Synthesis of Trifluoromethyl-1,2,4-triazine- and Trifluoromethylpyrimidine-Fused Uracils

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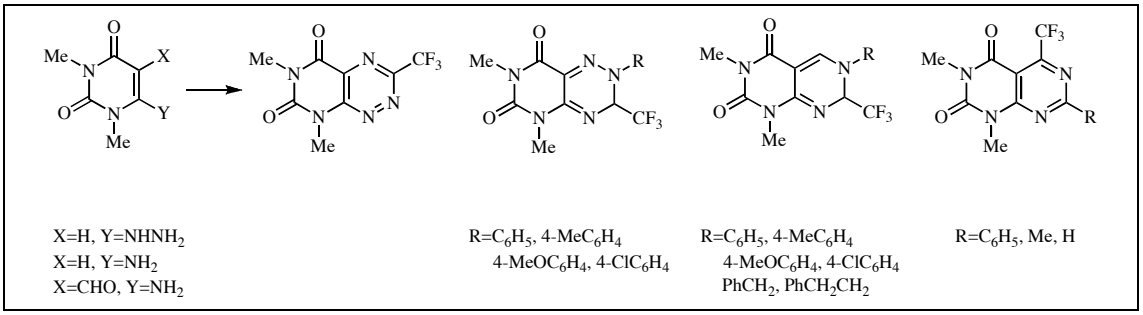

A variety of trifluoromethyl-1,2,4-triazine- and trifluoromethylpyrimidine-fused uracils (**9**), (**12**), (**15**) and (**18**) were synthesized from trifluoroacetaldehyde ethyl hemiacetal or trifluoroacetic anhydride and corresponding uracil derivatives.

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INTRODUCTION

Heterocycles containing fluorine and/or perfluoroalkyl groups have been target compounds because of their broad array of biological activities and specific chemical reactivities [1]. In our previous paper, we described the synthesis of condensed uracil derivatives having a trifluoromethyl group, *i.e.*, 5-trifluoromethylpyrido[2,3-*d*]-pyrimidine-2,4-diones (**1**) [2] and 4-trifluoromethyl-pyrimido[4,5-*c*]pyridazine-5,7-diones (**2**) [3] (Figure 1). Through the course of these studies we have prepared uracils condensed with trifluoromethyl-1,2,4-triazines (**9**) and (**12**) and with trifluoromethylpyrimidines (**15**) and (**18**).

Antibiotic fervenulin (6,8-dimethyl-5,6,7,8-tetrahydro-pyrimido[5,4-*e*]-1,2,4-triazine-5,7-dione) (**3**) [4], toxo-flavin (**4**) [5], and isofervenulin (5,7-dimethyl-5,6,7,8-tetrahydropyrimido[4,5-*e*]-1,2,4-triazine-6,8-dione) (**5**) [6] have been prepared by various methods. Introduction of a trifluoromethyl group into these compounds seems interesting from the point of view of biological activities and chemical behavior.

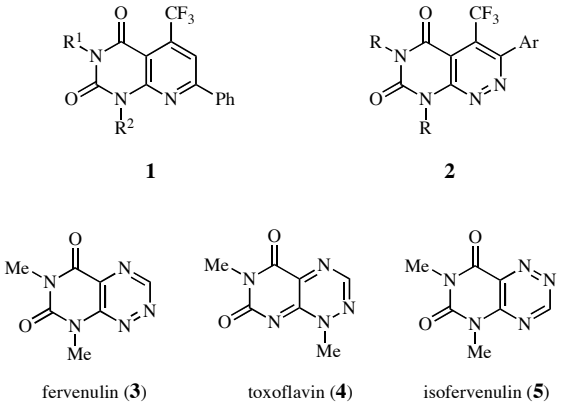
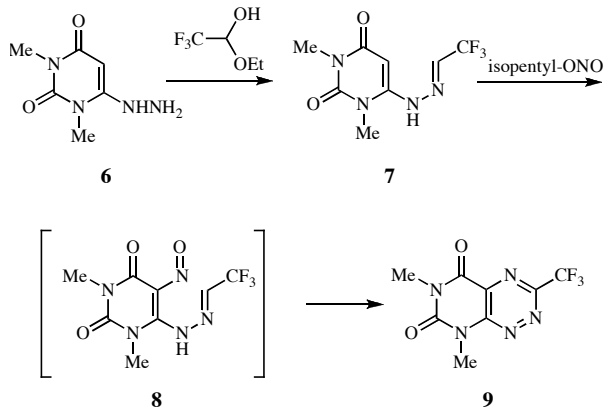


Figure 1

Several methods for synthesis of 3-substituted fervenulins have been published: the reaction of 5-arylazo-6-arylidenehydrazinouracils with dimethylform-amide diethylacetal [7], the reaction of 6-hydrazino-5-nitrosouracil with aldehydes [4a,c], cyclization of the adduct of 6-arylidenhydrazinouracil [8] to diethyl azodicarboxylate, the cyclization of 6-hydrazono-5-nitrosouracil [9], and the reaction of 6-amino-5-nitrosouracil with hydrazones [10]. We have synthesized 3-trifluoromethylfervenulin (**9**) principally according to Senga's method [4a] (Scheme 1). Trifluoroacetaldehyde hydrazone (**7**) [3], prepared from 6-hydrazino-1,3-dimethyluracil (**6**) and trifluoroacetaldehyde ethyl hemiacetal, was treated with isopentyl nitrite in ethanol to give **9** in one step in 44% yield. The ^{13}C nmr spectrum of **9** showed two quartet resonances at δ 119.30 ($^{1}J_{CF}$=274 Hz) and 153.74 ($^{2}J_{CF}$=38.0 Hz) ppm due to the trifluoromethyl carbon and the aromatic C3-carbon, respectively. The reaction would proceed *via* nitrosation to give the intermediate (**8**) followed by dehydration to **9** as reported in the synthesis of 3-substituted fervenulin [4a,9a].

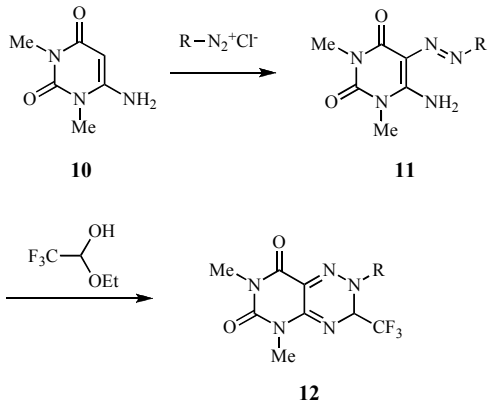
Derivatives of isofervenulin (**5**) have been prepared by the cyclization of 1-cyano-2-methyl-3-(6-uracilyl)iso-thiourea derivatives [11], 4-chloro-1,2,4-triazine-3-carboxylate [6a], 6-amino-5-arylazouracils [12], and 6-amino-5-nitrosouracil [6c], and from the addition product of uracil to azodicarboxylate diester [6b]. Photooxidation of 6-(aminomethylene)amino-5-arylazouracils has also been studied [13]. We have synthesized 2-substitutd 3-trifluoromethylisofervenulins starting from the readily

Scheme 1



available 6-amino-5-arylazouracils (**11**) [12] obtained from 6-amino-1,3-dimethyluracil (**10**) (Scheme 2). A mixture of **11**, trifluoroacetaldehyde ethyl hemiacetal, and a catalytic amount of *p*-toluenesulfonic acid in *N,N*-dimethylformamide was refluxed for 5 hours. After purification by column chromatography, the desired products (**12a**-**d**) were obtained in 39-58% yields. Nmr resonances due to the trifluoromethyl group of **12a** were observed at δ 6.46 (q, $^3J_{HF}$=5.6 Hz, C3-H) in the ^{1}H nmr spectrum along with δ 71.48 (q, $^2J_{CF}$=32.2 Hz, C3) and 123.00 (q, $^1J_{CF}$=289 Hz, CF_3) in the ^{13}C nmr spectrum.

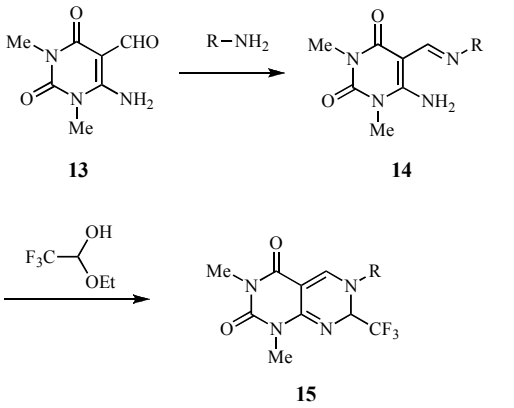
Scheme 2



11, **12a**: R = C_6H_5 **b**: R = 4-MeC_6H_4
c: R = 4-$MeOC_6H_4$ **d**: R = 4-ClC_6H_4

Next, we turned our attention to uracils condensed with 2-trifluoromethylpyrimidine. Cycloaddition reactions of 6-[(dimethylamino)methylene]aminouracil to heterocumulenes [14] or *N*-sulfonylimines [15] and the aza-Wittig reaction of iminophosphorane of 6-aminouracil with isocyanates [16] are recent synthetic approaches to 1,3-dimethyluracil condensed with a pyrimidine nucleus. 7-Trifluoromethyl-1,3-dimethylpyrimido[4,5-*d*]pyrimidine-2,4-dione is the only reported case of our target compounds [17], and it was prepared by treatment of 6-aminouracil with phosphorus oxychloride/*N,N*-dimethylformamide followed by heating with trifluoroacetamide. In order to introduce a trifluoromethyl group into the C7 position of 1,3-dimethylpyrimido[4,5-*d*]pyrimidine-2,4-diones (**15**), the choice of 6-amino-5-iminomethyluracils (**14**) as the starting material seems reasonable (Scheme 3). We have synthesized 6-substituted 7-trifluoromethyl derivatives (**15**) in 28-14% yields by heating a mixture of **14**, trifluoroacetaldehyde ethyl hemiacetal, and a catalytic amount of *p*-toluenesulfonic acid in dimethyl sulfoxide. Trial of the reaction under various conditions resulted in no improvement in yields. The ^{1}H nmr spectra of **15a** showed two absorptions due to C7-H at δ 6.14 (q, $^3J_{HF}$=5.5 Hz, 0.5 H) and 6.15 (q, $^3J_{HF}$=5.5 Hz, 0.5 H) and also two absorptions due to C4-H at 8.12 (s, 0.5H) and 8.13 (s, 0.5 H). Other products have a similar tendency. There would be two conformational isomers in these products due to the interaction between a trifluoromethyl group and a substituent at the N6 position.

Scheme 3

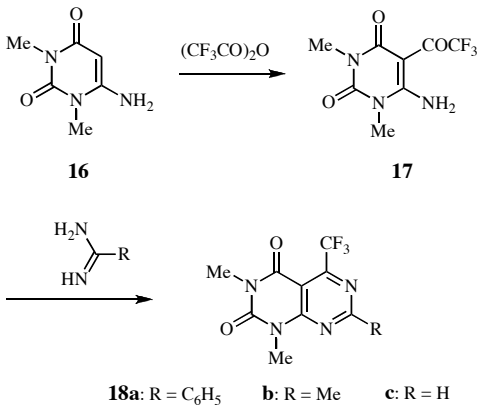


14, **15a**: R = C_6H_5 **b**: R = 4-MeC_6H_4 **c**: R = 4-$MeOC_6H_4$
d: R = 4-ClC_6H_4 **e**: R = $PhCH_2$ **f**: R = $PhCH_2CH_2$

5-Trifluoromethyl derivatives of pyrimido[4,5-*d*]pyrimidine-2,4-diones (**18**) were obtained from 6-amino-5-trifluoromethyluracil (**17**), which was prepared in 90% yield on treatment of 6-aminouracil (**16**) with trifluoroacetic anhydride at room temperature. The problem of acetylation of 6-aminouracils was discussed in an early report [18], and trifluoroacetyaltion in our experiment occurred at the C5 position as was expected. Heating a mixture of **17**, benzamidine hydrochloride or acetamidine hydrochloride, and sodium hydrogencarbonate in dimethylformamide at 130-140°C yielded the expected products **18a** and **b** in rather low yields (15% and 20%, respectively), whereas formamidine acetate gave **18c** in 66% yield. Attempted cyclization of **17** to other derivatives of **18** using reagents such as urea,

thiourea, amide, thioamide and guanidine resulted in the formation of an intractable complex mixture probably because of instability of **17** to heating. During our study, a 5,5-bis(trifluoromethyl) derivative of this class of compounds was prepared by the reaction of hexafluoroacetone (ethoxycarbonyl)imine with uracil by a Russian group [19].

Scheme 4



In conclusion, trfluoromethyl-1,2,4-triazine- and trifluoromethylpyrimidine-fused uracils, *i.e.*, (**9**), (**12**), (**15**) and (**18**) were obtained starting from readily available uracil derivatives (**6**), (**11**), (**14**) and (**17**), respectively.

EXPERIMENTAL

All melting points were determined with MRK MEL-TEMP II and are uncorrected. The ir spectra were measured on a JASCO FT/IR-420 spectrophotometer. Ms and nmr spectra were obtained with JEOL JMS DX-300 and JEOL GSX-400, respectively. Microanalysis was performed with YANACO CHN-CODER MT-5. Chloroform (carcinogenic) used as a solvent in the following experiment might easily be substituted by dichloromethane.

3-Trifluoromethyl-6,8-dimethyl-5,6,7,8-tetrahydropyrimido-[5,4-*e*]-1,2,4-triazine-5,7-dione (9). A suspension of **7** [3] (250 mg, 1.0 mmol) in ethanol (3 ml) was cooled by ice under nitrogen and was dropwise added by isopentyl nitrite (129 mg, 1.1 mmoles). The mixture was stirred at room temperature for 21 hours. After evaporation of the solvent, the residue was recrystallized from chloroform-hexane to give **9** as yellow needles, 115 mg (44%), mp 130-131 °C; ir (potassium bromide): CO 1743, CO 1691, 1576, 1294, 1201, 1161 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.58 (s, 3H, CH_3), 3.95 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 29.76, 30.35, 119.30 (q, $^1J_{CF}$=274 Hz, CF_3), 131.01, 148.89, 151.52, 153.74 (q, $^2J_{CF}$=38.0 Hz, C3), 157.84; ms: m/z (%) 261 (M^+, 61), 205 (71), 136 (46), 67 (100). *Anal.* Calcd. for $C_8H_6N_5O_2F_3$: C, 36.79; H, 2.32; N, 26.82. Found: C, 36.57; H, 2.48; N, 26.47.

3-Trifluoromethyl-5,7-dimethyl-2-phenyl-2,3,5,6,7,8-hexahydropyrimido[4,5-*e*]-1,2,4-triazine-6,8-dione (**12a**). A mixture of **11a** (1.56 g, 6.0 mmoles), trifluoroacetaldehyde ethyl hemiacetal (1.73 g, 12 mmoles), and a catalytic amount of *p*-toluensulfonic acid in *N,N*-dimethylformamide (15 ml) was refluxed for 5 hours. The reaction mixture was extracted by the use of water and $CHCl_3$, and the organic layer was separated and dried over magnesium sulfate. After evaporation of the solvent the solid residue was separated by column chromatography (silica gel-chloroform 1:ethyl acetate 1) to give **12a** as yellow prisms, 1.25 g (58%), mp 124-125 °C: ir (potassium bromide): CO 1722, CO 1678, 1622, 1508, 1223, 1149, 1099 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.42 (s, 3H, CH_3), 3.46 (s, 3H, CH_3), 6.46 (q, $^3J_{HF}$=5.6 Hz, 1H, C3-H), 7.26-7.55 (m, 5H, Ph); ^{13}C nmr (deuteriochloroform): δ 28.54, 29.19, 71.48 (q, $^2J_{CF}$=32.2 Hz, C3), 118.82, 122.66, 123.00 (q, $^1J_{CF}$=289 Hz, CF_3), 127.01, 129.54, 142.65, 147.70, 150.51, 157.79; ms: m/z (%) 339 (M^+, 5), 270 (100), 213 (5), 104 (18), 77. *Anal.* Calcd. for $C_{14}H_{12}N_5O_2F_3$: C, 49.56; H, 3.57; N, 20.64. Found: C, 49.59; H, 3.65; N, 20.80.

3-Trifluoromethyl-5,7-dimethyl-2-(4-methylphenyl)-2,3,5,6,7,8-hexahydropyrimido[4,5-*e*]-1,2,4-triazine-6,8-dione (**12b**). This compound was obtained in a manner similar to that of **12a** by which yellow prisms (39%) were obtained, mp 125-126 °C (chloroform-hexane); ir (potassium bromide): CO 1724, CO 1676, 1622, 1500, 1225, 1146, 1097 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.28 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 3.45 (s, 3H, CH_3), 6.43 (q, $^3J_{HF}$=5.6 Hz, 1H, C3-H), 7.23 (d, J=9.0 Hz, 2H), 7.42 (d, J=9.0 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 20.93, 28.49, 29.16, 71.71 (q, $^2J_{CF}$=32.2 Hz, C3), 118.83, 122.26, 123.00 (q, $^1J_{CF}$=291 Hz, CF_3), 130.06, 137.27, 140.44, 147.75, 150.57, 157.88. *Anal.* Calcd. for $C_{15}H_{14}N_5O_2F_3$: C, 50.99; H, 3.99; N, 19.82. Found: C, 50.98; H, 4.09; N, 20.01.

3-Trifluoromethyl-2-(4-methoxyphenyl)-5,7-dimethyl-2,3,5,6,7,8-hexahydropyrimido[4,5-*e*]-1,2,4-triazine-6,8-dione (**12c**). This compound was obtained in a manner similar to that of **12a** by which yellow prisms (49%) were obtained, mp 146-147 °C (chloroform-hexane); ir (potassium bromide): 1472, 1676, 1620, 1496, 1255, 1228, 1184, 1142 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.41 (s, 3H, CH_3), 3.45 (s, 3H, CH_3), 6.37 (q, $^3J_{HF}$=6.0 Hz, 1H, C3-H), 6.94 (d, J=10.0 Hz, 2H), 7.45 (d, J=10.0 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 28.48, 29.16, 55.62, 72.36 (q, $^2J_{CF}$=32.2 Hz, C3), 114.63, 120.90, 122.12, 123.00 (q, $^1J_{CF}$=289 Hz, CF_3), 136.32, 147.74, 150.60, 157.90, 158.75. *Anal.* Calcd. for $C_{15}H_{14}N_5O_3F_3$: C, 48.78; H, 3.82; N, 18.96. Found: C, 48.45; H, 3.86; N, 18.92.

2-(4-Chlorophenyl)-3-trifluoromethyl-5,7-dimethyl-2,3,5,6,7,8-hexahydropyrimido[4,5-*e*]-1,2,4-triazine-6,8-dione (**12d**). This compound was prepared in a manner to that of **12a** by which yellow prisms (54%) were obtained, mp 151-152 °C (chloroform-hexane); ir (potassium bromide): CO 1730, CO 1678, 1622, 1518, 1493, 1469, 1415, 1373, 1317, 1223, 1146, 1097 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.42 (s, 3H, CH_3), 3.46 (s, 3H, CH_3), 6.41 (q, $^3J_{HF}$=5.5 Hz, 1H, C3-H), 7.41 (d, J=8.2 Hz, 2H), 7.47 (d, J=8.2 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 28.48, 29.24, 71.30 (q, $^2J_{CF}$=32.2 Hz, C3), 119.83, 122.83 (q, $^1J_{CF}$=289 Hz, CF_3), 129.63, 132.71, 141.14, 147.55, 150.38, 157.60. *Anal.* Calcd. for $C_{14}H_{11}N_5O_2ClF_3$: C, 44.99; H, 2.97; N, 18.74. Found: C, 45.00; H, 3.14; N, 18.78.

6-Amino-5-[*N*-(benzyl)iminomethyl]-1,3-dimethyluracil (**14e**). This compound was prepared according to the literature method [16], white needles (52%), mp 167-168 °C (ethanol); ir (potassium bromide): NH 3286, CO 1707, 1618, 1549, 1495, 1450 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.33 (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 4.65 (s, 2H, CH_2), 5.92 (br s, 1H, NH), 7.24-

7.36 (m, 5H, ArH), 8.56 (s, 1H, HC=N). *Anal.* Calcd. for $C_{14}H_{16}N_4O_2$: C, 61.74; H, 5.93; N, 20.58. Found: C, 61.53; H, 5.87; N, 20.73.

6-Amino-1,3-dimethyl-5-[*N*-(2-phenylethyl)iminomethyl]-uracil (**14f**). This compound was prepared according to the literature method [16], white needles (68%), mp 157-158 °C (ethanol); ir (potassium bromide): NH 3288, CO 1699, 1624, 1545, 1360, 1182 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.93 (t, J=7.2 Hz, 2H, CH_2), 3.26 (s, 3H, CH_3), 3.33 (s, 3H, CH_3), 3.71 (t, J=7.2 Hz, 2H), 6.06 (br s, 1H, NH_2), 7.18-7.32 (m, 5H, ArH), 8.33 (s, 1H, HC=N). *Anal.* Calcd. for $C_{15}H_{18}N_4O_2$: C, 62.91; H, 6.35; N, 19.57. Found: C, 62.93; H, 6.44; N, 19.85.

7-Trifluoromethyl-1,3-dimethyl-6-phenyl-1,2,3,4,6,7-hexahydropyrimido[4,5-*d*]pyrimidine-2,4-dione (**15a**). A mixture of **14a** [16] (520 mg, 2.0 mmoles), trifluoroacetaldehyde ethylhemiacetal (640 mg, 4.0 mmoles), and a catalytic amount of *p*-toluenesulfonic acid monohydrate in dimethyl sulfoxide (4 ml) was refluxed for 12 hours. The reaction mixture was poured into a mixed solvent of water and chloroform, and the mixture was extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated to give an oily residue, which was solidified by addition of methanol. The solid was collected by filtration and recrystallized from methanol. The crystals were purified by column chromatography (silica gel- a mixed solvent of chloroform 1: ethyl acetate 1) to give **15a** (190 mg, 28%), light yellow powder, mp 183-184 °C (methanol); ir (potassium bromide): CO 1712, 1666, 1628, 1597, 1537, 1489, 1308, 1252, 1201, 1174, 1146 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.32 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.14 (q, $^3J_{HF}$=5.5 Hz, 0.5 H, C7-H), 6.15 (q, $^3J_{HF}$=5.3Hz, 0.5 H, C7-H), 7.30-7.50 (m, 5H, ArH), 8.12 (s, 0.5 H, C5-H), 8.12 (s, 0.5 H, C5-H); ^{13}C nmr (deuteriochloroform): δ 27.81, 28.93, 76.00 (q, $^2J_{CF}$=31.7 Hz, C7), 94.96, 123.28 (q, $^1J_{CF}$=289.1 Hz, CF_3), 122.59, 127.98, 130.17, 124.57, 149.40, 151.79, 153.44, 160.51; ms: m/z (%) 338 (M^+, 2), 269 (100), 212 (11), 104 (11), 77 (44). *Anal.* Calcd. for $C_{15}H_{12}O_2N_4F_3$: C, 53.26; 3.87; H, 3.87; N, 16.56. Found: C, 53.20; H, 4.00; N, 16.71.

7-Trifluoromethyl-1,3-dimethyl-6-(4-methylphenyl)-1,2,3,4,6,7-hexahydropyrimido[4,5-*d*]pyrimidine-2,4-dione (**15b**). This compound was obtained in a manner similar to that of **15a** by which light yellow powder (26%) was obtained, mp 156-157 °C (methanol); ir (potassium bromide): CO 1662, 1630, 1539, 1491, 1375, 1301, 1282, 1248, 1200, 1144 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.39 (s, 3H, CH_3), 3.32 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.09 (q, $^3J_{HF}$=5.5 Hz, 0.5H, C7-H), 6.19 (q, $^3J_{HF=}$5.5 Hz, C7-H), 7.18-7.27 (m, 4H, ArH), 8.08 (s, 0.5 H, C5-H), 8.09 (s, 0.5H, C5-H); ^{13}C nmr (deuteriochloroform): δ 21.01, 27.76, 28.91, 76.13 (q, $^2J_{CF}$=31.0 Hz, C7), 94.57, 122.56, 123.27 (q, $^1J_{CF}$ = 289.0 Hz, CF_3), 130.65, 138.22, 140.13, 149.61, 151.83, 153.46, 160.56. *Anal.* Calcd. for $C_{16}H_{15}N_4O_2F_3$: C, 54.55; H, 4.29; N, 15.90. Found: C, 54.58; H, 4.34; N, 16.09.

7-Trifluoromethyl-6-(4-methoxyphenyl)-1,3-dimethyl-1,2,3,4,6,7-hexahydropyrimido[4,5-*d*]pyrimidine-2,4-dione (**15c**) This compound was obtained in a manner similar to that of **15a** by which light yellow powder (14%) was obtained, mp 181-182 °C (methanol); ir (potassium bromide): CO 1716, CO 1662, 1635, 1493, 1373, 1250, 1203, 1182, 1136 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.14 (s, 3H, CH_3), 3.32 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 6.02 (q, $^3JC_{HF}$=5.5 Hz, 0.5H, C7-H), 6.03 (q, $^3J_{HF}$=5.3 Hz, 0.5H, C7-H), 6.96 (d, J=9.0 Hz, 2H), 7.24 (d, J=9.0 Hz, 2H), 8.03 (s, 0.5 H, C5-H), 8.04 (s, 0.5 H, C5-H); ^{13}C nmr (deuteriochloroform): δ 27.78, 28.93, 55.63, 76.59 (q, $^2J_{CF}$=29.6 Hz, C7), 94.34, 115.19, 123.28 (q, $^1J_{CF}$=290.1 Hz, CF_3), 124.70, 135.64, 150.02, 151.87, 153.44, 159.18, 160.59. *Anal.* Calcd. for $C_{16}H_{15}N_4O_3F_3$: C, 52.18; H, 4.11; N, 15.21. Found: C, 52.14; H, 4.19; N, 15.32.

6-(4-Chlorophenyl)-7-trifluoromethyl-1,3-dimethyl-1,2,3,4,6,7-hexahydropyrimido[4,5-*d*]pyrimidine-2,4-dione (**15d**). This compound was obtained in a manner similar to that of **15a** by which white powder (21%) was obtained, mp 183-184 °C (methanol); ir (potassium bromide): CO 1712, CO 1643, 1539, 1483, 1373, 1325, 1282, 1207, 1136, 1093 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.32 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.08 (q, $^3J_{HF}$=5.3 Hz, 0.5 H, C7-H), 6.09 (q, $^3J_{HF}$=5.3 Hz, 0.5 H, C7-H), 7.26 (d, J=8.8 Hz, 2H), 7.45 (d, J=8.8 Hz, 2H), 8.06 (s, 0.5 H, C5-H), 8.07 (s, 0.5 Hz, C5-H); ^{13}H nmr (deuteriochloroform): δ 28.68, 29.81, 76.83 (q, $^2J_{CF}$=31.2 Hz, C7), 96.26, 124.02 (q, $^1J_{CF}$=288.5 Hz, CF_3), 124.75, 131.17, 134.67, 141.87, 149.67, 152.51, 154.12, 161.21. *Anal.* Calcd. for $C_{15}H_{12}N_4O_2Cl F_3$: C, 48.34; H, 3.25; N, 15.03. Found: C, 48.41; H, 3.37; N, 15.18.

6-Benzyl-7-trifluoromethyl-1,3-dimethyl-1,2,3,4,6,7-hexahydropyrimido[4,5-*d*]pyrimidine-2,4-dione (**15e**). This compound was obtained in a manner similar to that of **15a** by which white needles (21%) were obtained, mp 144-145 °C (ethanol); ir (potassium bromide): CO 1720, CO 1652, 1635, 1506, 1417, 1389, 1171, 1142 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.31 (s, 3H, CH_3), 3.32 (s, 3H, CH_3), 4.59 (d, J=15.2 Hz, 1H, PhCH), 4.70 (d, J=15.2 Hz, 1H, PhCH), 5.54 (q, $^3J_{HF}$=5.5 Hz, 1H, C5-H), 7.23-7.44 (m, 4H, ArH), 7.95 (s, 1H, C5-H); ^{13}C nmr (deuteriochloroform): 27.65, 28.79, 58.93, 73.49 (q, $^2J_{CF}$=31.7 Hz, C7), 91.97, 123.59 (q, $^1J_{CF}$=288.5 Hz, CF_3), 128.05, 129.28, 129.47, 132.64, 151.97, 153.38, 160.54, 162.67. *Anal.* Calcd. for $C_{16}H_{15}N_4O_2F_3$: C, 54.54; H, 4.30; N, 15.90. Found: C, 54.53; H, 4.42; N, 15.76.

6-(2-Phenylethyl)-7-trifluoromethyl-1,3-dimethyl-1,2,3,4,6,8-hexahydropyrimido[4,5-*d*]pyrimidine-2,4-dione (**15f**). This compound was obtained in a manner similar to that of **15a** by which white prisms (23%) were obtained, mp 145-147 °C (ethanol); ir (potassium bromide) CO 1709, CO 1637, 1539, 1504, 1415, 1381, 1171, 1142, 1101 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.90-3.03 (m, 2H, CH_2), 3.26 (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 3.62-3.37 (m, 2H, CH_2), 5.51 (q, $^3J_{HF}$=5.6 Hz, 1H, C7-H), 7.13-7.33 (m, 5H, ArH), 7.65 (s, 1H, C5-H); ^{13}C nmr (deuteriochloroform): 27.60, 28.78, 35.36, 56.31, 74.33 (q, $^2J_{CF}$=31.2 Hz, C7), 92.00, 123.35 (q, $^1J_{CF}$=288.5 Hz, CF_3), 127.44, 128.54, 128.97, 135.83, 151.57, 151.94, 153.52, 160.34. *Anal.* Calcd. for $C_{17}H_{17}N_4O_2F_3$: C, 55.73; H, 4.69; N, 15.30. Found: C, 55.70; H, 4.59; N, 15.46.

6-Amino-5-trifluoroacetyl-1,3-dimethyluracil (**17**). To powdered **16** (3.10 g, 20 mmoles) without a solvent was dropwise added trifluoroacetic anhydride (14 ml, 101 mmoles) under nitrogen and the mixture was stirred at room temperature for 24 hours. The mixture was neutralized with 50% aqueous sodium hydroxide, and the resulting precipitates were collected by filtration to give **17** (4.50 g, 90%), white prisms, mp 180-181 °C (methanol); ir (potassium bromide): NH 3338, CO 1728, 1618, 1539, 1444, 1221, 1184, 1140 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.14 (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 8.79 (br s, 1H, NH), 10.20 (br s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 27.60, 30.10, 87.96, 117.35 (q, $^1J_{CF}$=285.9 Hz, CF_3), 149.33, 158.84, 158.87, 175.83 (q, $^2J_{CF}$=34.9 Hz, CO). *Anal.* Calcd. for $C_8H_8N_3O_3F_3$: C, 38.25; H, 3.21; N, 16.73. Found: C, 38.53; H, 3.28; N, 16.74.

5-Trifluoromethyl-1,3-dimethyl-7-phenyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4-dione (**18a**). A mixture of **17** (502 mg, 2.0 mmoles), benzamidine hydrochloride (626 mg, 4.0 mmoles), and sodium hydrogen carbonate (168 mg, 2.0 mmoles) in *N,N*-dimethylformamide (5 ml) was heated at 130°C for 14 hours. After cooling, the mixture was diluted with chloroform and extracted with water. The organic layer was dried over magnesium sulfate and evaporated to dryness. The solid residue was recrystallized from ethyl acetate to give **18a** (83 mg, 15%), white needles, mp 276-277 °C; ir (potassium bromide): CO 1736, CO 1689, 1570, 1410, 1356, 1225, 1169 cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 3.97 (s, 3H, CH_3), 4.33 (s, 3H, CH_3), 7.92-8.89 (m, 5H, ArH). *Anal.* Calcd. for $C_{15}H_{11}N_4O_2F_3$: C, 53.57; H, 3.30; N, 16.67. Found: C, 53.85; H, 3.47; N, 16.75.

5-Trifluoromethyl-1,3,7-trimethyl-1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4-dione (**18b**). This compound was obtained as described above for **18a** and was separated by column chromatography (silica gel-ethyl acetate 1: hexane 1) to give **18b** (20%), white crops, mp 120-121 °C; ir (potassium bromide): CO 1726, CO 1682, 1574, 1414, 1392, 1161 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.84 (s, 3H, CH_3), 3.48 (s, 3H, CH_3), 3.73 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 26.60, 28.84, 30.23, 103.33, 120.02 (q, $^1J_{CF}$=274.8 Hz, CF_3), 150,43, 155.32 (q, $^2J_{CF}$=37.5 Hz, C5), 156.95, 157.85, 171.67. *Anal.* Calcd. for $C_{10}H_9N_4O_2F_3$: C, 43.80; H, 3.31; N, 20.44. Found: C, 43.79; H, 3.39; N, 20.27.

5-Trifluoromethyl-1,3-dimethyl-1,2,3,4-tetrahydropyrimido-[4,5-*d*]pyrimidine-2,4-dione (**18c**) A mixture of **17** (251 mg, 1.0 mmoles) and formamidine acetate (208 mg, 2.0 mmoles) in *N,N*-dimethylformamide (3 ml) was heated with stirring at 140°C for 3 hours. After cooling, water was added to the reaction mixture and the resulting precipitates were collected by filtration to give **18c** (173 mg, 66%), white crops, mp 182-183 °C (ethyl acetate); ir (potassium bromide): CO 1730, CO 1676, 1581, 1496, 1402, 1338 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.49 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 9.21 (s, 1H, C7-H); ^{13}C nmr (deuteriochloroform): δ 29.00, 30.43, 106.03, 119.98 (q, $^1J_{CF}$=275 Hz, CF_3), 150.16, 155.74 (q, $^2J_{CF}$=38.0 Hz, C5), 156.69, 157.85, 160.20. *Anal.* Calcd. for $C_9H_7N_4O_2F_3$: C, 41.54; H, 2.71; N, 21.54. Found: C, 41.60; H, 2.83; N, 21.68.

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