Convenient Substitution of Hydroxypyridines with Trifluoroacetaldehyde Ethyl Hemiacetal

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Thermal substitution of 4-hydroxypyridine **1** with trifluoroacetaldehyde ethyl hemiacetal (TFAE) leads to a moderate yield of 3-(1-hydroxy-2,2,2-trifluoroethyl)-4-hydroxypyridine **7** in the presence of a catalytic amount of anhydrous potassium carbonate. Under similar conditions, several α-trifluoromethyl hydroxypyridinemethanols **8**-**15** are easily prepared from 2- or 3-hydroxypyridines **2**-**6**.

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In the last two decades, considerable attention has been given to the preparation of α-trifluoromethyl carbinols because of their unique physical, chemical and biological properties [1]. A number of synthetic methods have been established, mainly *via* reduction of α-trifluoromethyl ketones [2], addition of nucleophiles to trifluoroacetaldehyde [3] and addition of trifluoromethyl anion, such as trifluoromethyltrimethylsilane (CF_3TMS), to carbonyl compounds [4]. Trifluoroacetaldehyde ethyl hemiacetal (TFAE), as a synthetic equivalent of trifluoroacetaldehyde, has been widely used for this purpose [5]. In our work, its thermal substitution with a variety of electron-rich heteroarenes, such as indole, pyrrole, furan, thiophene, phenols and *N*,*N*-dimethylaniline, has proved to be an efficient way of preparing the corresponding α-trifluoromethyl arylmethanols [6].

As a continuous work, we are interested in the reaction of TFAE with pyridine because of the important bioactivities of their fluorinated derivatives. In fact, α-trifluoromethyl-3-pyridinemethanols, as fungicidal pyridine derivatives, have been prepared by addition of 3-pyridyllithium to α-trifluoromethyl ketone or by addition of alkyllithium to 2,2,2-trifluoro-1-(3-pyridyl)ethanone [7]. Pyridine derivatives are electron-deficient and generally resistent to electrophilic substitution under mild conditions, although trifluoroacetylation of dimethylamino-substituted pyridines using trifluoroacetic anhydride has been successful [8]. Actually in our experiments, pyridine and its hydroxy-substituted derivatives did not undergo substitution with TFAE, even in the presence of zinc chloride. However, we found that the substitution between hydroxypyridines and TFAE readily took place when a catalytic amount of anhydrous potassium carbonate was added. The details for the reaction are described as follows.

Results and Discussion.

Hydroxypyridines **1**-**6** used in this work are given in Scheme 1. We first tried the reaction of 4-hydroxypyridine **1** with TFAE without any solvents in the presence of 10 mmol % of potassium carbonate, and the results are given in Table 1 (runs 1-3). It was found that the reaction was greatly dependent upon the reaction temperature, and no detectable substituted product was formed when the reaction was carried out below 90 °C. However, a moderate yield of 3-(1-hydroxy-2,2,2-trifluoroethyl)-4-hydroxypyridine **7** was obtained when the reaction was carried out at 130 °C for 20 hours (Scheme 1). Under similar conditions, the reaction of 2-hydroxypyridine **2** with TFAE gave two substituted products, 2-hydroxy-5-(1-hydroxy-2,2,2-trifluoroethyl)pyridine **8** and 2-hydroxy-3-(1-hydroxy-2,2,2-trifluoroethyl)pyridine **9** (runs 4-5), and that of 2-hydroxy-5-carbethoxypyridine **3** gave 2-hydroxy-3-(1-hydroxy-2,2,2-trifluoroethyl)-5-carbethoxypyridine **10** (run 6). The chemical structures for all the substituted products were easily distinguished according to the chemical shifts and the coupling constants of the protons in the pyridine ring. The low isolated yields of products **7**-**10** were mainly attributed to the recovery of the corresponding hydroxypyridines used. In contrast, a high yield (89 %) of 2-(1-hydroxy-2,2,2-trifluoroethyl)-3-hydroxy-6-methylpyridine **11** was afforded from 3-hydroxy-6-methylpyridine **4** (run 7).

Scheme 1

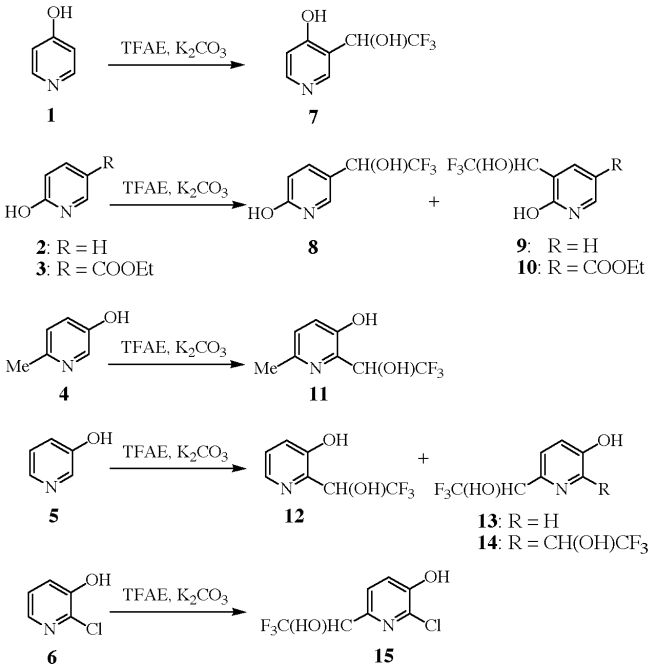
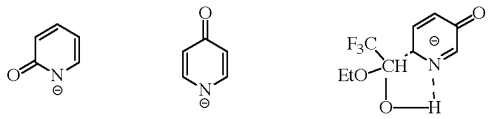


Table 1
Reaction of hydroxypyridines **1-6** with TFAE

Run	Substrate (S)	Molar Ratio (TFAE/S)	Temperature (°C)	Time (h)	Products (isolated yields, %)
1	**1**	1.1	100	16	**7** (11)
2	**1**	1.1	130	6	**7** (34)
3	**1**	1.1	130	20	**7** (49)
4	**2**	1.1	130	8	**8** (14) **9** (4)
5	**2**	1.5	130	20	**8** (23) **9** (7)
6	**3**	2.0	130	36	**10** (9)
7	**4**	1.1	130	8	**11** (89)
8	**5**	1.1	100	6	**12** (33) **13** (35) **14** (11)
9	**5**	1.0	90	8	**12** (27) **13** (29) **14** (5)
10	**5**	3.0	130	8	**12** (10) **13** (13) **14** (62)
11	**6**	1.1	130	8	**15** (93)

Apart from the marked difference in the reactivity of these substrates, the important orientation problem arises in the substitution reactions of 2- and 3-hydroxypyridines. In the case of 2-hydroxypyridine **2**, the formation of 5-substituted product **8** was obviously favored (runs 4-5). In the case of 3-hydroxy-6-methylpyridine **4**, an unexpected result was observed that no 4-substituted product was detected except 2-substituted product **11**. The specific orientation was also observed in other 3-hydroxypyridines. In fact, no detectable amount of 4-substituted product was formed in the reaction of 3-hydroxypyridine **5**, although the product distribution formed was greatly dependent upon the molar ratio of **5**/TFAE. Monosubstituted compounds, 2-(1-hydroxy-2,2,2-trifluoroethyl)-3-hydroxypyridine **12** and 3-hydroxy-6-(1-hydroxy-2,2,2-trifluoroethyl) pyridine **13**, were mainly generated when equivalent amounts of **1a** and TFAE were caused to react at 90 °C (run 9), whereas disubstituted compound, 2,6-bis(1-hydroxy-2,2,2-trifluoroethyl)-3-hydroxypyridine **14**, was the main product when an excess amount of TFAE was used (run 10). Moreover, blocking the 2-site of 3-hydroxypyridine with a chlorine atom **6** led to only the formation of 6-substituted product, 2-chloro-3-hydroxy-6-(1-hydroxy-2,2,2-trifluoroethyl)-pyridine **15**, in an excellent yield (93 %, run 11).

Based on these observations, we believe that the removal of the phenolic proton of hydroxypyridine by potassium carbonate, which increases the negative charge on the ring, greatly favors the substitution with TFAE. The low reactivity for 2-hydroxypyridine and 4-hydroxypyridine can be easily interpreted from the markedly important contribution of the pyridone canonical forms **16a** and **16b** (Fig. 1), which decrease the electron density on the carbons (C_3 and C_5) of the pyridine ring to a large extent. On the other hand, it seems to be difficult to understand why no 4-substituted product was generated in the reaction of 3-hydroxypyridines, though the regioselective substitution was commonly rationalized from the different electron density delocalized at each atom of the pyridine ring. We therefore suggested the possibility that 2- and 6-substituted products were given through a five-membered transition state outlined as **17** (Figure 1).



16a **16b** **17**

Figure 1

EXPERIMENTAL

The ^{1}H nmr spectra were recorded with tetramethylsilane (TMS) as an internal standard at 90 MHz on a Hitachi R-90H FT spectrometer. The ^{19}F nmr spectra were recorded with hexafluorobenzene as an internal standard at 84.7 MHz on the same spectrometer. All nmr spectra were measured in acetone-d_6. Mass spectra (70 eV) were measured on a Hitachi M-80 instrument. The ir spectra were recorded on a Shimadzu FTIR-8600PC instrument. Melting points were measured in a glass capillary on a heating block, and are uncorrected. High-resolution mass spectra were measured on a JEOL JMS-SX102A MS spectrometer.

3-(1-Hydroxy-2,2,2-trifluoroethyl)-4-hydroxypyridine (**7**).

A mixture of 1.90 g (0.020 mole) of 4-hydroxypyridine (**1**), 3.17 g (0.022 mole) of ethyl trifluoroacetaldehyde hemiacetal and 0.276 g (0.002 mole) of anhydrous potassium carbonate was heated with continuous stirring at 130 °C for 6 hours. After cooled, the mixture was dissolved in 30 ml of ethyl acetate and 20 ml of distilled water. The organic layer was separated, and the aqueous layer extracted twice with 20 ml of ethyl acetate. The combined organic layer was dried over sodium sulfate and evaporated to yield an oily residue. The residue was purified on a silica gel column with ethyl acetate:ethanol (98:2, v/v) as the elution to give a white solid, which was recrystallized from ethyl acetate to yield 1.30 g (34 %) of 3-(1-hydroxy-2,2,2-trifluoroethyl)-4-hydroxypyridine (**7**), white plates, mp 170-171 °C; ir: (potassium bromide): 3200 (OH), 1645 (pyridinol, CO), 1598, 1520, 1452, 1404, 1328, 1258, 1173, 1151, 1130, 1079, 847 cm^{-1}; ^{1}H nmr: δ 2.98 (br s, 1H, OH), 5.26 (q, 1H, $CHCF_3$, J = 7.7 Hz), 6.43 (d, 1H, 5-H, J = 7.3 Hz), 7.92 (d, 1H, 6-H, J = 7.3 Hz), 8.00 (s, 1H, 2-H), 11.20 (br s, 1H, PyOH); ^{19}F nmr: δ 84.96 (d, 3F, CF_3, J = 7.7 Hz); ms: m/z 193 (M^+, 20), 124 (M-CF_3, 100), 95 (M-CF_3CHO, 34).

Anal. Calcd. for $C_7H_6NO_2F_3$: C, 43.52; H, 3.13; N, 7.25. Found: C, 43.47; H, 3.12; N, 7.07.

The same procedure was taken for other hydroxy-substituted pyridines **2-6**.

2-Hydroxy-5-(1-hydroxy-2,2,2-trifluoroethyl)pyridine (**8**).

This compound was separated by column chromatography (silica gel-ethyl acetate) and recrystallized from ethyl aceate as a white solid, mp 205-206 °C; ir: (potassium bromide): 3257 (OH), 1667, 1626 (pyridone, CO), 1554, 1470, 1419, 1365, 1262, 1199, 1161, 1130, 1101, 826, 702 cm^{-1}; ^{1}H nmr: δ 2.80 (br s, 1H, OH), 5.05 (q, 1H, $CHCF_3$, J = 7.3 Hz), 6.43 (d, 1H, 3-H, J = 10.3 Hz), 7.57 (dd, 1H, 4-H, J = 10.3 Hz, 2.6 Hz), 7.63 (d, 1H, 6-H, J = 2.6 Hz), 11.30 (br s, 1H, PyOH); ^{19}F nmr: δ 85.43 (d, 3F, CF_3, J = 7.3 Hz); ms: m/z 193 (M^+, 33), 124 (M-CF_3, 100), 95 (M-CF_3CHO, 27), 69 (CF_3^+, 87).

Anal. Calcd. for $C_7H_6NO_2F_3$: C, 43.52; H, 3.13; N, 7.25. Found: C, 43.66; H, 3.14; N, 7.06.

2-Hydroxy-3-(1-hydroxy-2,2,2-trifluoroethyl)pyridine (**9**).

This compound was separated by silica gel column chromatography (ethyl acetate:hexane, 3:1, v/v) and recrystallized from chloroform:ethyl aceate as white plates, mp 165.5-166.5 °C; ir: (potassium bromide): 3300 (OH), 1652, 1598 (pyridone, CO), 1570, 1472, 1440, 1390, 1282, 1157, 1126, 1090, 1062, 778, 707 cm^{-1}; ^1H nmr: δ 5.28 (q, 1H, $CHCF_3$, J = 7.0 Hz), 6.41 (dd, 1H, 5-H, J = 6.8 Hz, 6.6 Hz), 6.48 (br s, 1H, OH), 7.56 (dd, 1H, 4-H, J = 6.6 Hz, 1.8 Hz), 7.69 (dd, 1H, 6-H, J = 6.8 Hz, 1.8 Hz), 11.20 (br s, 1H, PyOH); ^{19}F nmr: δ 85.52 (d, 3F, CF_3, J = 7.0 Hz); ms: m/z 193 (M^+, 22), 124 (M-CF_3, 100), 96 (M-CF_3CO, 13).

Anal. Calcd. for $C_7H_6NO_2F_3$: C, 43.52; H, 3.13; N, 7.25. Found: C, 43.55; H, 3.13; N, 6.93.

2-Hydroxy-3-(1-hydroxy-2,2,2-trifluoroethyl)-5-carbethoxypyridine (**10**).

This compound was separated by silica gel column chromatography (hexane:ethyl acetate, 1:1, v/v) and recrystallized from chloroform:ethyl aceate as white solid, mp 178.5-179 °C; ir: (potassium bromide): 3406 (OH), 1700 (CO_2Et), 1660, 1649 (pyridone, CO), 1624, 1437, 1376, 1284, 1253, 1218, 1170, 1127, 762, 657 cm^{-1}; ^1H nmr: δ 1.33 (t, 3H, CH_3, J = 7.2 Hz), 4.32 8q, 2H, CH_2, J = 7.2 Hz), 5.41 (q, 1H, $CHCF_3$, J = 6.2 Hz), 6.08 (br s, 1H, OH), 8.18 (d, 1H, 4-H, J = 2.2 Hz), 8.26 (d, 1H, 6-H, J = 2.2 Hz), 11.30 (br s, 1H, PyOH); ^{19}F nmr: δ 85.66 (d, 3F, CF_3, J = 6.2 Hz); ms: m/z 265 (M^+, 18), 196 (M-CF_3, 100), 168 (M-CF_3CO, 90). HRMS Calcd. for $C_{10}H_{10}NO_4F_3$: 265.0562. Found: 265.0561.

2-(1-Hydroxy-2,2,2-trifluoroethyl)-3-hydroxy-6-methylpyridine (**11**).

This compound was purified on a silica gel column with hexane:ethyl aceate (3:5, v/v) as the elution, and recrystallized from chloroform:ethyl aceate as white needles, mp 137.5-138.5 °C; ir: (potassium bromide): 3400 (OH), 1480, 1385, 1344, 1259, 1236, 1164, 1132, 1098, 938, 697, 662 cm^{-1}; ^1H nmr: δ 2.44 (s, 3H, CH_3), 2.89 (br s, 1H, OH), 5.34 (q, 1H, $CHCF_3$, J = 7.8 Hz), 7.16 (d, 1H, 4-H, J = 8.3 Hz), 7.35 (d, 1H, 5-H, J = 8.3 Hz), 9.0 (br s, 1H, PyOH); ^{19}F nmr: δ 86.69 (d, 3F, CF_3, J = 7.8 Hz); ms: m/z 207 (M^+, 39), 138 (M-CF_3, 100), 108 (M-CF_3CHOH, 23), 69 (CF_3^+, 40).

Anal. Calcd. for $C_8H_8NO_2F_3$: C, 46.37; H, 3.89; N, 6.76. Found: C, 46.45; H, 3.84; N, 6.60.

2-(1-Hydroxy-2,2,2-trifluoroethyl)-3-hydroxypyridine (**12**).

This compound was separated by silica gel column chromatography (hexane:ethyl acetate, 1:3, v/v) and recrystallized from chloroform:ethyl aceate as white plates, mp 116-116.5 °C; ir: (potassium bromide): 3528 (OH), 1607, 1582, 1469, 1423, 1302, 1259, 1185, 1162, 1138, 1075, 892, 804, 700, 642 cm^{-1}; ^1H nmr: 2.87 (br s, 1H, OH), 5.40 (q, 1H, $CHCF_3$, J = 6.4 Hz), 7.36 (m, 2H, 4-H, 5-H), 8.17 (dd, 1H, 6-H, J = 3.7 Hz, 2.2 Hz), 9.2 (br s, 1H, PyOH); ^{19}F nmr: δ 86.69 (d, 3F, CF_3, J = 6.4 Hz); ms: m/z 193 (M^+, 19), 124 (M-CF_3, 72), 94 (M-CF_3CHOH, 18), 69 (CF_3^+, 100).

Anal. Calcd. for $C_7H_6NO_2F_3$: C, 43.52; H, 3.13; N, 7.25. Found: C, 43.28; H, 3.06; N, 7.00.

3-Hydroxy-6-(1-hydroxy-2,2,2-trifluoroethyl)pyridine (**13**).

This compound was separated by silica gel column chromatography (hexane:ethyl acetate, 3:5, v/v) and recrystallized from chloroform:ethyl aceate as white plates, mp 135-136 °C; ir: (potassium bromide): 3442 (OH), 1617, 1577, 1496, 1339, 1287, 1250, 1214, 1171, 1119, 1103, 840, 816, 701, 655 cm^{-1}; ^1H nmr: δ 2.85 (br s, 1H, OH), 5.10 (q, 1H, $CHCF_3$, J = 6.9 Hz), 7.27 (dd, 1H, 4-H, J = 8.7 Hz, 2.2 Hz), 7.58 (d, 1H, 5-H, J = 8.7 Hz), 8.21 (d, 1H, 2-H, J = 2.2 Hz), 9.10 (br s, 1H, PyOH); ^{19}F nmr: δ 86.10 (d, 3F, CF_3, J = 6.9 Hz); ms: m/z 193 (M^+, 15), 124 (M-CF_3, 100), 94 (M-CF_3CHOH, 43), 69 (CF_3^+, 85).

Anal. Calcd. for $C_7H_6NO_2F_3$: C, 43.52; H, 3.13; N, 7.25. Found: C, 43.32; H, 3.08; N, 7.13.

2,6-Bis(1-hydroxy-2,2,2-trifluoroethyl)-3-hydroxypyridine (**14**).

This compound was separated by silica gel column chromatography (hexane:ethyl acetate, 1:3, v/v) and recrystallized from chloroform:ethyl aceate as white plates, mp 129-130 °C; ir: (potassium bromide): 3400 (OH), 1588, 1489, 1434, 1353, 1271, 1158, 1126, 1066, 995, 985, 835, 701, 638 cm^{-1}; ^1H nmr: δ 3.12 (br s, 1H, OH), 5.23 (q, 1H, $CHCF_3$, J = 6.6 Hz), 5.47 (q, 1H, $CHCF_3$, J = 6.6 Hz), 5.94 (br s, 1H, OH), 7.52 (s, 2H, 4-H, 5-H), 9.6 (br s, 1H, PyOH); ^{19}F nmr: δ 86.63 (d, 3F, CF_3, J = 6.6 Hz), 86.10 (d, 3F, CF_3, J = 6.6 Hz); ms: m/z 291 (M^+, 14), 222 (M-CF_3, 62), 204 (23), 184 (18), 128 (24), 69 (CF_3^+, 100).

Anal. Calcd. for $C_9H_7NO_3F_6$: C, 37.11; H, 2.42; N, 4.81. Found: C, 36.93; H, 2.49; N, 4.83.

2-Chloro-3-hydroxy-6-(1-hydroxy-2,2,2-trifluoroethyl)pyridine (**15**).

This compound was purified on a silica gel column with hexane:ethyl aceate (4:1, v/v) as the elution, and recrystallized from chloroform:ethyl aceate as white solid, mp 150-151 °C; ir: (potassium bromide): 3500 (OH), 1568, 1493, 1429, 1320, 1290, 1258, 1216, 1183, 1120, 1092, 839, 733, 686 cm^{-1}; ^1H nmr: δ 4.27 (br s, 1H, OH), 5.09 (q, 1H, $CHCF_3$, J = 7.0 Hz), 7.49 (s, 2H, 4-H, 5-H), 9.96 (br s, 1H, PyOH); ^{19}F nmr: δ 86.39 (d, 3F, CF_3, J = 7.0 Hz); ms: m/z 229 (M+2, 3.6), 227 (M^+, 10), 160 (36), 158 (M-CF_3, 100).

Anal. Calcd. for $C_7H_5ClNO_2F_3$: C, 36.93; H, 2.22; N, 6.16. Found: C, 36.86; H, 2.37; N, 5.88.

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REFERENCES AND NOTES

[1a] T. Kitazume and T. Yamazaki, Experimental Methods in Organic Fluorine Chemistry, Kodansha, Gordon & Breach Science Publishers, Tokyo, 1998. [b] R. Filler, Y. Kobayashi and L. M. Yagupolskii, Organofluorine Compounds in Medicinal Chemistry and Biomedical Application, Elsevier, Amsterdam, 1993; [c] R. E. Banks, Ed. Preparation, Properties and Industrial Applications of Organofluorine Compound, Ellis Horwood, Chichest, 1982; [d] H. Nohira, *J. Synth. Org.*

Chem. Jpn., **49**, 467 (1991); [e] D. M. Walba, H. A. Razavi, N. A. Clark and D. S. Parnar, *J. Am. Chem. Soc*., **110**, 8686 (1988).

[2a] R. P. Singh, G. F. Cao, R. L. Kirchmeier and J. M. Shreeve, *J. Org. Chem*., **64**, 2873 (1999); [b] Y. Yokoyama and K. Mochida, *Synlett*, 907 (1997); [c] F. A. J. Kerdesky and A. Basha, *Tetrahedron Lett*., **32**, 2003 (1991); [d] X. Creary, *J. Org. Chem*., **52**, 5027 (1987); [e] L. S. Chen, G. J. Chen and C. Tamborski, *J. Organometallic Chem*., **251**, 5027 (1983); [f] R. K. Mackie, S. Mhatre and J. M. Tedder, *J. Fluorine Chem*., **10**, 437 (1977).

[3a] A. Ishii, V. A. Soloshonok and K. Mikami, *J. Org. Chem*., **65**, 1597 (2000); [b] A. Ishii, J. Kojima and K. Mikami, *Org. Lett*., **1**, 2013 (1999); [c] A. Ishii and K. Mikami, *J. Fluorine Chem*., **97**, 51 (1999).

[4a] C. Mispelaere and N. Roques, *Tetrahedron Lett*., **40**, 6411 (1999); [b] R. P. Singh, G. Cao, R. L. Kirchmeier and J. M. Shreeve, *J. Org. Chem*., **64**, 2579 (1999); [c] G. K. S. Prakash and K. A. Yudin, *Chem. Rev*., **97**, 757 (1997); [d] S. Watanabe, T. Fujita, M. Sakamoto, Y. Mino and T. Kitazume, *J. Fluorine Chem.*, **73**, 21 (1995); [e] G. K. S. Prakash, R. Krishnamurti and G. A. Olah, *J. Am. Chem. Soc*., **111**, 393 (1989).

[5a] K. Sakumo, N. Kuki, T. Kuno, T. Takagi, M. Koyama, A. Ando and I. Kumadaki, *J. Fluorine Chem*., **93**, 165 (1999); [b] K. Funabi, M. Nojiri, M. Matsui and K. Shibata, *Chem. Commun*., 2051 (1998); [c] T. P. Loh and X. R. Li, *Tetrahedron Lett*., **38**, 869 (1997); [d] T. P. Loh and X. R. Li, *J. Chem. Soc*., *Chem. Commun*., 1929 (1996); [e] T. Kubota, M. Iijima and T. Tanaka, *Tetrahedron Lett.*, **33**, 1351 (1992); [f] A. Guy, A. Lobgeis and M. Lemaire, *J. Fluorine Chem*., **32**, 361 (1986).

[6a] Y. Gong, K. Kato and H. Kimoto, *Synlett* 1403 (1999); [b] Y. Gong, K. Kato and H. Kimoto, *Bull. Chem. Soc. Jpn*., **73**, 249 (2000); [c] Y. Maki, H. Kimoto, S. Fujii, M. Senga and L. A. Cohen, *J. Fluorine Chem*., **39**, 47 (1988); [d] S. Fujii, Y. Maki and H. Kimoto, *J. Fluorine Chem*., **30**, 415 (1986).

[7] F. Sauter, P. Stanetty, W. Ramer and W. Sittenthaler, *Monatsh. Chem*., **122**, 879 (1991).

[8] M. Kawase, J. Koyanagi and S. Saito, *Chem. Pharm. Bull*., **47**, 718 (1999).