A FACILE AND CONVENIENT SYNTHETIC METHOD FOR FLUORINE-CONTAINING 1,2-DIHYDROPYRIMIDINES AND PYRIMIDINES

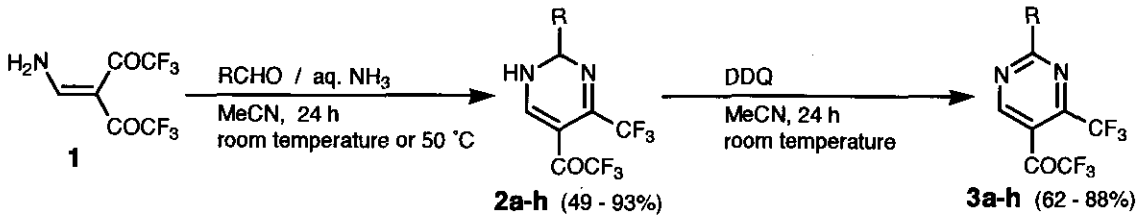
Etsuji Okada,* Tatsuhiko Kinomura, Hiroshi Takeuchi, and Masaru Hojo

Department of Chemical Science and Engineering, Faculty of Engineering, Kobe University, Kobe 657, Japan

Abstract - β, β-Bis(trifluoroacetyl)vinylamine (**1**) reacted easily with various aliphatic and aromatic aldehydes in the presence of aqueous ammonia under mild conditions to give 5-trifluoroacetyl-4-trifluoromethyl-1,2-dihydropyrimidines (**2**) in good yields. Dehydrogenation of **2** with DDQ afforded the corresponding pyrimidines (**3**) in excellent yields.

Pyrimidine and the related derivatives are important heterocycles because of their role in nucleic acid structure and their interesting pharmacological properties as antimalarial and antibacterial agents.[1,2] Besides, recently much attention has been paid to the development of new methodologies for the syntheses of many kinds of 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.[3-6] Furthermore, in the course of our extensive studies on the electrophilic[7-10] and nucleophilic[11-15] substitutions at olefinic carbon atoms, it was found that β, β-bis(trifluoroacetyl)vinylamine (**1**) can be easily prepared in two steps, bis(trifluoroacetylation) with trifluoroacetic anhydride[9] and subsequent *i*-BuO-NH_2 exchange reaction with ammonia,[14] starting from commercially available isobutyl vinyl ether. This situation prompted us to utilize β, β-bis(trifluoroacetyl)vinylamine (**1**)

as a new and convenient building block for construction of fluorine-containing heterocyclic compounds, and we report here that the title compounds (**2** and **3**) can be very easily synthesized by the reaction of **1** constituting the N-C-C-C fragment in the pyrimidine ring system with aldehydes providing the C-2 unit and ammonia used as the N-3 source of the ring.



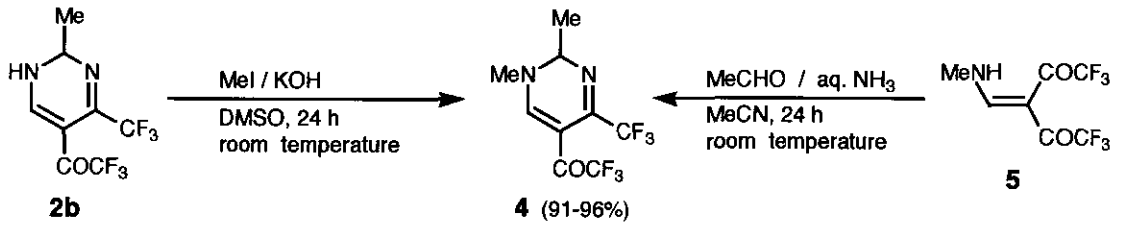
2, 3	a	b	c	d	e	f	g	h
R	H	Me	Et	*i*-Pr	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	Ph	*p*-ClC_6H_4

Scheme 1

The results are shown in Scheme 1. β, β-Bis(trifluoroacetyl)vinylamine (**1**) reacted at 50 ℃ within 24 h with formaldehyde in the presence of aqueous ammonia in acetonitrile to give 2-unsubstituted 5-trifluoroacetyl-4-trifluoromethyl-1,2-dihydropyrimidine (**2a**) in 75% yield. 2-Alkyl-5-trifluoroacetyl-4-trifluoromethyl-1,2-dihydropyrimidines (**2b-d**) were also easily obtained in 69-93% yields from **1**, aliphatic aldehydes such as acet-, propion-, and isobutyraldehydes, and ammonia. Similarly, such aromatic aldehydes as *p*-substituted benzaldehydes reacted with **1** and aqueous ammonia under mild conditions to afford the corresponding 2-aryl-1,2-dihydropyrimidines (**2e-h**) in 49-83% yields. Treatment of 1,2-dihydropyrimidines (**2a-h**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature for 24 h in acetonitrile caused smooth dehydrogenation to give the desired pyrimidines (**3a-h**) in 62-88% yields.

The structures of compounds (**2**, **3**) were determined on the basis of their ^{1}H-nmr and ir spectra, together

with elemental analyses. As representative cases, dihydropyrimidine (**2b**) and pyrimidine (**3d**) were further confirmed by ^{13}C-nmr spectral data. In particular, the structural distinction between 1,2-dihydropyrimidine (**2**) and its tautomeric form 2,3-dihydropyrimidine (**2'**) was confirmed as follows. In ^{1}H-nmr spectra of **2**, the olefinic proton (H-6) on the carbon atom (C-6) adjacent to the nitrogen atom (N-1) having an active hydrogen appeared as a broad singlet, which can possibly be interpreted by both H-H coupling with an amino proton and through-space H-F one with fluorine of the trifluoroacetyl group at the 5-position. Consequently, removal of the amino proton by *in situ* exchange with D_2O caused the disappearance of the signal assigned to it and also a simplification of the signal assigned to the H-6 to a sharp quartet (J_{HF}=1.9 Hz). Moreover, it was ascertained by comparing the ^{13}C-nmr spectrum of **2b** with that of the analogous 5-trifluoroacetyl-4-trifluoromethyl-1,2-dimethyl-1,2-dihydropyrimidine (**4**), which was prepared by two independent approaches as summarized in Scheme 2. The chemical shifts of C-6 (156.1 ppm), C-5 (98.5 ppm), and



Scheme 2

C-4 (152.6 ppm) in **2b** were very nearly equal to those (C-6: 156.8 ppm, C-5: 97.6 ppm, C-4: 151.8 ppm) in **4**. The possibility of the formation of its tautomer (**4'**) can be ruled out, especially on the route to **4** from **5**, because no nitrogen-nitrogen exchange reaction of methylamino derivative (**5**) with ammonia to yield amino derivative (**1**) occurs under such mild conditions.

Thus, the present synthetic method provides a facile and convenient access to pyrimidines having both trifluoromethyl and trifluoroacetyl groups which are not easily obtained by other methods. Further

utilization of **1** as a useful synthetic block for the preparation of various fluorine-containing heterocyclic compounds which are potentially medicinally active are now under investigation and will be presented elsewhere.

EXPERIMENTAL

All 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. 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 products for elemental analyses was done by recrystallization or Kugelrohr distillation.

Reaction of β,β-Bis(trifluoroacetyl)vinylamine (1) with Aldehydes in the Presence of Ammonia; General Procedure: To a solution of **1**[14](235 mg, 1 mmol) in MeCN (5 ml) were added the appropriate aldehyde (1.2 mmol) and aqueous ammonia (28 wt.%, 73 mg, 1.2 mmol). The mixture was stirred at room temperature for 24 h and the solvent was evaporated and the crude product was chromatographed using benzene/EtOAc (3:2) for **2a,b,d**, benzene/EtOAc (7:3) for **2c**, benzene/EtOAc (4:1) for **2e-g**, benzene/EtOAc (9:1) for **2h** as eluent.

In the synthesis of **2a**, 3 mmol of formaldehyde (37 wt.% in water) and 3 mmol of ammonia were used to 1 mmol of **1**, and the reaction was carried out at 50 ℃ for 24 h.

2a: yield 75%; oil; ir (film) 3228, 3198, 1638, 1593, 1535 cm^{-1}; ^{1}H-nmr ($CDCl_3$/CD_3CN) 8.67-6.63 (br, 1H, NH), 8.03 (br s, 1H, H-6), 5.04 (br s, 2H, H-2). Purification for microanalysis of **2a** was difficult; the structural assignment was confirmed by ^{1}H-nmr and ir spectra of the product which was purified by silica gel column chromatography.

2b: yield 93%; mp 117-118 ℃ (hexane/$CHCl_3$); ir (KBr) 3270, 1663, 1638, 1568 cm^{-1}; ^{1}H-nmr

($CDCl_3/CD_3CN$) 8.64-7.25 (br, 1H, NH), 7.98 (br s, 1H, H-6), 5.27 (br q, 1H, J=6, H-2), 1.57 (d, 3H, J=6, CH_3); ^{13}C-nmr (CD_3COCD_3) 171.4 (q, J_{CF}=31.7), 156.1 (dq, J_{CF}=4.9), 152.6 (q, J_{CF}=36.6), 120.6 (q, J_{CF}=275.9), 118.5 (q, J_{CF}=293.0), 98.5 (s), 66.5 (d), 21.1 (q). Anal. Calcd for $C_8H_6N_2OF_6$: C, 36.94; H, 2.32; N, 10.77. Found: C, 36.78; H, 2.19; N, 11.03.

2c: yield 69%; mp 111-112 ℃ (hexane/$CHCl_3$); ir (KBr) 3233, 1631, 1538 cm^{-1}; ^1H-nmr 8.51-5.97 (br, 1H, NH), 8.00 (br s, 1H, H-6), 5.16 (t, 1H, J=6, H-2), 2.15-1.68 (m, 2H, CH_2), 1.03 (t, 3H, J=7, CH_3). Anal. Calcd for $C_9H_8N_2OF_6$: C, 39.43; H, 2.94; N, 10.22. Found: C, 39.20; H, 2.51; N, 10.22.

2d: yield 83%; mp 119-120 ℃ (hexane/$CHCl_3$); ir (KBr) 3238, 1661, 1639, 1573, 1539 cm^{-1}; ^1H-nmr ($CDCl_3/CD_3CN$) 8.65-6.82 (br, 1H, NH), 8.00 (br s, 1H, H-6), 5.00 (br d, 1H, J=4.5, H-2), 2.53-1.89 (m, 1H, C<u>H</u>$(CH_3)_2$), 1.03 (d, 6H, J=6, CH_3). Anal. Calcd for $C_{10}H_{10}N_2OF_6$: C, 41.68; H, 3.50; N, 9.72. Found: C, 41.69; H, 3.57; N, 9.65.

2e: yield 83%; oil; ir (film) 3210, 1629, 1550, 1533, 1512 cm^{-1}; ^1H-nmr 8.23-7.40 (br, 1H, NH), 7.93 (br s, 1H, H-6), 7.33 (d, 2H, J=8, *p*-$MeOC_6$<u>H_4</u>), 6.95 (d, 2H, J=8, *p*-$MeOC_6$<u>H_4</u>), 5.91 (br s, 1H, H-2), 3.77 (s, 3H, OCH_3). Anal. Calcd for $C_{14}H_{10}N_2O_2F_6$: C, 47.74; H, 2.86; N, 7.95. Found: C, 47.84; H, 2.83; N, 7.89.

2f: yield 82%; mp 134-135 ℃ (hexane/$CHCl_3$); ir (KBr) 3292, 1668, 1640, 1588, 1550, 1510 cm^{-1}; ^1H-nmr ($CDCl_3/CD_3CN$) 8.66-6.96 (br, 1H, NH), 7.99 (br s, 1H, H-6), 7.23 (s, 4H, *p*-MeC_6<u>H_4</u>), 6.00 (br s, 1H, H-2), 2.34 (s, 3H, CH_3). Anal. Calcd for $C_{14}H_{10}N_2OF_6$: C, 50.01; H, 3.00; N, 8.33. Found: C, 49.98; H, 2.93; N, 8.43.

2g: yield 75%; mp 141-142 ℃ (hexane/$CHCl_3$); ir (KBr) 3278, 1638, 1544, 1518 cm^{-1}; ^1H-nmr ($CDCl_3/CD_3CN$) 8.59-7.63 (br, 1H, NH), 8.00 (br s, 1H, H-6), 7.38 (s, 5H, C_6H_5), 6.08 (br s, 1H, H-2). Anal. Calcd for $C_{13}H_8N_2OF_6$: C, 48.46; H, 2.50; N, 8.69. Found: C, 48.83; H, 2.31; N, 8.51.

2h: yield 49%; mp 140-141 ℃ (hexane/$CHCl_3$); ir (KBr) 3295, 1669, 1637, 1585, 1541, 1500 cm^{-1}; ^1H-nmr 8.57-7.69 (br, 1H, NH), 8.08 (br s, 1H, H-6), 7.34 (s, 4H, *p*-ClC_6H_4), 6.07 (br s, 1H, H-2). Anal. Calcd for $C_{13}H_7N_2OClF_6$: C, 43.78; H, 1.98; N, 7.86. Found: C, 43.67; H, 2.10; N, 7.84.

Dehydrogenation of 1,2-Dihydropyrimidines (2a-h) with DDQ; General Procedure: To a solution of **2a-h** (1 mmol) in MeCN (2 ml) was added DDQ (238 mg, 1.05 mmol) and the solution was stirred at room temperature for 24 h. The insoluble matter was separated from the solution by filtration and the solvent was evaporated to give the crude product which was purified by Kugelrohr distillation or by silica gel column chromatography. The following eluents were used; hexane/benzene (3:7) for **3f,g**, hexane/benzene (1:1) for **3h**, and hexane/benzene (4:1) for **3e**.

3a: yield 81%; oven temperature 70 ℃/30 mmHg; ir (film) 1755, 1554 cm^{-1}; ^{1}H-nmr 9.34 (s, 1H, H-2), 8.89 (s, 1H, H-6). **3a** was so volatile that its microanalysis could not be carried out.

3b: yield 62%; oven temperature 80 ℃/15 mmHg; ir (film) 1753, 1581 cm^{-1}; ^{1}H-nmr 8.94 (s, 1H, H-6), 2.91 (s, 3H, CH_3). Anal. Calcd for $C_8H_4N_2OF_6$: C, 37.23; H, 1.56; N, 10.85. Found: C, 37.05; H, 1.32; N, 11.27.

3c: yield 74%; oven temperature 80 ℃/10 mmHg; ir (film) 1751, 1578 cm^{-1}; ^{1}H-nmr 9.03 (s, 1H, H-6), 3.19 (q, 2H, J=8, CH_2), 1.44 (t, 3H, J=8, CH_3). Anal. Calcd for $C_9H_6N_2OF_6$: C, 39.72; H, 2.22; N, 10.29. Found: C, 40.04; H, 2.19; N, 10.26.

3d: yield 67%; oven temperature 80 ℃/10 mmHg; ir (film) 1751, 1578 cm^{-1}; ^{1}H-nmr 9.09 (s, 1H, H-6), 3.42 (hp, 1H, J=7, CH), 1.43 (d, 6H, J=7, CH_3); ^{13}C-nmr 181.6 (q, J_{CF}=39.1), 180.1 (s), 157.5 (br d), 154.4 (q, J_{CF}=36.6), 122.6 (s), 120.2 (q, J_{CF}=277.1), 115.8 (q, J_{CF}=290.5), 38.4 (d), 21.3 (q). Anal. Calcd for $C_{10}H_8N_2OF_6$: C, 41.97; H, 2.82; N, 9.79. Found: C, 41.60; H, 2.66; N, 10.32.

3e: yield 76%; mp 78-79 ℃ (hexane); ir (KBr) 1734, 1610, 1572 cm^{-1}; ^{1}H-nmr 9.11 (s, 1H, H-6), 8.52 (d, 2H, J=8, *p*-$MeOC_6\underline{H}_4$), 7.02 (d, 2H, J=8, *p*-$MeOC_6\underline{H}_4$), 3.91 (s, 3H, OCH_3). Anal. Calcd for $C_{14}H_8N_2O_2F_6$: C, 48.01; H, 2.30; N, 8.00. Found: C, 48.43; H, 2.14; N, 7.74.

3f: yield 87%; mp 82-83 ℃ (hexane); ir (KBr) 1738, 1577 cm^{-1}; ^{1}H-nmr 9.07 (s, 1H, H-6), 8.40 (d, 2H, J=8, *p*-$MeC_6\underline{H}_4$), 7.29(d, 2H, J=8, *p*-$MeC_6\underline{H}_4$), 2.43 (s, 3H, CH_3). Anal. Calcd for $C_{14}H_8N_2OF_6$: C, 50.31; H, 2.41; N, 8.38. Found: C, 50.50; H, 2.25; N, 8.36.

3g: yield 88%; mp 71-72 ℃ (hexane); ir (KBr) 1738, 1655, 1575 cm^{-1}; ^{1}H-nmr 9.10 (s, 1H, H-6), 8.67-

8.39 (m, 2H, $C_6\underline{H}_5$), 7.63-7.38 (m, 3H, $C_6\underline{H}_5$). Anal. Calcd for $C_{13}H_6N_2OF_6$: C, 48.77; H, 1.89; N, 8.75. Found: C, 48.74; H, 1.82; N, 8.85.

3h: yield 78%; mp 54-55 ℃ (hexane); ir (KBr) 1749, 1577 cm^{-1}; ^{1}H-nmr 8.98(s, 1H, H-6), 8.50 (d, 2H, J=8, *p*-$ClC_6\underline{H}_4$), 7.50 (d, 2H, J=8, *p*-$ClC_6\underline{H}_4$) . Anal. Calcd for $C_{13}H_5N_2OClF_6$: C, 44.03; H, 1.42; N, 7.90. Found: C, 43.85; H, 1.49; N, 8.60.

Synthesis of 5-Trifluoroacetyl-4-trifluoromethyl-1,2-dimethyl-1,2-dihydropyrimidine (4):

From 2b: Dihydropyrimidine derivative (**2b**) (130 mg, 0.5 mmol) and powdered KOH (31 mg, 0.55 mmol) were dissolved in DMSO (2 ml). To the solution was added MeI (710 mg, 5 mmol), and the mixture was stirred at room temperature for 24 h. The mixture was washed with water and extracted with CH_2Cl_2, the extract was dried over anhydrous sodium sulfate. The solvent was evaporated, and the crude mixture was chromatographed using benzene/EtOAc (3:2) as eluent to give **4** (132 mg, 0.48 mmol).

From 5: To a solution of **5**[14](249 mg, 1 mmol) in MeCN (5 ml) were added acetaldehyde (53 mg, 1.2 mmol) and aqueous ammonia (28 wt.%, 73 mg, 1.2 mmol). The mixture was stirred at room temperature for 24 h and the solvent was evaporated and the crude product was chromatographed using benzene/EtOAc (3:2) as eluent to afford **4** (249 mg, 0.91 mmol).

4: oven temperature 155 ℃/3 mmHg; ir (film) 1688, 1674, 1650, 1639, 1579 cm^{-1}; ^{1}H-nmr 7.69 (s, 1H, H-6), 5.34 (q, 1H, J=6, H-2), 3.24 (s, 3H, CH_3-1), 1.44 (d, 3H, J=6, CH_3-2); ^{13}C-nmr (CD_3COCD_3) 170.9 (q, J_{CF}=31.7), 156.8 (dq, J_{CF}=6.1), 151.8 (q, J_{CF}=35.4), 120.9 (q, J_{CF}=275.9), 118.7 (q, J_{CF}=291.8), 97.6 (s), 73.0 (d), 41.6 (q), 17.1 (q). Anal. Calcd for $C_9H_8N_2OF_6$: C, 39.43; H, 2.94; N, 10.22. Found: C, 39.41; H, 2.87; N, 10.31.

ACKNOWLEDGEMENTS

A financial support by a Grant-in-Aid for Scientific Research (No. 07651058) from the Ministry of Education, Science, and Culture, Japan is gratefully acknowledged.

REFERENCES

1. D. J. Brown, 'The Pyrimidines,' Wiley-Interscience, New York, 1970.
2. D. T. Hurst, 'An Introduction to the Chemistry and Biochemistry of Pyrimidines, Purines, and Pteridines,' Wiley, Chichester, 1980.
3. R. Filler, 'Organofluorine Chemicals and Their Industrial Applications,' ed. by R. E. Banks, Ellis Horwood, London, 1979.
4. R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry, 'Kodansha & Elsevier Biomedical, Tokyo, 1982.
5. J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
6. 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications,' ed. by R. Filler, Y. Kobayashi, and L. M. Yagupolskii , Elsevier, Amsterdam, 1993.
7. M. Hojo, R. Masuda, and E. Okada, *Tetrahedron Lett.*, 1986, **27**, 353.
8. M. Hojo, R. Masuda, and E. Okada, *Synthesis,* 1986, 1013.
9. M. Hojo, R. Masuda, and E. Okada, *Synthesis,* 1990, 347.
10. M. Hojo, R. Masuda, Y. Kamitori, and E. Okada, *J. Org. Chem.*, 1991, **56**, 1975.
11. M. Hojo, R. Masuda, E. Okada, S. Sakaguchi, H. Narumiya, and K. Morimoto, *Tetrahedron Lett.*, 1989, **30**, 6173.
12. M. Hojo, R. Masuda, E. Okada, H. Yamamoto, K. Morimoto, and K. Okada, *Synthesis*, 1990, 195.
13. M. Hojo, R. Masuda, and E. Okada, *Chem. Lett.*, 1990, 2095.
14. M. Hojo, R. Masuda, E. Okada, and Y. Mochizuki, *Synthesis,* 1992, 455.
15. E. Okada, R. Masuda, M. Hojo, and R. Inoue, *Synthesis*, 1992, 533.

Received, 1st March, 1996