SYNTHESES OF FLUORINE-CONTAINING 1,2-DIHYDROPYRIMIDINES AND PYRIDINES FROM β,β-BIS(TRIFLUOROACETYL)VINYLAMINE, KETONES AND AMMONIA

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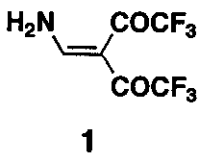
Abstract - β,β-Bis(trifluoroacetyl)vinylamine (**1**) reacted easily with various ketones in the presence of aqueous ammonia under mild conditions to give trifluoroacetylated 4-trifluoromethyl-1,2-dihydropyrimidines (**4**), α-trifluoromethylpyridines (**5**), and γ-trifluoromethylpyridines (**6**) in moderate yields.

Much attention has been focused on the development of new methodologies for the synthesis of various fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing interesting biological activities for their potential use in medicinal and agricultural scientific fields.[1] In the course of our systematic research program on the simple syntheses of CF_3-containing heterocyclic compounds, thus far we have found that fluorine-containing pyrroles,[2a] pyrazoles,[2b] pyridines,[2c] and 3,4-dihydro-2*H*-pyrans[2d,e] can be synthesized efficiently by making good use of the nucleophilic substitutions[3] at the olefinic carbon atoms and hetero Diels-Alder reaction[2d,e] of trifluoroacetylated alkenes. Recently, we have set about the investigations on utilization of β,β-bis(trifluoroacetyl)vinylamine (**1**), which can be easily prepared in two steps, bis(trifluoroacetylation)[2e] and subsequent *i*-BuO-NH_2 exchange reaction[3d] starting from isobutyl vinyl ether, as a new and convenient building block for construction of fluorine-containing heterocyclic compounds. In our preceding paper it was found that 5-trifluoroacetyl-4-trifluoromethyl-1,2-dihydropyrimidines (**2**) and pyrimidines (**3**) can be very easily synthesized by the reaction of **1** with aldehydes in the presence of ammonia and subsequent dehydrogenation.[4] As an extension of these works we report here the reaction of **1** with ketones, instead of aldehydes, in the presence of ammonia to give new trifluoroacetylated 4-trifluoromethyl-1,2-dihydropyrimidines (**4**), α-trifluoromethylpyridines (**5**), and γ-trifluoromethylpyridines (**6**), which are expected to exhibit interesting pharmacological activities.[5]



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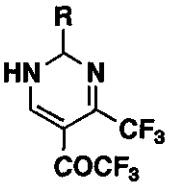

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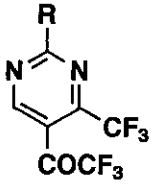

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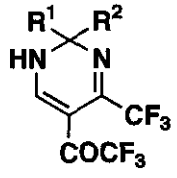

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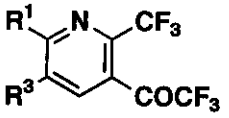

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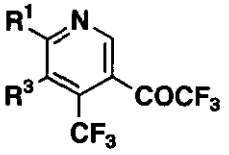

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Table 1. Reaction of **1** with Ketones in the Presence of Aqueous Ammonia [a)]

Entry	Ketone (equiv.)		aq. NH_3 / equiv.	Temp(℃)	R^1	R^2	R^3	Product	Yield (%)
1	MeCOMe	(30)	5	rt	Me	Me	–	**4a**	46
2	EtCOEt	(10)	2	50	Et	Et	Me	**4b / 5b**	49 / 7
3	Cyclopentanone	(5)	1	50	C_2H_4	C_2H_4	CH_2	**4c / 5c**	13 / 33
4	Cyclohexanone	(2)	1	50	C_3H_6	C_2H_4	CH_2	**4d / 5d**	53 / 15
5	Cycloheptanone	(5)	1	50	C_4H_8	C_2H_4	CH_2	**4e / 5e**	25 / 23
6	EtCOMe	(10)	2	50	Et	Me	–	**4f**	36
7	*i*-PrCOMe	(10)	2	50	*i*-Pr	Me	H	**4g / 6g**	47 / 11
8	PhCOMe	(10)	2	50	Ph	–	H	**6h**	42

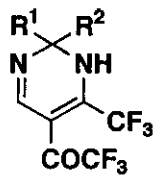
a) Reactions were caried out for 24 h in MeCN.

Reaction of β,β-bis(trifluoroacetyl)vinylamine (**1**) with acetone, a symmetrical acyclic ketone, in the presence of ammonia proceeded easily under mild conditions, similarly to that with aldehydes,[4] gave the expected 5-trifluoroacetyl-4-trifluoromethyl-2,2-dimethyl-1,2-dihydropyrimidine (**4a**) in 46% yield without being accompanied by any other product (Table 1). 5-Trifluoroacetyl-4-trifluoromethyl-2,2-diethyl-1,2-dihydropyrimidine (**4b**), however, was obtained in 49% yield with 7% of α-trifluoromethylpyridine (**5b**) in the reaction with diethyl ketone. Next, we tried the reactions of **1** with cyclic ketones such as cyclopentanone, cyclohexanone, and cycloheptanone. In all cases, spiro 1,2-dihydropyrimidines (**4c-e**) and cycloalkane-ring fused pyridines (**5c-e**) both were formed in 13-53% yields. Separation of the **4b-e** and **5b-e** mixtures was easily

carried out by column chromatography. Further, the present reaction was applicable to some unsymmetrical ketones. In analogy with acetone, **1** reacted with 2-butanone to provide only 1,2-dihydropyrimidine (**4f**) in 36% yield. However, 3-methyl-2-butanone afforded the mixture of 1,2-dihydropyrimidine (**4g**) and γ-trifluoromethylpyridine (**6g**) in 47 and 11% yields, respectively. There was no detectable amount of the expected α-trifluoromethylated regioisomer (**5g**). Interestingly, the reaction of **1** with acetophenone gave γ-trifluoromethyl-pyridine (**6h**) as a sole product in 42% yield without any formation of 1,2-dihydropyrimidine (**4h**), in striking contrast to the case of acetone mentioned above. It was unsuccessful replacing ammonia by other bases such as *N*,*N*-diisopropylethylamine for the sake of avoiding the formation of 1,2-dihydropyrimidines (**4**) and of obtaining pyridines (**5**, **6**) exclusively.

In the present pyrimidine ring synthesis, β,β-bis(trifluoroacetyl)vinylamine (**1**), ketone, and ammonia will probably be the source of N_1-C_6-C_5-C_4 fragment, of C_2, and of the other nitrogen atom (N_3), respectively. On the other hand, in the pyridine ring formation, **1** and ketone constitute the unit of C_α-C_β-C_γ and of $C_{\alpha'}$-$C_{\beta'}$, respectively. It is not certain at present whether the nitrogen atom (N_1) of the ring, especially of α-trifluoromethylpyridine, derives from ammonia or from **1**.

The structures of new compounds (**4-6**) were determined on the basis of their ^{1}H-NMR and IR spectra, together with elemental analyses. As representative cases, 1,2-dihydropyrimidine (**4a**), α-trifluoromethylpyridine (**5c**), and γ-trifluoromethylpyridines (**6g,h**) were further confirmed by ^{13}C-NMR spectral data. The structural distinction between 1,2-dihydropyrimidines (**4**) and its tautomeric form 2,3-dihydropyrimidines (**4'**) was clearly confirmed, similarly to the cases of **2**,[4] by the multiplicity (doublet or broad singlet) of the olefinic proton at the 6-position in the ^{1}H-NMR spectra. Moreover, ^{1}H- and ^{13}C-NMR spectra provided diagnostic information for the discrimination between α-trifluoromethyl-pyridines (**5**) and its regioisomeric form γ-trifluoromethylpyridines (**6**). In ^{1}H-NMR spectra, the chemical shifts of H- α in **6g,h** appeared in the downfield with respect to those of H- γ in **5b-e** by *ca.* 1.3-1.4 ppm. In ^{13}C-NMR spectrum of α-trifluoromethylpyridine (**5c**), there appeared two characteristic signals for C- α bearing a trifluoromethyl group appeared at 144.6 ppm as quartet (J_{CF}=35.4 Hz) and unsubstituted C- γ at 131.9 ppm as doublet. In contrast to this, ^{13}C-NMR spectra of γ-trifluoromethyl-pyridines (**6g,h**) showed double quartet (J_{CF}=3.7 Hz) for unsubstituted C- α at 149.2 and 150.0 ppm and quartet (J_{CF}=35.4 and 34.2 Hz) for C- γ bearing a trifluoromethyl group at 138.2 and 138.8 ppm.



4'

Thus, the present synthetic method provides a simple access to 1,2-dihydropyrimidines and pyridines having both trifluoromethyl and trifluoroacetyl groups which are not easily obtained by other methods. Further utilization of **1** as a useful synthetic block and investigations from the mechanistic standpoint of view are now in progress in our laboratory.

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. ^{1}H- 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 taken with a Yanaco CHN Corder MT-5 analyzer and were performed by the Microanalyses Center of Kyoto University. Chromatographic separations were carried out on a silica gel column (Fuji Silysia Chemical BW-127ZH; 100-270 mesh). 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 β,β-Bis(trifluoroacetyl)vinylamine (1) with Ketones in the Presence of Ammonia; General Procedure: To a solution of **1**[3d] (235 mg, 1 mmol) in MeCN (5 mL) were added the appropriate ketone (2 - 30 mmol) and aqueous ammonia (28 wt.%, 1 - 5 mmol). The mixture was stirred at rt or 50 ℃ for 24 h and the solvent was evaporated and the crude product was chromatographed using benzene/EtOAc (3:2) for **4a**, benzene/EtOAc (4:1) for **4b-g**, benzene for **5c-e** and **6g,h**, benzene /hexane (1:1) for **5b** as eluent.

4a: yield 46%; mp 165-166 ℃ ($CHCl_3$); IR (KBr) 3220, 1655, 1630, 1535 cm^{-1}; ^{1}H-NMR ($CDCl_3$ /CD_3CN) 7.81 (d, 1H, J=6, H-6), 7.95-7.12 (br, 1H, NH), 1.49 (s, 6H, CH_3); ^{13}C-NMR (CD_3COCD_3) 171.2 (q, J_{CF}=33.0), 154.7 (dq, J_{CF}=6.1), 150.4 (q, J_{CF}=35.4), 120.6 (q, J_{CF}=275.9), 118.5 (q, J_{CF}=291.8), 96.8 (s), 71.8 (s), 28.7 (q). Anal. Calcd for $C_9H_8N_2OF_6$: C, 39.43; H, 2.94; N, 10.22; F, 41.58. Found: C, 39.45; H, 2.82; N, 10.20; F, 41.55.

4b: yield 49%; mp 143-144 ℃ (hexane/$CHCl_3$); IR (KBr) 3243, 1637, 1541 cm^{-1}; ^{1}H-NMR 8.41-7.09 (br, 1H, NH), 8.03 (br s, 1H, H-6), 2.17-1.42 (m, 4H, CH_2), 0.94 (t, 6H, J=7, CH_3). Anal. Calcd for $C_{11}H_{12}N_2OF_6$: C, 43.72; H, 4.00; N, 9.27. Found: C, 43.84; H, 3.83; N, 9.32.

4c: yield 13%; mp 166-167 ℃ (hexane/$CHCl_3$); IR (KBr) 3243, 1634, 1535 cm^{-1}; ^{1}H-NMR ($CDCl_3$ /CD_3CN) 8.37-6.83 (br, 1H, NH), 7.89 (br s, 1H, H-6), 2.23-1.63 (m, 8H, CH_2). Anal. Calcd for $C_{11}H_{10}N_2OF_6$: C, 44.01; H, 3.36; N, 9.33. Found: C, 43.99; H, 3.25; N, 9.13.

4d: yield 53%; mp 163-164 ℃ ($CHCl_3$); IR (KBr) 3285, 1635, 1553 cm^{-1}; ^{1}H-NMR ($CDCl_3$/CD_3CN)

8.47-6.61 (br, 1H, NH), 7.87 (br s, 1H, H-6), 1.81-1.61 (m, 10H, CH_2). Anal. Calcd for $C_{12}H_{12}N_2OF_6$: C, 45.87; H, 3.85; N, 8.92. Found: C, 45.80; H, 3.66; N, 8.94.

4e: yield 25%; mp 181-182 ℃ (hexane/$CHCl_3$); IR (KBr) 3240, 1652, 1638, 1539 cm^{-1}; ^1H-NMR ($CDCl_3/CD_3CN$) 8.60-7.12 (br, 1H, NH), 7.72 (br s, 1H, H-6), 2.15-1.65 (m, 12H, CH_2). Anal. Calcd for $C_{13}H_{14}N_2OF_6$: C, 47.57; H, 4.30; N, 8.53. Found: C, 47.37; H, 4.08; N, 8.48.

4f: yield 36%; mp 149-150 ℃ (hexane/$CHCl_3$); IR (KBr) 3250, 1635, 1529 cm^{-1}; ^1H-NMR ($CDCl_3$ /CD_3CN) 8.27-6.94 (br, 1H, NH), 7.83 (br s, 1H, H-6), 2.03-1.47 (m, 5H, $C\underline{H_2}CH_3$, CH_3-2), 0.92 (t, 3H, J=7, $CH_2C\underline{H_3}$). Anal. Calcd for $C_{10}H_{10}N_2OF_6$: C, 41.68; H, 3.50; N, 9.72. Found: C, 41.50; H, 3.43; N, 9.81.

4g: yield 47%; mp 178-179 ℃ (hexane/$CHCl_3$); IR (KBr) 3250, 1634, 1529 cm^{-1}; ^1H-NMR ($CDCl_3$ /CD_3CN) 8.50-6.91 (br, 1H, NH), 7.88 (d, 1H, J=7, H-6), 2.32-1.68 (m, 1H, CH), 1.41 (s, 3H, CH_3-2), 1.31 (d, 3H, J=7, CH_3), 1.26 (d, 3H, J=7, CH_3). Anal. Calcd for $C_{11}H_{12}N_2OF_6$: C, 43.72; H, 4.00; N, 9.27. Found: C, 43.85; H, 3.81; N, 9.34.

5b: yield 7%; mp 164-165 ℃ (hexane/$CHCl_3$); IR (KBr) 1763, 1614, 1568 cm^{-1}; ^1H-NMR 7.58 (br s, 1H, H-γ), 2.90 (q, 2H, J=8, $C\underline{H_2}CH_3$), 2.42 (s, 3H, CH_3-β), 1.30 (t, 3H, J=8, $CH_2C\underline{H_3}$). Anal. Calcd for $C_{11}H_9NOF_6$: C, 46.33; H, 3.18; N, 4.91. Found: C, 46.58; H, 3.23; N, 5.10.

5c: yield 33%; oven temperature 90 ℃/3 mmHg; IR (film) 1746, 1601, 1554 cm^{-1}; ^1H-NMR 7.64 (br s, 1H, H-γ), 3.26-2.95 (m, 4H, CH_2), 2.49-1.95 (m, 2H, CH_2). ^{13}C-NMR 184.3 (q, J_{CF}=37.8), 171.1 (s), 144.6 (q, J_{CF}=35.4), 141.9 (s), 131.9 (d), 126.5 (s), 122.0 (q, J_{CF}=274.7), 116.4 (q, J_{CF}=290.5), 34.7 (t), 31.0 (t), 23.5 (t). Anal. Calcd for $C_{11}H_7NOF_6$: C, 46.66; H, 2.49; N, 4.95; F, 40.25. Found: C, 46.82; H, 2.42; N, 5.18; F, 40.32.

5d: yield 15%; oven temperature 100 ℃/3 mmHg; IR (film) 1749, 1599, 1558 cm^{-1}; ^1H-NMR 7.60 (br s, 1H, H-γ), 3.19-2.71 (m, 4H, CH_2), 2.13-1.68 (m, 4H, CH_2). Anal. Calcd for $C_{12}H_9NOF_6$: C, 48.50; H, 3.05; N, 4.71. Found: C, 48.44; H, 3.00; N, 4.82.

5e: yield 23%; oven temperature 110 ℃/3 mmHg; IR (film) 1746, 1591, 1540 cm^{-1}; ^1H-NMR 7.53 (br s, 1H, H-γ), 3.23-2.82 (m, 4H, CH_2), 1.85-1.57 (m, 6H, CH_2). Anal. Calcd for $C_{13}H_{11}NOF_6$: C, 50.17; H, 3.56; N, 4.50. Found: C, 50.46; H, 3.78; N, 4.63.

6g: yield 11%; oven temperature 50 ℃/3 mmHg; IR (film) 1740, 1590, 1551 cm^{-1}; ^1H-NMR 8.96 (s, 1H, H-α), 7.60 (s, 1H, H-β'), 3.26 (heptuplet, 1H, J=7, CH), 1.37 (d, 6H, J=7, CH_3). ^{13}C-NMR 180.2 (q, J_{CF}=36.6), 174.2 (s), 149.2 (dq, J_{CF}=3.7), 138.2 (q, J_{CF}=35.4), 123.1 (s), 122.1 (q, J_{CF}=274.7), 118.8 (dq, J_{CF}=4.9), 115.9 (q, J_{CF}=290.5), 37.2 (d), 22.0 (q). Anal. Calcd for $C_{11}H_9NOF_6$: C, 46.33; H, 3.18; N, 4.91. Found: C, 46.23; H, 3.09; N, 5.10.

6h: yield 42%; oven temperature 120 ℃/3 mmHg; IR (film) 1741, 1598, 1548 cm^{-1}; ^{1}H-NMR 8.96 (s, 1H, H-α), 8.08-7.90 (m, 3H, H-β ' or/and C_6H_5), 7.53-7.33 (m, 3H, H-β ' or/and C_6H_5). ^{13}C-NMR 181.6 (q, J_{CF}=37.8), 162.5 (s), 150.0 (dq, J_{CF}=3.7), 138.8 (q, J_{CF}=34.2), 136.5 (s), 131.8 (d), 129.4 (d), 127.9 (d), 123.6 (s), 122.5 (q, J_{CF}=274.7), 117.6 (dq, J_{CF}=4.9), 116.3 (q, J_{CF}=290.5). Anal. Calcd for $C_{14}H_7NOF_6$: C, 52.68; H, 2.21; N, 4.39. Found: C, 52.93; H, 2.13; N, 4.38.

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Received, 6th August, 1998