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Short communication

Trifluoromethylation of various aromatic compounds by CF_3I in the presence of Fe(II) compound, H_2O_2 and dimethylsulfoxide

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ABSTRACT

Trifluoromethylation of aromatic and hetero-aromatic compounds by CF_3I in the presence of Fe(II) compound, H_2O_2 and dimethylsulfoxide was investigated. Various trifluoromethylated benzene derivatives, six-membered nitrogen-containing aromatic compounds and five-membered hetero-aromatic compounds were obtained under mild conditions. General orientation of electrophilic substitution of aromatic compounds was observed similarly as reported in other radical trifluoromethylation previously.

1. Introduction

Trifluoromethylated aromatic, hetero-aromatic and *pseudo*-aromatic compounds are important intermediates for synthesis of pharmaceuticals and agricultural chemicals, and many synthetic methods have been explored thus far [1]. Among them, direct trifluoromethylation is simple and therefore promising as an industrial process. A trifluoromethyl radical is widely used in direct trifluoromethylation. It has electrophilic nature and can be readily generated from various radical sources [1,2]. In the previous methods of radical trifluoromethylation of aromatic, hetero-aromatic and *pseudo*-aromatic compounds, a trifluoromethyl radical is formed from CF_3Br photochemically [3] or in the presence of Zn/SO_2 or $Na_2S_2O_4$ [4], CF_3COOH electrochemically [5] or in the presence of XeF_2 [6], CF_3COOAg photochemically [7], CF_3SO_2M (M = Na or K) electrochemically [8], bis(trifluoroacetyl)-peroxide [9] or $Te(CF_3)_2$ [10]. However, these methods seem practically unsuitable because of the reagents and/or apparatus required.

CF_3I, which is one of the available radical sources of a trifluoromethyl radical [11], was also utilized for radical trifluoromethylation under photoirradiation [12] or in the presence of Zn/SO_2 [13]; trifluoromethylation by a trifluoromethyl radical formed from CF_3I thermally is also known despite the low yield [14]. Recently, we found that trifluoromethyl radicals can be generated from CF_3I with a reagent composed of $FeSO_4$, H_2O_2 and dimethylsulfoxide (DMSO), which is the alkylation reagent of aromatic and hetero-aromatic compounds with alkyl and perfluoroalkyl iodides [15], and that various nucleobases were able to be trifluoromethylated by CF_3I and this reagent [16]. Because this reagent for trifluoromethylation is very versatile, it can provide an industrial trifluoromethylation process. In fact, a single-step process for the manufacture of 5-trifluoromethyluracil from uracil and CF_3I on an industrial scale has been realized by the use of this reagent [16].

In this study, we examined trifluoromethylation using the reagent of Fe(II), H_2O_2 and DMSO reagent in order to verify the practical application to various aromatic and hetero-aromatic compounds. Further, we investigated the orientation of the products and the reactivity of the substrates on the basis of electrophilic substitution of aromatic compounds [17].

2. Results and discussion

2.1. Trifluoromethylation of benzene derivatives

In the previous study [16], we found that ferrocene (Cp_2Fe) was more effective than $FeSO_4$ for the trifluoromethylation of certain nucleobases and the addition of H_2SO_4 frequently improved the yield. Thereafter, we carried out trifluoromethylation of each

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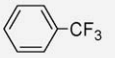
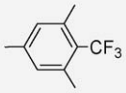
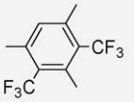
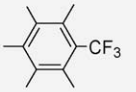
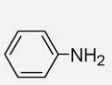
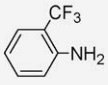
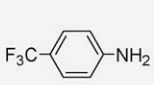
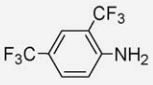
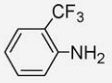
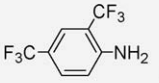
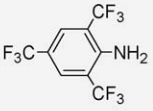
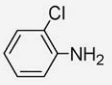
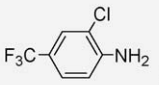
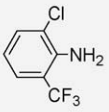
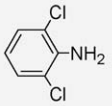
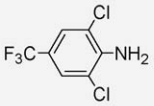
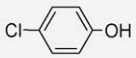
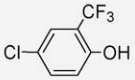
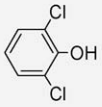
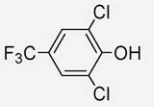
substrate by using the following four methods: (i) $FeSO_4$ in the presence of H_2SO_4 (method A), (ii) $FeSO_4$ in the absence of H_2SO_4 (method B), (iii) Cp_2Fe in the presence of H_2SO_4 (method C) and (iv) Cp_2Fe in the absence of H_2SO_4 (method D). Of them, the method giving the highest yield is listed in the tables hereafter.

Table 1 lists the results of trifluoromethylation of benzene derivatives. The reaction with benzene was carried out using method A. After the reaction, ^{19}F NMR spectrum revealed the formation of benzotrifluoride (**1a**) in 22% yield (entry 1). Because a trifluoromethyl radical is known to be an electrophile [1], benzene derivatives having an electron-donating group could exhibit the higher reactivity than benzene. The reaction with mesitylene, which possesses three electron-donating methyl groups, provided trifluoromethylmesitylnene (**2a**) and bis(tirifluoromethyl)mesitylene (**2b**) in 26% and 68% yields, respectively (entry 2). Since **2b** was presumably formed through consecutive trifluoromethylation from **2a**, the reactivity of **2a** can be considered to be higher than that of benzene. Probably the effect of an electron-donating methyl group was not cancelled by an electron-withdrawing trifluoromethyl group, for the decrease in electron density at *meta*-position of an electron-withdrawing group is negligible. The trifluoromethylation with pentamethylbenzene afforded a lower yield than that with mesitylene (entry 3). This is presumably because, as compared to mesitylene, pentamethylbenzene has fewer positions that can be trifluoromethylated. A mixture of 2-trifluoromethylaniline (**4a**), 4-trifluoromethylaniline (**4b**) and 2,4-bis(trifluoromethyl)aniline (**4c**) was obtained in the reaction with aniline (entry 4). Trifluoromethylated positions of these products were *ortho*- and *para*-positions of the electron-donating amino group. Other trifluoromethylation of aniline by a trifluoromethyl radical [**4a**,**4b**,**8a**] also showed the same orientation, indicating that the general trend of electrophilic substitution of aromatic compounds can be applied to the radical trifluoromethylation.

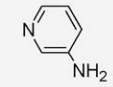
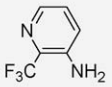
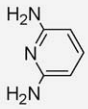
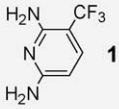
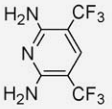
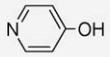
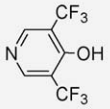
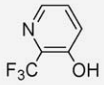
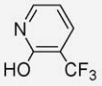
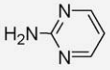
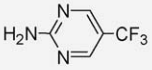
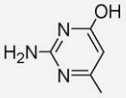
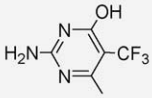
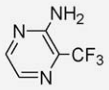
In the trifluoromethylation of aniline, method B (in the absence of H_2SO_4) was superior to method A (in the presence of H_2SO_4); method A afforded 9% for **4a**, 8% for **4b** and 5% for **4c**. This result suggests that a part of the amino group of aniline is protonated by H_2SO_4 into an aminium group. Therefore, the concentration of aniline in the reaction mixture should be lower with method A than with method B. In addition, the resulting anilinium ion is less reactive to an electrophile than aniline due to the strong electron-withdrawing nature of the aminium group. The higher reactivity of

Table 1
Trifluoromethylation of benzene derivatives.

entry	substrate	product (^{19}F-NMR yield)			method[a]
1		 **1a** (22%)			A
2		 **2a** (26%)	 **2b** (68%)		C
3		 **3a** (40%)			D
4		 **4a** (22%)	 **4b** (13%)	 **4c** (1%)	B
5		 **4c** (28%)	 **4d** (55%)		A
6		 **5a** (27%)	 **5b** (40%)		A[b]
7		 **6a** (40%)			C
8		 **7a** (38%)			C
9		 **8a** (20%)			C

[a]Substrate 1.0 mmol, CF_3I 3.0 mmol, DMSO 5.0 mL. Method A: $FeSO_4$ 0.3 mmol, H_2O_2 2.0 mmol, H_2SO_4 1.0 mmol. Method B: $FeSO_4$ 0.3 mmol, H_2O_2 2.0 mmol. Method C: Cp_2Fe 0.3 mmol, H_2O_2 2.0 mmol, H_2SO_4 1.0 mmol. Method D: Cp_2Fe 0.3 mmol, H_2O_2 2.0 mmol.
[b]$FeSO_4$ 0.5 mmol, H_2O_2 6.0 mmol.

Table 2
Trifluoromethylation of nitrogen-containing six-membered aromatics compounds.

entry	substrate	product (^{19}F-NMR yield)		method[a]
1			**9a** (41%)	D
2		 **10a** (40%)	 **10b** (56%)	A
3			**11a** (47%)	A[b]
4			**12a** (43%)	C[c]
5			**13a** (68%)	D
6			**14a** (22%)	A
7			**15a** (86%)	B
8			**16a** (57%)	A

[a]See footnote of Table 1.
[b]$FeSO_4$ 0.5 mmol, H_2O_2 6.0 mmol.
[c]Cp_2Fe 0.5 mmol, H_2O_2 10.0 mmol.

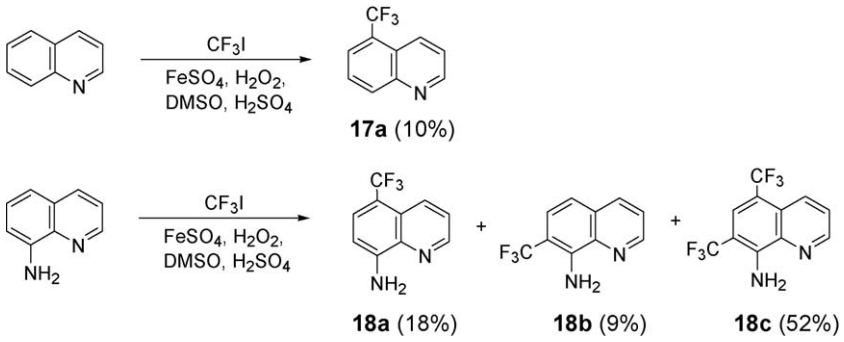
2-trifluoromethylaniline (entry 5), 2-chloroaniline (entry 6) and 2,6-dichloroaniline (entry 7) than aniline suggests that the electron-withdrawing trifluoromethyl or chlorine group suppress the protonation of the amino group. However, these substrates provided the higher yields with method A (in the presence of H_2SO_4) rather than method B (in the absence of H_2SO_4). Therefore, it can be said that aniline is exceptionally low reactive among the aniline derivatives tested in this trifluoromethylation and the effect of H_2SO_4 seems rather complex.

Ortho- or *para*-position of amino group in chloroanilines were trifluoromethylated moderately (entries 6 and 7). Chlorophenols also gave the *ortho*- and *para*-oriented products **7a** and **8a** (entries 8 and 9). These substrates are also more reactive than aniline.

2.2. Trifluoromethylation of nitrogen-containing six-membered aromatic compounds

We examined trifluoromethylation of nitrogen-containing six-membered aromatic compounds (Table 2). Because these substrates are electron-deficient, they are generally low reactive in electrophilic substitution. Indeed, the reaction using pyridine afforded a trace amount of certain trifluoromethylated products [18]. In contrast, 3-aminopyridine (entry 1) gave a moderate yield of *ortho*-oriented 3-amino-2-trifluoromethylpyridine (**9a**) in the absence of H_2SO_4 (method D) [13], suggesting that the amino group works effectively as an electron-donating group. Remarkably high total yield of *ortho*- and *para*-oriented trifluoromethylated products were obtained from 2,6-diaminopyridine even in the presence of H_2SO_4 (entry 2). The basicity of the nitrogen in the ring should be enhanced by the two amino groups at the 2- and 6-positions as expected generally, resulting in the protonation not at the amino groups but at the nitrogen atom in the ring. Although this protonation ought to cause the decrease in the reactivity to an electrophile, electron-donating character of two amino groups can cancel it and realized the high yields of **10a** and **10b**. At present, the role of proton in these high yields is unknown as well as in the reactions with aniline derivatives. Hydroxypyridines also gave the *ortho*-oriented products (entries 3–5) moderately. An electrophilically inactive 2-position of 3-hydroxypyridine was trifluoromethylated, though larger amounts of Cp_2Fe and H_2O_2 than those used typically in method C were necessary for the moderate yield (entry 4). This suggests that an electron-donating character of hydroxyl group is very effective in the trifluoromethylation. Pyrimidine and pyradine derivatives also provided *ortho*- or *para*-oriented products (entries 6–8). This orientation in the products suggests that the nitrogen atoms in the rings of 2-aminopyrimidine (entry 6) and aminopyradine (entry 8) were protonated by H_2SO_4 like 2,6-diaminopyridine.

In the reaction with quinoline, 5-trifluoromethylquinoline (**17a**) was exclusively obtained (Scheme 1), though electrophilic substitution of quinoline occurs generally at 5- and 8-positions. Moreover, the yield of **17a** (10%) was lower than **1a** (22%, entry 1 in Table 1), indicating that reactivity of benzene ring of quinoline is lower than that of benzene. The protonation possibly occurred



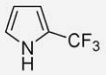
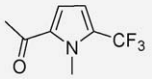
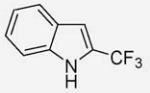
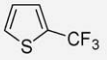
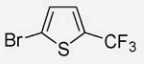
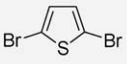
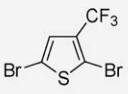
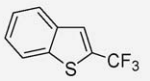
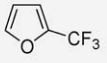
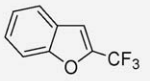
Scheme 1. Trifluoromethylation of quinoline and 8-aminoquinoline by the use of method A.

both at N atom in the ring and at the amino group. 8-Aminoquinoline exhibited much higher reactivity than quinoline and all the trifluoromethylated positions of the products were *ortho*- and *para*-positions of the amino group on benzene ring [13]. Therefore, the protonation possibly occurred at the nitrogen atom in the ring; this protonation should little affect the reactivity of the benzene ring. Such a high reactivity of 8-aminoquinoline also supports the exceptionally low reactivity of aniline in this trifluoromethylation.

2.3. Trifluoromethylation of five-membered hetero-aromatic compounds

Trifluoromethylation of various five-membered hetero-aromatic compounds were also investigated using this reagent. Table 3 shows the results of the trifluoromethylation with pyrrole, thiophene and furan derivatives. Pyrrole was readily trifluoromethylated at the 2-position as expected by the general trend of electrophilic substitution [**9b**,**12c**,**12h**,**17**]. The yield was slightly

Table 3
Trifluoromethylation of five-membered hetero-aromatic compounds (I).

entry	substrate	product (^{19}F-NMR yield)		method[a]
1			**19a** (96%)	A
2			**20a** (79%)	C
3			**21a** (36%)	A
4			**22a** (49%)	C
5			**23a** (47%)	C
6			**24a** (23%)	C
7			**25a** (17%)	C
8			**26a** (16%)	D
9			**27a** (30%)	D

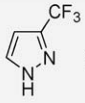
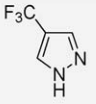
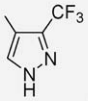
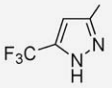
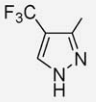
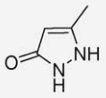
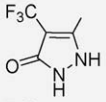
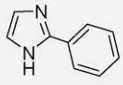
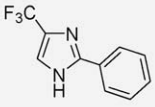
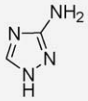
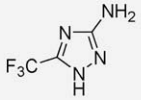
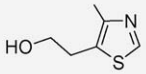
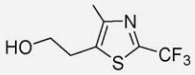
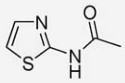
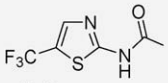
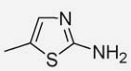
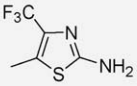
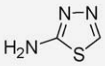
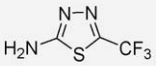
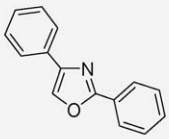
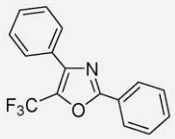
[a]See footnote of Table 1.

diminished by an electron-withdrawing acyl group (entry 2). Khanna and co-workers reported that trifluoromethylation of 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrrole by CF_3I in the presence of $FeSO_4$, H_2O_2 and DMSO gave the product trifluoromethylated at the 2-position in a yield of 43% [19]. We now assume that difference in yield occurs due to the addition of H_2SO_4. We performed the reactions in entries 1 and 2 in the presence of H_2SO_4 (method A for entry 1 and method C for entry 2). Although the effect of H_2SO_4 is unknown at present as described above, the addition of H_2SO_4 is one of the factors that improve a yield.

2-Trifluoromethylindole (**21a**) was exclusively obtained from indole despite the low yield (entry 3); the photochemical trifluoromethylation of indole by CF_3I afforded a mixture of 2- and 3-trifluoromethylindole [**12e**]. In this reaction, other products, which may have been trifluoromethylated on the phenyl ring, were also observed in ^{19}F NMR spectrum in *ca.* 10% total yield; however, those compounds have not been identified yet. Thiophene and 2-bromothiophene were trifluoromethylated at the 2-position, giving **22a** and **23a** in moderate yields. Interestingly, when 2- and 5-positions of thiophene were blocked with bromine, the product **24a** that was trifluoromethylated at the 3-position was obtained despite the lower yield (entry 6). 2-Trifluoromethylbenzo[*b*]thiophene (**25a**) was obtained selectively with this reagent, while the trifluoromethylation by CF_3Br photochemically [3] or using bis(trifluoromethyl)peroxide [**9a**] of benzo[*b*]thiophene afforded mixtures of 2-, 3-, 4- and 7-trifluoromathylated products. The present method seems superior to these trifluoromethylation in the selectivity for certain substrates.

Contrastingly, the selective trifluoromethylation at the 2-position of furan derivatives was observed similarly as other radical trifluoromethylation [**9a**,**12e**]. However, the reactivity was slightly unusual. The yield of 2-trifluoromethylfuran (**26a**) was

Table 4
Trifluoromethylation of five-membered hetero-aromatic compounds (II).

entry	substrate	product (^{19}F-NMR yield)			method[a]
1			**28a** (25%)	 **28b** (2%)	C
2			**29a** (49%)		C
3			**30a** (15%)	 **30b** (6%)	C
4			**31a** (63%)		A[b]
5			**32a** (16%)		B
6			**33a** (26%)		B
7			**34a** (45%)		D[c]
8			**35a** (53%)		D
9			**36a** (21%)		A
10			**37a** (33%)		D
11			**38a** (80%)		C

[a]See footnote of Table 1.
[b]$FeSO_4$ 1.0 mmol, H_2O_2 10.0 mmol.
[c]Cp_2Fe 0.5 mmol, H_2O_2 10.0 mmol.

lower than that of 2-trifluoromethylthiophene (**22a**). This differs from the general order of nucleophilicity, where furan > thiophene. On the other hand, the order of reactivity of benzo[*b*]furan > benzo[*b*]thiophene is reasonable (30% for **27a** in entry 9 > 17% for **25a** in entry 7).

Trifluoromethylation of pyrazole is unusual with respect to orientation and reactivity (entry 1 in Table 4). The main product was 3-trifluoromethyl (**28a**) with a concomitant formation of 4-trifluoromethylpyrazole (**28b**), though electrophilic substitution generally occurs at the 4-position. Moreover, rather low yields of **28a** and **28b** are unexpected, because pyrazole is highly electron-excessive. 4-Methylpyrazole having an electron-donating methyl group gave **29a** in 49% yield (entry 2), which implies that an electron-donating methyl group worked effectively toward a higher yield. On the other hand, 3-methylpyrazole afforded lower yields of the 5- and 4-trifluoromethylated products (entry 3) than entry 1. The substrate in entry 4, 3-methyl-3-pyrazolin-5-one which is the keto form of aromatic 5-hydroxy-3-methylpyrazole, is one of the α,β-unsaturated amides similar to uracil derivatives. Although larger amounts of $FeSO_4$ and H_2O_2 were required, the trifluoromethylated product at the α-position was obtained in a similar manner as were uracil derivatives [15]. Of the other electron-excessive compounds tested, only 2,4-diphenyloxazole provided a satisfactory yield (entry 11). Interestingly, no by-products trifluoromethylated on phenyl rings were found. Despite the low yields, electron-deficient compounds such as 1,2,4-triazole (entry 6) and 1,3,4-thiadiazole (entry 10) was able to be trifluoromethylated. In the reaction with 2-amino-5-methyl-1,3-triazole (entry 9), the position that can be trifluoromethylated is only the 4-position. Therefore, the protonation cannot be predicted by the reactivity or orientation, but possibly occurs at the nitrogen atom.

Therefore, when trifluoromethylation of five-membered hetero-aromatic compounds is performed with this reagent, the reactivity and orientation should be thoroughly noted.

Although some of the substrates that were tested afforded low yields, a simple trifluoromethylation process was achieved by using this reagent. We believe that this reagent can be applied to the synthesis of useful synthetic intermediates. For example, **6a**, **29a** and **37a** have been included in the structures of acetoprole (insecticide) [20], penthiopyrad (fungicide) [21] and thiazfluron (insecticide) [22], respectively (Fig. 1). Moreover, 13 new trifluoromethylated compounds were synthesized here by this reagent.

With regard to the reaction mechanism, we now consider as follows on the basis of the reported alkylation mechanism: (i) a hydroxyl radical is formed through the reduction of H_2O_2 by Fe(II) (Fe(III) is formed simultaneously); (ii) the hydroxyl radical is rapidly trapped by DMSO to form a methyl radical and (iii) the reaction of CF_3I and the methyl radical releases a trifluoromethyl radical [**15a**]. Supposing this mechanism, the reason why certain substrates favour Cp_2Fe and H_2SO_4 is unclear. The details of the mechanism are now under investigation.

3. Conclusion

Here, we presented the trifluoromethylation of various aromatic compounds by using the reagent comprising Fe(II), H_2O_2 and DMSO. The orientation of trifluoromethylated position was able to be predicted by the general trend of electrophilic substitution of aromatic compounds, though some substrates were exceptional. This method can provide economical process for industrial purposes, because (i) the reaction is simple and conventional single-step reaction, (ii) the reaction proceeds under mild conditions and (iii) the components of the reagent are inexpensive.

4. Experimental

4.1. General techniques

^1H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$, DMSO-d_6 or acetone-d_6 on Bruker DRX-500 (^{13}C 125 MHz) and DRX-250 (^1H 250 MHz, ^{19}F 235 MHz) spectrometers using tetramethylsilane as an internal reference for ^1H and ^{13}C NMR and fluorotrichloromethane as an external reference for ^{19}F NMR. Chemical shifts are expressed in ppm (δ). Multiplicities are indicated by s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), quint (quintet), hept (heptet), sept (septet), dd (doublet of doublet), ddd (doublet of doublet of doublet), ddq (doublet of doublet of quintet) and m (multiplet). ^{19}F NMR yields were calculated with 2,2,2-trifluoroethanol as an internal standard. The measurement of IR, high-resolution mass spectroscopy (HR-MS) and melting point (Mp) were carried out using HORIBA FT-720, JEOL JMS600 and BÜCHI 530, respectively. IR-spectra were obtained in the reflective mode. CF_3I was supplied by Tosoh F-Tech Co., Ltd. All the commercially available reagents were used without further purification.

4.2. Reaction procedures of trifluoromethylation

4.2.1. General procedure

In all the reactions, the amount of substrate was 1.0 mmol. DMSO solutions of CF_3I (3.0 mol/L) and H_2SO_4 (1.0 mol/L) were prepared just before use. $FeSO_4$ was dissolved in H_2O to a concentration of 1.0 mol/L. Cp_2Fe was used as a solid. Commercially available 30% H_2O_2 aqueous solution was used as received. During typical reactions, the molar ratio of [Fe]/[substrate], [CF_3I]/[substrate], [H_2O_2]/[substrate] and [H_2SO_4]/[substrate] were 0.3, 3.0, 2.0 and 1.0, respectively. An aqueous solution of $FeSO_4$ or Cp_2Fe, a DMSO solution of CF_3I and a DMSO solution of H_2SO_4 in some cases were charged in a two-neck flask in an argon atmosphere. The total amount of DMSO was adjusted to 5.0 mL by adding additional DMSO. Subsequently, a 30% aqueous solution of H_2O_2 was added drop-wise at the rate of 0.04 mL/min using a syringe pump. The temperature of the mixture thus obtained rose up to 40–50 °C; the mixture was stirred at this temperature for

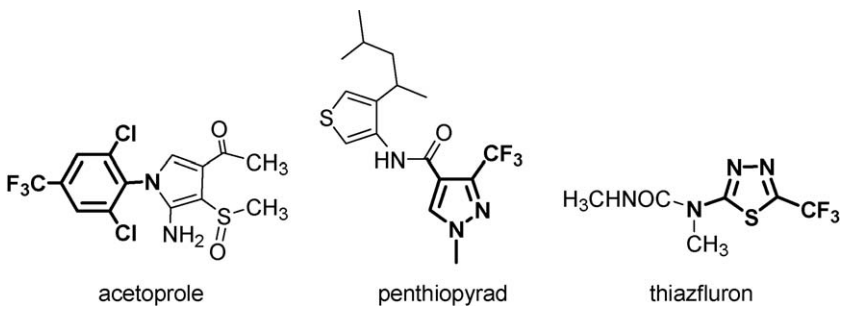


Fig. 1. Molecular structure of acetoprole, penthiopyrad and thiazfluron.

20 min. After cooling to room temperature, an aliquot of the solution was taken for measuring the ^{19}F NMR yield. Purification and isolation were carried out by means of thin layer silica chromatography, silica gel column chromatography or extraction.

The choice of method (A–D) has been listed in Tables 1–4 and Scheme 1. With respect to 2-chloroaniline (entry 5 in Table 1), 4-hydroxypyridine (entry 3 in Table 2), 3-hydroxypyridine (entry 4 in Table 2), 3-methyl-3-pyrazolin-5-one (entry 4 in Table 4) and 5-(2-hydroxyethyl)-4-methylthiazole (entry 7 in Table 4), the charged amount of Fe(II) compound and 30% aqueous solution of H_2O_2 was modified in order to obtain higher yields, as given in the footnotes of each table.

Typical procedures for **19a** (method A), **15a** (method B), **2a** and **2b** (method C) and **35a** (method D) are listed.

4.2.2. Method A: synthesis of 2-trifluoromethylpyrrole (19a)

Pyrrole (0.07 mL, 1.0 mmol), DMSO (2.0 mL), a DMSO solution of H_2SO_4 (0.5 mol/L, 2.0 mL), a DMSO solution of CF_3I (3.0 mol/L, 1.0 mL) and an aqueous solution of $FeSO_4$ (1.0 mol/L, 0.3 mL) were charged in a two-neck flask. A 30% aqueous solution of H_2O_2 (0.2 mL) was added subsequently. The reaction mixture was neutralized by adding an aqueous solution of Na_2CO_3, and the desired product was extracted into ethyl acetate. Purification and isolation of the product by thin layer silica chromatography (eluent hexane:ethyl acetate = 1:1) gave 2-trifluoromethylpyrrole (**19a**) as a colorless oil in an isolated yield of 72%.

4.2.3. Method B: synthesis of 2-amino-5-trifluoromethyl-4-hydroxy-6-mehylpyrimidine (15a)

2-Amino-4-hydroxy-6-methylpyrimidine (125 mg, 1.0 mmol), DMSO (4.0 mL) and a DMSO solution of CF_3I (3.0 mol/L, 1.0 mL) were charged in a two-neck flask. Then a 30% aqueous solution of H_2O_2 (0.2 mL) and an aqueous solution of $FeSO_4$ (1.0 mol/L, 0.3 mL) were added subsequently. The desired product was extracted into ethyl acetate. Removing the solvent under vacuo gave 2-amino-5-trifluoromethyl-4-hydroxy-6-mehylpyrimidine (**15a**) as a white solid in an isolated yield of 70%.

4.2.4. Method C: synthesis of 1,3,5-trimethyl-2-trifluoromethylbenzene (2a) and 1,3,5-trimethyl-2,4-bis(trifluoromethyl)benzene (2b)

1,3,5-Trimethylbenzene (140 μL, 1.0 mmol), Cp_2Fe (56 mg, 0.3 mmol), DMSO (2.0 mL), a DMSO solution of H_2SO_4 (0.5 mol/L, 2.0 mL) and a DMSO solution of CF_3I (3.0 mol/L, 1.0 mL) were charged in a two-neck flask. A 30% aqueous solution of H_2O_2 (0.2 mL) was added subsequently. The reaction mixture was neutralized by adding an aqueous solution of Na_2CO_3, and the desired product was extracted into ethyl acetate. Purification and isolation by passing through silica gel column (eluent hexane) gave 1,3,5-trimethyl-2-trifluoromethylbenzene (**2a**) as a pale yellow oil in an isolated yield of 48% and 1,3,5-trimethyl-2,4-bis(trifluoromethyl)benzene (**2b**) as a colorless oil in an isolated yield of 25%.

4.2.5. Method D: synthesis of N-(5-trifluoromethyl-1,3-thiazole-2-yl)acetoamide (35a)

N-(1,3-Thiazole-2-yl)acetoamide (142 mg, 1.0 mmol), Cp_2Fe (56 mg, 0.3 mmol), DMSO (4.0 mL) and a DMSO solution of CF_3I (3.0 mol/L, 1.0 mL) were charged in a two-neck flask. Then a 30% aqueous solution of H_2O_2 (0.2 mL) was added subsequently. The reaction mixture was neutralized by adding an aqueous solution of Na_2CO_3, and the desired product was extracted into ethyl acetate. Purification and isolation of the product by passing through silica gel column (eluent hexane:ethyl acetate = 1:1) gave *N*-(5-trifluoromethyl-1,3-thiazole-2-yl)acetoamide (**35a**) as a white solid in an isolated yield of 48%.

4.3. Characterization of products

The compounds **2b**, **10a**, **10b**, **11a**, **12a**, **15a**, **18a**, **18b**, **20a**, **31a**,**34a**,**35a** and **38a** are new compounds. These compounds except **2b** and **10a** have been fully characterized by NMR (^1H, ^{13}C and ^{19}F), IR and HR-MS herein. HR-MS and/or elementary analyses of **2b** and **10a** showed little reliability probably due to high volatility and/or low thermal and chemical stability. Therefore, EI–MS data were listed. The other compounds are not new and each compound is given a CAS number. Their characterization data are included in our patents previously reported [23].

4.3.1. 2,4-Bis(trifluoromethyl)-1,3,5-trimethylbenzene (2b)

Colorless oil. ^1H NMR ($CDCl_3$) δ 2.43–2.54 (m, 9H), 6.97 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 17.2 (hept, J_{CF} = 4.4 Hz), 21.9 (q, J_{CF} = 4.9 Hz), 125.6 (q, J_{CF} = 276.4 Hz), 127.8 (q, J_{CF} = 28.4 Hz), 134.5, 138.7 (hept, J_{CF} = 1.9 Hz), 140.1. ^{19}F NMR ($CDCl_3$) δ −53.2. IR 2927, 1743, 1601, 1456, 1429, 1387, 1367, 1308, 1149 (C–F) cm^{-1}. EI–MS Calcd for $C_{11}H_{10}F_6$ (*M*) 256 Found 256.

4.3.2. 2,6-Diamino-3-trifluoromethylpyridine (10a)

White solid. ^1H NMR ($CDCl_3$) δ 5.45 (brs, 2H), 5.71 (brs, 2H), 7.70 (d, J_{HH} = 5.9 Hz, 1H), 8.39 (d, J_{HH} = 5.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 105.6, 120.4 (q, J_{CF} = 31.4 H), 122.7 (q, J_{CF} = 271.3 Hz), 139.2, 140.7 (q, J_{CF} = 4.9 Hz), 161.4. ^{19}F NMR (DMSO-d_6) δ −61.4. IR 3421, 3016, 2933, 1628, 1577, 1417, 1176 (C–F) cm^{-1}. EI–MS Calcd for $C_6H_6N_3F_3$ 177. Found 177. Mp 98–100 °C.

4.3.3. 2,6-Diamino-3,5-bis(trifluoromethyl)pyridine (10b)

White solid. ^1H NMR ($CDCl_3$) δ 5.12 (brs. 4H), 7.70 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 98.0 (q, J_{CF} = 33.2 Hz), 124.5 (q, J_{CF} = 269.6 Hz), 135.6 (quint, J_{CF} = 4.7 Hz), 156.6. ^{19}F NMR ($CDCl_3$) δ −62.0. IR 3502, 3448, 3336, 3205, 1628, 1577, 1473, 1381, 1323, 1290, 1184 (C–F) cm^{-1}. HR-MS Calcd for $C_7H_5N_3F_6$ 245.0388. Found 245.0382. Mp 95–98 °C.

4.3.4. 4-Hydroxy-3,5-bis(trifluoromethyl)pyridine (11a)

White solid. ^1H NMR (acetone-d_6) δ 8.18 (s, 2H), 11.35 (brs, 1H). ^{13}C NMR (acetone-d_6) δ 120.6 (q, J_{CF} = 29.8 Hz), 124.0 (q, J_{CF} = 271.0 Hz), 139.9 (q, J_{CF} = 6.4 Hz), 170.6. ^{19}F NMR (acetone-d_6) δ −65.9. IR 3032, 2912, 2866, 1658, 1549, 1331, 1280, 1167 (C–F) cm^{-1}. HR-MS Calcd for $C_7H_4NOF_6$ (M+H) 232.0197. Found 232.0187. Mp 300 °C < .

4.3.5. 3-Hydroxy-2-trifluoromethylpyridine (12a)

White solid. ^1H NMR (acetone-d_6) δ 7.51 (dd, J_{HH} = 8.3, 3.8 Hz, 1H), 7.56 (dd, J_{HH} = 8.3, 2.0 Hz, 1H), 8.16 (dd, J_{HH} = 3.8, 2.0 Hz, 1H), 9.86 (brs, 1H). ^{13}C NMR (acetone-d_6) δ 122.6 (q, J_{CF} = 273.4 Hz), 122.5, 128.4, 134.6 (q, J_{CF} = 33.2 Hz), 140.1, 152.6. ^{19}F NMR (acetone-d_6) δ −66.8. IR 2900, 1592, 1340, 1298, 1174 (C–F) cm^{-1}. HR-MS Calcd for $C_6H_4NOF_3$ 163.0245. Found 163.0243. Mp 135–137 °C.

4.3.6. 2-Amino-4-hydroxy-6-methyl-5-trifluoromethylpyrimidine (15a)

White solid. ^1H NMR (DMSO-d_6) δ 2.23 (q, J_{HF} =2.8 Hz, 3H), 7.09 (brs, 2H), 11.23 (brs, 1H). ^{13}C NMR (DMSO-d_6) δ 22.8, 101.1 (q, J_{CF} = 29.2 Hz), 125.4 (q, J_{CF} = 271.0 Hz), 155.9, 160.9, 166.0. ^{19}F NMR (DMSO-d_6) δ −53.8. IR 3386, 3016, 2933, 1676, 1647, 1593, 1560, 1506, 1408, 1360, 1288, 1130 (C–F) cm^{-1}. HR-MS Calcd for $C_6H_7N_3OF_3$ (M+H) 194.0541. Found 194.0535. Mp < 300 °C.

4.3.7. 8-Amino-5-trifluoromethylquinoline (18a)

White solid. ^1H NMR ($CDCl_3$) δ 6.34 (brs, 2H), 6.95 (dd, J_{HH} = 8.2 Hz, J_{HF} = 0.2 Hz, 1H), 7.64 (dd, J_{HH} = 8.7, 4.1 Hz, 1H), 7.72 (dd, J_{HH} = 8.2 Hz, J_{HF} = 0.5 Hz, 1H), 8.39 (ddq, J_{HH} = 8.7, 1.5 Hz, J_{HF} = 1.8 Hz, 1H), 8.84 (dd, J_{HH} = 4.1, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 106.7, 111.6 (q, J_{CF} = 30.5 Hz), 123.8, 126.0, 126.4 (q,

J_{CF} = 268.9 Hz), 128.0 (q, J_{CF} = 5.8 Hz), 132.8 (q, J_{CF} = 2.3 Hz), 138.3, 148.5, 150.2. ^{19}F NMR ($CDCl_3$) δ −58.5. IR 3408, 3290, 1620, 1597, 1508, 1379, 1317, 1263, 1138 (C–F) cm^{-1}. HR-MS Calcd for $C_{10}H_7N_2F_3$ 212.0561. Found 212.0569. Mp 78–79 °C.

*4.3.8. 8-Amino-7-trifluoromethylquinoline (**18b**)*

White solid. ^{1}H NMR (acetone-d_6) δ 6.17 (brs, 2H), 7.06 (d, J_{HH} = 8.8 Hz, 1H), 7.37 (d, J_{HH} = 8.8 Hz, 1H), 7.49 (dd, J_{HH} = 8.4, 4.3 Hz, 1H), 8.14 (dd, J_{HH} = 8.4, 1.5 Hz, 1H), 8.71 (dd, J_{HH} = 4.3, 1.5 Hz, 1H). ^{13}C NMR (acetone-d_6) δ 106.0 (q, J_{CF} = 30.0 Hz), 113.9, 123.1 (q, J_{CF} = 4.7 Hz), 123.6, 125.9 (q, J_{CF} = 271.1 Hz), 130.2, 136.1, 138.1, 143.6, 148.3. ^{19}F NMR (acetone-d_6) δ −62.3. IR 3521, 3363, 1724, 1614, 1593, 1508, 1390, 1308, 1186 (C–F) cm^{-1}. HR-MS Calcd for $C_{10}H_7N_2F_3$ 212.0561. Found 212.0552. Mp 52–54 °C.

*4.3.9. 2-Acetyl-1-methyl-5-trifluoromethylpyrrole (**20a**)*

pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H), 4.02 (s, 3H), 6.54 (d, J_{HH} = 4.2 Hz, 1H), 6.89 (d, J_{HH} = 4.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 27.8, 34.2 (q, J_{CF} = 1.9 Hz), 110.2 (q, J_{CF} = 3.6 Hz), 113.6, 117.4, 120.6 (q, J_{CF} = 268.3 Hz), 128.0 (q, J_{CF} = 37.6 Hz), 189.7. ^{19}F NMR ($CDCl_3$) δ −60.1. IR 2670, 1670, 1541, 1389, 1346, 1147 (C–F) cm^{-1}. HR-MS Calcd for $C_8H_9NOF_3$ (M+H) 192.0636. Found 192.0645.

*4.3.10. 3-Methyl-4-trifluoromethyl-3-pyrazolin-5-one (**31a**)*

Pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 2.23 (q, J_{HF} = 1.2 Hz, 3H), 10.43 (brs, 1H), 12.05 (brs, 1H). ^{13}C NMR (DMSO-d_6) δ 10.8, 92.8 (q, J_{CF} = 36.0 Hz), 124.2 (q, J_{CF} = 265.0 Hz), 140.0, 158.7. ^{19}F NMR (DMSO-d_6) δ −54.1. IR 2933, 1734, 1558, 1456, 1439, 1363, 1290, 1151 (C–F) cm^{-1}. HR-MS Calcd for $C_5H_6N_2OF_3$ 167.0432 (M+H). Found 167.0428. Mp *ca.* 91 °C (decomp.).

*4.3.11. 2-Trifluoromethyl-5-(2-hydroxyethyl)-4-methylthiazole (**34a**)*

pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 2.54 (brs, 1H), 3.04 (t, J_{HH} = 6.0 Hz, 2H), 3.86 (t, J_{HH} = 6.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 14.9, 29.5, 62.0, 119.8 (q, J_{CF} = 271.6 Hz), 133.0, 150.5, 152.0 (q, J_{CF} = 40.4 Hz). ^{19}F NMR ($CDCl_3$) δ −61.4. IR 3300, 2931, 2881, 1734, 1716, 1541, 1466, 1302, 1184 (C–F) cm^{-1}. HR-MS Calcd for $C_7H_9NOSF_3$ (M+H) 212.0357. Found 212.0366.

*4.3.12. N-(5-Trifluoromethyl-1,3-thiazole-2-yl)acetoamide (**35a**)*

White solid. ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 7.75 (s, 1H), 11.76 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 23.1, 120.9 (q, J_{CF} = 38.2 Hz), 122.3 (q, J_{CF} = 268.5 Hz), 137.7 (q, J_{CF} = 4.5 Hz), 162.2, 168.3. ^{19}F NMR ($CDCl_3$) δ −54.8. IR 3167, 2929, 1703, 1564, 1529, 1371, 1335, 1290, 1273, 1176 (C–F) cm^{-1}. HR-MS Calcd for $C_6H_6N_2OSF_3$ (M+H) 211.0153. Found 211.0159. Mp 152–153 °C.

*4.3.13. 2,4-Diphenyl-5-trifluoromethyloxazole (**38a**)*

Pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.43–7.57 (m, 6H), 7.75–7.80 (m, 2H), 8.13–8.18 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 119.8 (q, J_{CF} = 267.8 Hz), 126.1, 127.1, 128.5 (q, J_{CF} = 1.6 Hz), 128.6, 129.0, 129.4, 129.6, 131.6, 133.5 (q, J_{CF} = 42.7 Hz), 142.5 (q, J_{CF} = 2.5 Hz), 161.7. ^{19}F NMR ($CDCl_3$) δ −60.4. IR 3062, 1610, 1558, 1489, 1387, 1367, 1325, 1163 (C–F) cm^{-1}. HR-MS Calcd for $C_{16}H_{11}NOF_3$ (M+H) 290.0793. Found 290.0783. Mp 46–48 °C.

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