

HETEROCYCLES, Vol. 68, No. 9, 2006, pp. 1875 - 1883. © The Japan Institute of Heterocyclic Chemistry
Received, 2nd May, 2006, Accepted, 18th July, 2006, Published online, 21st July, 2006. COM-06-10781

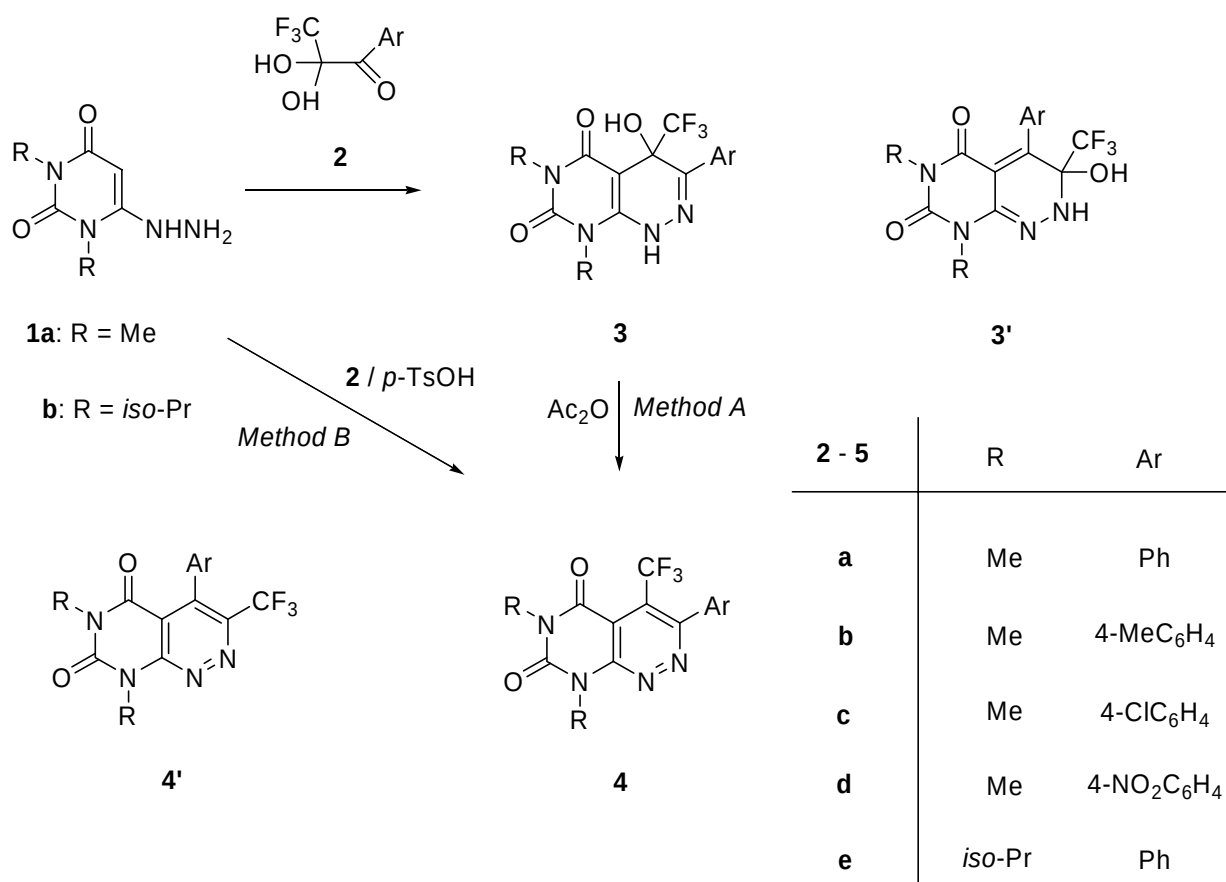
SYNTHESIS OF 4-TRIFLUOROMETHYLPYRIMIDO[4,5-*c*]- PYRIDAZINE-5,7-DIONES FROM URACILS

Masahiko Takahashi,* Yoshinobu Ogawa, and Kazuhiro Inoue

Department of Materials Science, Faculty of Engineering, Ibaraki University,
Hitachi, Ibaraki 316-8511, Japan
e-mail: takamasa@mx.ibaraki.ac.jp

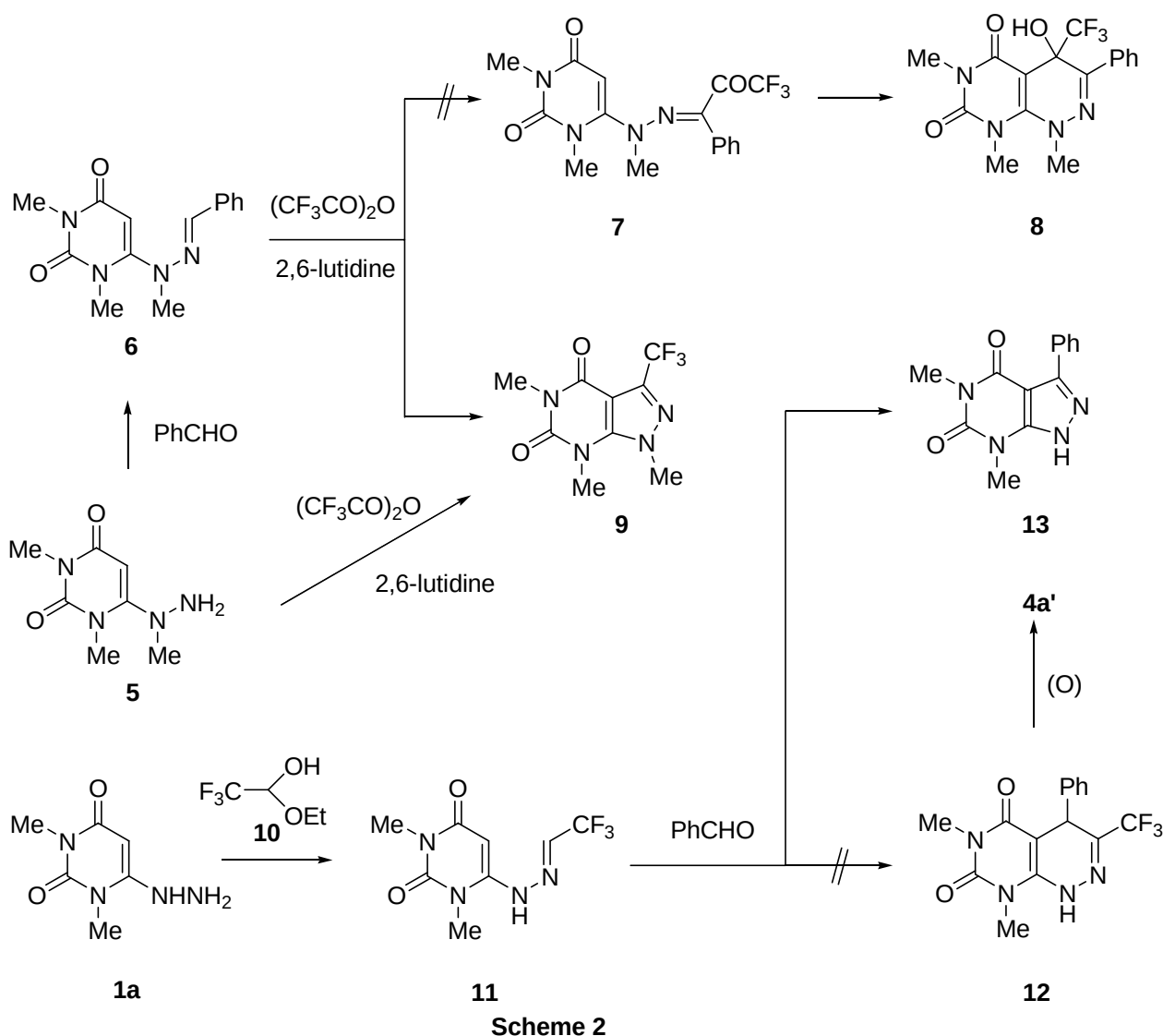
Abstract – The reaction of 6-hydrazinouracils (**1**) with 3-aryl-1,1,1-trifluoropropane-2,3-dione monohydrates (**2**) in refluxing ethanol in the presence of *p*-toluenesulfonic acid gave regioselectively 3-aryl-4-trifluoromethyl-5,6,7,8-tetrahydropyrimido[4,5-*c*]pyridazine-5,7-diones (**4a-e**) in moderate yields. The location of a trifluoromethyl group at the C4 position was elucidated on the basis of the chemical transformation of the derivatives.

Fluorine and/or perfluoroalkyl groups have attracted much attention because they modify the chemical and biological properties of organic compounds, especially heterocyclic compounds. The chemistry of heterocycles containing such fluorine groups has been well reviewed.¹ We have been interested in the chemistry of uracils (pyrimidine-2,4-diones)² and previously reported the preparation of trifluoromethylated pyrido[2,3-*d*]pyrimidine-2,4-diones starting from 6-aminouracils.³ In continuation of this work, we studied the synthesis of trifluoromethylated pyrimido[4,5-*c*]pyridazine-5,7-diones (**4**) starting from 6-hydrazinouracils. Pyrimido[4,5-*c*]pyridazine-5,7-diones have been prepared by the reaction of 6-hydrazinouracils with 1,2-diketones,⁴ α -bromomethylketones,⁵ or acetylene dicarboxylates.⁶ The condensed ring was also prepared on treatment of acetophenone hydrazones of 6-hydrazinouracil with *N*-bromosuccinimide.⁷ In order to introduce a trifluoromethyl group into pyrimido[4,5-*c*]pyridazine-5,7-diones, the reaction of 6-hydrazinouracils (**1**) with 3-aryl-1,1,1-trifluoropropane-2,3-dione monohydrates (**2**)⁸ as the suitable building block for the trifluoromethylation seems to be reasonable. However, it is possible that this reaction will yield two regioisomers, *i. e.*, 4-trifluoromethyl derivatives (**4**) and 3-trifluoromethyl derivatives (**4'**). We report here synthesis of the condensed heterocycles and identification of the regioisomers.



Scheme 1

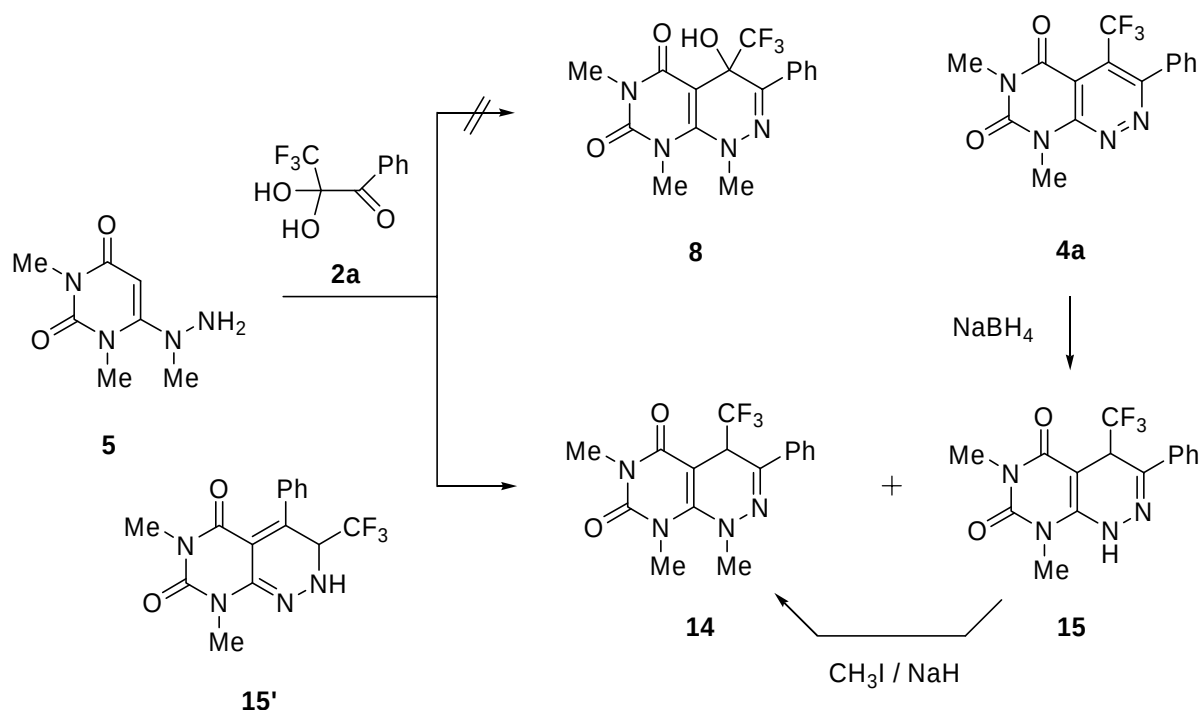
A mixture of 6-hydrazino-1,3-dimethyluracil (**1a**)⁹ and **2** in ethanol was refluxed for 12 h. The product (34% yield) appeared to be 4-trifluoromethyl-4-hydroxy-1,4,5,6,7,8-hexahydropyrimido[4,5-*c*]-pyridazine-5,7-dione (**3a**) or its regioisomer, 3-trifluoromethyl-3-hydroxy-2,3,5,6,7,8-hexahydropyrimido[4,5-*c*]pyridazine-5,7-dione (**3a'**) (Scheme 1). We tentatively assigned this product to be **3a** at this stage. Other derivatives, **3b** (50% yield) and **3c** (19% yield), were similarly obtained. Dehydration of the products (**3a** and **b**) to a fully unsaturated pyridazine ring (**4a** and **b**) was achieved in 74% and 66% yields, respectively, by refluxing of a mixture of **3** and acetic anhydride in toluene for 12 h (*Method A*). However, this method was unsatisfactory for **3c**. A direct route to pyridazine (**4a**) was accomplished in 84% yield by refluxing of a mixture of **1a** and **2** in ethanol in the presence of a catalytic amount of *p*-toluenesulfonic acid for 3 h (*Method B*). The reaction also proceeded in other solvents such as toluene, chloroform, or *N,N*-dimethylformamide under the same reaction conditions to give **4a** in 45%, 12%, or 52% yields, respectively, but isolable regioisomers were not found in the reaction mixture. The products (**4a-e**) were prepared in ethanol in moderate yields (55-84%) by this method. In the ¹³C-NMR spectra, the resonance of the C4 position of **3c** was observed at δ 70.28, while that of **4c** was observed at δ 146.67 in the aromatic region. Although the MS and analytical data supported the molecular formula of **4**, it was difficult to exclude another possible regioisomer (**4'**) formed from **3'** on the basis of the spectral data.



In order to differentiate between the structures (**4** and **4'**), some reactions were carried out. Comparison of the spectra of **3a** with those of its N1-methyl derivative (**8**), which would be the cyclization product of **7**, was expected to provide a solution (Scheme 2). Attempted trifluoroacetylation of benzaldehyde hydrazone (**6**)¹⁰ of 6-(1-methylhydrazino)uracil (**5**)¹¹ to **7** on treatment with trifluoroacetic anhydride in tetrahydrofuran in the presence of 2,6-lutidine at 0 °C was unsuccessful. Instead, 3-trifluoromethylpyrazolo[3,4-*d*]pyrimidine-4,6-dione (**9**) was obtained in 80% yield. This product (**9**) was directly obtained in 82% yield from **5** under the same reaction conditions. Preparation of dihydro derivative (**12**) of **4a'** followed by oxidation to the isomer (**4a'**) was the next approach to establish the structure of **4**. Treatment of **1a** with ethyl trifluoroacetaldehyde hemiacetal (**10**) in refluxing chloroform gave the expected hydrazone (**11**) (69% yield), which was then allowed to react with benzaldehyde, but the product was identified as 3-phenylpyrazolo [3,4-*d*]pyrimidine (**13**)¹⁰ (9% yield).

Finally, the problem of the isomers (**4** or **4'**) was solved as follows (Scheme 3). As mentioned before, **8** seemed to be the key compound, and an alternative route to **8** was a reaction of **5** with **2a**. However, when this reaction was carried out under the same conditions as those used for the preparation of **4a** (or

4a') and the reaction mixture was separated by column chromatography, a deoxygenated product (**14**) (7% yield) and a deoxygenated and demethylated product (**15**) (5% yield) were unexpectedly obtained. The structure of **14** was confirmed on the basis of the C4-H resonance at δ 5.27 (q, $^3J_{\text{FH}}=8.0$ Hz) in the ^1H -NMR spectrum and the C4 resonance at δ 36.04 (q, $^2J_{\text{CF}}=32$ Hz) in the ^{13}C -NMR spectrum, but the structure of **15** remained uncertain because of the possibility of an alternative isomeric structure (**15'**). Methylation of the deoxygenated and demethylated product (**15** or **15'**) by use of iodomethane in the presence of sodium hydride in tetrahydrofuran gave **14** (33% yield), establishing the structure (**15**). The confirmation of the structure of **15** led to the solution of the regioisomer problem of **4** or **4'**. The treatment of the condensed product (**4a** or **4a'**) with sodium borohydride in ethanol gave a reduction product (79% yield), which was identical to **15**, proving that the correct structure is **4a**. These results show that the reactions of **1** with **2** proceeded regioselectively to yield **3** and **4**. In connection with our synthesis of pyrimido[4,5-*c*]pyridazine-5,7-diones, it should be emphasized that 1,6-dimethyl-3-(*N*-(*R*)-phenylethylcarbamoyl)pyrimido[4,5-*c*]pyridazine-5,7(1*H*,6*H*)-dione has photo-induced oxidation ability to some amines¹² and 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione reacts with enamines in the presence of an oxidant to give pyrrole-ring annulation products to a pyridazine nucleus.¹³



Scheme 3

EXPERIMENTAL

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 taken with JEOL JMS DX-300 and JEOL GSX-400 spectrometers, respectively. Microanalyses were performed with

YANACO CHN-Coder MT-5.

4-Trifluoromethyl-4-hydroxy-6,8-dimethyl-3-phenyl-1,4,5,6,7,8-hexahydropyrimido[4,5-c]-pyridazine-5,7-dione (3a)

A mixture of **1** (340 mg, 2.0 mmol) and **2a** (440 mg, 2.0 mmol) in EtOH (7 mL) was refluxed for 12 h. After evaporation of the solvent, the residue was crystallized by slow addition of Et₂O. The product was collected by filtration and recrystallized from CHCl₃-hexane to give **3a** (120 mg, 34%), colorless prisms, mp 184-185°C (EtOH). IR (KBr): 3251, 1718, 1641, 1522, 1252, 1184, 1151 cm⁻¹. ¹H-NMR (DMSO-*d*₆): δ 3.21 (s, 3H, N-CH₃), 3.43 (s, 3H, N-CH₃), 7.41-7.91 (m, 5H, ArH), 8.35 (br s, 1H, OH), 12.08 (br s, 1H, NH). MS: *m/z* (%) 337 (M⁺-OH, 100), 286 (34), 279 (50), 224 (50), 208 (36), 155 (40). *Anal.* Calcd for C₁₅H₁₃N₄O₃F₃: C, 50.85; H, 3.70; N, 15.82. Found: C, 50.84; H, 3.77; N, 15.81.

4-Trifluoromethyl-4-hydroxy-6,8-dimethyl-3-(4-methylphenyl)-1,4,5,6,7,8-hexahydropyrimido[4,5-c]pyridazine-5,7-dione (3b)

This product (**3b**) was prepared from **1** and **2b** in a manner similar to that for **3a**. Colorless prisms, 50% yield, mp 203-204°C (EtOH). IR (KBr): 3413, 3329, 1693, 1641, 1523, 1252, 1184, 1151 cm⁻¹. ¹H-NMR (CDCl₃): δ 2.38 (s, 3H, C-CH₃), 3.33 (s, 3H, N-CH₃), 3.36 (s, 3H, N-CH₃), 7.21 (d, *J*=8.0 Hz, 2H, ArH), 7.80 (d, *J*=8.0 Hz, 2H, ArH), 7.92 (s, 1H, OH), 8.81 (br s, 1H, NH). MS: *m/z* (%) 350 (M⁺-H₂O, 68), 299 (100), 293 (54), 279 (35), 238 (20), 222 (22). *Anal.* Calcd for C₁₆H₁₅N₄O₃F₃: C, 52.17; H, 4.10; N, 15.22. Found: C, 52.10; H, 4.14; N, 15.23.

3-(4-Chlorophenyl)-4-trifluoromethyl-4-hydroxy-6,8-dimethyl-1,4,5,6,7,8-hexahydropyrimido[4,5-c]pyridazine-5,7-dione (3c)

This product (**3c**) was prepared from **1** and **2c** in a manner similar to that for **3a**. Colorless prisms, 19% yield, mp 193-194°C (EtOH). IR (KBr): 3261, 1716, 1641, 1522, 1252, 1186, 1153 cm⁻¹. ¹H-NMR (CDCl₃): δ 3.38 (s, 3H, N-CH₃), 3.53 (s, 3H, N-CH₃), 7.37 (d, *J*=7.0 Hz, 2H, ArH), 7.92 (d, *J*=7.0 Hz, 2H, ArH), 7.38 (s, 1H, OH), 8.56 (s, 1H, NH). ¹³C-NMR (DMSO-*d*₆): δ 27.58, 30.05, 70.28 (q, ²*J*_{CF}=33 Hz, C4), 75.20, 125.20 (q, ¹*J*_{CF}=292 Hz, CF₃), 128.02, 130.75, 132.45, 134.32, 140.63, 144.49, 149.57, 163.50. MS: *m/z* (%) 370 (M⁺-H₂O, 65), 319 (100), 313 (40), 258 (28), 223 (33), 138 (62). *Anal.* Calcd for C₁₅H₁₂N₄O₃ClF₃: C, 46.34; H, 3.11; N, 14.42. Found: C, 46.11; H, 3.16; N, 14.13.

4-Trifluoromethyl-6,8-dimethyl-3-phenyl-5,6,7,8-tetrahydropyrimido[4,5-c]pyridazine-5,7-dione (4a)

Method A. A mixture of **3a** (354 mg, 1.0 mmol) and Ac₂O (0.19 mL, 2.0 mmol) in toluene (5 mL) was refluxed for 10 h. After evaporation of the solvent, MeOH was added to the oily residue to yield a crystalline product, which was collected by filtration followed by recrystallization from CHCl₃-hexane to give **4a** (250 mg, 74%) as yellow needles, mp 156-157 °C.

Method B. A mixture of **1a** (340 mg, 2.0 mmol) and **2a** (440 mg, 2.0 mmol) in EtOH (7 mL) in the presence of *p*-TsOH (38 mg, 0.2 mmol) was refluxed for 3 h. After evaporation of the solvent, the residue was recrystallized from EtOH to give **4a** (564 mg, 84%). IR (KBr): 1726, 1684, 1460, 1442, 1200 cm⁻¹. ¹H-NMR (CDCl₃): δ 3.54 (s, 3H, N-CH₃), 3.93 (s, 3H, N-CH₃), 7.50-7.63 (m, 5H, ArH). ¹³C-NMR (DMSO-*d*₆): δ 28.86, 30.43, 112.11, 121.84 (q, ¹J_{CF}=276 Hz, CF₃), 123.60 (q, ²J_{CF}=35 Hz, C4), 128.31, 128.78, 129.29, 137.26, 149.79, 151.21, 154.26, 157.84. MS: *m/z* 336 (M⁺, 100), 279 (52), 250 (25), 224 (58), 155 (46), 139 (28), 104 (50). *Anal.* Calcd for C₁₆H₁₁N₄O₂F₃: C, 53.57; H, 3.30; N, 16.67. Found: C, 53.64; H, 3.38; N, 16.80.

4-Trifluoromethyl-6,8-dimethyl-3-(4-tolyl)-5,6,7,8-tetrahydropyrimido[4,5-*c*]pyridazine-5,7-dione (4b)

This compound (**4b**) was obtained from **1a** and **2b** in 66% yield by *Method A* and in 79% yield by *Method B* as yellow powders, mp 123-124 °C (CHCl₃-hexane). IR (KBr): 1728, 1680, 1728, 1441, 1220, 1159, 1120 cm⁻¹. ¹H-NMR (CDCl₃): δ 2.46 (s, 3H, C4'-CH₃), 3.53 (s, 3H, N-CH₃), 3.98 (s, 3H, N-CH₃), 7.34 (d, *J*=8.4 Hz, 2H, ArH), 7.52 (d, *J*=8.4 Hz, 2H, ArH). MS: *m/z* (%) 350 (M⁺, 100), 293 (79), 279 (53), 238 (29), 222 (32), 169 (30), 119 (36). *Anal.* Calcd for C₁₆H₁₃N₄O₂F₃: C, 54.86; H, 3.74; N, 16.00. Found: C, 54.80; H, 3.82; N, 16.08.

3-(4-Chlorophenyl)-4-trifluoromethyl-6,8-dimethyl-5,6,7,8-tetrahydropyrimido[4,5-*c*]pyridazine-5,7-dione (4c)

This compound (**4c**) was obtained from **1a** and **2c** by *Method B* in 83% as colorless needles, mp 169-170 °C (EtOH). IR (KBr): 1726, 1684, 1570, 1537, 1360, 1282 cm⁻¹. ¹H-NMR (CDCl₃): δ 3.36 (s, 3H, N-CH₃), 3.99 (s, 3H, N-CH₃), 7.13 (d, *J*=8.4 Hz, 2H, ArH), 7.49 (d, *J*=8.4 Hz, 2H, ArH). ¹³C-NMR (CDCl₃): δ 29.03, 30.84, 110.93, 121.24 (q, ¹J_{CF}=274 Hz, CF₃), 128.33, 128.63, 129.35, 135.42, 140.38, 146.67 (q, ²J_{CF}=32 Hz, C4), 149.78, 152.94, 158.42. MS: *m/z* (%) 370 (M⁺, 94), 278 (86), 257 (42), 192 (30), 189 (67), 138 (26), 81 (100). *Anal.* Calcd for C₁₅H₁₀N₄O₂ClF₃: C, 48.59; H, 2.72; N, 15.12. Found: C, 48.48; H, 2.86; N, 15.11.

4-Trifluoromethyl-6,8-dimethyl-3-(4-nitrophenyl)-5,6,7,8-tetrahydropyrimido[4,5-*c*]pyridazine-5,7-dione (4d)

This compound (**4d**) was obtained from **1a** and **2d** by *Method B* in 55% as thin yellow plates, mp 288-290 °C (MeOH-CHCl₃). IR (KBr): 1728, 1683, 1576, 1525, 1362, 1281, 1188, 1149 cm⁻¹. ¹H-NMR (DMSO-*d*₆): δ 3.16 (s, 3H, N-CH₃), 3.82 (s, 3H, N-CH₃), 7.58 (d, *J*=8.8 Hz, 2H, ArH), 8.35 (d, *J*=8.8 Hz, 2H, ArH). MS: *m/z* (%) 381 (M⁺, 88), 296 (35), 268 (24), 200 (100). *Anal.* Calcd for C₁₅H₁₀N₅O₄F₃: C, 47.25; H, 2.64; N, 18.37. Found: C, 47.11; H, 2.75; N, 18.57

4-Trifluoromethyl-6,8-diisopropyl-3-phenyl-5,6,7,8-tetrahydropyrimido[4,5-*c*]pyridazine-5,7-dione (4e)

This compound (**4e**) was obtained from **1b** and **2e** by *Method B* in 76% as thin yellow powders, mp 160-162 °C (MeOH-H₂O). IR (KBr): 1724, 1682, 1564, 1531, 1446, 1342, 1298, 1142 cm⁻¹. ¹H-NMR (CDCl₃): δ 1.40 (d, *J*=7.2 Hz, 6H, CH₃), 1.71 (d, *J*=6.8 Hz, 6H, CH₃), 5.02-5.09 (m, 1H, CH), 5.93-6.00 (m, 1H, CH), 7.18-7.54 (m, 5H, ArH). MS: *m/z* (%) 392 (M⁺, 58), 350 (44), 307 (100), 278 (58), 208 (53), 158 (53), 58 (95). *Anal.* Calcd for C₁₉H₁₉N₄O₂F₃: C, 58.16; H, 4.88; N, 14.28. Found: C, 58.19; H, 4.93; N, 14.39

3-Trifluoromethyl-1,5,7-trimethyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-*d*]pyrimidine-4,6-dione (9)

A mixture of **6**¹⁰ (270 mg, 1.0 mmol) and 2,6-lutidine (0.12 mL, 1.0 mmol) in dry THF (10 mL) was cooled to 0°C under a nitrogen atmosphere, and then trifluoroacetic anhydride (0.28 mL, 2.0 mmol) was added and the mixture was stirred at rt for 2 h. The mixture was diluted with water (100 mL) and extracted with CHCl₃. The organic layer was separated, dried over MgSO₄, and evaporated to give a solid, which was washed with CHCl₃ and separated by filtration to give **9** (211 mg, 80%), mp 219-220 °C (CHCl₃), colorless prisms. IR (KBr): 1711, 1676, 1593, 1564, 1304, 1190, 1144 cm⁻¹. ¹H-NMR (CDCl₃): δ 3.40 (s, 3H, N-Me), 3.80 (s, 3H, N-Me), 4.21 (s, 3H, N-Me). *Anal.* Calcd for C₉H₉N₄O₂F₃: C, 41.23; H, 3.46; N, 21.37. Found: C, 41.02; H, 3.62; N, 21.36.

The product (**9**) was also directly obtained in 82% yield from **5**¹¹ under the same conditions as those described above.

6-(2,2,2-Trifluoroethylidenehydrazino)-1,3-dimethyluracil (11)

A mixture of **1a** (340 mg, 2.0 mmol) and **10** (320 mg, 2.2 mmol) in CHCl₃ (7 mL) was refluxed for 6 h. After cooling, the precipitated crystals were separated by filtration and recrystallized from CHCl₃ to give **11** (347 mg, 69%), yellow needles, mp 178-179 °C (EtOH). IR (KBr): 3203, 3076, 1701, 1631, 1570, 1477, 1221, 1186, 1130, 1099 cm⁻¹. ¹H-NMR (DMSO-*d*₆): δ 3.14 (s, 3H, N-Me), 3.40 (s, 3H, N-Me), 5.31 (s, 1H, C5-H), 8.10 (br s, 1H, CF₃-CH=), 11.59 (br s, 1H, NH). MS: *m/z* (%) 250 (M⁺, 16), 193 (5), 181 (18), 124 (10), 110 (11), 55 (100). *Anal.* Calcd for C₈H₉N₄O₂F₃: C, 38.41; H, 3.63; N, 22.39.

Found: C, 38.41; H, 3.70; N, 22.52.

5,7-Dimethyl-3-phenyl-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine-4,6-dione (13)

A mixture of **11** (250 mg, 1.0 mmol), benzaldehyde (220 mg, 2.0 mmol), and *p*-TsOH · H₂O (19 mg, 0.1 mmol) in EtOH (3 mL) was refluxed for 6 h. The oily residue obtained after removal of the solvent was purified by column chromatography using silica gel with a solvent of AcOEt to give **13** (24 mg, 9%), yellow needles, mp 259-260 °C (CHCl₃-hexane, lit.,¹⁰ mp 242 °C).

4-Trifluoromethyl-1,6,8-trimethyl-3-phenyl-1,4,5,6,7,8-hexahydropyrimido[4,5-*c*]pyridazine-5,7-dione (14) and 4-Trifluoromethyl-6,8-dimethyl-3-phenyl-1,4,5,6,7,8-hexahydropyrimido[4,5-*c*]pyridazine-5,7-dione (15)

A mixture of **5** (184 mg, 1.0 mmol), **2a** (220 mg, 1.0 mmol), and *p*-TsOH · H₂O (190 mg, 1.0 mmol) in toluene (7 mL) was refluxed for 6 h. After evaporation of the solvent, the oily residue was separated by column chromatography using silica gel with a solvent of CHCl₃-AcOEt. The solid obtained from the first fraction was washed with Et₂O and recrystallized from EtOH to give **14** (26 mg, 7%), colorless plates, 175-176 °C. IR (KBr): 1707, 1649, 1622, 1504, 1471, 1236, 1113 cm⁻¹. ¹H-NMR (CDCl₃): δ 3.39 (s, 3H, N-Me), 3.54 (s, 3H, N-Me), 3.60 (s, 3H, N-Me), 5.27 (q, ³J_{HF}=8.0 Hz, 1H, C4-H), 7.42-7.94 (m, 5H, ArH). ¹³C-NMR (CDCl₃): δ 28.59, 35.32, 36.04 (q, ²J_{CF}=32 Hz, C4), 41.82, 82.37, 123.93 (q, ¹J_{CF}=284 Hz, CF₃), 126.81, 128.63, 130.65, 133.18, 145.23, 147.47, 152.33, 161.18. Anal. Calcd for C₁₆H₁₅N₄O₂F₃: C, 54.55; H, 4.29; N, 15.90. Found: C, 54.52; H, 4.37; N, 15.94.

The solid obtained from the second fraction was washed with Et₂O to give **15** (18 mg, 5%), white powder, mp 239-240 °C. IR (KBr): 3290, 1701, 1649, 1516, 1350, 1244, 1119 cm⁻¹. ¹H-NMR (CDCl₃): δ 3.42 (s, 3H, N-Me), 3.58 (s, 3H, N-Me), 5.27 (q, ³J_{HF}=8.8 Hz, 1H, C4-H), 7.32-7.86 (m, 5H, ArH), 9.10 (s, 1H, NH). ¹³C-NMR (DMSO-*d*₆): δ 27.31, 28.32, 34.25 (q, ²J_{CF}=29 Hz, C4), 69.34, 124.92, 126.94 (q, ¹J_{CF}=255 Hz, CF₃), 127.91, 128.21, 134.65, 137.38, 148.87, 151.55, 161.06. MS: *m/z* (%) 338 (M⁺, 5), 269 (100), 212 (12), 156 (11), 140 (17), 77 (19). Anal. Calcd for C₁₅H₁₃N₄O₂F₃: C, 53.26; H, 3.87; N, 16.56. Found: C, 53.25; H, 3.99; N, 16.56.

Methylation of 15 to 14

A mixture of **15** (100 mg, 0.30 mmol) and NaH in oil (50%) (14 mg, 0.33 mmol) was stirred for 30 min at 0 °C under a nitrogen atmosphere. Iodomethane (0.02 mL, 0.33 mmol) was then added to the cooled mixture, which was stirred for 4 h at rt. After evaporation of the solvent, the oily residue was triturated with AcOEt to give a solid, which was washed with water and recrystallized from EtOH to afford **14** (35 mg, 33%).

Reduction of **4a** to **15**

A mixture of **4a** (336 mg, 1.0 mmol) and NaBH₄ (38 mg, 1.0 mmol) in EtOH (3 mL) was stirred for 1.5 h at rt. After evaporation of the solvent, the residue was triturated with CHCl₃ to give a solid, which was separated by filtration and washed with Et₂O to afford **15** (134 mg, 79%).

REFERENCES

1. A. W. Erian, *J. Heterocycl. Chem.*, 2001, **38**, 793; T. Katagiri and K. Uneyama, *J. Fluorine Chem.*, 2000, **105**, 285; K. Uneyama, *J. Fluorine Chem.*, 1999, **97**, 11; J. Elguero, A. Fruchier, N. Jagerovic, and A. Werner, *Org. Prep. Peoced. Int.*, 1995, **27**, 35; K. C. Joshi, R. Jain, and A. Dandia, *J. Fluorine Chem.*, 1992, **56**, 1; K. Burger, U. Wucherpfennig, and E. Brunner, 'Advances in Heterocyclic Chemistry: Fluoro Heterocycles with Five-Membered Rings,' Vol. 60, ed. by A. R. Katritzky, Academic Press, Inc., San Diego, 1994, pp. 2-64.
2. M. Takahashi, Y. Kadowaki, Y. Uno, and Y. Nakano, *Heterocycles*, 1999, **51**, 2035; N. Matsumoto and M. Takahashi, *Tetrahedron*, 2002, **58**, 10073; N. Matsumoto and M. Takahashi, *Heterocycles*, 2003, **60**, 2677; N. Matsumoto and M. Takahashi, *Tetrahedron Lett.*, 2005, **46**, 5551.
3. M. Takahashi, H. Nagaoka, and K. Inoue, *J. Heterocycl. Chem.*, 2004, **41**, 525.
4. W. Pfeleiderer and H. Ferch, *Liebigs Ann. Chem.*, 1958, **615**, 48; B. K. Billings, J. A. Wagner, P. D. Cook, and R. N. Castle, *J. Heterocycl. Chem.*, 1975, **12**, 1221.
5. F. Yoneda, M. Higuchi, M. Kawamura, and Y. Nitta, *Heterocycles*, 1978, **9**, 1571; K. Senga, J. Sato, Y. Kanamori, M. Ichiba, S. Nishigaki, M. Noguchi, and F. Yoneda, *J. Heterocycl. Chem.*, 1978, **15**, 781; S. Naya, K. Shibayama, and M. Nitta, *Heterocycles*, 2004, **63**, 1393.
6. P. J. Bhuyan, K. C. Lekhok, and J. S. Sandhu, *Tetrahedron Lett.*, 1999, **40**, 1793.
7. H. Kanazawa, S. Nishigaki, and K. Senga, *J. Heterocycl. Chem.*, 1984, **21**, 969.
8. Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, S. Ohara, and T. Yokoyama, *J. Org. Chem.*, 1988, **53**, 129.
9. W. Pfeleiderer and K-H.Schündehütte, *Liebigs Ann. Chem.*, 1958, **612**, 158.
10. F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1481.
11. F. Yoneda and T. Nagamatsu, *Heterocycles*, 1974, **2**, 153.
12. S. Naya, K. Shibayama, and M. Nitta, *Heterocycles*, 2004, **63**, 1393.
13. A. V. Gulevskaya, D. V. Besedin, A. F. Pozharskii, and Z. A. Starikova, *Tetrahedron Lett.*, 2001, **42**, 5981; A. V. Gulevskaya, O. V. Serduke, A. F. Pozharskii, and D. V. Besedin, *Tetrahedron*, 2003, **59**, 7669; O. V. Serduke, A. V. Gulevskaya, A. F. Pozharskii, Z. A. Starikova, and I. A. Profatilova, *Tetrahedron*, 2006, **62**, 652.