A FACILE AND CONVENIENT SYNTHETIC METHOD FOR FLUORINE-CONTAINING PYRIDINES, 1,2-DIHYDROPYRIDINES, AND 2-PYRIDONES

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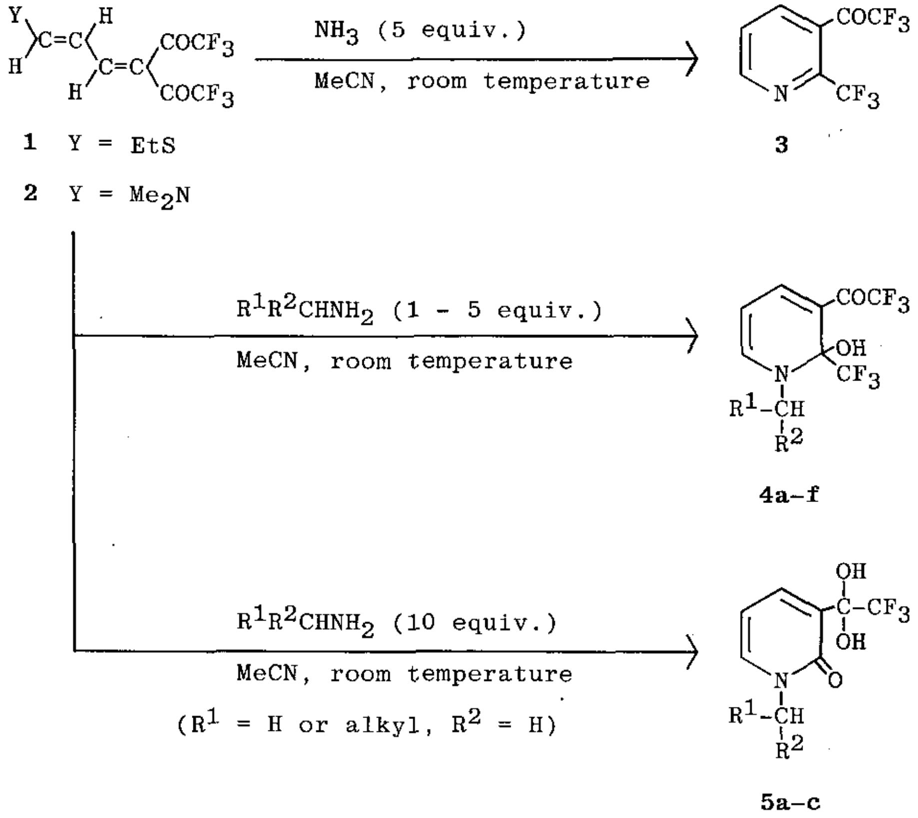
Abstract - 1-Ethylthio- and 1-dimethylamino-4,4-bis(trifluoroacetyl)-1,3-butadienes (**1, 2**) reacted easily with aqueous ammonia and various primary amines under mild conditions to afford selectively the corresponding fluorine-containing pyridines (**3**), 1,2-dihydropyridines (**4**), and 2-pyridones (**5**) in excellent yields.

Pyridine and its derivatives constitute an important class of heterocyclic compounds and this ring system is found in a great number of naturally occurring products, for example alkaloids having interesting biological activities.[1-7] Besides, in recent years the development of new methodologies for the synthesis of various fluorine-containing heterocycles has received an increasing interest, since many kinds of these compounds are now widely recognized as important organic materials showing interesting functionalities for use in medicinal and agricultural sciences.[8-10] In the course of our extensive studies[11-14] on the nucleophilic substitutions at olefinic carbon atoms activated by trifluoroacetyl group, it was found that the S-N and N-N exchange reactions of 1-ethylthio- and 1-dimethylamino-4,4-bis(trifluoroacetyl)-1,3-butadienes (**1, 2**) with various secondary amines proceed easily under mild conditions to give the corresponding 4,4-bis(trifluoroacetyl)-1,3-butadienylamines in high yields.[14] As an extension and generalization of this work, we now describe a facile and convenient synthetic method for pyridines (**3**), 1,2-dihydropyridines (**4**), and 2-pyridones (**5**) bearing trifluoromethyl group by nucleophilic substitution of **1** and **2** with ammonia and primary amines.

The results are shown in Scheme 1 and summarized in Table 1. Both sulfide (**1**)[15] and amine



Scheme 1

(**2**)[16] reacted quite easily at room temperature with 5 mole equivalents of aqueous ammonia (28%) in acetonitrile to give 3-trifluoroacetyl-2-trifluoromethylpyridine (**3**) in high yields (Entries 1 and 2). Aliphatic primary amines such as methyl-, ethyl-, isopropyl-, isobutyl-, and *sec*-butylamines (with 1-5 mole equivalents) reacted also cleanly to afford desired fluorine-containing 1,2-dihydropyridines (**4a-e**) in 53-100% yields (Entries 3, 4, 7, 9, 11, and 12). Aromatic primary amine, *p*-anisidine, reacted readily with **1** even at room temperature within 1 h to provide the corresponding 1,2-dihydropyridine (**4f**) in 89% yield, though considerably less reactive than aliphatic amines (Entry 13). In contrast to this, instead of expected 1,2-dihydropyridines such as **4a-c**, 2-pyridones (**5a-c**) were obtained exclusively or predominantly in 68-84% yields when treated with a large excess (10 mole equiv.) of aliphatic primary amines whose carbon atoms adjacent to nitrogen are

Table 1. Synthesis of Fluorine-Containing Pyridines (**3**), 1,2-Dihydropyridines (**4**), and 2-Pyridones (**5**)

Entry	Substrate	Amine ($R^1R^2CHNH_2$)a)			Time (h)	Product	Yield (%)b)
		R^1	R^2	equiv.			
1	**1**	(R^1R^2CH = H)		5	1	**3**	89
2	**2**	(R^1R^2CH = H)		5	4	**3**	96
3	**1**	H	H	1.2	1	**4a**	100
4	**2**	H	H	1.2	4	**4a** / **5a**	81/15 (7)
5	**1**	H	H	10	4	**5a**	68
6	**2**	H	H	10	4	**5a**	84
7	**2**	Me	H	3	1	**4b** / **5b**	89/ 7 (4)
8	**2**	Me	H	10	4	**4b** / **5b**	28/71
9	**2**	i-Pr	H	1.2	4	**4c**	53
10	**2**	i-Pr	H	10	4	**5c**	79
11	**1**	Me	Me	5	1	**4d**	100
12	**2**	Et	Me	5	4	**4e**	76
13	**1**	p-$MeOC_6H_4$	H	1.2	1	**4f**	89

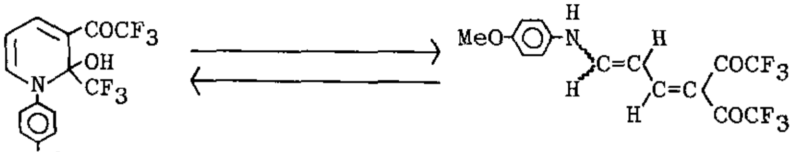
a) Aqueous solutions of ammonia (28%), methylamine (40%), and ethylamine (70%) were used. b) Isolated yields of products purified by column chromatography on silica gel. Values in parentheses are the yields of recovered substrates.

not branched (R^1=H or alkyl, R^2=H in $R^1R^2CHNH_2$) such as methyl-, ethyl-, and isobutylamines (Entries 5, 6, 8, and 10). The trifluoroacetyl group of 2-pyridones (**5**) was found to exist as hydrated form.

A possible reaction course is as follows. Nucleophilic S-N or N-N exchange reaction of **1** or **2** with primary amines takes place to give intermediate N-monosubstituted 1-amino-4,4-bis(trifluoroacetyl)-1,3-butadienes, which undergo intramolecular nucleophilic attack of the amino nitrogen onto the carbonyl carbon of the trifluoroacetyl group to afford 1,2-dihydropyridines (**4**). In the case of using ammonia, **4** (R^1R^2CH=H) easily loses water to give pyridine (**3**). 2-Pyridones (**5**) are formed by elimination of fluoroform from 1,2-dihydropyridine (**4**) only where R^1 is hydrogen or alkyl group and R^2 is hydrogen, as similar to the well-known haloform reaction. The reaction is probably initiated with deprotonation of 2-hydroxy group of **4** in the presence of amines in large excess. When both R^1 and R^2 are alkyl groups in **4**, the elimination of fluoroform seems to be difficult to proceed under such mild conditions.

The structures of compounds (**3-5**) were determined from their ^1H-nmr and ir spectra, together with elemental analyses. As representative cases, dihydropyridine (**4e**) and 2-pyridone (**5a**) were further confirmed by ^{13}C-nmr spectral data. In particular, ^{13}C-nmr spectrum of **4e** showed a characteristic signal for the hemiaminal carbon (C-2) bearing trifluoromethyl group at δ=86.1 (q, J_{CF}=33.6 Hz). This presented unambiguous evidence supporting the dihydropyridine ring formation. In the ^{13}C-nmr spectrum of **5a**, there appeared two diagnostic signals for the hydrated trifluoroacetyl carbonyl carbon at δ=93.4 (q, J_{CF}=32.0 Hz) and amide carbonyl carbon at δ=163.0 (s), which supported that the hydration occurs not at the carbonyl of the pyridone ring but at that of the trifluoroacetyl group.

In connection to this, it seems of interest to note here that 1-p-methoxyphenyl derivative (**4f**) in crystalline state was found to exist in the acyclic form (**6**), although it is in the cyclic form (**4f**) both in pure liquid state and in solution as depicted below. This



4f **6**

(in liquid state and in solution) (in crystalline state)

was apparently ascertained by its ir and ^1H-nmr spectroscopic data as follows. In the ^1H-nmr spectrum of **4f** in $CDCl_3$ there were observed characteristic peaks for the three olefinic hydrogens and coupling constants for these protons were small (J=7 Hz) similar to the case of 1-alkyl derivatives (**4a-e**). The ir spectrum of **4f** taken as oily film showed broad O-H stretching band at 3520-2750 cm^{-1} and strong absorption bands for C=O and C=C at 1630 and 1500 cm^{-1}, respectively, which are similar to those of oily 1-alkyl derivatives (**4a-c**). Oily **4f** crystallized gradually to **6** and its ir spectrum (KBr tablet) exhibited the characteristic absorption bands at 3180 cm^{-1} (N-H), at 1685 and 1630 cm^{-1} (C=O), and at 1558 cm^{-1} (C=C). Among them, particularly the medium peak at 1685 cm^{-1} is diagnostic for 1-amino-4,4-bis(trifluoroacetyl)-1,3-butadiene system.[16] When this crystalline **6** was dissolved in $CDCl_3$ the ^1H-nmr spectrum showed conversion of **6** back again to its cyclic form (**4f**). In contrast, in the case of crystalline 1-alkyl derivatives (**4d** and **4e**), the phenomenon of such ring-opening and ring-closing was not observed. Their ir spectra (KBr tablet) showed that **4d** and **4e** exist in the cyclic form even in the solid state.

In conclusion, the present method is experimentally very simple, convenient and useful for the synthesis of CF_3-containing pyridine and its derivatives which are not easily obtained by other methods. Evaluation of biological activities for **3-5** is now under way.

EXPERIMENTAL

Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. Ir spectra were recorded on a Hitachi EPI-G3 spectrophotometer. ^1H- and ^{13}C-nmr spectra were obtained with JEOL PMX 60SI and FX 90Q instruments using $CDCl_3$ as a solvent unless otherwise indicated. All chemical shifts are reported in ppm downfield from internal tetramethylsilane; coupling constants (J) are given in Hz. Elemental analyses were performed by the Microanalyses Center of Kyoto University. Chromatographic separations were carried out on silica gel column (Wakogel C-200; 100-200 mesh). Acetonitrile was dried over molecular sieves. All reagents were obtained commercially and used without further purification. Final purification of all products for elemental analyses was done by Kugelrohr distillation or recrystallization.

Reaction of 1-Ethylthio- and 1-Dimethylamino-4,4-bis(trifluoroacetyl)-1,3-butadienes (1 and 2) with Amines (Refer to Table 1); General Procedure: To a solution of **1**[15] or **2**[16] (2 mmol) in MeCN (10 ml) was added an amine (1-10 equiv.). The solution was stirred at room temperature for 1 or 4 h. After evaporation of the solvent under reduced pressure, the crude products were separated by column chromatography as eluted with benzene for **4a-f**, ethyl acetate for **3** and **5a-c**, and benzene/ethyl acetate (1:1) for recovered substrate **2**.

3-Trifluoroacetyl-2-trifluoromethylpyridine (3): oven temperature 120 °C/110 mmHg; ir (film) 1750 cm^{-1}; ^1H-nmr 8.92 (1H, d, J=5, H-6), 8.00 (1H, d, J=8, H-4), 7.67 (1H, dd, J=5, 8, H-5). Anal. Calcd for $C_8H_3NOF_6$: C, 39.52; H, 1.24; F, 46.89. Found: C, 39.88; H, 1.19; F, 46.61.

3-Trifluoroacetyl-2-trifluoromethyl-2-hydroxy-1-methyl-1,2-dihydropyridine (4a): oven temperature 100 °C/20 mmHg; ir (film) 3540-2710, 1621, 1508 cm^{-1}; ^1H-nmr 8.70-8.17 (1H, br, OH), 7.72 (1H, dq, J=2, 7, H-4), 7.02 (1H, d, J=7, H-6), 5.27 (1H, t, J=7 H-5), 3.33 (3H, s, CH_3). Anal. Calcd for $C_9H_7NO_2F_6$: C, 39.29; H, 2.56; N, 5.09; F, 41.43. Found: C, 39.45; H, 2.53; N, 5.00; F, 41.31.

1-Ethyl-3-trifluoroacetyl-2-trifluoromethyl-2-hydroxy-1,2-dihydropyridine (4b): oven temperature 100 °C/30 mmHg; ir (film) 3700-2725, 1622, 1508 cm^{-1}; ^1H-nmr 8.77-7.93 (1H, br, OH), 7.57 (1H, dq, J=2, 7, H-4), 7.10 (1H, d, J=7, H-6), 5.32 (1H, t, J=7, H-5), 4.27-3.13 (2H, m, CH_2), 1.35 (3H, t, J=7, CH_3). Anal. Calcd for $C_{10}H_9NO_2F_6$: C, 41.54; H, 3.14; N, 4.84; F, 39.42. Found: C, 41.74; H, 3.08; N, 4.77; F, 39.51.

3-Trifluoroacetyl-2-trifluoromethyl-2-hydroxy-1-isobutyl-1,2-dihydropyridine (4c): oven temperature 120 °C/20 mmHg; ir (film) 3580-2475, 1621, 1505 cm^{-1}; ^1H-nmr 8.67-7.83 (1H, br, OH), 7.53 (1H, dq, J=2, 7, H-4), 7.03 (1H, d, J=7, H-6), 5.30 (1H, t, J=7, H-5), 3.82 (1H, dd, J=7, 14, CH_2), 3.02 (1H, dd, J=8, 14, CH_2), 2.37-1.68 (1H, m, CH), 0.93 (6H, d, J=7, CH_3). Anal. Calcd for $C_{12}H_{13}NO_2F_6$: C, 45.43; H, 4.13; N, 4.42. Found: C, 45.54; H, 4.06; N, 4.53.

3-Trifluoroacetyl-2-trifluoromethyl-2-hydroxy-1-isopropyl-1,2-dihydropyridine (4d): mp 108-109 °C (hexane); ir (KBr) 3600-2540, 1622, 1593, 1504 cm^{-1}; ^1H-nmr 9.10-7.73 (1H, br, OH), 7.57 (1H, dq, J=2, 7, H-4), 7.25 (1H, d, J=7, H-6), 5.35 (1H, t, J=7, H-5), 4.52 (1H, hp, J=7, CH), 1.40 (3H, d, J=7, CH_3), 1.30 (3H, d, J=7, CH_3). Anal. Calcd for $C_{11}H_{11}NO_2F_6$: C, 43.58; H, 3.66; N, 4.62; F, 37.59. Found: C, 43.67; H, 3.57; N, 4.76; F, 37.64.

3-Trifluoroacetyl-2-trifluoromethyl-2-hydroxy-1-sec-butyl-1,2-dihydropyridine (4e): mp 77-78 °C (hexane); ir (KBr) 3650-2780, 1618, 1590, 1508 cm^{-1}; ^1H-nmr 8.47 (1H, s, OH), 7.50 (1H, dq, J=2, 7, H-4), 7.10 (1H, d, J=7, H-6), 5.30 (1H, t, J=7, H-5), 4.42-3.97 (1H, m, NCH), 1.85-0.77 (8H, m, CH_3, C_2H_5); ^{13}C-nmr 179.9 (q, J_{CF}=32.1), 146.1(d), 145.3 (d), 124.7(q, J_{CF}=296.0), 117.2 (q, J_{CF}=289.9), 101.7 (s), 97.8 (d), 86.1 (q, J_{CF}=33.6), 53.3 (d), 32.2 (t), 20.0 (q), 10.5 (q). Anal. Calcd for $C_{12}H_{13}NO_2F_6$: C, 45.43; H, 4.13; N, 4.42; F, 35.93. Found: C, 45.70; N, 4.10; N, 4.46; F, 36.00.

3-Trifluoroacetyl-2-trifluoromethyl-2-hydroxy-1-p-methoxyphenyl-1,2-dihydropyridine (4f): oil; ir (film) 3520-2750, 1630, 1500 cm^{-1}; ^1H-nmr 8.43-8.07 (1H, br, OH), 7.58 (1H, dq, J=2, 7, H-4), 7.20 (2H, d, J=9, H_{arom}), 7.02 (1H, d, J=7, H-6), 6.80 (2H, d, J=9, H_{arom}), 5.37 (1H, t, J=7, H-5), 3.77 (3H, s, CH_3).

3-(2,2,2-Trifluoro-1,1-dihydroxyethyl)-1-methyl-2-pyridone (5a): mp 134-135 °C ($CHCl_3$); ir (KBr) 3200, 1640, 1570, 1550 cm^{-1}; ^1H-nmr (CD_3CN-DMSO-d_6) 8.30 (2H, br s, OH), 7.83 (1H, br d, J=7, H-4), 7.67 (1H, dd, J=2, 7, H-6), 6.40 (1H, t, J=7, H-5), 3.55 (3H, s, CH_3); ^{13}C-nmr (DMSO-d_6) 163.0 (s), 141.8 (d), 141.2 (d), 123.9 (s), 123.8 (q, J_{CF}=289.9), 106.8 (d), 93.4 (q, J_{CF}=32.0), 32.4 (q). Anal. Calcd for $C_8H_8NO_3F_3$: C, 43.06; H, 3.61; N, 6.28; F, 25.54. Found: C, 43.17, H, 3.65; N, 6.42; F, 25.17.

1-Ethyl-3-(2,2,2-trifluoro-1,1-dihydroxyethyl)-2-pyridone (5b): mp 114-115 °C ($CHCl_3$); ir (KBr) 3320, 1644, 1575, 1552 cm^{-1}; ^1H-nmr ($CDCl_3$-CD_3CN) 7.70 (1H, br d, J=7, H-4), 7.40 (1H, dd, J=2, 7, H-6), 7.17 (2H, br s, OH), 6.30 (1H, t, J=7, H-5), 4.17 (2H, q, J=7, CH_2), 1.35 (3H, t, J=7, CH_3). Anal. Calcd for $C_9H_{10}NO_3F_3$: C, 45.58; H, 4.25; N, 5.91; F, 24.03. Found: C, 45.83; H, 4.19; N, 6.02; F, 24.07.

3-(2,2,2-Trifluoro-1,1-dihydroxyethyl)-1-isobutyl-2-pyridone (5c): mp 97-98 °C ($CHCl_3$); ir (KBr) 3350, 1642, 1571, 1551 cm^{-1}; ^1H-nmr ($CDCl_3$-CD_3CN) 7.73 (1H, br d, J=7, H-4), 7.35 (1H, dd, J=2, 7, H-6), 7.16 (2H, br s, OH), 6.30 (1H, t, J=7, H-5), 3.77 (2H, d, J=7, CH_2), 2.40-1.83 (1H, m, CH), 0.93 (6H, d, J=6, CH_3). Anal. Calcd for $C_{11}H_{14}NO_3F_3$: C, 49.81; H, 5,32; N, 5.28; F, 21.49. Found: C, 49.84; H, 5.26; N, 5.46; F, 22.01.

1-p-Methoxyphenylamino-4,4-bis(trifluoroacetyl)-1,3-butadiene (6): mp 127-128 °C (benzene); ir (KBr) 3180, 1685, 1630, 1558 cm^{-1}. Anal. Calcd for $C_{15}H_{11}NO_3F_6$: C, 49.06; H, 3.02; N, 3.82; F, 31.05. Found: C, 48.72; H, 2.93; N, 3.76; F, 31.10.

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