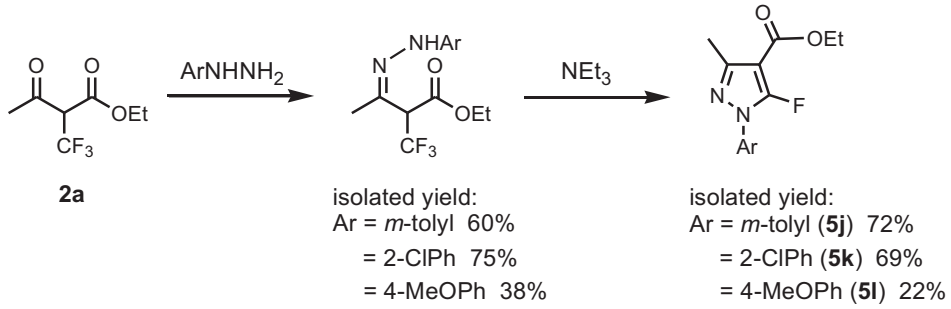
N-[2-(1,3-Dimethyl)butylphenyl]-5-fluoro-1,3-dimethylpyrazole-4-carboxamide is a commercially available fungicide[17] and derivatives of this compound having isopropyl[17] or aryl[18] group in the *ortho*-position of *N*-phenyl group are also known to be biologically active. The compounds **7a**–**j** are potential analogues of these fungicides. A previously reported synthesis of *N*-aryl-5-fluoro-1,3-dimethylpyrazole-4-carboxamide[19] involves the following processes; (i) cycloaddition of methylhydrazine to 3-oxobutyrates to give 5-hydroxy-1,3-dimethylpyrazole derivatives, (ii) chlorination at the 5-position with $POCl_3$, and (iii) the substitution of this chlorine by fluorine with KF. The present method is undisputedly simpler than the reported method. Moreover, this method is highly versatile, furnishing a variety of derivatives, because *N*-aryl-3-oxobutyramides, which are used as the starting



Scheme 5.



Scheme 6.



Scheme 7.

materials are readily obtainable from diketene and the corresponding aniline compounds.[20]

3. Conclusion

We achieved direct trifluoromethylation at the 2-position of 1,3-dicarbonyl compounds with CF_3I in the presence of the Fenton reagent in DMSO. Furthermore, we were able to demonstrate that the obtained 2-trifluoromethyl-1,3-dicarbonyl compounds are very useful C3 unit for the synthesis of biologically active fluorinated pyrazole derivatives. 4-(Trifluoromethyl)pyrazole, 5-fluoropyrazole-4-carboxylates or carboxamides derivatives were readily obtained by cycloaddition of hydrazine derivatives to these 2-(trifluoromethyl)-1,3-dicarbonyl compounds. The simplicity of this method makes it applicable to the synthesis of novel fluorinated heteroaromatic compounds. Other applications of 2-(trifluoromethyl)-1,3-dicarbonyl compounds are now under investigation.

4. Experimental

4.1. General techniques

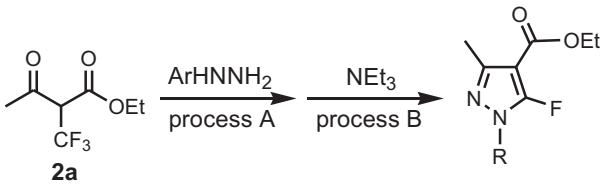
^1H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 using Bruker DRX-500 (^1H 500 MHz, ^{13}C 125 MHz) and DRX-250 (^{19}F 235 MHz) spectrometers. Tetramethylsilane was used as an internal reference for ^1H and ^{13}C NMR. The chemical shift of ^{19}F NMR was referenced to the resonance frequency, ^{19}F 376.27 MHz, with a negative sign indicating an upfield shift. Chemical shifts were expressed in parts per million (δ). Multiplicties were indicated by s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), and m (multiplet). ^{19}F NMR yields were calculated with 2,2,2-trifluoroethanol as an internal standard. IR, high-resolution mass spectroscopy (HRMS), X-ray crystallography, and melting point (mp) measurements were carried out using HORIBA FT-720, Waters LCT Premier XE, Rigaku R-AXIS PAPID II and Stanford Research Systems MPA100, respectively. IR spectra were obtained in the reflective mode. All the commercially available reagents were used without further purification.

4.2. General procedure

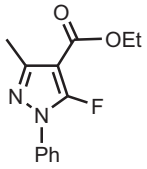
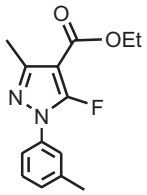
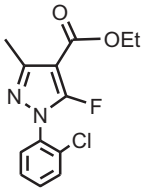
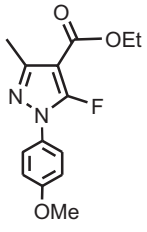
4.2.1. Trifluoromethylation of 1,3-dicarbonyl compounds. The procedure for synthesis of 3-(trifluoromethyl)pentane-2,4-dione (**1a**) is used as a representative example. A 30% H_2O_2 aqueous solution (2.0 mL) was added dropwise to the mixture of pentane-2,4-dione (10 mmol), DMSO (40 mL), 3.0 M DMSO solution of CF_3I (10 mL), and 1.0 M aqueous solution of $FeSO_4$ (3.0 mL) in an Ar atmosphere. The resulting mixture was stirred for 1 h at room temperature. After the reaction, an aliquot of the mixture was analyzed using ^{19}F NMR, confirming the formation of 3-(trifluoromethyl)pentane-2,4-dione (**1a**) in 71% yield. The reaction mixture was poured into H_2O and the product was extracted to diethyl ether. The diethyl ether layer was washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4, and then concentrated by distillation. The product was isolated using silica gel chromatography.

4.2.2. Successive trifluoromethylation of ethyl 3-oxobutanoate. A 30% H_2O_2 aqueous solution (1.0 mL) was added dropwise to the mixture of ethyl 3-oxobutanoate (5.0 mmol), DMSO (20 mL), 3.0 M DMSO solution of CF_3I (5.0 mL), and 1.0 M aqueous solution of

Table 6
Cycloaddition of various arylhydrazines to **2a**[a]



2a

Entry	Ar	Product		Isolated yield/%
1	Ph		**5i**	43 (46[c]) (38[d])
2[b]	*m*-Tolyl		**5j**	44
3[b]	2-ClPh		**5k**	58
4[b]	4-MeOPh		**5l**	33

[a] The reaction conditions of process A: **2a** 0.5 mmol, hydrazine 0.5–0.75 mmol, EtOH 3 mL. All the reactions were carried out at room temperature or 80 °C for 2 h. The reaction conditions of process B: NEt_3 0.5–0.75 mmol. All the reactions were carried out at 80 °C for 1 h.

[b] Since *m*-tolylhydrazine, (*o*-chlorophenyl)hydrazine, and (*p*-methoxyphenyl) hydrazine were supplied as a HCl salt, their EtOH solutions including the same equivalent of NEt_3 were used in process A.

[c] ^{19}F NMR yield.

[d] ^{19}F NMR yield in the reaction with K_2CO_3 (1.0 mmol) instead of NEt_3.

$FeSO_4$ (1.5 mL) in an Ar atmosphere. The resulting mixture was stirred for 1 h at room temperature. After the reaction, an aliquot of the mixture was analyzed using ^{19}F NMR, confirming the formation of ethyl 3-oxo-2-(trifluoromethyl)butanoate (**2a**) in 43% yield. To this reaction mixture were added 3.0 M DMSO solution of CF_3I (5.0 mL), 1.0 M aqueous solution of $FeSO_4$ (1.5 mL), and 30% H_2O_2 aqueous solution (1.0 mL). After stirring for 1 h, **2a** was formed in ^{19}F NMR 61% yield. Furthermore, the same reagent was added to this reaction mixture and **2a** formation was confirmed by ^{19}F NMR in 73%. Finally, the resulting mixture was poured into H_2O and the product was extracted to diethyl ether. The diethyl ether layer was washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4, and then concentrated by distillation. The product was isolated using silica gel chromatography.

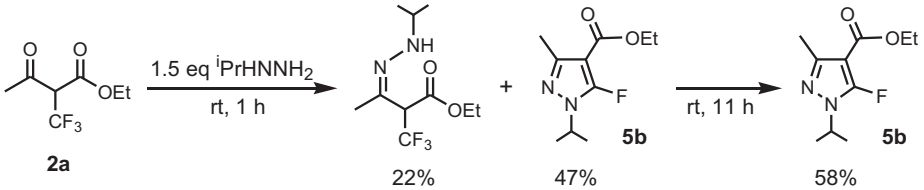
*4.2.3. Cycloaddition of hydrazine derivatives to 3-(trifluoromethyl) pentane-2,4-dione (**1a**).* The procedure for synthesis of 3,5-dimethyl-4-(trifluoromethyl)-1*H*-pyrazole (**4a**) is used as a representative example. Hydrazine monohydrate (2.5 mmol) was added to a mixture of 3-(trifluoromethyl)pentane-2,4-dione (2.5 mmol), and EtOH (4.0 mL) in an Ar atmosphere. The resulting mixture was stirred for 5 h at 60 °C. After cooling to room temperature, the product was extracted to ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4 and, then concentrated under vacuo. The product was isolated using silica gel chromatography.

4.2.4. Cycloaddition of hydrazine derivatives to 3-oxo-2-(trifluoromethyl)butanoates. The procedure for synthesis of ethyl 5-fluoro-1,3-dimethylpyrazole-4-carboxylate (**5a**) is used as a representative example. A mixture of methylhydrazine (0.75 mmol), ethyl 3-oxo-2-(trifluoromethyl)butanoate (0.50 mmol), and EtOH (3.0 mL) in an Ar atmosphere was stirred for 2 h at 80 °C. After cooling to room temperature, the product was extracted to ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4, and then concentrated under vacuo. The product was isolated using silica gel chromatography.

*4.2.5. Synthesis of ethyl 3-(phenylhydrazono)-2-(trifluoromethyl) butanoate (**6**) from ethyl 3-oxo-2-(trifluoromethyl)butanoate (**2a**).* A mixture of phenylhydrazine (2.0 mmol), ethyl 3-oxo-2-(trifluoromethyl)butanoate (1.0 mmol), and EtOH (5.0 mL) in an Ar atmosphere was stirred for 2 h at 80 °C. After cooling to room temperature, the product was extracted to ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4, and then concentrated under vacuo. The product was isolated using silica gel chromatography.

*4.2.6. Synthesis of ethyl 5-fluoro-3-methyl-1-phenyllpyrazole-4-carboxylate (**5i**) from ethyl 3-phenylhydrazono-2-(trifluoromethyl) butanoate (**6**).* A mixture of ethyl 3-(phenylhydrazono)-2-(trifluoromethyl)butanoate (0.50 mmol), NEt_3 (0.75 mmol), and EtOH (3.0 mL) in an Ar atmosphere was stirred for 1 h at 80 °C. After cooling to room temperature, the product was extracted to ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4, and then concentrated under vacuo. The product was isolated using silica gel chromatography.

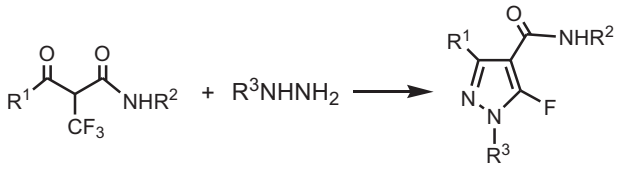
*4.2.7. Cycloaddition of arylhydrazines to ethyl 3-oxo-2-(trifluoromethyl)butanoates (**2a**).* The procedure for synthesis of ethyl 5-fluoro-3-methyl-1-phenylpyrazole-4-carboxylate (**5i**) is used as a representative example. A mixture of phenylhydrazine (0.50 mmol), ethyl 3-oxo-2-(trifluoromethyl)butanoate

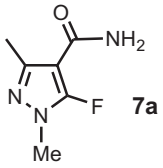
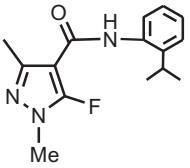
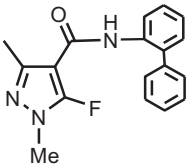
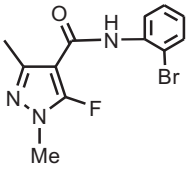
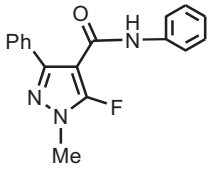
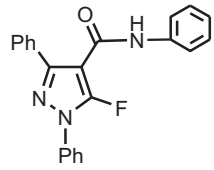


2a

Scheme 8.

Table 7
Cycloaddition of methyl or phenylhydrazine to 3-oxopropinonamides[a]



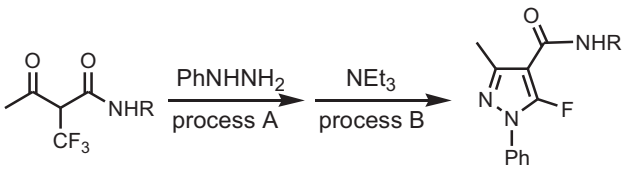
Entry	R^1	R^2	R^3	Product	Isolated yield/%
1	Me	H (**3a**)	Me	 **7a**	75
2	Me	2-^{i}PrPh (**3b**)	Me	 **7b**	52
3[b]	Me	Biphenyl-2-yl (**3c**)	Me	 **7c**	44
4	Me	2-BrPh (**3d**)	Me	 **7d**	85
5[c]	Ph	Ph (**3e**)	Me	 **7e**	74
6[d]	Ph	Ph (**3f**)	Ph	 **7f**	58

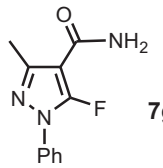
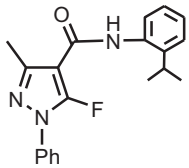
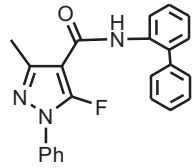
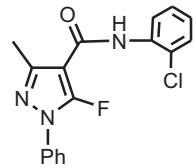
[a] The used amounts of a 3-oxo-2-(trifluoromethyl)carboxiamide derivative and methylhydrazine were 0.5 mmol and 0.75 mmol, respectively. All the reactions were carried out in 3.0 mL of EtOH for 2 h at 80 °C.
[b] EtOH (6.0 mL) was used.
[c] Methylhydrazine (1.0 mmol) was used in 2.0 mL of EtOH and 1.0 mL of DMSO.
[d] Phenylhydrazine (1.5 mmol) was used in 2.0 mL of EtOH and 1.0 mL of DMSO.

(0.50 mmol), and EtOH (3.0 mL) in an Ar atmosphere was stirred for 2 h at 80 °C (process A). NEt_3 (0.75 mmol) was subsequently added to the mixture and was further stirred for 1 h at 80 °C (process B). After cooling to room temperature, the product was extracted to ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4, and then concentrated under vacuo. The product was isolated using silica gel chromatography.

4.2.8. Cycloaddition of hydrazine derivatives to 3-oxo-2-(trifluoromethyl)butanamide derivatives. The procedure for synthesis of 5-fluoro-1,3-dimethylpyrazole-4-carboxamide (**7a**) is used as a representative example. A mixture of methylhydrazine (0.75 mmol), 3-oxo-2-(trifluoromethyl)butanamide (0.50 mmol), and EtOH (3.0 mL) in an Ar atmosphere was stirred for 2 h at 80 °C. After cooling to room temperature, the product was extracted to ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4, and then concentrated under vacuo. The product was isolated using silica gel chromatography.

Table 8
Cycloaddition of phenylhydrazine to 3-oxo-2-(trifluoromethyl)butyramide derivatives[a]

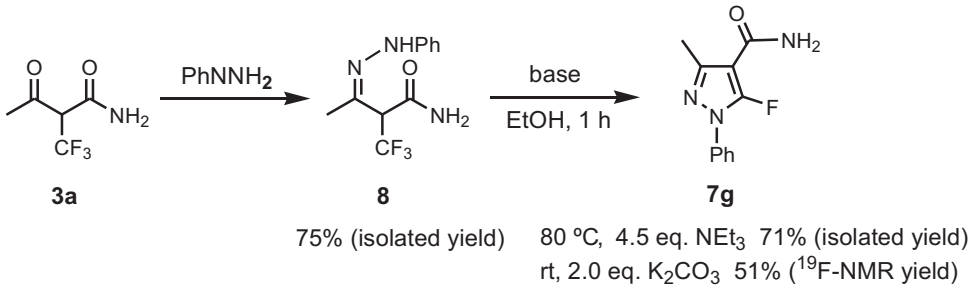


Entry	R	Product	Isolated yield/%
1	H (**3a**)	 **7g**	57
2	2-^{i}PrPh (**3b**)	 **7h**	76
3	Biphenyl-2-yl (**3c**)	 **7i**	68
4	2-ClPh (**3e**)	 **7j**	80

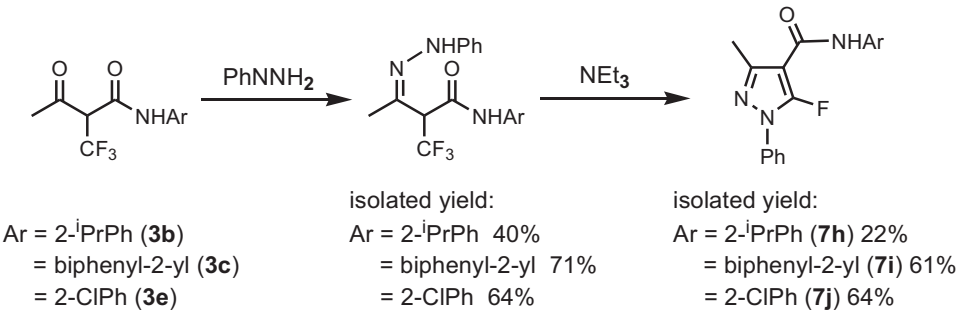
[a] The reaction conditions of process A: substrate 0.5 mmol, phenylhydrazine 0.5–0.75 mmol, EtOH 3–6 mL. All the reactions were carried out at room temperature for 2 h. The reaction conditions of process B: NEt_3 1.5–2.25 mmol. All the reactions were carried out at 80 °C for 2 h.

*4.2.9. Synthesis of 3-(phenylhydrazono)-2-(trifluoromethyl)butanamide (**8**) from 3-oxo-2-(trifluoromethyl)butanamide (**3a**).* A mixture of phenylhydrazine (0.50 mmol), 3-oxo-2-(trifluoromethyl)butanamide (0.50 mmol), and EtOH (3.0 mL) in an Ar atmosphere was stirred for 2 h at room temperature. After the reaction, the product was extracted to ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4, and then concentrated under vacuo. The product was isolated using silica gel chromatography.

*4.2.10. Synthesis of 5-fluoro-3-methyl-1-phenylpyrazole-4-carboxamide (**7h**) from 3-(phenylhydrazono)-2-(trifluoromethyl)butanamide (**8**).* A mixture of 3-(phenylhydrazono)-2-(trifluoromethyl) butanamide (0.25 mmol), NEt_3 (1.13 mmol), and EtOH (2.0 mL) in an Ar atmosphere was stirred for 2 h at 80 °C. After cooling to room



Scheme 9.



Scheme 10.

temperature, the product was extracted to ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4, and then concentrated under vacuo. The product was isolated using silica gel chromatography.

4.2.11. Cycloaddition of phenylhydrazine to 3-oxo-2-(trifluoromethyl) butanamide derivatives. The procedure for synthesis of 5-fluoro-3-methyl-1-phenylpyrazole-4-carboxamide (**7h**) is used as a representative example. A mixture of phenylhydrazine (0.50 mmol), 3-oxo-2-(trifluoromethyl)butanamide (0.50 mmol), and EtOH (3.0 mL) in an Ar atmosphere was stirred for 2 h at room temperature (process A). NEt_3 (1.50 mmol) was subsequently added to the mixture and was further stirred for 2 h at 80 °C (process B). After cooling to room temperature, the product was extracted to ethyl acetate. The ethyl acetate layer was washed with a saturated aqueous solution of NaCl, dried with Na_2SO_4, and then concentrated under vacuo. The product was isolated using silica gel chromatography.

4.3. Characterization of products

*4.3.1. 3-(Trifluoromethyl)pentane-2,4-dione (**1a**).* Colorless oil. ^{1}H NMR (DMSO-d_6) δ 2.30 (6H, s), 5.47 (1H, q, J_{HF}=9.4 Hz). ^{13}C NMR (DMSO-d_6) δ 31.0, 66.9 (q, J_{CF}=23.7 Hz), 122.7 (q, J_{CF}=280.4 Hz), 196.9. ^{19}F NMR (DMSO-d_6) δ −62.7 (d, J_{FH}=9.4 Hz). IR 1718, 1560, 1419, 1346, 1248, 1151, 1097, 1016, 922, 741 cm^{-1}. HRMS: calcd for $C_6H_6F_3O_2$ (M−H$^-$): 167.0325; found: *m*/*z* 167.0331.

*4.3.2. 3-(Trifluoromethyl)nonane-2,4-dione (**1b**).* Pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 0.85 (3H, t, J=7.1 Hz), 1.17−1.31 (4H, m), 1.49 (2H, quint, J=7.2 Hz), 2.28 (3H, s), 2.65 (2H, t, J=7.2 Hz), 5.45 (1H, q, J_{HF}=9.3 Hz). ^{13}C NMR (DMSO-d_6) δ 13.9, 22.0, 22.3, 30.4, 30.8, 43.4, 66.3 (q, J_{CF}=23.5 Hz), 122.7 (q, J_{CF}=280.4 Hz), 196.7, 199.0. ^{19}F NMR (DMSO-d_6) δ −62.6 (d, J_{FH}=9.3 Hz). IR 1743, 1718, 1560, 1415, 1340, 1261, 1247, 1146, 1099, 1016, 739 cm^{-1}. HRMS: calcd for $C_{10}H_{14}F_3O_2$ (M−H$^-$): 223.0951; found: *m*/*z* 223.0938.

*4.3.3. 1-Phenyl-2-(trifluoromethyl)butane-1,3-dione (**1c**).* Pale yellow solid. Mp 40.5−42.9 °C. ^{1}H NMR (DMSO-d_6) δ 2.29 (3H, s), 6.44 (1H, q, J_{HF}=8.8 Hz), 7.56−7.66 (2H, m), 7.71−7.80 (1H, m), 8.04−8.12 (2H, m). ^{13}C NMR (DMSO-d_6) δ 30.3, 62.3 (q, J_{CF}=23.8 Hz), 123.1 (q, J_{CF}=280.6 Hz), 129.2, 129.3, 134.9, 135.6, 189.5, 196.5. ^{19}F NMR (DMSO-d_6) δ −62.2 (d, J_{FH}=8.8 Hz). IR 1724, 1687, 1597, 1450, 1360, 1261, 1232, 1147, 1119, 827, 766, 687, 642 cm^{-1}. HRMS: calcd for $C_{11}H_8F_3O_2$ (M−H$^-$): 229.0482; found: *m*/*z* 229.0477.

*4.3.4. 2,2,6,6-Tetramethyl-4-(trifluoromethyl)heptane-3,5-dione (**1d**).* Pale yellow solid. Mp 79.8−82.2 °C. ^{1}H NMR (DMSO-d_6) δ 1.14 (18H, s), 5.91 (1H, q, J_{HF}=8.3 Hz). ^{13}C NMR (DMSO-d_6) δ 26.5, 45.2, 56.7 (q, J_{CF}=23.8 Hz), 122.6 (q, J_{CF}=281.3 Hz), 202.8. ^{19}F NMR (DMSO-d_6) δ −60.4 (d, J_{FH}=8.3 Hz). IR 1734, 1481, 1342, 1282, 1250, 1153, 1130, 1043, 999, 874, 852, 785, 631 cm^{-1}. HRMS: calcd for $C_{12}H_{19}F_3O_2$ (M+H$^+$): 253.1415; found: *m*/*z* 253.1411.

*4.3.5. Ethyl 3-oxo-2-(trifluoromethyl)butanoate (**2a**).* Colorless oil. ^{1}H NMR (DMSO-d_6) δ 1.21 (3H, t, J=7.1 Hz), 2.31 (3H, s), 4.23 (2H, q, J=7.1 Hz), 5.34 (1H, q, J_{HF}=9.0 Hz). ^{13}C NMR (DMSO-d_6) δ 13.8, 30.3, 60.9 (q, J_{CF}=25.7 Hz), 62.5, 122.6 (q, J_{CF}=279.6 Hz), 162.6 (q, J_{CF}=3.1 Hz), 195.5. ^{19}F NMR (DMSO-d_6) δ −63.8 (d, J_{FH}=9.0 Hz). IR 1751, 1732, 1371, 1348, 1223, 1167, 1144, 1109, 1034, 916, 702, 671 cm^{-1}. HRMS: calcd for $C_7H_8F_3O_3$ (M−H$^-$): 197.0431; found: *m*/*z* 197.0435.

*4.3.6. Ethyl 4-methyl-3-oxo-2-(trifluoromethyl)pentanoate (**2b**).* Colorless oil. ^{1}H NMR (DMSO-d_6) δ 1.06 (6H, d, J=6.8 Hz), 1.19 (3H, t, J=7.1 Hz), 2.86 (1H, sept, J=6.8 Hz), 4.20 (2H, q, J=7.1 Hz), 5.59 (1H, q, J_{HF}=8.8 Hz). ^{13}C NMR (DMSO-d_6) δ 13.8, 17.4, 17.5, 41.4, 58.0 (q, J_{CF}=25.7 Hz), 62.4, 122.7 (q, J_{CF}=279.6 Hz), 162.7 (q, J_{CF}=3.2 Hz), 201.8. ^{19}F NMR (DMSO-d_6) δ −63.7 (d, J_{FH}=8.8 Hz). IR 2981, 1757, 1728, 1346, 1261, 1227, 1159, 1113, 1020,

920, 837 cm^{-1}. HRMS: calcd for $C_9H_{14}F_3O_3$ ($M+H^+$): 227.0895; found: *m*/*z* 227.0912.

*4.3.7. Ethyl 3-oxo-3-phenyl-2-(trifluoromethyl)propionate (**2c**).* Colorless oil. ^1H NMR (DMSO-d_6) δ 1.09 (3H, t, *J*=7.1 Hz), 4.17 (2H, q, *J*=7.1 Hz), 6.31 (1H, q, J_{HF}=8.5 Hz), 7.58–7.63 (2H, m), 7.72–7.77 (1H, m), 8.05–8.09 (2H, m). ^{13}C NMR (DMSO-d_6) δ 13.7, 56.0 (q, J_{CF}=25.8 Hz), 62.5, 122.9 (q, J_{CF}=279.9 Hz), 129.1, 129.3, 134.9, 135.2, 162.9 (q, J_{CF}=2.9 Hz), 188.3. ^{19}F NMR (DMSO-d_6) δ −63.4 (d, J_{FH}=8.5 Hz). IR 1747, 1693, 1599, 1450, 1234, 1155, 1111, 1026, 687 cm^{-1}. HRMS: calcd for $C_{12}H_{10}F_3O_3$ ($M-H^-$): 259.0588; found: *m*/*z* 259.0580.

*4.3.8. Ethyl 3-oxo-3-(p-tolyl)-2-(trifluoromethyl)propionate (**2d**).* Colorless oil. ^1H NMR (DMSO-d_6) δ 1.09 (3H, t, *J*=7.1 Hz), 2.40 (3H, s), 4.16 (2H, q, *J*=7.1 Hz), 6.27 (1H, q, J_{HF}=8.5 Hz), 7.41 (2H, d, *J*=8.2 Hz), 7.97 (2H, d, *J*=8.2 Hz). ^{13}C NMR (DMSO-d_6) δ 13.8, 21.4, 55.8 (q, J_{CF}=25.7 Hz), 62.4, 123.0 (q, J_{CF}=279.9 Hz), 129.3, 129.8, 132.8, 145.9, 163.1 (q, J_{CF}=2.9 Hz), 187.7. ^{19}F NMR (DMSO-d_6) δ −63.4 (d, J_{FH}=8.5 Hz). IR 1749, 1685, 1606, 1346, 1234, 1155, 1109, 1026, 827, 622 cm^{-1}. HRMS: calcd for $C_{13}H_{14}F_3O_3$ ($M+H^+$): 275.0895; found: *m*/*z* 275.0889.

*4.3.9. Ethyl 3-(4-chlorophenyl)-3-oxo-2-(trifluoromethyl)propionate (**2e**).* Colorless oil. ^1H NMR (DMSO-d_6) δ 1.09 (3H, t, *J*=7.1 Hz), 4.17 (2H, q, *J*=7.1 Hz), 6.34 (1H, q, J_{HF}=8.4 Hz), 7.70 (2H, d, *J*=8.5 Hz), 8.08 (2H, d, *J*=8.5 Hz). ^{13}C NMR (DMSO-d_6) δ 13.7, 56.0 (q, J_{CF}=25.8 Hz), 62.6, 122.8 (q, J_{CF}=279.9 Hz), 129.5, 131.0, 133.9, 140.2, 162.7 (q, J_{CF}=2.9 Hz), 187.4. ^{19}F NMR (DMSO-d_6) δ −63.3 (d, J_{FH}=8.4 Hz). IR 1751, 1697, 1589, 1346, 1236, 1153, 1111, 1092, 1024, 835, 631 cm^{-1}. HRMS: calcd for $C_{12}H_9ClF_3O_3$ ($M-H^-$): 293.0192; found: *m*/*z* 293.0198.

*4.3.10. 3-Oxo-2-(trifluoromethyl)butanamide (**3a**).* Colorless solid. Mp 116.7–117.6 °C. ^1H NMR (DMSO-d_6) δ 2.20 (3H, s), 4.62 (1H, q, J_{HF}=8.9 Hz), 7.75 (1H, br s), 8.00 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 29.0, 61.8 (q, J_{CF}=24.3 Hz), 123.2 (q, J_{CF}=279.7 Hz), 162.9 (q, J_{CF}=2.4 Hz), 196.1. ^{19}F NMR (DMSO-d_6) δ −63.9 (d, J_{FH}=8.9 Hz). IR 3386, 3197, 1730, 1674, 1352, 1252, 1159, 1109, 984, 804, 741, 665 cm^{-1}. HRMS: calcd for $C_5H_7F_3NO_2$ ($M+H^+$): 170.0429; found: *m*/*z* 170.0425.

*4.3.11. N-(2-Isopropylphenyl)-3-oxo-2-(trifluoromethyl)butanamide (**3b**).* Colorless solid. Mp 132.6–134.1 °C. ^1H NMR (DMSO-d_6) δ 1.13 (3H, d, *J*=6.9 Hz), 1.16 (3H, d, *J*=6.9 Hz), 2.30 (3H, s), 3.13 (1H, sept, *J*=6.9 Hz), 4.94 (1H, q, J_{HF}=8.7 Hz), 7.18–7.23 (1H, m), 7.24–7.29 (2H, m), 7.34–7.38 (1H, m), 10.14 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 23.19, 23.22, 27.4, 29.1, 62.1 (q, J_{CF}=24.5 Hz), 123.2 (q, J_{CF}=279.9 Hz), 125.9, 126.2, 126.9, 127.4, 133.6, 143.6, 160.7 (q, J_{CF}=2.3 Hz), 195.8. ^{19}F NMR (DMSO-d_6) δ −63.7 (d, J_{FH}=8.7 Hz). IR 3240, 1732, 1657, 1529, 1244, 1155, 1115, 760 cm^{-1}. HRMS: calcd for $C_{14}H_{17}F_3NO_2$ ($M+H^+$): 288.1211; found: *m*/*z* 288.1210.

*4.3.12. N-(Biphenyl-2-yl)-3-oxo-2-(trifluoromethyl)butanamide (**3c**).* Colorless solid. Mp 146.5–147.8 °C. ^1H NMR (DMSO-d_6) δ 2.08 (3H, s), 4.77 (1H, q, J_{HF}=8.7 Hz), 7.33–7.48 (9H, m), 10.11 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 29.0, 61.9 (q, J_{CF}=24.5 Hz), 123.1 (q, J_{CF}=279.9 Hz), 127.1, 127.2, 127.6, 128.2, 128.6, 129.0, 130.7. 133.6, 137.4, 138.6, 160.5, 195.6. ^{19}F NMR (DMSO-d_6) δ −63.6 (d, J_{FH}=8.7 Hz). IR 3248, 1736, 1657, 1529, 1255, 1232, 1151, 1107, 744, 702 cm^{-1}. HRMS: calcd for $C_{17}H_{15}F_3NO_2$ ($M+H^+$): 322.1055; found: *m*/*z* 322.1058.

*4.3.13. N-(2-Bromophenyl)-3-oxo-2-(trifluoromethyl)butanamide (**3d**).* Colorless solid. Mp 132.5–134.3 °C. ^1H NMR (DMSO-d_6) δ 2.33 (3H, s), 5.06 (1H, q, J_{HF}=8.7 Hz), 7.20–7.25 (1H, m), 7.39–7.44 (1H, m), 7.54–7.58 (1H, m), 7.69–7.73 (1H, m), 10.37 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 29.4, 62.0 (q, J_{CF}=24.6 Hz), 118.6, 123.0 (q, J_{CF}=280.1 Hz), 127.7, 128.4, 128.5, 133.1, 135.1, 160.3, 195.5. ^{19}F NMR (DMSO-d_6) δ −63.5 (d, J_{FH}=8.7 Hz). IR 3240, 1739, 1658, 1541, 1369, 1259, 1151, 1111, 752 cm^{-1}. HRMS: calcd for $C_{11}H_{10}BrF_3NO_2$ ($M+H^+$): 323.9847; found: *m*/*z* 323.9849.

*4.3.14. N-(2-Chlorophenyl)-3-oxo-2-(trifluoromethyl)butanamide (**3e**).* Colorless solid. Mp 127.6–128.7 °C. ^1H NMR (DMSO-d_6) δ 2.32 (3H, s), 5.09 (1H, q, J_{HF}=8.7 Hz), 7.26–7.31 (1H, m), 7.35–7.40 (1H, m), 7.53–7.57 (1H, m), 7.63–7.67 (1H, m), 10.40 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 29.3, 62.0 (q, J_{CF}=24.8 Hz), 123.0 (q, J_{CF}=279.6 Hz), 126.9, 127.4, 127.9, 129.9, 133.7, 160.4 (q, J_{CF}=2.4 Hz), 195.6. ^{19}F NMR (DMSO-d_6) δ −63.6 (d, J_{FH}=8.7 Hz). IR 3249, 1734, 1660, 1541, 1377, 1261, 1144, 1111, 746 cm^{-1}. HRMS: calcd for $C_{11}H_{10}ClF_3NO_2$ ($M+H^-$): 280.0352; found: *m*/*z* 280.0348.

*4.3.15. 3-Oxo-N,3-diphenyl-2-(trifluoromethyl)propanamide (**3f**).* Colorless solid. Mp 183.0–184.4 °C. ^1H NMR (DMSO-d_6) δ 5.79 (1H, q, J_{HF}=8.3 Hz), 7.07–7.16 (1H, m), 7.27–7.37 (2H, m), 7.45–7.61 (4H, m), 7.63–7.73 (1H, m), 7.96–8.04 (2H, m), 10.85 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 58.5 (q, J_{CF}=24.4 Hz), 119.7, 123.5 (q, J_{CF}=280.1 Hz), 124.8, 128.3, 129.19, 129.24, 134.5, 135.2, 138.0, 159.6, 187.9. ^{19}F NMR (DMSO-d_6) δ −63.2 (d, J_{FH}=8.3 Hz). IR 3275, 1693, 1664, 1533, 1446, 1333, 1250, 1149, 1115, 901, 868, 737, 685 cm^{-1}. HRMS: calcd for $C_{16}H_{13}F_3NO_2$ ($M+H^+$): 308.0898; found: *m*/*z* 308.0896.

*4.3.16. 3,5-Dimethyl-4-(trifluoromethyl)-1H-pyrazole (**4a**).* Pale yellow solid. Mp 80.5–82.3 °C. ^1H NMR ($CDCl_3$) δ 2.35 (6H, q, J_{HF}=1.2 Hz), 11.47 (1H, br s). ^{13}C NMR ($CDCl_3$) δ 11.4, 108.2 (q, J_{CF}=36.0 Hz), 124.0 (q, J_{CF}=266.4 Hz), 143.9. ^{19}F NMR ($CDCl_3$) δ −56.1. IR 2945, 2889, 1601, 1527, 1329, 1308, 1147, 1093, 1045, 777, 742 cm^{-1}. HRMS: calcd for $C_6H_8F_3N_2$ ($M+H^+$): 165.0640; found: *m*/*z* 165.0658.

*4.3.17. 1,3,5-Trimethyl-4-(trifluoromethyl)pyrazole (**4b**).* Colorless oil. ^1H NMR ($CDCl_3$) δ 2.28 (3H, q, J_{HF}=0.9 Hz), 2.32 (3H, q, J_{HF}=0.7 Hz), 3.72 (3H, s). ^{13}C NMR ($CDCl_3$) δ 10.1, 12.5, 35.8, 108.5 (q, J_{CF}=35.8 Hz), 123.9 (q, J_{CF}=266.4 Hz), 139.1 (q, J_{CF}=2.8 Hz), 145.7 (q, J_{CF}=2.1 Hz). ^{19}F NMR ($CDCl_3$) δ −55.8. IR 1572, 1493, 1439, 1392, 1333, 1271, 1149, 1095, 1051, 742 cm^{-1}. HRMS: calcd for $C_7H_{10}F_3N_2$ ($M+H^+$): 179.0796; found: *m*/*z* 179.0787.

*4.3.18. 3,5-Dimethyl-1-phenyl-4-(trifluoromethyl)pyrazole (**4c**).* Pale yellow oil. ^1H NMR ($CDCl_3$) δ 2.36 (3H, q, J_{HF}=1.3 Hz), 2.38 (3H, q, J_{HF}=1.2 Hz), 7.36–7.40 (2H, m), 7.41–7.45 (1H, m), 7.46–7.51 (2H, m). ^{13}C NMR ($CDCl_3$) δ 11.1, 12.5, 109.7 (q, J_{CF}=35.7 Hz), 123.9 (q, J_{CF}=266.8 Hz), 125.6, 128.4, 129.1, 138.5, 139.6 (q, J_{CF}=2.8 Hz), 147.1. ^{19}F NMR ($CDCl_3$) δ −56.0. IR 1570, 1506, 1429, 1335, 1259, 1153, 1101, 1053, 764, 696 cm^{-1}. HRMS: calcd for $C_{12}H_{12}F_3N_2$ ($M+H^+$): 241.0953; found: *m*/*z* 241.0941.

*4.3.19. 1,3-Dimethyl-5-phenyl-4-(trifluoromethyl)pyrazole (**4d**).* Colorless oil. ^1H NMR ($CDCl_3$) δ 2.39 (3H, q, J_{HF}=1.0 Hz), 3.63 (3H, s), 7.31–7.35 (2H, m), 7.45–7.49 (3H, m). ^{13}C NMR ($CDCl_3$) δ 12.7, 36.7, 109.3 (q, J_{CF}=35.7 Hz), 123.3 (q, J_{CF}=267.0 Hz), 128.5, 128.6, 129.5, 129.6, 143.4 (q, J_{CF}=2.9 Hz), 146.2. ^{19}F NMR ($CDCl_3$) δ −54.6. IR 1495, 1338, 1273, 1207, 1149, 1101, 1051, 764, 737, 700 cm^{-1}. HRMS: calcd for $C_{12}H_{12}F_3N_2$ ($M+H^+$): 241.0953; found: *m*/*z* 241.0936.

*4.3.20. 1,5-Dimethyl-3-phenyl-4-(trifluoromethyl)pyrazole (**4e**).* Colorless oil. ^1H NMR ($CDCl_3$) δ 2.43 (3H, q, J_{HF}=1.2 Hz), 3.85 (3H, s), 7.35–7.42 (3H, m), 7.54–7.59 (2H, m). ^{13}C NMR ($CDCl_3$) δ 10.4, 36.3, 107.9 (q, J_{CF}=35.9 Hz), 123.6 (q, J_{CF}=267.0 Hz), 128.1,

128.3, 128.6, 132.4, 139.8 (q, J_{CF}=2.9 Hz), 149.1 (q, J_{CF}=2.1 Hz). ^{19}F NMR ($CDCl_3$) δ −53.6. IR 1556, 1456, 1333, 1167, 1097, 1034, 972, 775, 698 cm^{-1}. HRMS: calcd for $C_{12}H_{12}F_3N_2$ (M+H$^+$): 241.0953; found: *m*/*z* 241.0935.

*4.3.21. 3-Methyl-1,5-diphenyl-4-(trifluoromethyl)pyrazole (**4f**).* Pale yellow solid. Mp 50.7–52.0 °C. ^{1}H NMR ($CDCl_3$) δ 2.49 (3H, q, J_{HF}=1.3 Hz), 7.13–7.18 (2H, m), 7.21–7.29 (5H, m), 7.30–7.40 (3H, m). ^{13}C NMR ($CDCl_3$) δ 12.9, 110.9 (q, J_{CF}=35.8 Hz), 123.3 (q, J_{CF}=267.5 Hz), 125.2, 127.8, 128.3, 128.6, 128.8, 129.3, 130.1, 138.9, 143.1 (q, J_{CF}=3.0 Hz), 147.6. ^{19}F NMR ($CDCl_3$) δ −54.3. IR 1508, 1487, 1427, 1313, 1248, 1142, 1109, 1047, 762, 692 cm^{-1}. HRMS: calcd for $C_{17}H_{14}F_3N_2$ (M+H$^+$): 303.1109; found: *m*/*z* 303.1095.

*4.3.22. Ethyl 5-fluoro-1,3-dimethylpyrazole-4-carboxylate (**5a**).* Colorless solid. Mp 42.8–43.9 °C. ^{1}H NMR (DMSO-d_6) δ 1.24 (3H, t, *J*=7.1 Hz), 2.25 (3H, s), 3.63 (3H, d, J_{HF}=1.5 Hz), 4.19 (2H, q, *J*=7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.6, 33.7, 59.9, 98.3 (d, J_{CF}=7.6 Hz), 149.8 (d, J_{CF}=6.4 Hz), 153.8 (d, J_{CF}=289.0 Hz), 161.8 (d, J_{CF}=5.5 Hz). ^{19}F NMR (DMSO-d_6) δ −123.1. IR 1699, 1576, 1560, 1421, 1311, 1261, 1182, 1093, 775, 687 cm^{-1}. HRMS: calcd for $C_8H_{12}FN_2O_2$ (M+H$^+$): 187.0883; found: *m*/*z* 187.0878.

*4.3.23. 5-Fluoro-1,3-dimethylpyrazole-4-carboxylic acid (**5a′**).* Colorless solid. Mp 208 °C (dec). ^{1}H NMR (DMSO-d_6) δ 2.24 (3H, s), 3.62 (3H, d, J_{HF}=1.2 Hz), 12.51 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 14.4, 33.9, 93.6 (d, J_{CF}=7.8 Hz), 148.5 (d, J_{CF}=6.7 Hz), 153.3 (d, J_{CF}=286.8 Hz), 162.6 (d, J_{CF}=5.1 Hz). ^{19}F NMR (DMSO-d_6) δ −123.8. IR 1701, 1579, 1556, 1421, 1306, 1269, 1184, 1099, 899, 762, 681 cm^{-1}. HRMS: calcd for $C_6H_8FN_2O_2$ (M+H$^+$): 159.0570; found: *m*/*z* 159.0568.

*4.3.24. Ethyl 5-fluoro-1-isopropyl-3-methylpyrazole-4-carboxylate (**5b**).* Pale yellow solid. Mp 49.6–51.3 °C. ^{1}H NMR ($CDCl_3$) δ 1.34 (3H, t, *J*=7.1 Hz), 1.47 (6H, d, *J*=6.7 Hz), 2.40 (3H, s), 4.29 (2H, q, *J*=7.1 Hz), 4.47 (1H, sept, *J*=6.7 Hz). ^{13}C NMR (DMSO-d_6) δ 14.3, 14.7, 21.5, 49.4, 59.7, 93.1 (d, J_{CF}=8.2 Hz), 148.3 (d, J_{CF}=6.8 Hz), 152.1 (d, J_{CF}=287.0 Hz), 161.2 (d, J_{CF}=5.6 Hz). ^{19}F NMR ($CDCl_3$) δ −123.4. IR 2989, 1707, 1574, 1529, 1487, 1454, 1306, 1228, 1136, 1088, 1066, 822, 773, 625 cm^{-1}. HRMS: calcd for $C_{10}H_{16}FN_2O_2$ (M+H$^+$): 215.1196; found: *m*/*z* 215.1197.

*4.3.25. Ethyl 5-fluoro-3-isopropyl-1-phenylpyrazole-4-carboxylate (**5c**).* Yellow solid. Mp 45.5–47.2 °C. ^{1}H NMR (DMSO-d_6) δ 1.25 (6H, d, *J*=6.9 Hz), 1.28 (3H, t, *J*=7.1 Hz), 3.43 (1H, sept, *J*=6.9 Hz), 4.26 (2H, q, *J*=7.1 Hz), 7.41–7.69 (5H, m). ^{13}C NMR (DMSO-d_6) δ 14.3, 21.2, 27.5, 60.1, 93.8 (d, J_{CF}=7.7 Hz), 122.3 (d, J_{CF}=3.5 Hz), 128.4, 129.7, 135.9, 152.7 (d, J_{CF}=293.0 Hz), 158.4 (d, J_{CF}=5.4 Hz), 160.8 (d, J_{CF}=5.9 Hz). ^{19}F NMR (DMSO-d_6) δ −119.6. IR 2962, 2931, 1716, 1577, 1520, 1456, 1342, 1232, 1134, 1090, 1041, 752, 687 cm^{-1}. HRMS: calcd for $C_{15}H_{18}FN_2O_2$ (M+H$^+$): 277.1352; found: *m*/*z* 277.1343.

*4.3.26. Ethyl 5-fluoro-1,3-diphenylpyrazole-4-carboxylate (**5d**).* Colorless solid. Mp 73.8–75.1 °C. ^{1}H NMR (DMSO-d_6) δ 1.21 (3H, t, *J*=7.1 Hz), 4.22 (2H, q, *J*=7.1 Hz), 7.40–7.79 (10H, m). ^{13}C NMR (DMSO-d_6) δ 14.1, 60.4, 94.8 (d, J_{CF}=7.8 Hz), 122.6 (d, J_{CF}=3.1 Hz), 128.0, 128.8, 129.11, 129.14, 129.8, 132.0, 135.7 (d, J_{CF}=2.7 Hz), 151.3 (d, J_{CF}=6.7 Hz), 153.1 (d, J_{CF}=292.8 Hz), 160.5 (d, J_{CF}=5.8 Hz). ^{19}F NMR (DMSO-d_6) δ −118.6. IR 1728, 1570, 1510, 1456, 1313, 1149, 1090, 1022, 785, 754, 687, 654 cm^{-1}. HRMS: calcd for $C_{18}H_{16}FN_2O_2$ (M+H$^+$): 311.1196; found: *m*/*z* 311.1198.

*4.3.27. Ethyl 5-fluoro-1-(4-chlorophenyl)-3-phenylpyrazole-4-carboxylate (**5e**).* Orange solid. Mp 92.9–93.7 °C. ^{1}H NMR (DMSO-d_6) δ 1.21 (3H, t, *J*=7.1 Hz), 4.22 (2H, q, *J*=7.1 Hz), 7.41–7.49 (3H, m), 7.62–7.82 (6H, m). ^{13}C NMR (DMSO-d_6) δ 14.1, 60.4, 95.0 (d, J_{CF}=7.7 Hz), 124.1 (d, J_{CF}=3.6 Hz), 128.0, 129.1, 129.2, 129.8, 131.8, 133.1, 134.6 (d, J_{CF}=2.5 Hz), 151.4 (d, J_{CF}=6.8 Hz), 153.2 (d, J_{CF}=293.6 Hz), 160.4 (d, J_{CF}=5.8 Hz). ^{19}F NMR (DMSO-d_6) δ −117.8. IR 1730, 1572, 1508, 1485, 1323, 1302, 1149, 1086, 825, 758, 687, 654 cm^{-1}. HRMS: calcd for $C_{18}H_{15}ClFN_2O_2$ (M+H$^+$): 345.0806; found: *m*/*z* 345.0806.

*4.3.28. Ethyl 5-fluoro-1-methyl-3-phenylpyrazole-4-carboxylate (**5f**).* Colorless solid. Mp 48.0–50.0 °C. ^{1}H NMR (DMSO-d_6) δ 1.18 (3H, t, *J*=7.1 Hz), 3.77 (3H, d, J_{HF}=1.4 Hz), 4.17 (2H, q, *J*=7.1 Hz), 7.36–7.44 (3H, m), 7.58–7.66 (2H, m). ^{13}C NMR (DMSO-d_6) δ 14.1, 34.4, 60.0, 92.9 (d, J_{CF}=7.8 Hz), 127.9, 128.7, 128.9, 132.4, 150.0 (d, J_{CF}=6.8 Hz), 153.9 (d, J_{CF}=288.1 Hz), 160.7 (d, J_{CF}=5.7 Hz). ^{19}F NMR (DMSO-d_6) δ −121.5. IR 1711, 1545, 1450, 1389, 1306, 1142, 1053, 766, 696, 654 cm^{-1}. HRMS: calcd for $C_{13}H_{14}FN_2O_2$ (M+H$^+$): 249.1039; found: *m*/*z* 249.1031.

*4.3.29. Ethyl 5-fluoro-1-methyl-3-(p-tolyl)pyrazole-4-carboxylate (**5g**).* Colorless solid. Mp 83.2–85.1 °C. ^{1}H NMR (DMSO-d_6) δ 1.19 (3H, t, *J*=7.1 Hz), 2.33 (3H, s), 3.75 (3H, d, J_{HF}=1.5 Hz), 4.17 (2H, q, *J*=7.1 Hz), 7.20 (2H, d, *J*=8.1 Hz), 7.53 (2H, d, *J*=8.1 Hz). ^{13}C NMR (DMSO-d_6) δ 14.2, 21.0, 34.4, 60.0, 92.8 (d, J_{CF}=7.8 Hz), 128.5, 128.7, 129.6, 138.1, 149.9 (d, J_{CF}=7.0 Hz), 153.9 (d, J_{CF}=288.2 Hz), 160.7 (d, J_{CF}=5.7 Hz). ^{19}F NMR (DMSO-d_6) δ −121.5. IR 1703, 1579, 1541, 1442, 1321, 1182, 1051, 829, 777, 681 cm^{-1}. HRMS: calcd for $C_{14}H_{16}FN_2O_2$ (M+H$^+$): 263.1196; found: *m*/*z* 263.1187.

*4.3.30. Ethyl 5-fluoro-3-(4-chlorophenyl)-1-methylpyrazole-4-carboxylate (**5h**).* Pale yellow solid. Mp 83.8–85.8 °C. ^{1}H NMR (DMSO-d_6) δ 1.19 (3H, t, *J*=7.1 Hz), 3.77 (3H, d, J_{HF}=1.4 Hz), 4.18 (2H, q, *J*=7.1 Hz), 7.47 (2H, d, *J*=8.6 Hz), 7.67 (2H, d, *J*=8.6 Hz). ^{13}C NMR (DMSO-d_6) δ 14.1, 34.5, 60.1, 93.0 (d, J_{CF}=8.0 Hz), 128.0, 130.6, 131.2, 133.6, 148.7 (d, J_{CF}=7.1 Hz), 154.0 (d, J_{CF}=288.6 Hz), 160.6 (d, J_{CF}=5.7 Hz). ^{19}F NMR (DMSO-d_6) δ −121.0. IR 1705, 1545, 1439, 1298, 1140, 1092, 1038, 849, 783, 642 cm^{-1}. HRMS: calcd for $C_{13}H_{13}ClFN_2O_2$ (M+H$^+$): 283.0650; found: *m*/*z* 283.0643.

*4.3.31. Ethyl 5-fluoro-3-methyl-1-phenylpyrazole-4-carboxylate (**5i**).* Colorless solid. Mp 51.5–52.2 °C. ^{1}H NMR (DMSO-d_6) δ 1.28 (3H, t, *J*=7.1 Hz), 2.38 (3H, s), 4.25 (2H, q, *J*=7.1 Hz), 7.41–7.49 (1H, m), 7.50–7.59 (2H, m), 7.60–7.68 (2H, m). ^{13}C NMR (DMSO-d_6) δ 14.3, 14.7, 60.1, 94.9 (d, J_{CF}=8.0 Hz), 122.2 (d, J_{CF}=3.5 Hz), 128.4, 129.7, 135.8 (d, J_{CF}=2.8 Hz), 149.9 (d, J_{CF}=6.9 Hz), 152.5 (d, J_{CF}=292.2 Hz), 160.9 (d, J_{CF}=5.7 Hz). ^{19}F NMR (DMSO-d_6) δ −119.8. IR 1709, 1577, 1518, 1489, 1309, 1240, 1134, 1099, 762, 687, 648 cm^{-1}. HRMS: calcd for $C_{13}H_{14}FN_2O_2$ (M+H$^+$): 249.1039; found: *m*/*z* 249.1031.

*4.3.32. Ethyl 5-fluoro-3-methyl-1-(m-tolyl)pyrazole-4-carboxylate (**5j**).* Pale yellow solid. Mp 44.8–45.2 °C. ^{1}H NMR (DMSO-d_6) δ 1.28 (3H, t, *J*=7.1 Hz), 2.37 (6H, s), 4.25 (2H, q, *J*=7.1 Hz), 7.22–7.31 (1H, m), 7.38–7.49 (3H, m). ^{13}C NMR (DMSO-d_6) δ 14.3, 14.6, 21.0, 60.1, 94.9 (d, J_{CF}=8.0 Hz), 119.1 (d, J_{CF}=4.0 Hz), 122.5 (d, J_{CF}=3.1 Hz), 129.0, 129.5, 135.7 (d, J_{CF}=2.6 Hz), 139.5, 149.8 (d, J_{CF}=6.7 Hz), 152.4 (d, J_{CF}=292.2 Hz), 160.9 (d, J_{CF}=5.6 Hz). ^{19}F NMR (DMSO-d_6) δ −119.7. IR 1714, 1585, 1516, 1483, 1462, 1333, 1254, 1101, 1082, 771, 681, 650 cm^{-1}. HRMS: calcd for $C_{14}H_{16}FN_2O_2$ (M+H$^+$): 263.1196; found: *m*/*z* 263.1191.

*4.3.33. Ethyl 5-fluoro-1-(2-chlorophenyl)-3-methylpyrazole-4-carboxylate (**5k**).* Pale yellow solid. Mp 70.1–71.6 °C. ^{1}H NMR (DMSO-d_6) δ 1.27 (3H, t, *J*=7.1 Hz), 2.38 (3H, s), 4.26 (2H, q, *J*=7.1 Hz), 7.52–7.77 (4H, m). ^{13}C NMR (DMSO-d_6) δ 14.3, 14.7, 60.2, 94.0 (d, J_{CF}=7.4 Hz), 128.7, 129.9, 130.4, 130.5, 132.3, 132.6 (d, J_{CF}=2.3 Hz), 150.5 (d, J_{CF}=6.5 Hz), 153.3 (d, J_{CF}=290.1 Hz), 160.9 (d, J_{CF}=5.7 Hz). ^{19}F NMR (DMSO-d_6) δ −119.2. IR 1711, 1585, 1529, 1485,

1321, 1242, 1126, 1084, 1041, 758, 717 cm^{-1}. HRMS: calcd for $C_{13}H_{13}ClFN_2O_2$ ($M+H^+$): 283.0650; found: *m*/*z* 283.0643.

*4.3.34. Ethyl 5-fluoro-1-(4-methoxyphenyl)-3-methylpyrazole-4-carboxylate (**5l**).* Pale yellow solid. Mp 68.5–69.2 °C. ^1H NMR (DMSO-d_6) δ 1.27 (3H, t, J=7.1 Hz), 2.36 (3H, s), 3.80 (3H, s), 4.24 (2H, q, J=7.1 Hz), 7.08 (2H, d, J=9.0 Hz), 7.54 (2H, d, J=9.0 Hz). ^{13}C NMR (DMSO-d_6) δ 14.3, 14.6, 55.6, 60.0, 94.5 (d, J_{CF}=8.1 Hz), 114.8, 124.1 (d, J_{CF}=2.7 Hz), 128.7 (d, J_{CF}=2.3 Hz), 149.5 (d, J_{CF}=6.7 Hz), 152.2 (d, J_{CF}=290.8 Hz), 159.2, 161.0 (d, J_{CF}=5.5 Hz). ^{19}F NMR (DMSO-d_6) δ −120.7. IR 1701, 1579, 1525, 1500, 1446, 1306, 1238, 1136, 1093, 1020, 825, 777 cm^{-1}. HRMS: calcd for $C_{14}H_{16}FN_2O_3$ ($M+H^+$): 279.1145; found: *m*/*z* 279.1138.

*4.3.35. Ethyl 3-(phenylhydrazono)-2-(trifluoromethyl)butanoate (**6**).* Yellow oil. ^1H NMR (DMSO-d_6) δ 1.20 (3H, t, J=7.1 Hz), 1.98 (3H, s), 4.20 (2H, q, J=7.1 Hz), 4.66 (1H, q, J_{HF}=9.0 Hz), 6.71–6.79 (1H, m), 7.03–7.09 (2H, m), 7.14–7.21 (2H, m), 9.25 (1H, br s). ^{13}C NMR ($CDCl_3$) δ 12.6 (d, J_{CF}=1.4 Hz), 14.0, 58.3 (d, J_{CF}=28.1 Hz), 62.1, 113.2, 120.8, 123.6 (d, J_{CF}=280.8 Hz), 129.2, 133.6 (d, J_{CF}=2.1 Hz), 144.3, 165.2 (d, J_{CF}=2.6 Hz). ^{19}F NMR (DMSO-d_6) δ −65.0 (d, J_{CF}=9.0 Hz). IR 1739, 1601, 1236, 1161, 1134, 1107, 1026, 750, 692 cm^{-1}. HRMS: calcd for $C_{13}H_{16}F_3N_2O_2$ ($M+H^+$): 289.1164; found: *m*/*z* 289.1159.

*4.3.36. 5-Fluoro-1,3-dimethylpyrazole-4-carboxamide (**7a**).* Colorless solid. Mp 139.4–141.4 °C. ^1H NMR (DMSO-d_6) δ 2.23 (3H, s), 3.61 (3H, d, J_{HF}=1.2 Hz), 6.89 (1H, br s), 7.12 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 14.3, 33.8, 96.3 (d, J_{CF}=9.9 Hz), 147.1 (d, J_{CF}=7.9 Hz), 151.3 (d, J_{CF}=281.8 Hz), 162.4 (d, J_{CF}=4.6 Hz). ^{19}F NMR (DMSO-d_6) δ −127.4. IR 3437, 3167, 1662, 1618, 1585, 1541, 1477, 1404, 1119, 793, 733 cm^{-1}. HRMS: calcd for $C_6H_9FN_3O$ ($M+H^+$): 158.0730; found: *m*/*z* 158.0727.

X-ray crystal data: $C_6H_8FN_3O$, M=157.15, monoclinic, space group, $P2_1/c$, Z=4, a=6.5182(1), b=12.9452(2), c=8.4421(2), β=95.813(1)°, V=708.69(2) Å^3, d=1.473 g cm^{-3}, 1086 independence reflections were collected with Cu Kα radiation on a Rigaku R-AXIS RAPID II. Data analysis was carried out with the Rigaku Crystal Structure, the structure was solved by direct methods using SHELXS and refined on F^2 using SHELXL to $R1$=0.0524, $wR2$=0.1522. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited with the Cambridge Crystallographic Database Service. Please quote reference number CCDC 859473.

*4.3.37. 5-Fluoro-N-(2-isopropylphenyl)-1,3-dimethylpyrazole-4-carboxamide (**7b**).* Colorless solid. Mp 110.8–112.7 °C. ^1H NMR (DMSO-d_6) δ 1.15 (6H, d, J=6.9 Hz), 2.28 (3H, s), 3.16 (1H, sept, J=6.9 Hz), 3.66 (3H, d, J_{HF}=1.1 Hz), 7.13–7.26 (2H, m), 7.30–7.36 (2H, m), 9.02 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 14.1, 23.1, 27.5, 33.8, 96.9 (d, J_{CF}=10.2 Hz), 125.6, 125.9, 126.5, 127.2, 134.8, 143.7, 147.0 (d, J_{CF}=7.9 Hz), 151.2 (d, J_{CF}=281.6 Hz), 160.1 (d, J_{CF}=4.8 Hz). ^{19}F NMR (DMSO-d_6) δ −127.0. IR 1672, 1576, 1523, 1446, 1417, 1317, 1171, 1097, 1066, 931, 752 cm^{-1}. HRMS: calcd for $C_{15}H_{19}FN_3O$ ($M+H^+$): 276.1512; found: *m*/*z* 276.1504.

*4.3.38. N-(Biphenyl-2-yl)-5-fluoro-1,3-dimethylpyrazole-4-carboxamide (**7c**).* Colorless solid. Mp 145.2–146.5 °C. ^1H NMR (DMSO-d_6) δ 2.12 (3H, s), 3.58 (3H, d, J_{HF}=1.2 Hz), 7.24–7.48 (8H, m), 7.75–7.81 (1H, m), 8.63 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 14.1, 33.8, 96.4 (d, J_{CF}=9.8 Hz), 125.4, 125.7, 127.6, 128.0, 128.7, 129.0, 130.3, 134.9, 136.0, 138.7, 147.0 (d, J_{CF}=7.6 Hz), 151.0 (d, J_{CF}=282.3 Hz), 159.4 (d, J_{CF}=4.6 Hz). ^{19}F NMR (DMSO-d_6) δ −127.1. IR 3392, 1672, 1577, 1522, 1435, 1319, 1273, 1078, 930, 750, 706 cm^{-1}. HRMS: calcd for $C_{18}H_{17}FN_3O$ ($M+H^+$): 310.1356; found: *m*/*z* 310.1356.

*4.3.39. N-(2-Bromophenyl)-5-fluoro-1,3-dimethylpyrazole-4-carboxamide (**7d**).* Colorless solid. Mp 149.3–151.4 °C. ^1H NMR (DMSO-d_6) δ 2.33 (3H, s), 3.68 (3H, d, J_{HF}=1.2 Hz), 7.10–7.18 (1H, m), 7.35–7.43 (1H, m), 7.65–7.71 (1H, m), 7.84–7.90 (1H, m), 8.89 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 14.5, 33.9, 96.2 (d, J_{CF}=9.5 Hz), 117.2, 125.6, 126.7, 128.3, 132.7, 136.2, 147.5 (d, J_{CF}=7.6 Hz), 151.4 (d, J_{CF}=282.2 Hz), 159.2 (d, J_{CF}=4.7 Hz). ^{19}F NMR (DMSO-d_6) δ −125.5. IR 3404, 1674, 1577, 1529, 1417, 1319, 1167, 1086, 1018, 748 cm^{-1}. HRMS: calcd for $C_{12}H_{12}BrFN_3O$ ($M+H^+$): 312.0148; found: *m*/*z* 312.0151.

*4.3.40. 5-Fluoro-1-methyl-N,3-diphenylpyrazole-4-carboxamide (**7e**).* Colorless solid. Mp 147.9–150.1 °C. ^1H NMR (DMSO-d_6) δ 3.81 (3H, d, J_{HF}=1.0 Hz), 7.04–7.12 (1H, m), 7.28–7.45 (5H, m), 7.58–7.74 (4H, m), 10.29 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 34.4, 98.1 (d, J_{CF}=11.9 Hz), 119.8, 123.9, 127.3, 128.5, 128.6, 128.9, 132.5, 139.1, 147.3 (d, J_{CF}=7.7 Hz), 151.4 (d, J_{CF}=280.8 Hz), 159.5 (d, J_{CF}=4.2 Hz). ^{19}F NMR (DMSO-d_6) δ −128.2. IR 1670, 1591, 1537, 1439, 1383, 1331, 1246, 1167, 754, 690 cm^{-1}. HRMS: calcd for $C_{17}H_{15}FN_3O$ ($M+H^+$): 296.1199; found: *m*/*z* 296.1198.

*4.3.41. 5-Fluoro-N,1,3-triphenylpyrazole-4-carboxamide (**7f**).* Pale yellow solid. Mp 160.9–162.5 °C. ^1H NMR (DMSO-d_6) δ 7.06–7.16 (1H, m), 7.30–7.55 (6H, m), 7.57–7.68 (4H, m), 7.72–7.84 (4H, m), 10.50 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 100.1 (d, J_{CF}=12.4 Hz), 119.7, 122.1 (d, J_{CF}=3.2 Hz), 124.1, 127.5, 128.5, 128.7, 129.0, 129.1, 130.0, 132.0, 136.1, 138.9, 148.8 (d, J_{CF}=7.9 Hz), 150.5 (d, J_{CF}=285.2 Hz), 159.0. ^{19}F NMR (DMSO-d_6) δ −124.8. IR 1653, 1597, 1549, 1485, 1448, 1321, 1259, 1074, 989, 883, 831, 750, 687. HRMS: calcd for $C_{22}H_{17}FN_3O$ ($M+H^+$): 358.1356; found: *m*/*z* 358.1351.

*4.3.42. 5-Fluoro-3-methyl-1-phenylpyrazole-4-carboxamide (**7g**).* Colorless solid. Mp 164.9–167.0 °C. ^1H NMR (DMSO-d_6) δ 2.35 (3H, s), 7.16 (1H, br s), 7.36 (1H, br s), 7.37–7.46 (1H, m), 7.48–7.64 (4H, m). ^{13}C NMR (DMSO-d_6) δ 14.5, 98.5 (d, J_{CF}=10.2 Hz), 121.8 (d, J_{CF}=3.6 Hz), 128.0, 129.8, 136.1, 149.0 (d, J_{CF}=7.8 Hz), 150.5 (d, J_{CF}=287.1 Hz), 162.1 (d, J_{CF}=4.5 Hz). ^{19}F NMR (DMSO-d_6) δ −123.9. IR 3388, 3192, 1635, 1614, 1514, 1495, 1444, 1267, 1109, 1051, 750, 685. HRMS: calcd for $C_{11}H_{11}FN_3O$ ($M+H^+$): 220.0886; found: *m*/*z* 220.0885.

*4.3.43. 5-Fluoro-N-(2-isopropylphenyl)-3-methyl-1-phenylpyrazole-4-carboxamide (**7h**).* Pale yellow solid. Mp 112.6–114.0 °C. ^1H NMR (DMSO-d_6) δ 1.17 (6H, d, J=6.8 Hz), 2.40 (3H, s), 3.21 (1H, sept, J=6.8 Hz), 7.18–7.69 (9H, m), 9.32 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 14.3, 23.2, 27.5, 99.1 (d, J_{CF}=10.5 Hz), 121.9 (d, J_{CF}=3.4 Hz), 125.7, 126.0, 126.7, 127.1, 128.1, 129.8, 134.6, 136.1 (d, J_{CF}=2.5 Hz), 143.7, 148.8 (d, J_{CF}=7.9 Hz), 150.5 (d, J_{CF}=286.1 Hz), 159.8 (d, J_{CF}=4.5 Hz). ^{19}F NMR (DMSO-d_6) δ −123.7. IR 1651, 1577, 1533, 1514, 1452, 1248, 1051, 823, 752, 687. HRMS: calcd for $C_{20}H_{21}FN_3O$ ($M+H^+$): 338.1669; found: *m*/*z* 338.1670.

*4.3.44. N-(Biphenyl-2-yl)-5-fluoro-3-methyl-1-phenylpyrazole-4-carboxamide (**7i**).* Pale yellow solid. Mp 104.6–106.1 °C. ^1H NMR (DMSO-d_6) δ 2.23 (3H, s), 7.27–7.60 (13H, m), 7.69–7.77 (1H, m), 9.04 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 14.2, 98.7 (d, J_{CF}=10.2 Hz), 121.8 (d, J_{CF}=3.4 Hz), 126.0, 126.1, 127.6, 128.1, 128.2, 128.6, 129.0, 129.8, 130.4, 134.7, 136.0 (d, J_{CF}=2.4 Hz), 136.6, 138.8, 148.8 (d, J_{CF}=7.7 Hz), 150.3 (d, J_{CF}=289.0 Hz), 159.3 (d, J_{CF}=4.4 Hz). ^{19}F NMR (DMSO-d_6) δ −123.9. NMR (DMSO-d_6) δ −123.7. IR 1676, 1579, 1514, 1435, 1313, 1273, 1232, 1134, 893, 837, 750, 702. HRMS: calcd for $C_{23}H_{19}FN_3O$ ($M+H^+$): 372.1512; found: *m*/*z* 382.1512.

*4.3.45. N-(2-Chlorophenyl)-5-fluoro-3-methyl-1-phenylpyrazole-4-carboxamide (**7j**).* Pale yellow solid. Mp 128.6–129.0 °C. ^1H NMR (DMSO-d_6) δ 2.43 (3H, s), 7.18–7.27 (1H, m), 7.33–7.70 (7H, m), 7.90–7.96 (1H, m), 9.27 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 14.5, 98.5 (d, J_{CF}=10.2 Hz), 122.0 (d, J_{CF}=3.4 Hz), 125.5, 126.47, 126.50, 127.8, 128.3, 129.6, 129.8, 134.8, 136.0 (d, J_{CF}=2.5 Hz), 149.2 (d, J_{CF}=7.5 Hz), 150.7 (d, J_{CF}=287.0 Hz), 159.1 (d, J_{CF}=4.9 Hz). ^{19}F NMR (DMSO-d_6) δ −122.3. IR

3133, 1649, 1577, 1535, 1516, 1439, 1244, 1047, 829, 750, 683. HRMS: calcd for $C_{17}H_{14}ClFN_3O$ ($M+H^+$): 330.0809; found: *m*/*z* 330.0810.

*4.3.46. 3-(Phenylhydrazono)-2-(trifluoromethyl)butanamide (**8**).* Colorless solid. Mp 118 °C (dec). ^{1}H NMR (DMSO-d_6) δ 1.99 (3H, s), 4.18 (1H, q, J_{HF}=9.5 Hz), 6.70–6.78 (1H, m), 7.06–7.13 (2H, m), 7.14–7.23 (2H, m), 7.42 (1H, br s), 7.76 (1H, br s), 9.13 (1H, br s). ^{13}C NMR (DMSO-d_6) δ 14.0, 57.2 (d, J_{CF}=25.5 Hz), 113.0, 119.4, 124.8 (d, J_{CF}=280.6 Hz), 129.0, 135.6, 145.9, 165.8. ^{19}F NMR (DMSO-d_6) δ −64.6 (d, J_{FH}=9.5 Hz). IR 3431, 3290, 1660, 1603, 1329, 1246, 1155, 1128, 1099, 850, 744, 692, 654 cm^{-1}. HRMS: calcd for $C_{11}H_{13}F_3N_3O$ ($M+H^+$): 260.1011; found: *m*/*z* 260.1010.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2012.01.075.

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