A Trial toward the Synthesis of γ-Fluorinated β-Amino-α-thiohydroxyamino Acid: A Finding of Desulfurizative C−C Bond Formation in Thio-Wittig-Type Rearrangement of *S*-(*N*-Aryl-trifluoroacetimidoyl)thioglycolates

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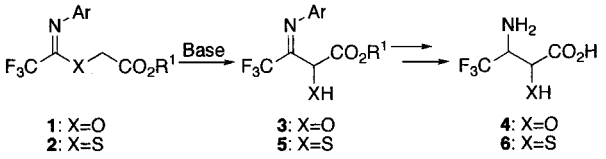
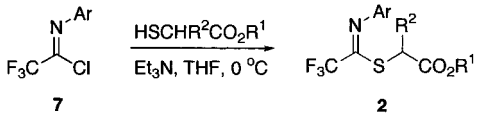
The study of the chemistry and biological activity of antibiotics and enzyme inhibitors of fluorinated β-amino acids[1,2] has gained considerable interest during the last two decades. On this basis, unnatural and structurally new fluorinated amino acids are current synthetic targets. Recently, we reported the synthesis of α-hydroxy-β-amino acids *via* Wittig rearrangement[3,4] of *O*-(*N*-arylimidoyl)glycolates **1** to α-hydroxy-β-iminocarboxylates **3** (Scheme 1). As an extension of the *O*-Wittig rearrangement (**1** → **3**), it is interesting to see whether the corresponding thio-analogues **2** undergo the same type of rearrangement to β-imino-α-thiohydroxycarboxylates **5**, which would be promising precursors of α-thiohydroxy-β-amino-γ,γ,γ-trifluorobutanoic acid, a new class of α-thiohydroxyamino acids (Scheme 1). Here, we describe the preparation and the base-promoted reactions of thioglycolates **2** in which unexpected desulfurization[5] and intramolecular ring closure with *N*-aromatic rings were discovered.

The thioglycolates **2** were prepared in good yields by the nucleophilic displacement of the fluorinated imidoyl chlorides **7**[6,7] with the commercially available thioglycolates under the basic conditions (Scheme 2). ^{19}F NMR of **2a** showed two broad peaks for CF_3 group at 96.5 and 100.0 ppm in DMSO-d_6 at room temperature, which coalesced to one peak when the NMR temperature was raised to 50 °C. This phenomenon may arise from the stereoisomerism of an *N*-aryl group, *anti* or *syn* to the trifluoromethyl group.

Scheme 1



Scheme 2



2a R^1=Me R^2= H Ar= 4-MeOC$_6$H$_4$(92%)
2b R^1= Bn R^2= H Ar= 4-MeOC$_6$H$_4$(89%)
2c R^1=Me R^2=Me Ar= 4-MeOC$_6$H$_4$(85%)
2d R^1=Me R^2= H Ar= 3-ClC$_6$H$_4$(91%)
2e R^1=Me R^2= H Ar= 3,5-Cl$_2$C$_6$H$_3$(90%)
2f R^1=Me R^2= H Ar= 3,5-Me$_2$C$_6$H$_3$(90%)
2g R^1=Me R^2= H Ar= 4-NO$_2$C$_6$H$_4$(84%)

Scheme 3

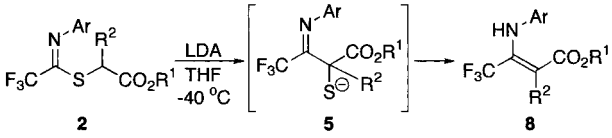


Table 1. Effect of Temperature and Bases in the Conversion of 2a to 8a

entry	base	*T* (°C)	time (h)	yield (%) of **8a**
1	LTMP	−40	9	62
2	NaH	−40	9	62
3	KO^{t}Bu	−40	9	60
4	LDA	−20	9	61
5	LDA	−40	9	71
6	LDA	−60	9	20[a]
7	LDA	−80	9	no reaction[a]
8	LDA	−40	1	25[a]
9	LDA	−40	3	49[a]
10	LDA	−40	4	57[a]
11	LDA	−40	6	65[a]

[a] The amounts of recovered **2a** were 75, 98, 69, 33, 17, and 11% in entries 6, 7, 8, 9, 10, and 11, respectively.

The thioglycolates **2** were subjected to the lithium diisopropylamide (LDA)-promoted Wittig-type rearrangement. Surprisingly, the reaction provided enamino esters **8** bearing no sulfur moiety and no expected β-imino-α-thiohydroxyesters **5** (Scheme 3). The effects of bases and the reaction conditions for the yield of **8** are shown in Table 1. The LDA was the best base for this enamine formation in our estimation. The lower reaction temperature (Table 1, entries 6 and 7) and the shorter reaction time (Table 1, entries 8−10) resulted in mostly recovery of **2a**. Results of the desulfurizative rearrangement of some ring-substituted compounds **2** are summarized in Table 2. Both electron-withdrawing (Table 2, entries 4 and 5) and electron-donating substituents (Table 2, entries 1 and 6) provided the products **8** in reasonable yields, suggesting that the electronic effect in the rear-

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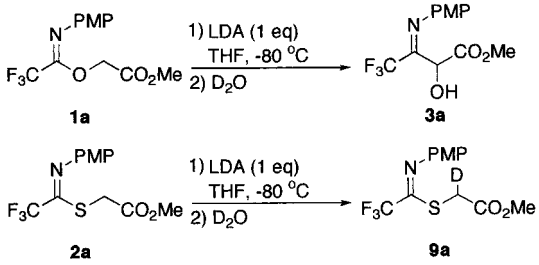
Table 2. Yield of 8 in Desulfurizative Rearrangement of 2

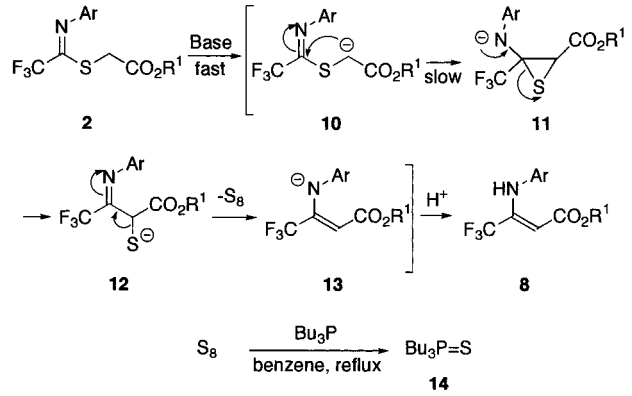
entry	R^1	R^2	Ar	yield (%) of **8**
1	Me	H	4-$MeOC_6H_4$	**8a** (71)
2	Bn	H	4-$MeOC_6H_4$	**8b** (91)
3	Me	Me	4-$MeOC_6H_4$	**8c** (54[a])
4	Me	H	3-ClC_6H_4	**8d** (90)
5	Me	H	3,5-$Cl_2C_6H_3$	**8e** (77)
6	Me	H	3,5-$Me_2C_6H_3$	**8f** (70)
7	Me	H	4-$NO_2C_6H_4$	**8g** (7)

[a] A mixture of **8c** and its tautomer (3-iminoester).

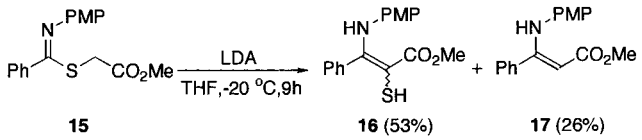
Scheme 4



Scheme 5



Scheme 6



rangement is small. However, the nitro compound mostly decomposed under the experimental conditions. Meanwhile, one-pot reaction (**7a** → **2a** → **8a**) by using 2.5 equiv of LDA also gave a reasonable yield of compound **8a** (59%).

In Wittig-type rearrangement of *O*-(*N*-arylimidoyl)-glycolates **1** to α-hydroxy-*β*-iminocarboxylates **3**, the best result was obtained under the conditions of lithium 2,2,6,6-tetramethylpiperidide (LTMP) in a mixed solvent (DME/THF = 3:1) at the temperature between −70 and −105 °C for 1 h. The reaction of **2** proceeded at the higher temperature with a longer reaction time (−40 °C for 9 h) than that of oxygen compound **1**. To clarify the relative reactivities between **1** and **2**, and the reaction mechanism of the transformation of **2** to **8**, several additional experiments were conducted. At first, both **1a** and **2a** were separately treated with LDA at −80 °C for 1 h and the reaction was quenched with D_2O. This experiment revealed **1a** provided the rearranged product **3a** (Scheme 4), but **2a** was simply deuterated on α-carbon to carboxyl group and did not undergo the expected rearrangement to **8**. Next, a mixture of **1a** (0.5 mmol) and **2a** (0.5 mmol) was treated with 0.5 mmol of LDA at −80 °C for 1 h and then was added deuterium oxide. Surprisingly, deuterium was incorporated in **2a** to give **9a**, but **1a** was recovered intact. These results suggest that deprotonation from **2a** occurs much more easily than that from **1a**,[8] but the carbanion of **2a** rearranges more slowly at −80 °C as compared with **1a**. It is plausible that the imino esters **2** undergo Wittig type rearrangement only at the higher temperature. The next questions to be solved are what the sulfur moiety is transformed to and when desulfurization occurs. If the reaction proceeds stepwise as shown in Scheme 5, elemental sulfur must be eliminated. In fact, the crude product mixture in ether was decanted and a slightly yellow solid was obtained. The mass spectrum of the solid clearly revealed a typical fragment of elemental sulfur that was consistent with that of the authentic elemental sulfur. Moreover, the reaction of the solid with tributylphosphine produced the phosphine sulfide[9] **14** (Scheme 5).

Then, the trapping of thiolate intermediate **12** by benzoylation was examined. After treating **2a** with LDA at −40 °C for 4 h, benzoyl chloride was added at once into the reaction mixture, which was then stirred at −40 °C for another 30 min. 2-Thiobenzoyloxy-3-(*N*-benzoylamino)-2-butenoate **18** was isolated in 34% yield along with compounds **8a** (30%) and **2a** (16%). Meanwhile, when the reaction mixture was quenched with aqueous NH_4Cl under the same conditions, the yield of **8a** was 57% (Table 1, entry 10) and the crude sample did not show absorption of thiohydroxyl group in the IR spectrum. These experimental results suggest that desulfurization occurs not only under the reaction conditions but also under the workup conditions. Enamine **18** was isolable as a final product, because of the high acidity of α-methine proton of *S*-benzoyl compound of **12** and thermodynamically more favorable trifluoromethyl enamine form **18** rather than the imine form.[10] Isolation of **18** clearly suggests that thiolate **12** is an initial rearrangement intermediate that gradually undergoes desulfurization under the reaction conditions. Due to the strong electron-withdrawing nature of both trifluoroiminyl and carboalkoxyl groups, desulfurization as shown in **12** would occur easily. A similar type of desulfurization from 1,3-dicarbonyl-2-thiol is known.[11] It is interesting that 2-thiol compound **16** was isolated along with *β*-aminocinnamate **17** in the reaction of **15** with LDA (Scheme 6). The lower stability of **12** is presumably due to the stronger electron-withdrawing nature of trifluoromethyl group in **12** than that of the phenyl group in **16**.

The another interesting phenomenon observed in the chemistry of thiolate **12** was the oxidative intramolecular cyclization (**2a** → **12a** → **19**). Thiolate **12a** could be oxidized with elemental iodine to the corresponding

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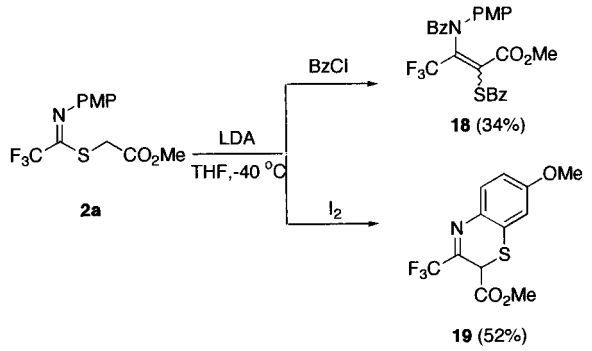
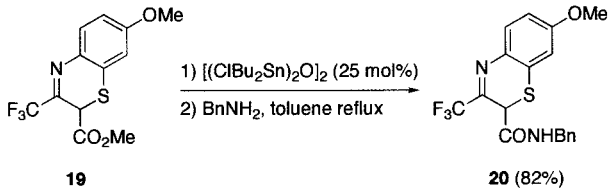
Scheme 7



Scheme 8



thioalkoxyl radical which subsequently underwent intramolecular cyclization *via* a radical addition to the aryl ring, affording compound **19** (Scheme 7). The structure of **19** was determined by X-ray crystallography of the corresponding amide **20** (Figure 1, Supporting Information), which was prepared by ester−amide exchange reaction[12] with benzylamine (Scheme 8).

In conclusion, the base-catalyzed Wittig type rearrangement of *S*-(*N*-aryltrifluoroacetimidoyl)acetates **2** proceeded smoothly at −40 °C, affording 3-amino-4,4,4-trifluoro-2-butenoates **8**. The intermediate 3-amino-4,4,4-trifluoro-2-thiohydroxybutanoates underwent a facile desulfurization to give 3-amino-4,4,4-trifluoro-2-butenoate **12**. The same type rearrangement of the corresponding 2-*S*-(*N*-arylbenzoimidoyl)acetate **15** proceeded likewise under the same reaction conditions at −20 °C, where 3-amino-2-thiohydroxycinnamate **16** was produced as a major product. The facile desulfurization would arise from the stronger electron-withdrawing nature of trifluoromethyl group for **2** than that of phenyl group for **15**. This rearrangement provides us a possible synthethic route to 3-amino-2-thiohydroxycarboxylic acid derivatives.

Experimental Section

General Methods. All reactions were performed under a dry argon atmosphere. THF was freshly distilled from sodium-benzophenone ketyl under nitrogen. All other reagents were used as obtained and without further purification. Glassware and syringes used for the reaction were oven dried before use. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at 200, 50.3, and 188 MHz, respectively. The chemical shifts are reported in δ (ppm) values relative to $CDCl_3$ (δ 7.26 ppm for ^{1}H NMR, δ 77.0 ppm for ^{13}C NMR) and C_6F_6 (δ 0 ppm for ^{19}F NMR). For TLC and column chromatography E. Merck silica gel (Kieselegel 60 F254 and Kieselgel 60, 230−400 mesh) was used.

General Procedure for the Reaction of Imidoyl Chlorides 7 with Thioglycolates. To a solution of thioglycolate (2.440 g, 23 mmol)/THF (25 mL) in a 50 mL reaction flask under N_2 were added trifluoroacetimidoyl chloride **7a** (4.948 g, 21 mmol) and Et_3N (3.2 mL, 23 mmol). The reaction mixture was then stirred at 0 °C (ice water bath) for 1 h. After all of the imidoyl chloride was consumed (monitored by TLC), the reaction was stopped and the insoluble salt formed in the reaction was filtered off. The usual workup and distillation under reduced pressure provided the product **2a** (92%, 5.931 g) as a yellowish product

Methyl *S*-(1-((*N*-4-methoxyphenyl)imino)-2,2,2-trifluoroethyl)thioglycolate (2a): IR (neat) 1746, 1634 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.2−6.9 (m, 4 H), 3.89 (s, 2 H), 3.78 (s, 3 H), 3.64 (s, 3 H); ^{19}F NMR (DMSO-d_6, 60 °C) δ 96.5 (brs, CF_3); MS *m*/*z* 307 (3) [M]$^+$, 202 (100). Anal. Calcd for $C_{12}H_{12}F_3NO_3S$: C, 46.90; H, 3.94; N, 4.56. Found: C, 46.98; H, 4.21; N, 4.55.

General Procedure for Rearrangement Reaction of 2. To a solution of diisopropylamine (0.75 mmol) in freshly distilled THF (3 mL) cooled to −40 °C under argon atmosphere was added dropwise *n*-BuLi in hexane (0.75 mmol), and then the mixture was stirred for an additional 30 min. Trifluoromethylated imino thioglycolate **2** (0.5 mmol, 0.156 g) in freshly distilled THF (2 mL) was added dropwise to the LDA solution over 10 min. The reaction mixture was stirred for 9 h. After almost all the starting material was gone (checked by TLC), 10 mL of diethyl ether was added and the reaction was quenched with 10 mL of aqueous NH_4Cl. The organic layer was then washed with water until the color of water layer became light yellowish and was dried over $MgSO_4$. Purification through column chromatography (silica gel, AcOEt/hexane = 1:10) gave the yellowish product **8a** (71%, 0.098 g).

Methyl 3-(*N*-4-methoxyphenyl)amino-4,4,4-trifluoro-2-butenoate (8a): IR (neat) 3232, 1746, 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.64 (brs, 1 H), 7.11 (d, J = 9 Hz, 2 H), 6.84 (d, J = 9 Hz, 2 H), 5.27 (s, 1 H), 3.79 (s, 3 H), 3.74 (s, 3 H); ^{19}F NMR ($CDCl_3$) δ 97.9 (s, CF_3); MS *m*/*z* 275 (74) [M]$^+$, 206 (100), 149 (81). Anal. Calcd for $C_{12}H_{12}F_3NO_3$: C, 52.37; H, 4.39; N, 5.09. Found: C, 52.17; H, 4.62; N, 5.16.

Preparation and Procedure for Rearrangement Reaction of 15. To a solution of (*N*-4-methoxyphenyl)thiobenzanilide[13] (1.001 g, 4.12 mmol)/CH_2Cl_2 (25 mL) in a 50 mL reaction flask under N_2 were added methyl bromoacetate (0.702 g, 4.53 mmol) and Et_3N (1.3 mL, 12.4 mmol). The reaction mixture was then stirred at 0 °C (ice water bath) for 3 h and concentrated, and compound **15** was obtained in 92% (1.193 g) yield by column chromatography (silica gel, AcOEt/hexane = 1:5). The compound **15** (1.0 mmol, 0.317 g) in freshly distilled THF (2 mL) was added dropwise to the LDA solution at −20 °C. The reaction mixture was stirred for 9 h at −20 °C. After almost all of the starting material was gone (checked by TLC), 10 mL of diethyl ether and aqueous NH_4Cl were added at once. The organic layer was then washed with water until the color of the water layer became light red and was dried over $MgSO_4$. Purification by column chromatography (silica gel, AcOEt/hexane) gave the yellowish products **16** (53%, 0.168 g) and **17** (26%, 0.074 g).

Methyl *S*-(1-((*N*-4-methoxyphenyl)imino)phenyl)thioglycolate (15): IR (neat) 1742, 1614 cm^{-1}; ^{1}H NMR (DMSO-d_6, 70 °C) δ 7.6−7.2 (m, 5H), 6.9−6.5 (m, 4 H), 3.88 (brs, 2 H), 3.68 (s, 3 H), 3.63 (s, 3 H); MS *m*/*z* 315 (10) [M]$^+$, 210 (100), 77 (12). Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.43; H, 5.58; N, 4.74.

Methyl 3-(*N*-4-methoxyphenyl)amino-2-thiohydroxycinnamate (16): IR (neat) 3180, 2280, 1738, 1648 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.59 (brs, 1 H), 7.4−7.2 (m,5 H), 7.1 (brs, 1H), 6.7−6.5 (m, 4 H), 3.77 (brs, 3 H), 3.68 (s, 3 H). Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.37; H, 5.43; N, 4.18.

Methyl 3-(*N*-4-methoxyphenyl)aminocinnamate (17): IR (neat) 3280, 1652, 1616 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.19 (brs, 1 H), 7.4−7.2 (m,5 H), 6.7−6.6 (m, 4 H), 4.93 (s, 1 H), 3.74 (s, 3 H), 3.70 (s, 3 H); MS *m*/*z* 283 (100) [M]$^+$, 251 (63), 210 (56). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.80; H, 6.31; N, 5.31.

A Procedure for Trapping Intermediate 12 with Benzoyl Chloride. A mixture of **2a** (0.154 g, 0.5 mmol) and LDA (0.75 mmol) was stirred at −40 °C for 4 h and was then added benzoyl chloride (0.18 mL, 1.5 mmol) at once. After being stirred

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at −40 °C for 30 min, 10 mL of diethyl ether and 10 mL of aqueous NH_4Cl were added. The ether solution was dried over $MgSO_4$ and concentrated. The residue was column chromatographed (silica gel, AcOEt/hexane = 1:5) to give **18** as colorless crystal in 34% (0.088 g) yield.

Methyl 3-(*N*-4-methoxyphenyl-*N*-benzoyl)amino-4,4,4-trifluoro-2-benzoylthio-2-butenoate (18): mp = 123−125 °C; IR (KBr) 1746, 1682, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.0−6.6 (m, 14 H), 3.94 (s, 3 H), 3.73 (s, 3 H); ^{19}F NMR ($CDCl_3$) δ 101.8 (s, CF_3); MS *m*/*z* 515 (9) $[M]^+$, 484 (7), 456 (7), 378 (21) 105(100). Anal. Calcd for $C_{26}H_{20}F_3NO_5S$: C, 60.58; H, 3.91; N, 2.72. Found: C, 60.42; H, 3.92; N, 2.83.

Synthesis of 19 by Iodine Oxidation of Intermediate 12. After the reaction of **2a** (0.1538 g, 0.5 mmol) with LDA (0.75 mmol) for 6 h as described above, the mixture was treated with I_2 (0.2571 g, 1 mmol) in THF (2 mL). The reaction was quenched with 10 mL of aqeous $Na_2S_2O_3$. After the usual workup and chromatography (silica gel, Et_2O/hexane = 1/2), **19** was isolated as a red oil in 52% (0.0804 g) yield.

3-Trifluoromethyl-7-methoxy-2-methoxycarbonylbenzo[*e*]thiazine (19): IR (neat) 1746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 (d, *J* = 10 Hz, 1 H), 6.9−6.7 (m, 2 H), 4.34 (s, 1 H), 3.82 (s, 3 H), 3.68 (s, 3 H); ^{19}F NMR ($CDCl_3$) δ 90.0 (s, CF_3); MS *m*/*z* 305 (13) $[M]^+$, 246 (100). Anal. Calcd for $C_{12}H_{10}F_3N_3O_3S$: C, 47.21; H, 3.30; N, 4.59. Found: C, 47.0; H, 3.20; N, 4.36.

Preparation of 20. A mixture of **19** (0.6289 g, 2 mmol), 1,3-dichlorotetrabutyldistannoxane (0.4049 g, 0.5 mmol), and benzylamine (0.25 mL, 2 mmol) in toluene (7 mL) was refluxed under N_2 for 1 day. Purification by column chromatography (silica gel, AcOEt/hexane = 1:2) gave product **20** as white crystals in 82% (0.6232 g) yield.

2-Benzylcarbamoyl-3-trifluoromethyl-7-methylbenzo[*e*]thiazine (20): mp = 152−153 °C; IR (KBr) 3400, 1678, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6−6.4 (m, 8 H), 4.43 (dd, *J* = 15, 7 Hz, 1 H), 4.34 (s, 1 H), 4.19 (dd, *J* = 15, 7 Hz, 1 H), 3.80 (s, 3 H); ^{19}F NMR ($CDCl_3$) δ 91.0 (s, CF_3); MS *m*/*z* 380 (1) $[M]^+$, 247 (100), 91 (34). Anal. Calcd for $C_{18}H_{15}F_3N_2O_2S$: C, 56.84; H, 3.97; N, 7.36. Found: C, 57.13; H, 4.18; N, 7.61.

X-ray crystal data for 20: $C_{18}H_{15}F_3N_2O_2S$, M = 380.38, orthorhombic, space group $P2_12_12_1$ (#19), a = 14.033(2) Å, b = 22.164(4) Å, c = 5.5190(5) Å, V = 1716.5(4) $Å^3$, Z = 4, D_{calc} = 1.47 (2) g cm^{-3}, R = 0.0790 for 1060 observed reflections [$I > 3.00\sigma(I)$] and 235 variable parameters. All measurements were made on a Rigaku RAXIS-IV imaging plate area detector with Mo Kα radiation.

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Supporting Information Available: Data of IR, ^1H and ^{19}F NMR, MS, and elemental analysis for compounds **2b**−**g** and **8b**−**g** and the detailed X-ray data for compound **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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