Brominated 4-(Trifluoromethyl)pyrimidines: A Convenient Access to Versatile Intermediates

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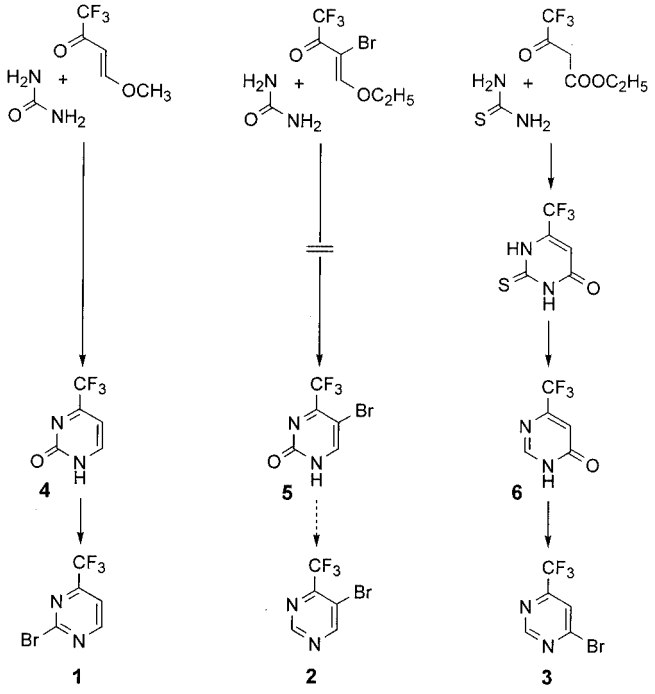
An expedient route to all three monobrominated and all three dibrominated isomers of 4-(trifluoromethyl)pyrimidine, and to several other halogenated pyrimidines, is described. Key steps are the electrophilic introduction of the halogen in the 5-position of 2- or 4-pyrimidinones, the bromodeoxygenation of pyrimidinones or thiopyrimidinones using phosphorus tribromide, and the partial debromination of dibromo-4-(trifluoromethyl)pyrimidines.

Recently, we have devoted much attention to the preparation and subsequent functionalization of chlorinated and brominated (trifluoromethyl)pyrazoles,[1] (trifluoromethyl)pyridines[2−6] and (trifluoromethyl)quinolines.[2,7−9] We now report the extension of this work to the pyrimidine analogs carrying a trifluoromethyl group and an additional halogen as substituents. To our surprise, only one monochlorinated and one dichlorinated derivative of 4-(trifluoromethyl)pyrimidine, 2-chloro-4-(trifluoromethyl)-pyrimidine[10−12] and 2,6-dichloro-4-(trifluoromethyl)pyrimidine,[13,14] and no bromo derivatives, were found in the literature. However, this was not the only motivation for the present study. Fluorine-containing pyrimidine derivatives exhibit attractive biological activities. They are applied in the agrochemical sector as insecticides, herbicides, fungicides and plant growth regulators (e.g., Flufenerim[15], Primsulfuron-methyl[16], Diflumetorim[17] and Fluoroprimidol[18]). 5-Fluorouracil, 5-(trifluoromethyl)uracil and their congeners belong to a family of the most potent anticancer and antiviral drugs.[19,20]

Two of the three possible bromo-4-(trifluoromethyl)pyrimidines, isomers **1** and **3**, could be readily prepared. The preparation of the third one, isomer **2**, was more troublesome.

The condensation of urea with 1,1,1-trifluoro-4-methoxy-3-buten-2-one afforded 4-(trifluoromethyl)pyrimidin-2(1*H*)-one (**4**), a known compound,[21] in 78% yield. This was converted into 2-bromo-4-(trifluoromethyl)pyrimidine (**1**; 81%) by reaction with phosphorus tribromide. The analogous condensation of urea with 3-bromo-4-ethoxy-1,1,1-trifluoro-3-buten-2-one[22] produced tars rather than the expected 5-bromo-4-(trifluoromethyl)-2(1*H*)-pyrimidinone (**5**), which is a potential precursor of 5-bromo-4-(trifluoromethyl)pyrimidine (**2**). Heating thiourea together with ethyl 4,4,4-trifluoroacetoacetate gave 2-thioxo-6-(trifluoromethyl)-2,3-dihydropyrimidin-4(1*H*)-one[14] (81%). The sulfur atom was readily removed by reduction with hydrogen peroxide. The resulting 6-(trifluoromethyl)pyrimidin-4(3*H*)-one[23] (**6**; 84%) provided 4-bromo-6-(trifluoromethyl)pyrimidine (**3**; 62%) upon heating with phosphorus tribromide.



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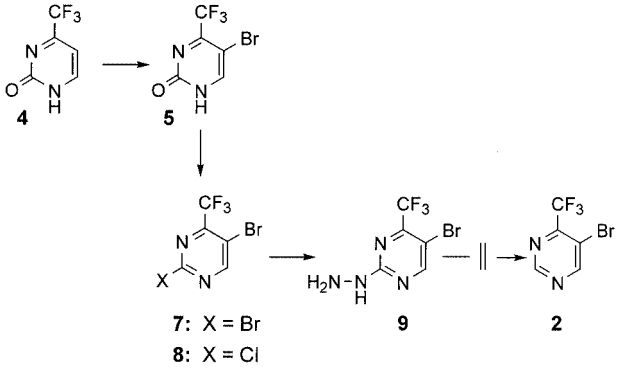
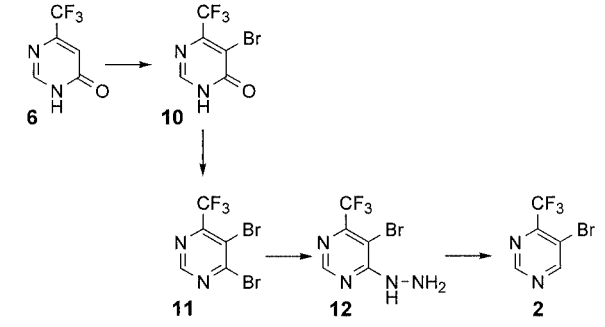
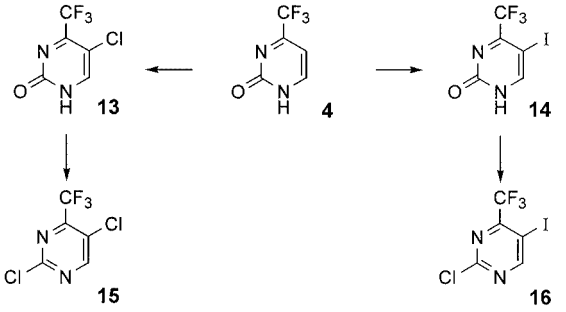
The bromo derivative **5** was nevertheless readily obtained by the treatment of 4-(trifluoromethyl)pyrimidin-2(1*H*)-one (**4**) with bromine. Subsequent reaction with phosphorus tribromide or phosphorus trichloride provided 2,5-dibromo-4-(trifluoromethyl)pyrimidine (**7**; 80%) and 5-bromo-2-chloro-4-(trifluoromethyl)pyrimidine (**8**; 89%), respectively. Both products **7** and **8** reacted with hydrazine to give the 2-hydrazinopyrimidine (**9**; 95%). However, its attempted oxidative dediazotization[24−26] to the bromopyrimidine **2** failed.



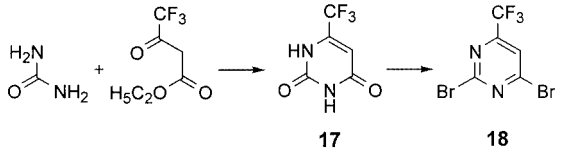
The hydrazine route proved successful when starting with 6-(trifluoromethyl)pyrimidin-4(3*H*)-one (**6**), which underwent smooth bromination at the 5-position to afford the intermediate (**10**; 86%). Compound **10**, when heated in the presence of phosphorus tribromide, exchanged the oxygen atom for a second bromine atom. The resulting 4,5-dibromo-6-(trifluoromethyl)pyrimidine (**11**; 77%) was condensed with hydrazine to furnish the hydrazino compound (**12**; 72%), which was transformed into the desired 5-bromo-4-(trifluoromethyl)pyrimidine (**2**; 77%) by oxidative dediazotization with manganese dioxide.[26]



The electrophilic substitution of 2(1*H*)- and 4(1*H*)-pyrimidinones is not restricted to bromination. 4-(Trifluoromethyl)pyrimidin-2(1*H*)-one (**4**) was converted analogously into its 5-chloro and 5-iodo derivatives (**13** and **14**; 80% and 60%) which, when heated with phosphorus trichloride, gave 2,5-dichloro-4-(trifluoromethyl)pyrimidine (**15**; 81%) and 2-chloro-5-iodo-4-(trifluoromethyl)pyrimidine (**16**; 77%), respectively.



Having already obtained the two dibromo-4-(trifluoromethyl)pyrimidines **8** and **11**, we wanted to prepare the third isomer, 2,6-dibromo-4-(trifluoromethyl)pyrimidine (**18**). This was accomplished by treating 6-(trifluoromethyl)-pyrimidine-2,4(1*H*,3*H*)-dione[27] (**17**), which is readily made from urea and ethyl trifluoroacetoacetate in 79% yield, with phosphorus tribromide.



Halopyrimidines are extremely versatile building blocks for life science oriented synthetic work. They can be subjected to an immense variety of nucleophilic (het)aromatic substitution reactions[28] but also be employed in Suzuki coupling reactions.[29−35] Moreover, they may be used to generate reactive organometallic intermediates by metalation[36,37] or halogen/metal permutations.[38,39] We shall report on these attractive options in due course.

Experimental Section

Details concerning standard operations and abbreviations have been given in previous publications from this laboratory.[40−42] ^{1}H and (^{1}H-decoupled) ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively. If not specified otherwise, samples were dissolved in deuteriochloroform or, if marked by an asterisk, in hexadeuterioacetone. Mass spectra were obtained at an ionization potential of 70 eV with a source temperature of 200 °C. If no molecular peak could be observed under these conditions, chemical ionization (c.i.) in an ammonia atmosphere at 100 °C source temperature was applied. To avoid redundancy, in all cases only the [^{35}Cl] and [^{79}Br] fragments and not the [^{37}Cl] or [^{81}Br] isotopomers are listed.

2-Bromo-4-(trifluoromethyl)pyrimidine (1): 4-(Trifluoromethyl)pyrimidin-2(1*H*)-one[15] (**1**; 16 g, 0.10 mol) and phosphorus tribromide (29 g, 0.10 mol) were heated together at 150 °C for 2 h, after which the mixture was poured on crushed ice (0.2 kg) and extracted with hexane (3 × 0.10 L). The combined organic layers were washed with brine (1 × 50 mL) and dried with anhydrous sodium sulfate. Distillation afforded a colorless oil. Yield: 18.3 g (81%). B.p. 55−56 °C/10 Torr; m.p. 21−23 °C. n_D^{20} = 1.4754. d_4^{20} = 1.826. ^{1}H NMR: δ = 8.85 (d, *J* = 5.1 Hz, 1 H), 7.66 (d, *J* = 5.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 161.9 (s), 157.7 (q, *J* = 38 Hz), 153.7 (s), 119.5 (q, *J* =

276 Hz), 116.1 (s) ppm. MS: *m/z* (%) = 227 (4) [M^+ + 1], 226 (15) [M^+], 147 (100), 132 (20), 121 (15), 97 (18) ppm. $C_5H_2BrF_3N_2$ (226.98): calcd. C 26.46, H 0.89; found C 26.36, H 0.72.

4-Bromo-6-(trifluoromethyl)pyrimidine (3): Prepared analogously from 6-(trifluoromethyl)pyrimidin-4(3*H*)-one (**6**; see following paragraph; 16 g, 0.10 mol). Colorless oil. Yield: 14.0 g (62%). B.p. 36−37 °C/10 Torr; m.p. 13−15 °C. n_D^{20} = 1.4714. d_4^{20} = 1.808. ^{1}H NMR: δ = 9.12 (s, 1 H), 7.89 (s, 1 H) ppm. ^{13}C NMR: δ = 159.4 (s), 156.2 (q, *J* = 37 Hz), 154.9 (s), 122.4 (s), 119.6 (q, *J* = 275 Hz) ppm. MS: *m/z* (%) = 227 (100) [M^+ + 1], 209 (9), 189 (24), 145 (26), 115 (24), 98 (40). $C_5H_2BrF_3N_2$ (226.98): calcd. C 26.46, H 0.89; found C 26.29, H 0.63.

6-(Trifluoromethyl)pyrimidin-4(3*H*)-one (6): A solution of commercial 2-thioxo-6-(trifluoromethyl)-2,3-dihydropyrimidin-4(1*H*)-one (49 g, 0.25 mol) and 30% aqueous hydrogen peroxide (0.20 L) in water (0.30 L) and tetrahydrofuran (50 mL) was kept at 80 °C for 2 h, before being concentrated to one third of its volume. The pH was adjusted to 6 with sodium hydrogen carbonate (38 g), the reaction mixture was saturated with sodium chloride and extracted with ethyl acetate (3 × 0.20 L). The combined organic layers were dried, filtered and concentrated. Colorless platelets (from ethyl acetate). Yield: 28.7 g (70%). M.p. 158−159 °C (reprod.). ^{1}H NMR*: δ = 8.40 (s, 1 H), 6.79 (s, 1 H) ppm. ^{13}C NMR*: δ = 161.2 (s), 153.2 (q, *J* = 35 Hz), 152.7 (s), 121.8 (q, *J* = 274 Hz), 115.0 (s) ppm. MS: *m/z* (%) = 165 (22) [M^+ + 1], 164 (100) [M^+], 145 (23), 136 (86), 117 (21). $C_5H_3F_3N_2O$ (164.09): calcd. C 36.60, H 1.84; found C 36.59, H 1.70.

5-Bromo-4-(trifluoromethyl)pyrimidin-2(1*H*)-one (5): Bromine (21 mL, 64 g, 0.40 mol) was added dropwise over a period of 20 min to a mixture of 4-(trifluoromethyl)pyrimidin-2(1*H*)-one[21] (**4**; 66 g, 0.40 mol) and potassium acetate (0.12 kg, 1.2 mol) in glacial acetic acid (0.40 L) under continuous stirring after which the reaction mixture was heated at 80 °C for 2 h. After the solvent was evaporated, the residue was taken up in ethyl acetate (0.60 L) and washed with water (2 × 0.20 L). Concentration of the solvent to one seventh of its volume afforded tiny colorless needles by cooling to 0 °C. Yield: 77.8 g (80%). M.p. 208−209 °C (dec.). ^{1}H NMR*: δ = 8.76 (s, 1 H) ppm. ^{13}C NMR*: δ = 160.7 (s), 160.5 (s), 157.1 (q, *J* = 35 Hz), 120.7 (q, *J* = 277 Hz), 100.5 (s) ppm. MS: *m/z* (%) = 243 (28) [M^+ + 1], 242 (67) [M^+], 216 (22), 163 (100), 121 (100), 93 (38). $C_5H_2BrF_3N_2O$ (242.98): calcd. C 24.72, H 0.83; found C 24.63, H 0.72.

5-Bromo-2-chloro-4-(trifluoromethyl)pyrimidine (7): 5-Bromo-4-(trifluoromethyl)pyrimidin-2(1*H*)-one (**5**; 18 g, 75 mmol) and phosphorus trichloride (40 mL, 60 g, 0.40 mol) were heated under reflux for 2 h. Then excess reagent was evaporated under reduced pressure. Ice (80 g) was added and the mixture was extracted with hexanes (3 × 80 mL). The combined organic layers were washed with brine (40 mL). Distillation gave a colorless oil. Yield 17.4 g (89%). B.p. 53−54 °C/5 Torr; m.p. −6 to −5 °C. n_D^{20} = 1.4840. d_4^{20} = 1.879. ^{1}H NMR: δ = 8.98 (s, 1 H) ppm. ^{13}C NMR: δ = 164.8 (s), 159.8 (s), 155.3 (q, *J* = 37 Hz), 119.4 (q, *J* = 277 Hz), 115.5 (s) ppm. MS: *m/z* (%) = 262 (100), 260 (78) [M^+], 193 (15), 154 (10), 93 (25). $C_5HBrClF_3N_2$ (261.43): calcd. C 22.97, H 0.39; found C 22.58, H 0.25.

2,5-Dibromo-4-(trifluoromethyl)pyrimidine (8): 5-Bromo-4-(trifluoromethyl)pyrimidin-2(1*H*)-one (**3b**; 36 g, 0.15 mol) and phosphorus tribromide (43 g, 0.15 mol) were heated at 150 °C for 45 min then poured onto crushed ice (0.20 kg) and extracted with hexanes (3 × 0.15 L). The combined organic layers were washed with brine (75 mL). Distillation afforded a colorless oil. Yield: 36.7 (80%). B.p. 50−51/0.38 Torr; m.p. −36 to −35 °C. n_D^{20} = 1.4956. d_4^{20} = 1.921. ^{1}H NMR: δ = 8.87 (s, 1 H) ppm. ^{13}C NMR: δ = 164.2 (s), 155.0 (q, *J* = 37 Hz), 150.6 (s), 119.2 (q, *J* = 277 Hz), 116.3 (s) ppm. MS: *m/z* (%) = 304 (43) [M^+], 246 (25), 150 (39), 137 (23), 121 (100). $C_5HBr_2F_3N_2$ (305.88): calcd. C 19.63, H 0.33; found C 19.39, H 0.29.

5-Bromo-2-hydrazino-4-(trifluoromethyl)pyrimidine (9): 2,5-Dibromo-4-(trifluoromethyl)pyrimidine (**8**; 4 mL, 7.7 g, 25 mmol) was dissolved in ethanol (5.0 mL) and added dropwise during 15 min to an ice/salt-cooled solution of hydrazine monohydrate (2.4 mL, 2.5 g, 50 mmol) in ethanol (20 mL). Water (0.12 L) was added, the product was filtered and washed with water (2 × 10 mL). Tiny pale yellow prisms (from aqueous ethanol). Yield: 6.11 g (95%). M.p. 116−118 °C (reprod.). ^{1}H NMR: δ = 8.57 (s, 1 H), 6.68 (s, broad, 1 H), 3.97 (s, 2 H) ppm. ^{13}C NMR: δ = 163.2 (s), 162.3 (s), 153.5 (q, *J* = 35 Hz), 120 (q, *J* = 277 Hz), 102.7 (s) ppm. MS: *m/z* (%) = 257 (55) [M^+ + 1], 256 (67) [M^+], 227 (19), 177 (11), 157 (12), 120 (15). $C_5H_4BrF_3N_4$ (257.01): calcd. C 23.37, H 1.57; found C 23.26, H 1.35.

5-Bromo-6-(trifluoromethyl)pyrimidin-4(3*H*)-one (10): Prepared as described for pyrimidinone **5** from 6-(trifluoromethyl)pyrimidin-4(3*H*)-one (**6**; 49 g, 0.30 mol). Colorless prisms (from acetone). Yield: 63.0 g (86%). M.p. 214−215 °C (decomp.). ^{1}H NMR*: δ = 8.41 (s, 1 H) ppm. ^{13}C NMR*: δ = 158.4 (s), 150.9 (q, *J* = 34 Hz), 149.7 (s), 121.8 (q, *J* = 276 Hz), 115.1 (s) ppm. MS: *m/z* (%) = 243 (27) [M^+ + 1], 242 (100) [M^+], 214 (7), 146 (61), 135 (36), 115 (27). $C_5H_2BrF_3N_2O$ (242.98): calcd. C 24.72, H 0.83; found C 24.71, H 0.65.

4,5-Dibromo-6-(trifluoromethyl)pyrimidine (11): Prepared as described for pyrimidine **8** from 5-bromo-6-(trifluoromethyl)pyrimidin-4(3*H*)-one (**7**; 15 g, 60 mmol). Colorless needles (from pentane). Yield: 14.2 g (77%). M.p. 47−49 °C (reprod.). ^{1}H NMR: δ = 8.96 (s, 1 H) ppm. ^{13}C NMR: δ = 158.6 (s), 155.5 (s), 154.6 (q, *J* = 36 Hz); 121.7 (s), 119.7 (q, *J* = 277 Hz) ppm. MS: *m/z* (%) = 305 (6) [M^+ + 1], 304 (8) [M^+], 258 (8), 225 (16), 148 (20), 121 (100). $C_5HBr_2F_3N_2$ (305.88): calcd. C 19.63, H 0.33; found C 19.29, H 0.28.

5-Bromo-4-hydrazino-6-(trifluoromethyl)pyrimidine (12): Prepared as described for pyrimidine **9** from 4,5-dibromo-6-(trifluoromethyl)pyrimidine (**11**; 23 g, 75 mmol). Tiny golden yellow needles (from aqueous ethanol). Yield: 13.9 g (72%). M.p. 124−125 °C (reprod.). ^{1}H NMR: δ = 8.64 (s, 1 H), 7.12 (s, broad, 1 H), 4.15 (s, 2 H) ppm. ^{13}C NMR: δ = 160.9 (s), 155.3 (s), 151.1 (q, *J* = 35 Hz), 120.6 (q, *J* = 277 Hz), 100.0 (s) ppm. MS: *m/z* (%) = 257 (55) [M^+ + 1], 256 (86) [M^+], 144 (5), 132 (18), 121 (30), 120 (100). $C_5H_4BrF_3N_4$ (257.01): calcd. C 23.37, H 1.57; found C 23.52, H 1.40.

5-Bromo-4-(trifluoromethyl)pyrimidine (2): 5-Bromo-4-hydrazino-6-(trifluoromethyl)pyrimidine (**12**; 6.4 g, 25 mmol) in chloroform (50 mL) was added dropwise to a stirred suspension of manganese(IV) oxide (22 g, 0.25 mol) in chloroform (50 mL) at 0 °C over a period of 15 min. After additional 30 min of stirring, the manganese oxide was removed by filtration and washed with chloroform (25 mL). Distillation of the combined filtrates gave a colorless oil. Yield: 4.37 g (77%). B.p. 43−44 °C/16 Torr; m.p. −4 to −2 °C. n_D^{20} = 1.4819. d_4^{20} = 1.821. ^{1}H NMR: δ = 9.26 (s, 1 H), 9.08 (s, 1 H) ppm. ^{13}C NMR: δ = 162.4 (s), 156.5 (s),153.2 (q, *J* = 36 Hz), 120.1 (q, *J* = 275 Hz), 117.3 (s) ppm. MS: *m/z* (%) = 227 (24) [M^+ + 1], 225 (12), 131 (100), 98 (90), 81 (32). $C_5H_2BrF_3N_2$ (226.98): calcd. C 26.46, H 0.89; found C 26.30, H 0.79.

5-Chloro-4-(trifluoromethyl)pyrimidin-2(1*H*)-one (13): A solution of 4-(trifluoromethyl)pyrimidin-2(1*H*)-one (**4**; 25 g, 0.15 mol), sulfuryl chloride (20 g, 12 mL, 0.15 mol) and iron(III) chloride (2.4 g, 15 mmol) in glacial acetic acid (0.15 L) was heated at 80 °C for 2 h before the solvent was evaporated. The residue was triturated with water (0.10 mL), collected by filtration, washed with water (2 × 0.20 L) again and dried in a desiccator. Colorless prisms (from ethyl acetate). Yield: 23.8 g (80%). M.p. 177−178 °C (reprod.). ^{1}H NMR*: δ = 8.71 (s, 1 H) ppm. ^{13}C NMR*: δ = 160.7 (s), 158.6 (s), 155.6 (q, *J* = 35 Hz), 120.6 (q, *J* = 277 Hz), 115.3 (s) ppm. MS: *m*/*z* (%) = 119 (10) [M$^+$ + 1], 198 (21) [M$^+$], 170 (28), 131 (43), 129 (100), 101 (15). $C_5H_2ClF_3N_2O$ (198.53): calcd. C 30.25, H 1.02; found C 30.28, H 0.79.

2,5-Dichloro-4-(trifluoromethyl)pyrimidine (15): Prepared as described for pyrimidine **7** from 5-chloro-4-(trifluoromethyl)pyrimidin-2(1*H*)-one (**13**; 20 g, 0.10 mol). Colorless oil. Yield: 17.6 g (81%). B.p. 40−41 °C/5 Torr. n_D^{20} = 1.4691. d_4^{20} = 1.606. ^{1}H NMR: δ = 8.86 (s, 1 H). ^{13}C NMR: δ = 162.1 (s), 159.0 (s), 153.8 (q, *J* = 37 Hz), 127.8 (s), 119.2 (q, *J* = 276 Hz), 115.7 (s). MS: *m*/*z* (%) = 217 (45) [M$^+$ + 1], 216 (100) [M$^+$], 189 (7), 147 (12), 128 (12). $C_5HCl_2F_3N_2$ (216.98): calcd. C 27.68, H 0.46; found C 27.69, H 0.25.

5-Iodo-4-(trifluoromethyl)pyrimidin-2(1*H*)-one (14): A solution of 4-(trifluoromethyl)pyrimidin-2(1*H*)-one[15] (**4**; 25 g, 0.15 mol) and iodine chloride (26 g, 0.15 mol) in glacial acetic acid (0.15 L) were heated at 80 °C for 2 h, then the solvent was evaporated. The residue was triturated with water (0.10 L), collected by filtration, washed with water (2 × 0.20 L) again and dried in a desiccator. Colorless platelets (from ethyl acetate). Yield: 24.8 g (60%). M.p. 214−216 °C (dec.). ^{1}H NMR*: δ = 8.81 (s, 1 H) ppm. ^{13}C NMR*: δ = 164.0 (s), 160.1 (q, *J* = 35 Hz), 158.8 (s), 137.4(s), 120.2 (q, *J* = 278 Hz) ppm. MS: *m*/*z* (%) = 308 (8), 291 (17) [M$^+$ + 1], 290 (100) [M$^+$], 239 (50), 221 (36), 163 (13), 127 (38). $C_5H_2F_3IN_2O$ (289.98): calcd. C 20.71, H 0.70; found C 20.84, H 0.64.

2-Chloro-5-iodo-4-(trifluoromethyl)pyrimidine (16): Prepared as described for pyrimidine **7** from 5-iodo-4-(trifluoromethyl)pyrimidin-2(1*H*)-one (**14**; 22 g, 75 mmol). Colorless oil. Yield: 17.8 g (77%). B.p. 66−67 °C/2 Torr. n_D^{20} = 1.5493. d_4^{20} = 2.086. ^{1}H NMR: δ = 9.1 (s, 1 H) ppm. ^{13}C NMR: δ = 170.4 (s), 160.6 (s), 158.4 (q, *J* = 36 Hz), 119.3 (q, *J* = 272 Hz), 85.8 (s) ppm. MS: *m*/*z* (%) = 309 (50) [M$^+$ + 1], 308 (100) [M$^+$], 239 (5), 220 (18), 178 (10), 161 (18), 127 (66). $C_5HClF_3IN_2$ (308.42): calcd. C 19.46, H 0.33; found C 19.36, H 0.33.

2,4-Dibromo-6-(trifluoromethyl)pyrimidine (18): Prepared as described for pyrimidine **1** from 6-(trifluoromethy)pyrimidine-2,4(1*H*,3*H*)-dione [21] (**17**; 9 g, 50 mmol) with a stoichiometric amount of phosphorus tribromide (29 g, 0.10 mol). Colorless prisms (from methanol). Yield: 12.1 g (79%). M.p. 81−83 °C (reprod.). ^{1}H NMR: δ = 7.83 (s, 1 H) ppm. ^{13}C NMR: δ = 157.5 (q, *J* = 38 Hz), 155.5 (s), 152.5 (s), 120.8 (s), 118.9 (q, *J* = 278 Hz) ppm. MS: *m*/*z* (%) = 305 (67) [M$^+$ + 1], 304 (47) [M$^+$], 285 (26), 225 (58), 131 (100), 122 (92), 95 (88). $C_5HBr_2F_3N_2$ (305.88): calcd. C 19.63, H 0.33; found C 19.40, H 0.34.

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