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# Nucleophilic replacement of *p*-(1-chloro-2,2,2-trifluoroethyl)phenols: novel synthesis of β-trifluoromethyl-tyrosine

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**Abstract**

Three *para*-(1-chloro-2,2,2-trifluoroethyl)phenols **2a–c** were prepared by selective α-chlorination of the corresponding alcohols **1a–c**. Substitution of **2a** by active methylene compound **4** proceeds smoothly in the presence of an appropriate base at room temperature, giving substituted products **5–9** in good yields. On the basis of this finding, both the important β-trifluoromethyl-tyrosine **15** and its derivatives have been successfully synthesized.


*Keywords:* Nucleophilic replacement; Trifluoromethyl-tyrosine; Amino acid

## 1. Introduction

Preparation of fluorine-substituted compounds is of interest because of the striking effects that selective fluorine substitution has on bioactive molecules' bioactivity [1–3]. Lately, the preparation and bioactivities of fluorinated amines and amino acids have become of great interest, and several studies have been published. α-Trifluoromethylated amines have been prepared by reductive amination of trifluoromethyl ketones [4–6], the nucleophilic addition of trimethyl(trifluoromethyl)silane to aldimines [7–10], the ene reaction of *N*-tosyl trifluoromethylated imine [11], and the Friedel-Crafts reaction of *N*-alkyl trifluoromethylated imines or hemiaminals [12,13]. Of the α-amino acids, fluorinated phenylalanine [14,15] and fluorinated threonine [16,17] have been studied in detail. In addition, methods for the preparation of fluorinated β-amino acids, the Reformatsky reaction of aldimine with ethyl bromodifluoroacetate [18] and nucleophilic addition to trifluoromethylated imine [19], have been established.

Recently, we reported the easy preparation of β-trifluoromethyl-*N*-acetyltryptophan by the substitution reaction of 2,2,2-trifluoro-1-(indol-3-yl)ethanol and diethyl 2-acetoamidomalonate in the presence of sodium ethoxide or sodium hydride [20]. We therefore used 4-(1-hydroxy-2,2,2-trifluoroethyl)phenol as the starting material to synthesize the interesting fluorinated tyrosine derivative, β-trifluoromethyl-tyrosine. The 4-(1-hydroxy-2,2,2-trifluoroethyl)phenol readily obtained from phenol and trifluoroacetaldehyde ethyl hemiacetal [21,22] does not, however, react with diethyl 2-acetoamidomalonate under the same conditions, mainly because of the poor leaving ability of the side-chain hydroxyl group. For this reason, we have tried to selectively convert this hydroxyl group into a good leaving group, such as an acetoxy or a halogen group, but it is difficult to selectively acylate the side-chain hydroxyl group in acetic anhydride because of competitive acylation of the phenolic group. Selective chlorination of the side-chain hydroxyl group was made possible by the use of the common chlorination agent, $SOCl_2$ and pyridine. The substitution of *para*- or *ortho*-(1-chloro-2,2,2-trifluoroethyl)phenols by various nucleophiles and a convenient method for preparing β-trifluoromethyl-tyrosine are reported.

## 2. Results and discussion

Three *para*-(1-chloro-2,2,2-trifluoroethyl)phenols, **2a–c**, were prepared by the reactions of the corresponding alcohols **1a–c** with $SOCl_2$ and pyridine (Scheme 1). First, substitution

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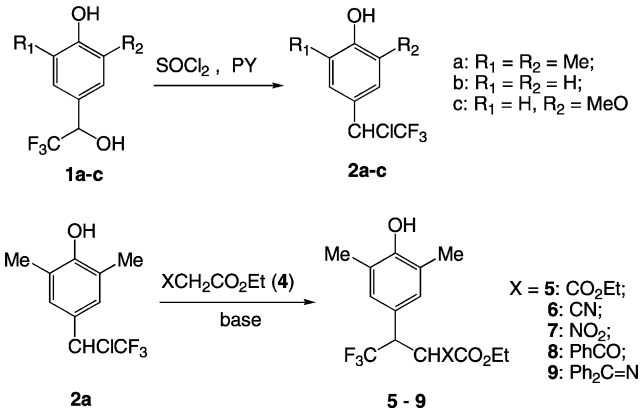



Scheme 1.

reactions of **2a** with the weakly acidic compounds **4** and nitromethane were examined at room temperature in the presence of an appropriate base. With diethyl malonate, there was a high yield of substituted product **5** when sodium hydride was the base (Table 1, Entry 1). Under the same conditions, similar reactions of **2a** with ethyl cyanoacetate, ethyl benzoylacetate, ethyl (benzhydrylidene-amino)acetate, and nitromethane gave the corresponding substituted products **6**, **8**–**10a** in high yields (Entries 2 and 4–6). With ethyl nitroacetate substituted product **7** was produced in high yield when potassium carbonate was the base (Entry 3), whereas no simple substituted product was detected in the corresponding reaction of **2a** with sodium cyanide (Entry 7). Stereochemical analysis of substituted products **6**–**9** by $^{1}H$ and $^{19}F$ NMR showed that *anti*-isomer formation was somewhat more preferential than *syn*-isomer formation, albeit in low ratios (Entries 2–5).

Based on these findings, the reactions of 4-(1-chloro-2,2,2-trifluoroethyl)phenol **2b** with nitromethane, ethyl (benzhydrylidene-amino)acetate, and ethyl nitroacetate were investigated under the above conditions to obtain the target compounds β-trifluoromethylated tyrosine and tyramine. Substituted product **10b** (Fig. 1) was generated with nitromethane, but only in about 20% yield (Entry 8). Product analysis showed that the low yield mainly was due to the formation of side-products caused by condensation of **2b** in the presence of the base. The same side-products were produced in the reaction with ethyl (benzhydrylidene-amino)acetate, giving product **11** in 55% yield (Entry 9). In contrast, a 70% yield of product **12** was obtained with ethyl nitroacetate (Entry 10). A low yield of substituted product **10c**, a useful precursor of β-trifluoromethylated dopamine was obtained when 4-(1-chloro-2,2,2-trifluoroethyl)-2-methoxy-phenol **2c** was used in the reaction with nitromethane (Entry 11), whereas with ethyl nitroacetate substituted product **13** was produced in high yield (Entry 12).

It is very difficult for nucleophiles to substitute directly for the chlorine atom in an alkyl chloride bearing a bulky trifluoromethyl group. In fact, we found that no substitution reaction occurred between 1-chloro-2,2,2-trifluoroethylbenzene and diethyl malonate in the presence of sodium hydride. The above replacement therefore probably proceeds along a pathway via the generation and reaction of quinone methides.

The benzhydrylidene group next was removed from products **9** and **11**. When a mixture of **9** (3.0 mmol), 4N aqueous HCl (5.0 l), and acetic acid (8.0 ml) was stirred at room temperature for 24 h, the β-trifluoromethyl-tyrosine analogue **14** was afforded in 87% yield (Scheme 2). Under the same conditions, hydrolysis of **11** gave β-trifluoromethyl-tyrosine **15** in 85% yield. Moreover, tyrosine **15** was obtained in 83% yield when nitro compound **12** was hydrogenated in methanol in the presence of a catalytic amount of palladium–charcoal under a hydrogen atmosphere (Scheme 3). Palladium-catalyzed hydrogenation of **10c** and **13** gave the corresponding reduction products **16** and **17**, respectively, in 77 and 79% yields.

Table 1
Reaction of (1-chloro-2,2,2-trifluoroethyl)phenol with various nucleophiles

| Entry | Substrate | Nucleophile | Conditions | Product (yield %) | *anti*:*syn* |
|---|---|---|---|---|---|
| 1 | **2a** | $CH_2(CO_2Et)_2$ | NaH/toluene, RT, 6 h | **5** (80) | |
| 2 | **2a** | $NCCH_2CO_2Et$ | NaH/THF, RT, 6 h | **6** (97) | 66:34 |
| 3 | **2a** | $O_2NCH_2CO_2Et$ | $K_2CO_3$/DMF, RT, 36 h | **7** (87) | 55:45 |
| 4 | **2a** | $PhCOCH_2CO_2Et$ | NaH/THF, RT, 8 h | **8** (88) | 57:43 |
| 5 | **2a** | $Ph_2CH{=}NCH_2CO_2Et$ | NaH/THF, RT, 8 h | **9** (80) | 58:42 |
| 6 | **2a** | $CH_3NO_2$ | NaH/THF, RT, 8 h | **10a** (87) | |
| 7 | **2a** | NaCN | DMF, RT, 36 h | None | |
| 8 | **2b** | $CH_3NO_2$ | NaH/THF, RT, 8 h | **10b** (20) | |
| 9 | **2b** | $Ph_2CH{=}NCH_2CO_2Et$ | NaH/THF, RT, 8 h | **11** (55) | 65:35 |
| 10 | **2b** | $O_2NCH_2CO_2Et$ | $K_2CO_3$/DMF, RT, 36 h | **12** (70) | 61:39 |
| 11 | **2c** | $CH_3NO_2$ | NaH/THF, RT, 8 h | **10c** (30) | |
| 12 | **2c** | $O_2NCH_2CO_2Et$ | $K_2CO_3$/DMF, RT, 36 h | **13** (85) | 64:36 |
| 13 | **2b** | $PhCH(CH_3)NH_2$ | $CH_2Cl_2$, 0–5 °C, 8 h | **18** (61) | 74:26 |
| 14 | **3a** | $NH_3$ (aq) | $CH_2Cl_2$, 0–5 °C, 8 h | **19** (43) | |
| 15 | **3a** | $PhCH(CH_3)NH_2$ | $CH_2Cl_2$, 0–5 °C, 8 h | **20a** (51) | >99:1 |
| 16 | **3b** | $PhCH(CH_3)NH_2$ | $CH_2Cl_2$, 0–5 °C, 8 h | **20b** (62) | >99:1 |

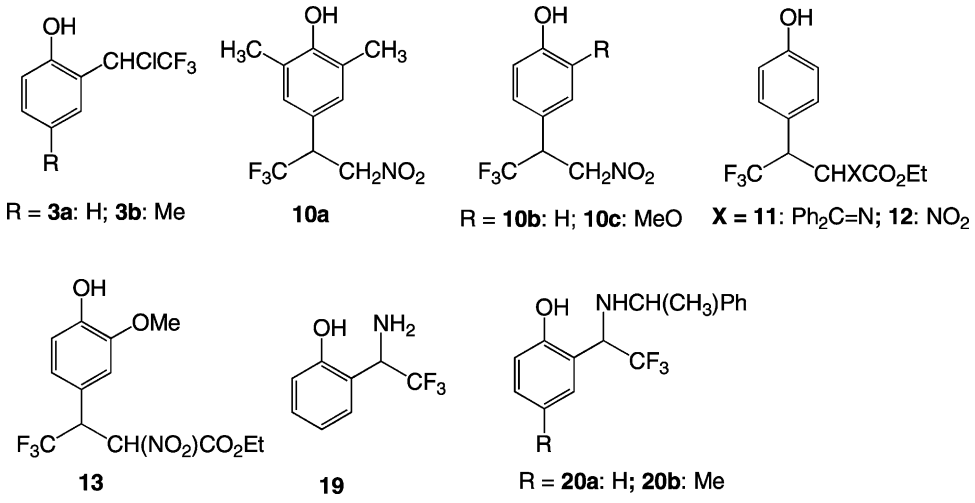
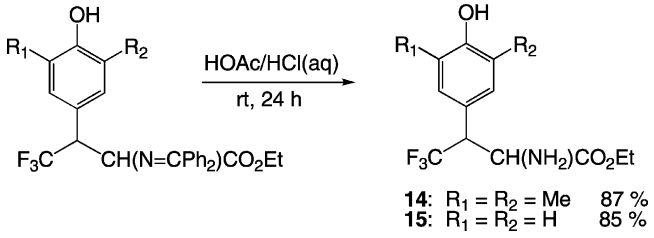
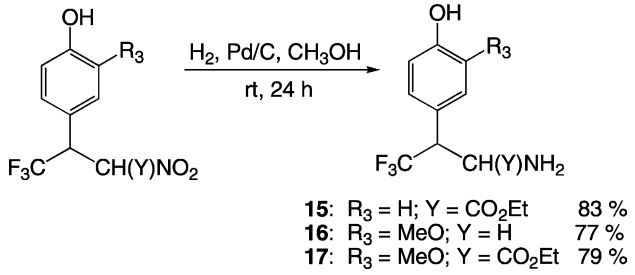



Fig. 1. Structures of substituted products of *p*- and *o*-(1-chloro-2,2,2-trifluoroethyl)phenols with nucleophiles.

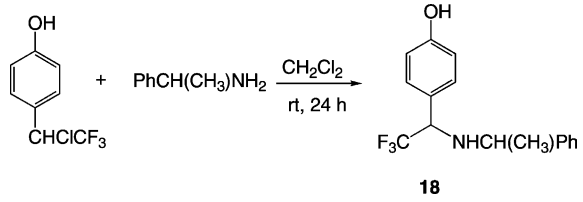
In addition to the C-centered nucleophiles, substitution of **2b** with an N-centered nucleophile was examined. The addition of **2b** (5.0 mmol) to an excess of 1-phenylethylamine (15.0 mmol) in dichloromethane at 0–5 °C gave *N*-alkyl 1-aryl-2,2,2-trifluoroethylamine, **18**, in 61% yield (Scheme 4). The diastereomer ratio determined by $^{19}F$ NMR was 74:26 (Entry 13). The corresponding reaction




Scheme 2.




Scheme 3.




Scheme 4.

of 2-(1-chloro-2,2,2-trifluoroethyl)phenol, **3a** (Fig. 1), readily obtained in high yield by the chlorination of 2-(1-hydroxy-2,2,2-trifluoroethyl)phenol with $SOCl_2$ and pyridine, was investigated under these conditions because of the importance of *o*-aminoalkylphenols in asymmetric synthesis. The reaction of **3a** with ammonia afforded α-trifluoromethylamine, **19**, in 43% yield (Entry 14). A similar reaction with (*S*)-1-phenylethylamine produced a moderate yield of *N*-alkyl 1-aryl-2,2,2-trifluoroethylamine, **20**, in high diastereoselectivity (up to 99:1) (Entry 15). High diastereoselectivity also occurred in the corresponding reaction of 2-(1-chloro-2,2,2-trifluoroethyl)-*p*-cresol, **3b** (Entry 16).

In conclusion, we consider that the substitution reaction of *para*- and *ortho*-(1-chloro-2,2,2-trifluoroethyl)phenols using various nucleophiles is an efficient, novel method for preparing β-trifluoromethyl-tyrosine, dopamine, and α-trifluoromethylamines.

## 3. Experimental

### 3.1. General

All the starting materials were obtained commercially and used without purification. Tetrahydrofuran was treated with sodium wires and preserved on 4 Å molecular sieves. $^1H$ NMR spectra were recorded with tetramethylsilane (TMS) as the internal standard at 90 MHz by a Hitachi R-90H FT spectrometer and at 299.95 MHz by a Varian INOVA-300 FT spectrometer. $^{19}F$ NMR spectra were recorded, at 84.7 and 282.22 MHz, respectively, by the same spectrometers with hexafluorobenzene as the internal standard. Mass spectra (70 eV) were measured with a Shimadzu QP-5000 instrument, and high-resolution mass spectra with a JEOL JMS-SX102A MS spectrometer. Melting points, measured in a glass capillary tube on a heating block, are uncorrected.

### 3.2. Preparation of p-(1-chloro-2,2,2-trifluorethyl) phenols **2a–c**

A mixture of 4-(1-hydroxy-2,2,2-trifluoroethyl)-2,6-dimethyl-phenol **1a** (2.20 g, 10 mmol) and thionyl chloride (1.67 g, 14 mmol) in dry toluene (15 ml) was cooled to 0–5 °C in an ice–water bath. Pyridine (0.79 g, 10 mmol) was added slowly to keep the reaction temperature below 10 °C. This reaction mixture was stirred at 0–5 °C for 1 h then heated at 70 °C for 2 h with continuous stirring. After being cooled, it was poured into about 20 g of ice–water and stirred for another 30 min. The organic layer was separated, and the aqueous layer treated twice with ethyl acetate. The combined organic layer was dried over sodium sulfate then evaporated under reduced pressure, giving an oily residue. It was purified by silica gel column chromatography (hexane:ethyl acetate: 7:1 (v/v)), yielding 2.26 g (95%) of chlorinated product **2a** as a colorless oil. The same procedures were used to prepare **2b**, **2c**, **3a**, and **3b**, the yields being 91% for **2b**, 95% for **2c**, 90% for **3a**, and 81% for **3b**.

### 3.3. General procedures for nucleophilic replacement with **2a–c**

Procedure (A): Diethyl malonate (0.88 g, 5.5 mmol) was added to a suspension of sodium hydride (60%, 0.22 g, 5.5 mmol) in dried toluene (25 ml) and stirred at 0–5 °C for 30 min. A solution of compound **2a** (1.19 g, 5.0 mmol) in toluene (10 ml) was added, and the whole stirred at room temperature for 6 h. The reaction mixture then was poured into distilled water (15 ml) and neutralized with dilute aqueous HCl. The organic layer was separated, and the aqueous layer treated twice with ethyl acetate. The organic phases were combined, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography. Elution with hexane:ethyl acetate (7:1 (v/v)) gave 1.45 g of product **5** in 80% yield.

Procedure (B): A mixture of ethyl nitroacetate (0.73 g, 5.5 mmol) and potassium carbonate (1.38 g, 10.0 mmol) was stirred in dry DMF (20 ml) at room temperature for 30 min. Compound **2a** (1.19 g, 5.0 mmol) was added, and the whole stirred vigorously for 36 h. The reaction mixture, worked-up as above, gave 1.46 g (87%) of product **7**.

Procedure (A) was followed when the ethyl cyanoacetate, ethyl benzoylacetate, ethyl (benzhydrylidene-amino)acetate and nitromethane reactions with **2a**, **2b**, or **2c** took place in THF. Procedure (B) was followed when ethyl nitroacetate was used. The products obtained and their spectral data follow.

2-[2,2,2-Trifluoro-1-(4-hydroxy-3,5-dimethyl-phenyl)-ethyl]-malonic acid diethyl ester (**5**): a colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.91 (2H, s), 4.92 (1H, s), 4.26 (2H, q, $J = 7.2$ Hz), 4.12 (1H, m), 4.09 (1H, d, $J = 7.0$ Hz), 3.91 (2H, q, $J = 7.2$ Hz), 2.20 (6H, s), 1.30 (3H, t, $J = 7.2$ Hz), 0.96 (3H, t, $J = 7.2$ Hz). $^{19}$F NMR ($CDCl_3$) $\delta$ 93.48 (3F, d, $J = 8.6$ Hz). MS *m/z* 362 ($M^+$, 27), 314 (24), 288 (36), 271 (29), 269 (100), 241 (72), 215 (23), 203 (76), 175 (30), 153 (22). HRMS. Anal. calcd: 362.1341. Found: 362.1340.

2-Cyano-4,4,4-trifluoro-3-(4-hydroxy-3,5-dimethyl-phenyl)-butyric acid ethyl ester (**6**): a colorless oil. Main isomer: $^1$H NMR ($CDCl_3$) $\delta$ 7.05 (2H, s), 4.91 (1H, s, br), 4.23 (2H, q, $J = 7.0$ Hz), 4.15 (1H, d, $J = 7.2$ Hz), 3.94 (1H, m), 2.23 (6H, s), 1.23 (3H, t, $J = 7.0$ Hz). $^{19}$F NMR ($CDCl_3$) $\delta$ 93.81 (3F, d, $J = 7.9$ Hz). MS *m/z* 315 ($M^+$, 9), 203 (100), 153 (9). HRMS. Anal. calcd: 315.1082. Found: 315.1080. Minor isomer (distinguishable data): $^1$H NMR ($CDCl_3$) $\delta$ 6.97 (2H, s). $^{19}$F NMR ($CDCl_3$) $\delta$ 95.15 (3F, d, $J = 7.9$ Hz).

4,4,4-Trifluoro-3-(4-hydroxy-3,5-dimethyl-phenyl)-2-nitro-butyric acid ethyl ester (**7**): minor isomer first diluted with hexane:ethyl acetate (1:5 (v/v)): colorless grains, mp 84–86 °C. $^1$H NMR ($CDCl_3$) $\delta$ 6.94 (2H, s), 5.65 (1H, d, $J = 11.0$ Hz), 4.80 (1H, s, br), 4.40 (1H, m), 4.34 (2H, q, $J = 7.2$ Hz), 2.21 (6H, s), 1.34 (3H, t, $J = 7.2$ Hz). $^{19}$F NMR ($CDCl_3$) $\delta$ 95.51 (3F, d, $J = 7.9$ Hz). Main isomer (second fraction) diluted with hexane:ethyl acetate (1:5 (v/v)): a yellowish oil. $^1$H NMR ($CDCl_3$) $\delta$ 6.93 (2H, s), 5.69 (1H, d, $J = 10.8$ Hz), 5.14 (1H, s), 4.43 (1H, m), 3.96 (2H, q, $J = 7.0$ Hz), 2.20 (6H, s), 0.96 (3H, t, $J = 7.0$ Hz). $^{19}$F NMR ($CDCl_3$) $\delta$ 93.34 (3F, d, $J = 7.9$ Hz). MS *m/z* 335 ($M^+$, 33), 288 (44), 243 (84), 215 (100), 203 (23), 175 (15), 147 (11). HRMS. Anal. calcd: 335.0981. Found: 335.0981.

2-Benzoyl-4,4,4-trifluoro-3-(4-hydroxy-3,5-dimethyl-phenyl)-butyric acid ethyl ester (**8**): main isomer (first fraction): a yellowish oil. $^1$H NMR ($CDCl_3$) $\delta$ 7.92 (2H, d, $J = 7.2$ Hz), 7.43 (3H, m), 6.87 (2H, s), 5.40 (1H, s, br), 5.25 (1H, d, $J = 11.4$ Hz), 4.48 (1H, m), 4.17 (2H, q, $J = 7.2$ Hz), 2.05 (6H, s), 1.18 (3H, t, $J = 7.2$ Hz). $^{19}$F NMR ($CDCl_3$) $\delta$ 94.48 (3F, d, $J = 8.8$ Hz). Minor isomer (second fraction): a yellowish oil. $^1$H NMR ($CDCl_3$) $\delta$ 8.14 (2H, d, $J = 7.2$ Hz), 7.55 (3H, m), 7.05 (2H, s), 5.41 (1H, s, br), 5.23 (1H, d, $J = 11.0$ Hz), 4.55 (1H, m), 3.81 (2H, q, $J = 7.0$ Hz), 2.23 (6H, s), 0.84 (3H, t, $J = 7.0$ Hz). $^{19}$F NMR ($CDCl_3$) $\delta$ 94.07 (3F, d, $J = 8.8$ Hz). MS *m/z* 394 ($M^+$, 4), 301 (11), 243 (15), 203 (4), 105 (100), 77 (39). HRMS. Anal. calcd: 394.1392. Found: 394.1387.

2-(Benzhydrylidene-amino)-4,4,4-trifluoro-3-(4-hydroxy-3,5-dimethyl-phenyl)-butyric acid ethyl ester (**9**): a yellowish oil. Main isomer: $^1$H NMR ($CDCl_3$) $\delta$ 7.42 (10H, m), 7.02 (2H, s), 4.63 (1H, d, $J = 4.8$ Hz), 4.62 (1H, s, br), 4.08 (1H, m), 3.92 (2H, q, $J = 7.0$ Hz), 2.22 (6H, s), 0.88 (3H, t, $J = 7.0$ Hz). $^{19}$F NMR ($CDCl_3$) $\delta$ 95.65 (3F, d, $J = 8.3$ Hz). MS *m/z* 469 ($M^+$, 0), 396 16), 280 (95), 266 (63), 250 (17), 238 (42), 202 (24), 193 (100), 165 (48), 105 (50), 77 (52). Minor isomer (distinguishable data): $^1$H NMR ($CDCl_3$) $\delta$ 6.79 (2H, s), 4.12 (2H, q, $J = 7.0$ Hz), 2.15 (6H, s), 0.88 (3H, t, $J = 7.0$ Hz). $^{19}$F NMR ($CDCl_3$) $\delta$ 97.44 (3F, d, $J = 8.3$ Hz).

2,6-Dimethyl-4-(2,2,2-trifluoro-1-nitromethyl-ethyl)phenol (**10a**): colorless plates, mp 140–142 °C. $^1$H NMR

($CDCl_3$) $\delta$ 6.91 (2H, s), 4.87 (1H, d, $J = 6.2$ Hz), 4.81 (1H, d, $J = 5.5$ Hz), 4.20 (1H, m), 2.24 (6H, s). $^{19}F$ NMR ($CDCl_3$) $\delta$ 92.63 (3F, d, $J = 7.8$ Hz). MS *m/z* 263 ($M^+$, 33), 217 (34), 216 (100), 203 (17), 153 (40), 147 (30). Anal. calcd for $C_{11}H_{12}F_3NO_3$: C, 50.19; H, 4.60; N, 5.32. Found: C, 50.11; H, 4.59; N, 5.23.

4-(2,2,2-Trifluoro-1-nitromethyl-ethyl)phenol (**10b**): a yellowish oil. $^1H$ NMR ($CDCl_3$) $\delta$ 7.19 (2H, d, $J = 8.7$ Hz), 6.84 (2H, d, $J = 8.7$ Hz), 5.30 (1H, s, br), 4.89 (1H, d, $J = 6.1$ Hz), 4.82 (1H, d, $J = 7.0$ Hz), 4.26 (1H, m). $^{19}F$ NMR ($CDCl_3$) $\delta$ 92.55 (3F, d, $J = 8.3$ Hz). MS *m/z* 235 ($M^+$, 13), 189 (18), 188 (100), 175 (16), 149 (24), 125 (75), 119 (69), 91 (46). HRMS. Anal. calcd: 235.0456. Found: 235.0455.

2-Methoxy-4-(2,2,2-trifluoro-1-nitromethyl-ethyl)phenol (**10c**): colorless plates, mp 78–79 °C. $^1H$ NMR ($CDCl_3$) $\delta$ 6.94 (1H, d, $J = 8.4$ Hz), 6.82 (1H, d, $J = 8.4$ Hz), 6.77 (1H, s), 4.90 (1H, d, $J = 4.6$ Hz), 4.82 (1H, d, $J = 6.6$ Hz), 4.20 (1H, m), 3.89 (3H, s). $^{19}F$ NMR ($CDCl_3$) $\delta$ 92.69 (3F, d, $J = 8.6$ Hz). MS *m/z* 265 ($M^+$, 40), 219 (29), 218 (100), 203 (34), 155 (28), 175 (12), 135 (32), 109 (41). Anal. calcd for $C_{10}H_{10}F_3NO_4$: C, 45.29; H, 3.80; N, 5.28. Found: C, 45.12; H, 3.79; N, 5.18.

4,4,4-Trifluoro-3-(4-hydroxy-phenyl)-2-nitro-butyric acid ethyl ester (**12**): a colorless oil. Main isomer: $^1H$ NMR ($CDCl_3$) $\delta$ 7.21 (2H, d, $J = 8.6$ Hz), 6.83 (2H, d, $J = 8.6$ Hz), 5.66 (1H, d, $J = 10.8$ Hz), 5.50 (1H, s, br), 4.50 (1H, dq, $J = 10.8$ and 8.8 Hz), 3.96 (2H, q, $J = 7.2$ Hz), 0.99 (3H, t, $J = 7.2$ Hz). $^{19}F$ NMR ($CDCl_3$) $\delta$ 93.31 (3F, d, $J = 8.8$ Hz). MS *m/z* 307 ($M^+$, 10), 261 (11), 260 (44), 231 (11), 215 (93), 187 (100), 175 (31), 147 (51), 125 (39), 119 (47), 109 (30), 91 (50). HRMS. Anal. calcd: 307.0668. Found: 307.0666. Minor isomer (distinguishable data): $^1H$ NMR ($CDCl_3$) $\delta$ 4.36 (2H, q, $J = 7.2$ Hz), 1.35 (3H, t, $J = 7.2$ Hz). $^{19}F$ NMR ($CDCl_3$) $\delta$ 95.39 (3F, d, $J = 8.8$ Hz).

4,4,4-Trifluoro-3-(4-hydroxy-3-methoxy-phenyl)-2-nitro-butyric acid ethyl ester (**13**): a colorless oil. Main isomer: $^1H$ NMR ($CDCl_3$) $\delta$ 6.94 (1H, d, $J = 7.0$ Hz), 6.84 (1H, d, $J = 7.0$ Hz), 6.80 (1H, s), 5.67 (1H, d, $J = 10.6$ Hz), 4.54 (1H, m), 4.05 (2H, q, $J = 7.0$ Hz), 3.91 (3H, s), 0.99 (3H, t, $J = 7.0$ Hz). $^{19}F$ NMR ($CDCl_3$) $\delta$ 93.34 (3F, d, $J = 8.9$ Hz). MS *m/z* 337 ($M^+$, 11), 290 (16), 245 (15), 217 (100), 203 (8), 177 (12), 145 (12), 127 (10). HRMS. Anal. calcd: 337.0773. Found: 337.0772. Minor isomer (distinguishable data): $^1H$ NMR ($CDCl_3$) $\delta$ 4.37 (2H, q, $J = 7.0$ Hz), 1.35 (3H, t, $J = 7.0$ Hz). $^{19}F$ NMR ($CDCl_3$) $\delta$ 95.42 (3F, d, $J = 8.9$ Hz).

### *3.4. Preparation of β-trifluoromethyl-tyrosine **15** via acid-catalyzed hydrolysis*

A mixture of compound **11** (1.32 g, 3.0 mmol), 4N aqueous HCl (5.0 ml), and acetic acid (8.0 ml) was vigorously stirred at room temperature for 24 h. After the reaction ended, 10 ml of cold water was added and the mixture neutralized with saturated aqueous $NaHCO_3$ solution. About 20 ml of ethyl acetate next was added, and the whole stirred for several minutes. The organic layer was separated, and the aqueous layer treated twice with ethyl acetate. The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified in a silica gel column and eluted with hexane:ethyl acetate (3:1 (v/v)), giving 0.71 g (85%) of β-trifluoromethyl-tyrosine ester **15**.

Compound **9**, hydrolyzed under the same conditions, gave β-trifluoromethylated amino ester **14** in 87% yield.

2-Amino-4,4,4-trifluoro-3-(4-hydroxy-3,5-dimethyl-phenyl)-butyric acid ethyl ester (**14**): colorless crystals, mp 130–133 °C. Main isomer: $^1H$ NMR ($CDCl_3$) $\delta$ 6.93 (2H, s), 4.12 (2H, q, $J = 7.0$ Hz), 4.04 (1H, d, $J = 6.8$ Hz), 3.65 (1H, m), 2.22 (6H, s), 1.65 (2H, s, br), 0.95 (3H, t, $J = 7.0$ Hz). $^{19}F$ NMR ($CDCl_3$) $\delta$ 95.48 (3F, d, $J = 9.2$ Hz). MS *m/z* 305 ($M^+$, 5), 203 (4), 184 (8), 116 (22), 102 (38), 74 (100). Minor isomer (distinguishable data): $^1H$ NMR ($CDCl_3$) $\delta$ 4.20 (2H, q, $J = 7.0$ Hz), 1.28 (3H, t, $J = 7.0$ Hz). $^{19}F$ NMR ($CDCl_3$) $\delta$ 98.14 (3F, d, $J = 9.2$ Hz). Anal. calcd for $C_{14}H_{18}F_3NO_3$: C, 55.08; H, 5.94; N, 4.59. Found: C, 55.02; H, 5.92; N, 4.53.

2-Amino-4,4,4-trifluoro-3-(4-hydroxy-phenyl)-butyric acid ethyl ester (**15**): colorless crystals, mp 122–125 °C. Main isomer: $^1H$ NMR ($CDCl_3$) $\delta$ 7.22 (2H, d, $J = 8.4$ Hz), 6.79 (2H, d, $J = 8.4$ Hz), 4.10 (1H, d, $J = 6.3$ Hz), 3.69 (1H, m), 4.18 (2H, q, $J = 7.2$ Hz), 2.20 (2H, br), 1.26 (3H, t, $J = 7.2$ Hz). $^{19}F$ NMR ($CDCl_3$) $\delta$ 95.36 (3F, d, $J = 9.4$ Hz). MS *m/z* 277 ($M^+$, 1), 204 (13), 175 (5), 135 (8), 116 (22), 102 (87), 74 (100). Anal. calcd for $C_{12}H_{14}F_3NO_3$: C, 51.99; H, 5.09; N, 5.05. Found: C, 51.03; H, 5.08; N, 4.98. Minor isomer (distinguishable data): $^1H$ NMR ($CDCl_3$) $\delta$ 6.72 (2H, d, $J = 8.4$ Hz), 3.94 (2H, q, $J = 7.2$ Hz), 1.08 (3H, t, $J = 7.2$ Hz). $^{19}F$ NMR ($CDCl_3$) $\delta$ 97.91 (3F, d, $J = 9.4$ Hz).

### *3.5. Preparation of β-trifluoromethyl-tyrosine **15** via palladium-catalyzed hydrogenolysis*

A mixture of nitro compound **12** (0.61 g, 2.0 mmol) and 5% palladium-charcoal (0.42 g) in methanol (10 ml) was stirred for 24 h at room temperature under a hydrogen atmosphere then filtered through a Celite pad, and the filtrate concentrated by evaporation under reduced pressure. The residue was separated by elution through a silica gel column with hexane:ethyl acetate/hexane (from 4:1 to 2:1 (v/v)), giving 0.46 g (83%) of β-trifluoromethyl-tyrosine ester **15**.

Pd-catalyzed hydrogenolysis of nitro compounds **10c** and **13**, done by the same procedures, gave amine **16** in 77% yield and amino ester **17** in 79% yield.

4-(1-Aminomethyl-2,2,2-trifluoro-ethyl)-2-methoxy-phenol (**16**): colorless crystals, mp 103–105 °C. $^1H$ NMR ($CDCl_3$) $\delta$ 6.93 (1H, d, $J = 7.7$ Hz), 6.85 (1H, s), 6.74 (1H, d, $J = 7.7$ Hz), 3.89 (3H, s), 3.10–3.45 (3H, m), 2.40 (2H, br). $^{19}F$ NMR ($CDCl_3$) $\delta$ 93.25 (3F, d, $J = 9.9$ Hz). MS *m/z* 235 ($M^+$, 11), 206 (100), 205 (25), 186 (89), 171 (29). Anal. calcd for $C_{10}H_{12}F_3NO_2$: C, 51.07; H, 5.14; N, 5.96. Found: C, 51.04; H, 5.14; N, 5.93.

2-Amino-4,4,4-trifluoro-3-(4-hydroxy-3-methoxy-phenyl)-butyric acid ethyl ester (**17**): a yellowish oil. Main isomer: $^1$H NMR ($CDCl_3$) $\delta$ 6.85 (3H, s), 3.44–4.30 (6H, m), 3.87 (3H, s), 1.26 (3H, t, $J = 7.0$ Hz). $^{19}$F NMR ($CDCl_3$) $\delta$ 95.42 (3F, d, $J = 9.3$ Hz). MS *m/z* 307 ($M^+$, 3), 306 (13), 232 (6), 205 (100), 186 (13), 155 (11), 116 (31). Anal. calcd for $C_{13}H_{16}F_3NO_4$: C, 50.82; H, 5.25; N, 4.56. Found: C, 50.58; H, 5.13; N, 4.33. Minor isomer (distinguishable data): $^1$H NMR ($CDCl_3$) $\delta$ 1.09 (3H, t, $J = 7.0$ Hz). $^{19}$F NMR ($CDCl_3$) $\delta$ 98.02 (3F, d, $J = 9.3$ Hz).

### *3.6. Reaction of p-(1-chloro-2,2,2-trifluoro-ethyl)phenol **2b** with 1-phenylethylamine*

Compound **2b** (1.05 g, 5.0 mmol) was added slowly with continuous stirring to a solution of 1-phenylethylamine (1.81 g, 15.0 mmol) in dichloromethane (25 ml) at 0–5 °C, and the whole stirred for 8 h. The solvent was removed under reduced pressure, and the oily residue separated by silica gel column chromatography with hexane:ethyl acetate (5:1 (v/v)) as the eluting solvent gave 0.90 g of *N*-alkyl 1-aryl-2,2,2-trifluoroethylamine **18** in 61% yield.

The same procedures were followed for the corresponding reactions of **3a** and **3b** with 1-phenylethylamine. Products **20a** and **20b** were obtained, respectively, in 51 and 62% yields.

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