Synthesis of Trifluoromethylated Pyrido[2,3-*d*]pyrimidine-2,4-diones from 6-Aminouracils and Trifluoromethylated Pyrazolo[3,4-*b*]-pyridines from 5-Aminopyrazoles

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5 or 7-Trifluoromethyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-2,4-diones **3**, **5**, **10**, **13** and 4- or 6-trifluoromethylpyrazolo[3,4-*b*]pyridines **15**, **16**, **19**, **21** were prepared from 6-aminouracils and 5-aminopyrazoles, respectively, in good yields by the use of building blocks such as 4,4,4-trifluoro-1-phenyl-1,3-butanedione, 1,1,1-trifluoro-4-phenyl-3-buten-2-one, 4-ethoxy-1,1,1-trifluoro-3-buten-2-one, and ethyl trifluoroacetoacetate.

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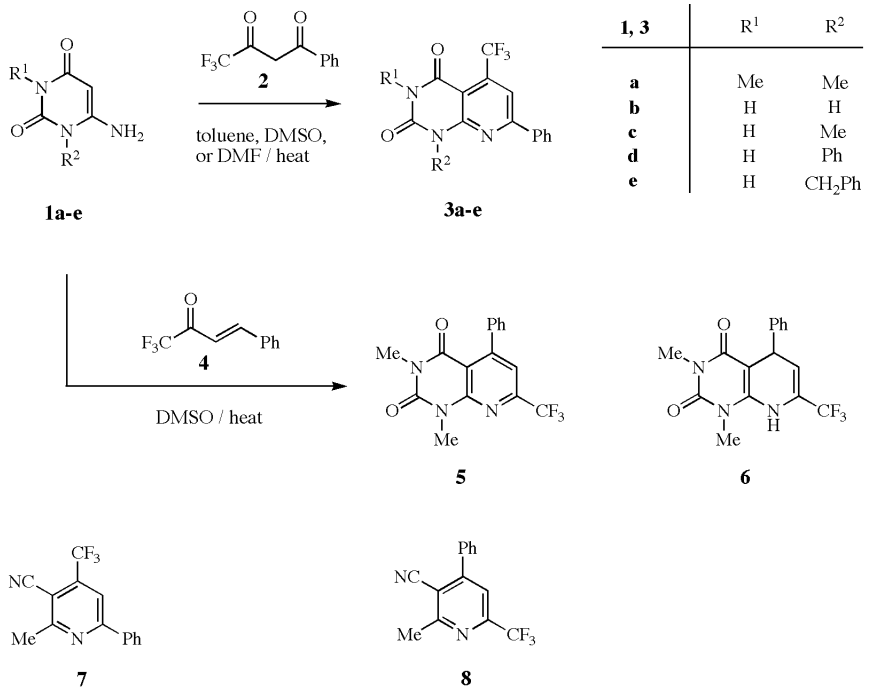
1,2,3,4-Tetrahydropyrido[2,3-*d*]pyrimidine-2,4-diones, uracil derivatives condensed with a pyridine ring [1], have been a class of target compounds in uracil chemistry because of their biological and pharmaceutical activities [2] and because of relationship to 5-deaza derivatives of pteridines and lumazines [3]. Most of these compounds were prepared starting from readily available 6-aminouracils, which are well known as heterocyclic enamines, by condensation with bifunctional compounds. Nucleophilic attack of the C-5 position of uracils at the bifunctional building block followed by cyclocondensation at the unsubstituted C-6 amino group results in the formation of a pyridine ring. As bifunctional groups, simple α,β-unsaturated carbonyls and nitriles [4], β-functionalized-α,β-unsaturated ketones [5], acetylenic ketones and esters [6], 1,3-dicarbonyl compounds [7], and combinations of formaldehyde and active methylenes [8] have been reported. During our studies on the synthesis of uracil derivatives [9], we have become interested in the introduction of trifluoromethyl groups into these heterocycles, since heterocycles bearing trifluoromethyl groups sometimes show modified chemical reactivity and biological activity [10]. It appears essential in the preparation of these heterocycles to use suitable building blocks bearing trifluoromethyl groups. A convenient and regioselective synthesis of trifluoromethylpyridines by the reaction of trifluoromethylated 1,3-diketones with β-aminocrotononitrile or ethyl β-aminocrotonate has recently been reported [11]. At first, we applied this method to 6-aminouracils [12].

Scheme 1



1, 3	R^1	R^2
a	Me	Me
b	H	H
c	H	Me
d	H	Ph
e	H	CH_2Ph

A mixture of 6-aminouracils **1a**-**e** and 4,4,4-trifluoro-1-phenyl-1,3-butanedione **2** in toluene, dimethyl sulfoxide, or *N,N*-dimethylformamide was heated for 7-10 hours to give 5-trifluoromethyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-2,4-diones **3a**-**e** in one step in 67-91% yields (Scheme 1). In the case of **1a**, addition of acetic acid was effective, but no additives were necessary in other cases. The results are summarized in Table 1. The reaction proceeded regiospecifically to afford the 5-trifluoromethyl derivatives. In order to obtain regioisomeric 7-trifluoromethyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-2,4-diones **5**, the Michael addition reaction of **1a** with 1,1,1-trifluoro-4-phenyl-3-buten-2-one **4** was carried out in dimethyl sulfoxide at 60-70 °C for 3 hours, giving **5** (32% yield) and its dihydro derivative **6** (20% yield) after separation by column chromatography. The dihydro derivative **6** seems to be the intermediate to **5**, and, in fact, **6** was converted to **5** when heated in dimethyl sulfoxide without any oxidizing agent. The regiochemistry of **3a** and **5** was deduced on the basis of the ^{13}C nmr spectra. The resonance of the carbon bearing a trifluoromethyl group of **3a** was observed at δ 140.03 (q, $^2J_{CF}$=35 Hz), while that of **5** appeared at δ 149.54 (q, $^2J_{CF}$=35 Hz). This tendency of a chemical shift of the carbon bearing a trifluoromethyl group in the two regioisomers **3a** and **5** is in accordance with the results obtained for the isomers of 3-cyano-4-trifluoromethyl-2-methyl-6-phenylpyridine **7** (δ 141.3, q, $^2J_{CF}$=33.9 Hz) and 3-cyano-6-trifluoromethyl-2-methyl-4-phenylpyridine **8** (δ 149.7, q, $^2J_{CF}$=35.6 Hz) [11a]. Thus, the regiochemistry was determined and higher reactivity of a trifluoromethyl ketone than phenyl ketone of **2** towards enamine **1** was shown. Trifluoromethylated pyrido[2,3-*d*]pyrimidine-2,4,7-trione **10** was also obtained from the reaction of **1a** with ethyl trifluoroacetoacetate **9** in 66% yield (Scheme 2).

Table 1

Preparation of Compound **3**

Compound No.	Reaction Conditions: Solvent	Additive	Temp. (°C)	Hours	Yield %
3a	toluene	acetic acid	reflux	7	67
3b	dimethyl sulfoxide	none	100	10	87
3c	*N,N*-dimethylformamide	none	90	10	84
3d	dimethyl sulfoxide	none	90	7	79
3e	*N,N*-dimethylformamide	none	90	10	91

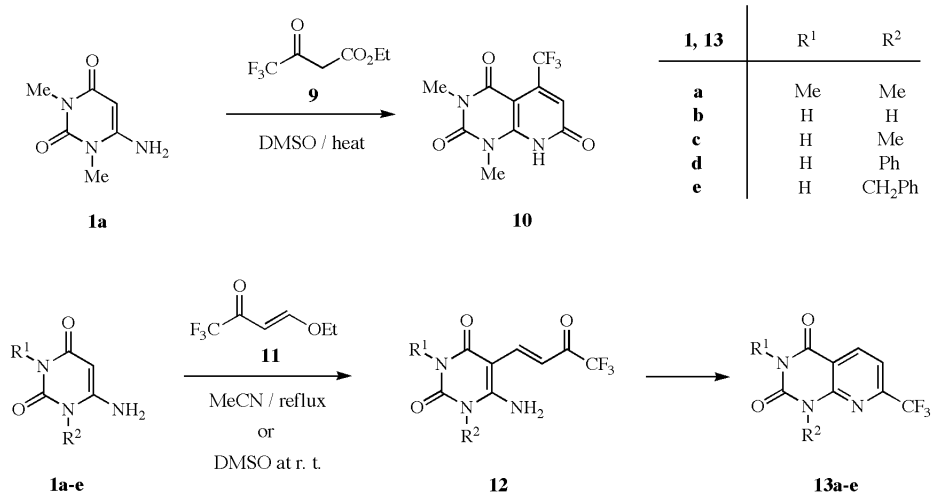
Table 2

Preparation of Compound **13**

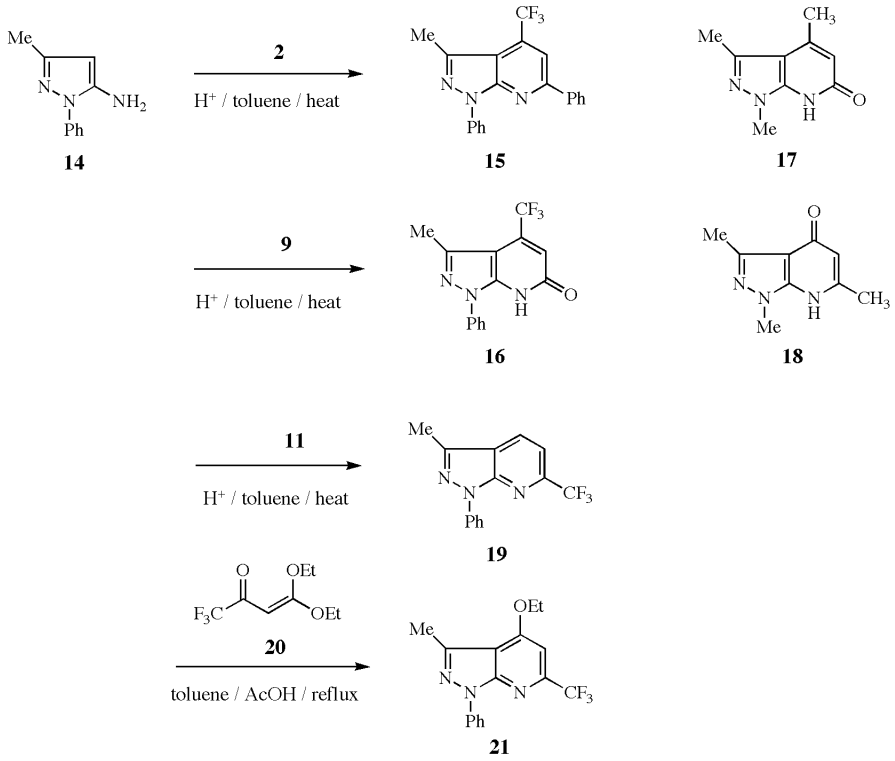
Compound No.	Reaction Conditions: Solvent	Temp.(°C)	Hours	Yield %
13a	acetonitrile	reflux	11	81
13b	dimethyl sulfoxide	room temp.	43	91
13c	dimethyl sulfoxide	60	12	87
13d	*N,N*-dimethylformamide	100	8	61
13e	dimethyl sulfoxide	60	15	76

4-Ethoxy-1,1,1-trifluoro-3-buten-2-one **11** [13] is also a useful building block for the synthesis of trifluoromethyl-containing molecules, and many heterocycles have been prepared by cycloaddition [14] or cyclocondensation [15]. Electrophilic attack of **11** at indole in the presence of $ZnCl_2$ occurred at the C-3 position of indole to give 1,1,1-trifluoro-4-(1*H*-indol-3-yl)-3-buten-2-one [16]. Similarly, the reaction of **11** with enaminonitriles has been reported to give trifluoroacetyldienamines, which were converted into 6-trifluoromethyl-3-pyridinecarbonitrile on heating [17]. The reaction of **1a**-**e** with **11** proceeded very smoothly at room temperature or at a higher temperature to afford 1,3-disubstituted 7-trifluoromethyl-1,2,3,4-tetrahydro-

Scheme 2



Scheme 3



pyrido[2,3-*d*]pyrimidine-2,4-diones **13a**-**e** in 61-91% yields. The results are summarized in Table 2. Since the chemical shift (δ 151.41, q, $^2J_{CF}$=36 Hz) of the carbon bearing a trifluoromethyl group in the nmr spectrum of **13a** is close to those of **5** (δ 149.54) and **8** (δ 149.7), the position of a trifluoromethyl group was assigned to the C-7 position. This was demonstrated as follows by isolation of the intermediate in the reaction. The intermediary 6-amino-5-(4,4,4-trifluoro-3-oxo-1-buten-1-yl)uracil **12a** (R^1=R^2=Me) was isolated in 28% yield as an unstable solid when the reaction was carried out in an ice-bath for 3 days. The structure of **12a** was established on the basis of the ^{1}H nmr spectrum. The intermediate **12a** was converted into **13a** by subsequent heating, excluding the possibility of formation of a regioisomeric 5-trifluoromethyl derivative as a product.

5-Amino-3-methyl-1-phenylpyrazole **14** has an enamine structure and is expected to behave in a manner similar to **1** (Scheme 3). In fact, diazotization and nitrosation of 1-substituted 5-aminopyrazoles has been reported to occur at the 4-position [18,19]. Thus, the reaction of **1** with trifluoromethyl-building blocks **2**, **9**, and **11** yielded the corresponding trifluoromethyl-substituted pyrazolo[3,4-*b*]-pyridines, **15** (53%), **16** (64%), and **19** (10%), respectively. Similarly to **3a**, **5** and **13a**, the position of a trifluoromethyl group was assigned by comparison of the chemical shift of a quartet carbon of **15** (δ 132.06) with that of **19** (δ 138.87). The problem of formation of regioisomeric products in the reaction with **9** was resolved by comparison of the chemical shift of the carbonyl carbon in the ^{13}C nmr spectra. The chemical shift of the carbonyl carbon of **16** (δ 162.49) is more in accordance with the model compound **17** (δ 163.2) than the isomeric **18** (δ 178.5) [20]. The results show that enamine **14** selectively attacks at the ketone rather than the ester group of **9**, and also support the structure of the product **10** from **1a** and **9**. Further cyclization of **1** or **14** by use of 4,4-diethoxy-1,1,1-trifluoro-3-buten-2-one **20** [21] which behaves similarly to **11** was attempted. However, only 4-ethoxy-6-trifluoromethylpyrazolo[3,4-*b*]pyridine **21** was obtained in 36% yield from **14**.

EXPERIMENTAL

Melting points were determined with MRK MEL-TEMP II and are uncorrected. Ir spectra were recorded using a JASCO FT/IR-420 spectrophotometer. Ms spectra were recorded using a JEOL JMS DX-300 spectrometer, and ^{1}H and ^{13}C nmr spectra were recorded using a JEOL GSX-400 spectrometer. Microanalyses were performed using a YANACO CHN-CODER MT-5. The compounds **1a**-**b**, **2**, **4**, and **9** are commercially available, and **1c**-**e** [22], **11** [13], and **20** [21] were prepared according to the methods described in the literature.

5-Trifluoromethyl-1,3-dimethyl-7-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-2,4-dione (**3a**).

A mixture of **1a** (155 mg, 1.0 mmole) and **2** (238 mg, 1.1 mmoles) in toluene (3 ml) in the presence of acetic acid (0.3 ml)

was refluxed for 7 hours. After removal of the solvent the residue was recrystallized from chloroform-hexane to give **3a** (225 mg, 67%), white needles, mp 264-265 °C; ir (potassium bromide): 1724, 1676, 1570, 1369, 1167 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.51 (s, 3H), 3.87 (s, 3H), 7.55-7.57 (m, 3H), 7.97 (s, 1H), 8.13-8.16 (m, 2H); ^{13}C nmr (deuteriochloroform): δ 28.86, 30.57, 105.23, 113.11 (q, $^3J_{CF}$=6 Hz), 122.01 (q, $^1J_{CF}$=273 Hz, CF_3), 127.52, 129.12, 131.58, 136.13, 140.03 (q, $^2J_{CF}$=35 Hz, C-5), 150.81, 152.33, 158.10, 161.34; ms: m/z 335 (M^+, 100), 307 (18), 266 (21), 223 (83), 154 (24).

Anal. Calcd. for $C_{16}H_{12}F_3N_3O_2$: C, 57.32; H, 3.61; N, 12.53. Found: C, 57.23; H, 3.70; N, 12.55.

5-Trifluoromethyl-7-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]-pyrimidine-2,4-dione (**3b**).

A mixture of **1b** (127 mg, 1.0 mmole) and **2** (238 mg, 1.1 mmoles) in dimethyl sulfoxide (2 ml) was heated at 100 °C for 10 hours. After cooling, water was added to the reaction mixture, and the precipitates were collected by filtration to give **3b** (267 mg, 87%). Recrystallization from tetrahydrofuran gave white needles, mp 300 °C (sublimation); ir (potassium bromide): 3058, 1738, 1693, 1603, 1404, 1371, 1265, 1174, 1132 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.55-7.61 (m, 3H), 8.03 (s, 1H), 8.22-8.26 (m, 2H), 11.55 (broad s, 1H), 11.99 (broad s, 1H).

Anal. Calcd. for $C_{14}H_8F_3N_3O_2$: C, 54.73; H, 2.62; N, 13.68. Found: C, 54.67; H, 2.74; N, 13.67.

5-Trifluoromethyl-1-methyl-7-phenyl-1,2,3,4-tetrahydropyrido-[2,3-*d*]pyrimidine-2,4-dione (**3c**).

This compound was prepared in a manner similar to **3b**. White needles, mp 325-326 °C (tetrahydrofuran); ir (potassium bromide): 3041, 2844, 1728, 1705, 1597, 1568, 1392, 1373, 1269, 1182, 1128 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.63 (s, 3H), 7.59-7.60 (m, 3H), 8.11 (s, 1H), 8.30-8.32 (m, 2H), 11.81 (s, 1H); ms: m/z 321 (M^+, 88), 292 (16), 252 (12), 223 (100), 154 (32).

Anal. Calcd. for $C_{15}H_{10}F_3N_3O_2$: C, 56.08; H, 3.14; N, 13.08. Found: C, 56.25; H, 3.28; N, 13.10.

5-Trifluoromethyl-1,7-diphenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]-pyrimidine-2,4-dione (**3d**).

This compound was prepared in a manner similar to **3b**. White needles, mp 284-285 °C (methanol); ir (potassium bromide): 3053, 1738, 1693, 1595, 1564, 1375, 1263, 1174 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.38-7.85 (m, 10H), 8.11 (s, 1H), 11.94 (s, 1H); ms: m/z 383 (M^+, 87), 382 (89), 339 (20), 312 (100), 291 (13), 140 (19), 77 (86).

Anal. Calcd. for $C_{20}H_{12}F_3N_3O_2$: C, 62.67; H, 3.16; N, 10.96. Found: C, 62.78; H, 3.30; N, 11.06.

1-Benzyl-5-trifluoromethyl-7-phenyl-1,2,3,4-tetrahydropyrido-[2,3-*d*]pyrimidine-2,4-dione (**3e**).

This compound was prepared in a manner similar to **3b**. White needles, mp 248-249 °C (methanol); ir (potassium bromide): 3180, 3054, 1728, 1693, 1568, 1392, 1369, 1263, 1167 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.67 (s, 2H), 7.23-7.59 (m, 8H), 7.95 (s, 1H), 8.04-8.07 (m, 2H), 8.72 (s, 1H); ms: m/z 397 (M^+, 41), 329 (18), 325 (44), 292 (12), 91 (100).

Anal. Calcd. for $C_{21}H_{14}F_3N_3O_2$: C, 63.48; H, 3.55; N, 10.58. Found: C, 63.63; H, 3.73; N, 10.59.

7-Trifluoromethyl-1,3-dimethyl-5-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-2,4-dione (**5**) and 7-Trifluoromethyl-1,3-dimethyl-5-phenyl-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]-pyrimidine-2,4-dione (**6**).

A mixture of **1a** (155 mg, 1.0 mmole) and **4** (220 mg, 1.1 mmoles) in dimethyl sulfoxide (2 ml) was heated at 60-70 °C for 3 hours with stirring. After addition of water to the mixture it was extracted with chloroform. Drying over $MgSO_4$ followed by removal of the solvent gave a solid residue, which was subjected to column-chromatography on silica gel with chloroform. The first fraction gave **5** (107 mg, 32%), colorless needles, mp 134-135 °C (methanol); ir (potassium bromide): 1720, 1670, 1566, 1261, 1192, 1147 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.39 (s, 3H), 3.80 (s, 3H), 7.27-7.32 (m, 2H), 7.35 (s, 1H), 7.44-7.50 (m, 3H); ^{13}C nmr (deuteriochloroform): δ 28.73, 30.44, 110.02, 118.03, 120.52 (q, $^1J_{CF}$=274 Hz, CF_3), 127.55, 127.98, 128.78, 138.02, 149.54 (q, $^2J_{CF}$=35 Hz, C-7), 150.81, 151.90, 156.95, 159.47; ms: m/z 335 (M^+, 55), 334 (100), 223 (25), 140 (8).

Anal. Calcd. for $C_{16}H_{12}F_3N_3O_2$: C, 57.32; H, 3.61; N, 12.53. Found: C, 57.26; H, 3.64; N, 12.67.

From the second fraction, **6** (67 mg, 20%) was obtained as colorless plates, mp 246-247 °C (methanol); ir (potassium bromide): 3270, 1689, 1630, 1531, 1483, 1186, 1126 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.26 (s, 3H), 3.49 (s, 3H), 4.77-4.79 (m, 1H), 5.69 (d, J=5.2 Hz, 1H), 5.75 (s, 1H), 7.21-7.32 (m, 5H); ms: m/z 337 (M^+, 31), 334 (36), 268 (7), 260 (100), 240 (8), 203 (21).

Anal. Calcd. for $C_{16}H_{14}F_3N_3O_2$: C, 56.97; H, 4.18; N, 12.46. Found: C, 56.91; H, 4.21; N, 12.46.

5-Trifluoromethyl-1,3-dimethyl-1,2,3,4,7,8-hexahydropyrido-[2,3-*d*]pyrimidine-2,4,7-trione (**10**).

A mixture of **1a** (155 mg, 1.0 mmole) and **9** (368 mg, 2.0 mmoles) in dimethyl sulfoxide (2 ml) was heated at 100 °C with stirring for 5 hours. After cooling, the precipitates were collected by filtration, washed with water, and dried to give **10** (182 mg, 66%). Recrystallization from chloroform-hexane gave colorless needles, mp 173-174 °C; ir (potassium bromide): 3072, 1702, 1658, 1604, 1286, 1269, 1244, 1184, 1153 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.50 (s, 3H), 3.71 (s, 3H), 7.01 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 28.05, 30.12, 98.21, 104.73, 120.37 (q, $^1J_{CF}$=274 Hz, CF_3), 150.32, 151.78, 152.25 (q, $^2J_{CF}$=35 Hz, C-5), 165.36, 169.69; ms: m/z 275 (M^+, 46), 247 (38), 246 (39), 163 (100), 115 (21).

Anal. Calcd. for $C_{10}H_8F_3N_3O_3$: C, 43.65; H, 2.93; N, 15.27. Found: C, 43.72; H, 2.95; N, 15.37.

6-Amino-5-(4,4,4-trifluoro-3-oxo-1-buten-1-yl)-1,3-dimethyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (**12**).

To a mixture of **1a** (310 mg, 2.0 mmoles) and *N,N*-dimethylformamide (3 ml) was dropwise added **11** (470 mg, 3.0 mmoles). The mixture was stirred for 3 days in a ice bath, and poured into water (80 ml) to form precipitates, which were collected by filtration and washed with diethyl ether to give a crude product **12** (157 mg, 28%); ir (potassium bromide): 3537, 3352, 1707, 1684, 1639, 1572, 1518, 1452 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.30 (s, 3H), 3.32 (s, 3H), 7.77 (d, J=14.2 Hz, 1H), 8.17 (d, J=14.2 Hz, 1H), 8.25 (broad s, 2H). This compound was unstable and was easily converted into **13a** on heating in methanol.

7-Trifluoromethyl-1,3-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*d*]-pyrimidine-2,4-dione (**13a**).

To a mixture of **1a** (465 mg, 3.0 mmoles) and acetonitrile (5 ml) was added **11** (564 mg, 3.6 mmoles). The mixture was

refluxed under nitrogen for 11 hours. After removal of the solvent, the resultant solid was recrystallized from methanol to give **13a** (629 mg, 81%), colorless needles, mp 117-119 °C: ir (potassium bromide): 1720, 1676, 1608, 1485, 1277, 1138 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.51 (s, 3H,), 3.75 (s, 3H), 7.56 (d J=8.0 Hz, 1H), 8.64 (d, J=8.0 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 28.73, 29.76, 112.86, 114.84, 120.25 (q, $^1J_{CF}$=273 Hz, CF_3), 139.71, 150.80, 150.94, 151.41 (q, $^2J_{CF}$=36 Hz, C-7), 160.20; ms: m/z 259 (M^+, 100), 231 (15), 202 (7), 174 (25), 147 (80).

Anal. Calcd. for $C_{10}H_8F_3N_3O_2$: C, 46.34; H, 3.11; N, 16.21. Found: C, 46.21; H, 3.22; N, 16.17.

7-Trifluoromethyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-2,4-dione (**13b**).

To a mixture of **1b** (381 mg, 3.0 mmoles) and dimethyl sulfoxide (3 ml) was added **11** (564 mg, 3.6 mmoles). The mixture was stirred at room temperature under nitrogen for 43 hours. Water (80 ml) was added to the mixture to precipitate the product, which were collected by filtration and washed with hexane to give **13b** (631 mg, 91%). Recrystallization from methanol gave white needles, mp 207 °C (sublimation); ir (potassium bromide): 3784, 3662, 1741, 1685, 1614, 1282, 1192, 1149 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.67 (d, J=8.0 Hz, 1H), 8.50 (d, J=8.0 Hz, 1H), 11.68 (broad s, 1H), 12.04 (broad s, 1H); ms: m/z 231 (M^+, 100), 212 (7), 188 (47), 161 (46), 160 (42).

Anal. Calcd. for $C_8H_4F_3N_3O_2$: C, 41.57; H, 1.74; N, 18.18. Found: C, 41.42; H, 1.84; N, 18.41.

7-Trifluoromethyl-1-methyl-1,2,3,4-tetrahydropyrido[2,3-*d*]-pyrimidine-2,4-dione (**13c**).

This compound was prepared in a manner similar to **13b**. White needles, mp 201 °C (sublimation) (methanol); ir (potassium bromide): 3180, 3066, 1713, 1689, 1606, 1469, 1415, 1350, 1275, 1182, 1159 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.74 (s, 3H), 7.58 (d, J=7.8 Hz, 1H), 8.65 (d, J=7.8 Hz, 1H), 9.46 (broad s, 1H, NH); ms: m/z 245 (M^+, 82), 216 (14), 174 (21), 147 (100), 127 (23).

Anal. Calcd. for $C_9H_6F_3N_3O_2$: C, 44.09; H, 2.47; N, 17.14. Found: C, 44.23; H, 2.55; N, 17.29.

7-Trifluoromethyl-1-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]-pyrimidine-2,4-dione (**13d**).

This compound was prepared in a manner similar to **13b**. Colorless needles, mp 263-264 °C (methanol); ir (potassium bromide): 3184, 3068, 1705, 1608, 1444, 1421, 1344, 1282, 1163 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.27-7.58 (m, 6H), 8.68 (d, J=8.0 Hz, 1H), 8.78 (broad s, 1H); ms: m/z 307 (M^+, 88), 264 (35), 236 (100), 77 (97).

Anal. Calcd. for $C_{14}H_8F_3N_3O_2$: C, 54.73; H, 2.62; N, 13.68. Found: C, 54.69; H, 2.78; N, 13.72.

1-Benzyl-7-trifluoromethyl-1,2,3,4-tetrahydropyrido[2,3-*d*]-pyrimidine-2,4-dione (**13e**).

This compound was prepared in a manner similar to **13b**. Colorless needles, mp 194-195 °C (ethanol); ir (potassium bromide): 3192, 3068, 1712, 1689, 1610, 1466, 1277 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.51 (s, 2H), 7.23-7.62 (m, 5H), 7.55 (d, J=7.8 Hz, 1H), 8.61 (d, J=7.8 Hz, 1H), 9.43 (broad s, 1H, NH); ms: m/z 321 (M^+, 39), 249 (12), 216 (5), 91 (100).

Anal. Calcd. for $C_{15}H_{10}F_3N_3O_2$: C, 56.08; H, 3.14; N, 13.08. Found: C, 56.05; H, 3.22; N, 13.16.

4-Trifluoromethyl-3-methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]-pyridine (**15**).

A mixture of **14** (173 mg, 1.0 mmole), **2** (216 mg, 1.0 mmole), and acetic acid (0.5 ml) in toluene (3 ml) was heated with stirring at 90 °C for 20 hours. The mixture was washed with water, dried over $MgSO_4$, and evaporated to give a solid residue, which was washed with a small amount of methanol and recrystallized from hexane to afford **15** (277 mg, 53%), thin yellowish green prisms, mp 151-152 °C; ir (potassium bromide): 1599, 1574, 1506, 1421, 1367, 1261, 1190, 1169, 1124 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.75 (s, 3H), 7.30-7.56 (m, 7H), 7.89 (s, 1H), 8.13-8.33 (m, 3H); ^{13}C nmr (deuteriochloroform): δ 14.49, 109.99, 110.70 (q, $^3J_{CF}$=5 Hz), 121.29, 122.74 (q, $^1J_{CF}$=273 Hz, CF_3), 125.99, 127.48, 128.93, 128.97, 130.12, 132.06 (q, $^2J_{CF}$=35 Hz, C-4), 137.81, 139.02, 141.08, 151.86, 156.76; ms: m/z 353 (M^+, 100), 338 (14), 312 (11), 177 (6), 77 (22).

Anal. Calcd. for $C_{20}H_{14}F_3N_3$: C, 67.98; H, 3.99; N, 11.89. Found: C, 68.26; H, 4.08; N, 11.92.

4-Trifluoromethyl-3-methyl-1-phenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-one (**16**).

A mixture of **14** (173 mg, 1.0 mmole), **9** (221 mg, 1.2 mmoles), and trifluoroacetic acid (114 mg, 1.0 mmole) in toluene (3 ml) was heated at 100 °C with stirring for 20 hours. The solid obtained after removal of the solvent was washed with hexane and recrystallized from chloroform-hexane to give **16** (188 mg, 64%); colorless needles, mp 177-178 °C; ir (potassium bromide): 3064, 1657, 1610, 1585, 1510, 1267, 1165, 1138 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.55 (s, 3H), 6.75 (s, 1H), 7.22-7.63 (m, 5H), 10.28 (broad s, 1H); ^{13}C nmr (deuteriochloroform): δ 14.03, 103.49, 107.69, 121.92 (q, $^1J_{CF}$=271 Hz, CF_3), 122.43, 127.46, 129.14, 135.82 (q, $^2J_{CF}$=35 Hz, C-4), 136.96, 142.74, 145.25, 162.49; ms: m/z 293 (M^+, 100), 278 (9), 252 (8), 118 (12), 77 (28).

Anal. Calcd. for $C_{14}H_{10}F_3N_3O$: C, 57.34; H, 3.44; N, 14.33. Found: C, 57.53; H, 3.49; N, 14.35.

6-Trifluoromethyl-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (**19**).

A mixture of **14** (173 mg, 1.0 mmole), **11** (202 mg, 1.2 mmoles), and trifluoroacetic acid (114 mg, 1.0 mmole) in toluene (3 ml) was heated at 100 °C with stirring for 3 hours. The mixture was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the solid residue was purified by column chromatography on silica gel with chloroform to give **19** (27 mg, 10%) as colorless needles, mp 103-104 °C; ir (potassium bromide): 1597, 1510, 1421, 1302, 1184, 1140, 1097 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.67 (s, 3H), 7.28-8.33 (m, 7H); ^{13}C nmr (deuteriochloroform): δ 14.48, 112.91, 113.16 (q, $^3J_{CF}$=5 Hz), 120.41, 121.67, 122.55 (q, $^1J_{CF}$=274 Hz, CF_3), 125.81, 126.38, 129.05, 130.88, 138.87 (q, $^2J_{CF}$=37 Hz, C-6), 148.81; ms: m/z 277 (M^+, 100), 252 (14), 236 (16), 131 (18), 77 (39).

Anal. Calcd. for $C_{14}H_{10}F_3N_3$: C, 60.65; H, 3.64; N, 15.16. Found: C, 60.68; H, 3.80; N, 15.14.

4-Ethoxy-6-trifluoromethyl-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (**21**).

A mixture of **14** (173 mg, 1.0 mmole), **20** (316 mg, 1.5 mmoles), and acetic acid (0.5 ml) in toluene (3 ml) was refluxed for 10 hours. The mixture was washed with water, dried over $MgSO_4$, and evap-

orated to give a solid, which was washed with a small amount of methanol and recrystallized from methanol to afford **21** (117 mg, 36%), colorless needles, mp 96-97 °C; ir (potassium bromide): 1612, 1581, 1510, 1429, 1381, 1327, 1257, 1165, 1128 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.46 (t, J=7.2 Hz, 3H), 4.50 (q, J=7.2 Hz, 2H), 6.91 (s, 1H), 7.26-8.20 (m, 5H); ^{13}C nmr (deuteriochloroform): δ 14.32, 14.35, 63.02, 104.60, 106.90, 120.87, 122.35 (q, $^1J_{CF}$=271, CF_3), 125.72, 128.84, 133.74 (q, $^2J_{CF}$=35 Hz, C-6), 139.05, 141.44, 150.19, 163.02 (C=O); ms: m/z 321 (M^+, 100), 306 (43), 293 (48), 118 (17), 77 (91).

Anal. Calcd. for $C_{16}H_{14}F_3N_3O$: C, 59.81; H, 4.39; N, 13.08. Found: C, 60.14; H, 4.40; N, 13.08.

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