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Metal-Bearing and Trifluoromethyl-Substituted Pyrimidines: Generation and Functionalization

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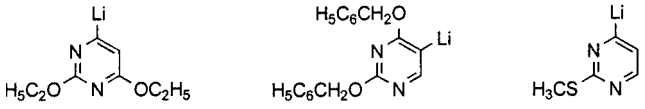
5-Pyrimidyllithium species are fairly stable when the metal is flanked by two electron-withdrawing substituents such as trifluoromethyl and chlorine or bromine. Thus, the corresponding 5-carboxylic acids are produced in high yields from 4,5-dibromo-6-(trifluoromethyl)pyrimidine and 5-bromo-4-chloro-6-(trifluoromethyl)pyrimidine upon halogen/metal permutation accomplished with isopropylmagnesium chloride or butyllithium followed by carboxylation. Satisfactory or excellent yields of 5-carboxylic acids are equally obtained when 4-chloro-, 2,4-dichloro- and 2,4-dibromo-6-(trifluoromethyl)pyrimidine are deprotonated with lithium diisopropylamide before being allowed to react with dry ice. In contrast, consecutive treatment of 2-bromo-4-(trifluoromethyl)-pyrimidine and 2-chloro-5-iodo-4-(trifluoromethyl)pyrimidine with butyllithium affords the expected carboxylic acids in only poor yields and not even trace amounts of acid were detected when 4-bromo-6-(trifluoromethyl)pyrimidine served as the substrate. The formation of bipyrimidines, emerging from either one of two competing mechanistic pathways, is a permanently menacing side reaction.

Introduction

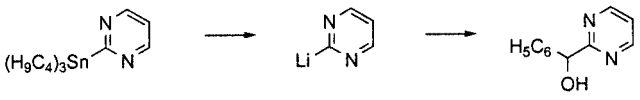
Pyrimidines[1–3] belong to the most prominent classes of heterocyclic compounds. They are well represented in the realm of natural products and their derivatives occupy a privileged position among commercial substances having pharmaceutical or agricultural applications.

The heterocyclic core of pyrimidines is in general readily accessible by a Pinner–Traube-like condensation of urea, thiourea or *S*-methylthiourea with a malonate or another twofold electrophile. However, the subsequent functionalization or structural elaboration may prove troublesome. At this stage it can be helpful to dispose of smartly designed organometallic intermediates as these should enable shortcuts and provide flexibility in synthesis. The potential of organometallic chemistry in the pyrimidine field was recognized already half a century ago (Scheme 1). 2,6-Diethoxypyrimid-4-yllithium, the first prototype species, was generated from 4-bromo-2,6-diethoxypyrimidine and butyllithium by permutational halogen/metal interconversion.[4] [2,4-Bis(benzyloxy)pyrimidyl-5-yl]lithium was set free analogously from 2,4-bis(benzyloxy)-5-bromopyrimidine.[5] The yields of products obtained upon trapping with standard electrophiles such as carbon dioxide or aldehydes were moderate (20–50%) and did not significantly improve when the reaction was carried out at –95 °C rather than at –75 °C and the brominated substrate was replaced by an iodo analog. Thus, 4-iodo-2-(methylthio)pyrimidine was converted via the lithio species into 4-tributylstannyl-2-(methylthio)-pyrimidine in not more than 52% yield.[6]



Scheme 1. The first heterosubstituted pyrimidyllithiums.

More satisfactory results were achieved when the lithiated intermediate was generated by metalloid/metal permutation. Thus, 2-(tributylstannyl)pyrimidine afforded the adduct in 78% yield upon consecutive treatment with butyllithium (in tetrahydrofuran at –95 °C) and benzaldehyde[6] (Scheme 2). This option is nevertheless not very attractive as the tin compound had to be prepared from a suitable precursor by halogen/metal permutation and condensation with tributylchlorostannane.



Scheme 2. 2-Pyrimidyllithium by metalloid/metal permutation.

The vast majority of lithiated pyrimidines was directly made by hydrogen/metal permutation ("metalation"). First results were disclosed in the very early nineties (Scheme 3). Kanatomo et al.[7] were able to isolate 4-(*tert*-butoxycar-

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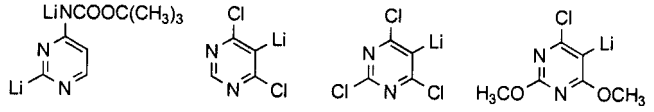
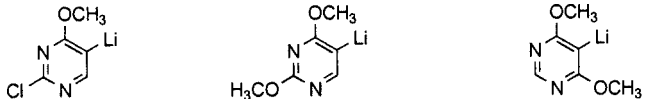
bonyl)amino-2-(trimethylsilyl)pyrimidine in 11% yield after having exposed 4-(*tert*-butoxycarbonyl)aminopyrimidine consecutively to the action of lithium 2,2,6,6-tetramethylpiperidide (LITMP) and chlorotrimethylsilane. This remained the sole example of a pyrimidine deprotonation at the 2-position. Radinov et al.[8] reported the selective 5-lithiation of 4,6-dichloropyrimidine and 2,4,6-trichloropyrimidine using lithium diisopropylamide (LIDA) or butyllithium as the base. According to Quéguiner et al.,[9,10] both butyllithium and LITMP promote similarly the metalation of 4-chloro-2,6-dimethoxypyrimidine at the 5-position, again the only vacant site.



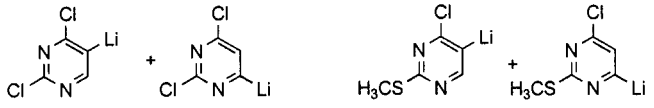
Scheme 3. Heterosubstituted pyrimidyllithiums generated by hydrogen/metal permutation (metalation).

Analogously 2-chloro-4-methoxypyrimid-5-yllithium[11] 2,4-dimethoxypyrimid-5-yllithium[12] and 4,6-dimethoxypyrimid-5-yllithium[12] were obtained and characterized (Scheme 4). LITMP served as the base in all three cases.



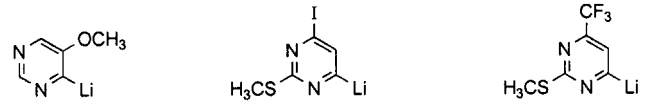
Scheme 4. More heterosubstituted pyrimidyllithiums generated by hydrogen/metal permutation (metalation).

Concomitant deprotonation at the 5- and 6-position was found to occur with 2,4-dichloropyrimidine[8,13] and 4-chloro-2-(methylthio)pyrimidine[13] (Scheme 5). In the latter case, the 5-/6-ratio varied strongly depending on the base employed, approximating 20:1 with LIDA and 1:2 with LITMP.[13]



Scheme 5. Regiochemically unselective metalation of two chloropyrimidines.

Only a few examples of clean 6-metalations have been reported so far (Scheme 6). They comprise "5-methoxypyrimid-6-yllithium"[10] (correct name: 5-methoxypyrimid-4-yllithium) and two intermediates derived from pyrimidines carrying bulky substituents at the 4-position, 6-iodo-2-(methylthio)pyrimid-4-yllithium[14] and 2-(methylthio)-6-(trifluoromethyl)pyrimid-4-yllithium.[15]



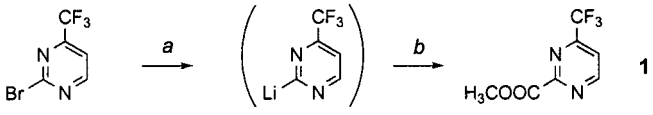
Scheme 6. The scarce 6-lithiated pyrimidine derivatives.

The latter species was so far the sole metalated pyrimidine having a CF_3 substituent. Pyrimidyllithiums carrying single fluorine atoms are also a curiosity. The only examples known are 4-fluoro-2-(methylthio)pyrimid-5-yllithium[16] and 2,4-difluoropyrimid-5-yllithium.[16]

Having more than half a dozen of chloro- or bromo-substituted 4-(trifluoromethyl)pyrimidines at hand,[17] we thought to convert them into lithiated species either by halogen/metal or hydrogen/metal permutation in order to pave the way toward functionalization. The intermediates, once formed, would be trapped as usual with our standard electrophile carbon dioxide.

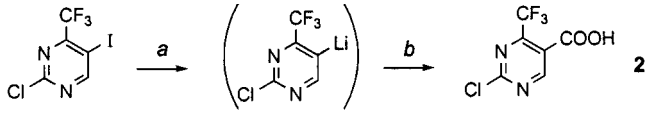
Results

Consecutive treatment of 2-bromo-4-(trifluoromethyl)-pyrimidine[17] with butyllithium in toluene at –90 °C and carbon dioxide followed by neutralization and esterification with an ethereal solution of diazomethane afforded methyl 4-(trifluoromethyl)pyrimidine-2-carboxylate (**1**) in moderate yield (36%) (Scheme 7). Under the same conditions, the isomeric 5-bromo-4- and 4-bromo-6-(trifluoromethyl)pyrimidines[17] gave only tars.



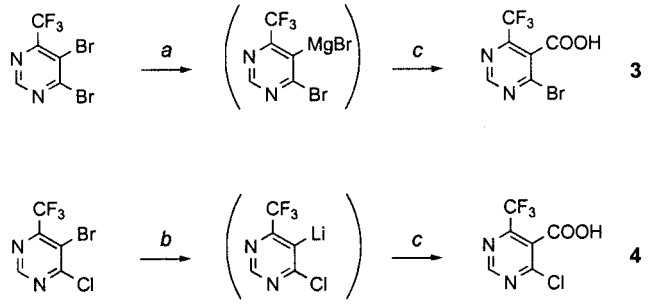
Scheme 7. Bromo/lithium permutation between 2-bromo-4-(trifluoromethyl)pyrimidine and butyllithium followed by carboxylation. Reaction conditions: *a* butyllithium in toluene at –90 °C for 15 min; *b* (1.) carbon dioxide, (2.) hydrochloric acid, (3.) diazomethane in diethyl ether.

We hoped to achieve a better result after replacing the bromo by the supposedly more reactive iodo substituent and by introducing a chlorine atom to block the possibly vulnerable 2-position. However, the yield of 2-chloro-4-(trifluoromethyl)pyrimidine-5-carboxylic acid (**2**; 29%) obtained from 2-chloro-5-iodo-4-(trifluoromethyl)pyrimidine[17] was again disappointing (Scheme 8).



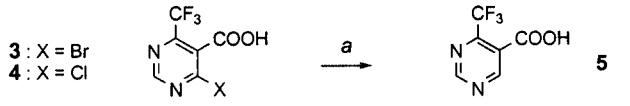
Scheme 8. Iodo/lithium permutation applied to 2-chloro-5-iodo-4-(trifluoromethyl)pyrimidine followed by carboxylation. Reaction conditions: *a* butyllithium in tetrahydrofuran at –75 °C for 15 min; *b* (1.) carbon dioxide, (2.) hydrochloric acid.

In contrast, clean reactions were encountered with 4,5-dibromo-6-(trifluoromethyl)pyrimidine[17] and 5-bromo-4-chloro-6-(trifluoromethyl)pyrimidine as the substrates when isopropylmagnesium chloride in diethyl ether and, respectively, butyllithium in toluene were employed as the exchange reagents (Scheme 9). 4-Bromo-6-(trifluoromethyl)-pyrimidine-5-carboxylic acid (**3**) and 4-chloro-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (**4**) were isolated in 54% and 73% yield. The rigorous discrimination between the two bromine atoms by the Grignard reagent is, even if not unexpected,[18] still noteworthy.



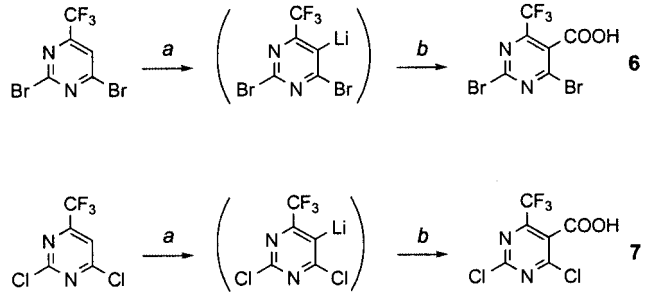
Scheme 9. Selective 5-bromo/metal permutation with 4,5-dibromo- and 5-bromo-4-chloro-6-(trifluoromethyl)pyrimidine. Reaction conditions: *a* isopropylmagnesium chloride in diethyl ether at 0 °C for 2 h; *b* butyllithium in toluene at –75 °C for 45 min; *c* (1.) carbon dioxide, (2.) hydrochloric acid.

The heavy halogen could be removed from both acids **3** and **4** by catalytic hydrogenation (Scheme 10). 4-(Trifluoromethyl)pyrimidine-5-carboxylic acid (**5**) was formed in 72% and 83% yield.



Scheme 10. Hydrogenolytic debromination and, respectively, dechlorination of 4-bromo- and 4-chloro-6-(trifluoromethyl)pyrimidine-5-carboxylic acid. Reaction conditions: *a* atmospheric catalytic hydrogenation, using palladium on charcoal at +25 °C in methanol in the presence of triethylamine.

The acid **4** was further obtained by simple treatment of 4-chloro-6-(trifluoromethyl)pyrimidine with LIDA followed by carboxylation, although in only moderate yield (31%). On the other hand, excellent results were achieved with 2,4-dibromo- and 2,4-dichloro-6-(trifluoromethyl)pyrimidine (Scheme 11). The 2,4-dihalo-6-(trifluoromethyl)pyrimidine-5-carboxylic acids **6** (X = Br) and **7** (X = Cl) were isolated in 79% and 89% yield.

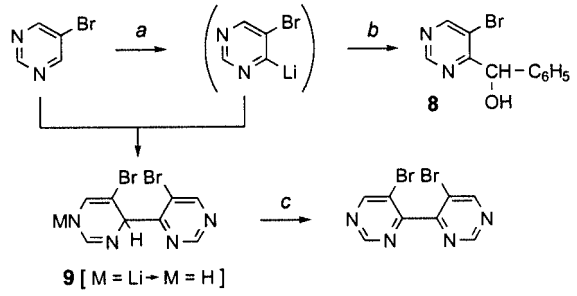


Scheme 11. Metalation and subsequent carboxylation of 2,4-dibromo- and 2,4-dichloro-6-(trifluoromethyl)pyrimidine. Reaction conditions: *a* lithium diisopropylamide in tetrahydrofuran at –75 °C for 45 min; *b* (1.) carbon dioxide, (2.). hydrochloric acid.

Discussion

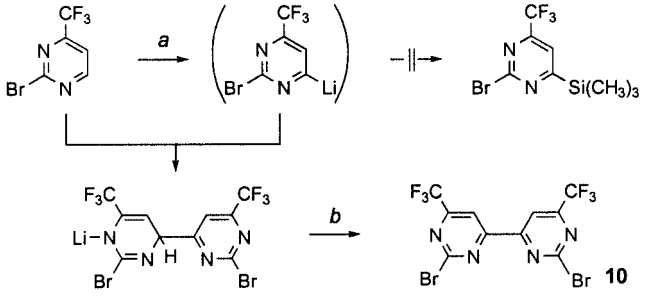
In general, it does not matter very much whether a pyrimidyllithium species is obtained by halogen/metal or hydrogen/metal permutation. Apparently the stability of the intermediate rather than the method of its generation is the critical issue. In other words, possible modes of decomposition play a key role.

It depends often just on the reaction conditions whether electron-rich species act as bases or nucleophiles. For example, butyllithium in tetrahydrofuran metalates 2,4-dimethoxypyrimidine at the 5-position,[12] whereas in diethyl ether it undergoes addition at the 6-position thus leading to 6-butyl-substituted uracil upon hydrolysis.[19,20] In the same way, a metalated pyrimidine may combine with its precursor. When 5-bromopyrimidine was treated with LIDA *in the presence* of benzaldehyde, the adduct **8** was formed in 36–41% yield, whereas in the absence of an external electrophile 32% of the dimer **9** (M = H) and, after oxidation with potassium permanganate, 5,5′-dibromo-4,4′-dipyrimidyl were produced[21] (Scheme 12).



Scheme 12. Nucleophilic addition of a pyrimidyllithium to its precursor thus giving ultimately rise to 5,5′-dibromo-4,4′-dipyrimidyl. Reaction conditions: *a* lithium diisopropylamide in diethyl ether at –10 °C for 2 h; *b* (1.) benzaldehyde, (2.) hydrochloric acid; *c* potassium permanganate in acetone at 25 °C for 6 h.

A similar dehydrodimer (**10**) was identified as a by-product (19%) when 2-bromo-4-(trifluoromethyl)pyrimidine was treated with a large excess of LITMP in the presence of chlorotrimethylsilane (3.0 equivalents of both reagents) (Scheme 13). No silylated pyrimidine was detected in the reaction mixture.



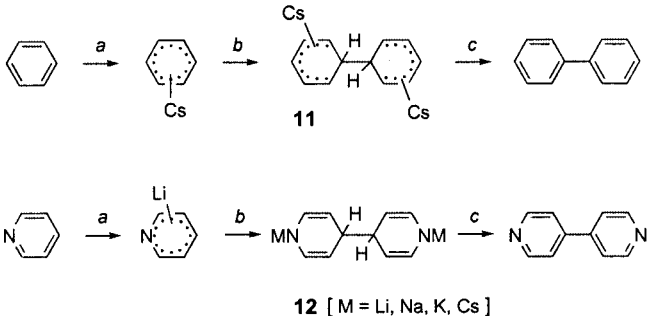
Scheme 13. 2,2′-Dibromo-6,6′-bis(trifluoromethyl)-4,4′-bipyrimidyl from 2-bromo-4-(trifluoromethyl)pyrimidine in the presence of lithium 2,2,6,6-tetramethylpiperidide (LITMP). Reaction conditions: *a* lithium 2,2,6,6-tetramethylpiperidide and chlorotrimethylsilane in tetrahydrofuran at –100 °C for 2 h; *b* lithium hydride elimination.

Such "cannibalization mechanisms" can explain why simple pyrimidyllithiums are too labile for straightforward application to practical organic synthesis. They nucleophilically attack their metal-free precursors unless heterosubstit-

uents such as a CF_3 group or halogen (e.g., chlorine and bromine) atoms provide steric and electronic stabilization.

However, this argument does not account for all scenarios encountered. If nucleophilic addition to metal-free precursors was the sole menace for the survival of metalated pyrimidines, 2,4-difluoropyrimid-5-yllithium[16] should be less and not more stable than the 2,4-dichloro analog[13] as the lightest halogen is the better nucleofugal leaving group.[22] It is also not immediately intelligible why reactions involving 4,6-dichloropyrimid-5-yllithium give excellent yields but those passing through 2,4,6-trichloropyrimid-5-yllithium only miserable ones.

All such incongruities suggest to consider, in addition to the combination of a (nucleophilic) pyrimidylmetal with its (electrophilic) pyrimidine precursor, the dimerization of "radical anions" as a second, alternative decomposition mode. In this way, benzene[23,24] or pyridine[25–29] produce, via alkali metal adducts, 6,6′-bis(2,4-cyclohexadienylcesium) (**11**) or (4,4′,*N*,*N*′-tetrahydro-4,4′-bipyridyl-*N*,*N*′-diyl)dilithium (**12**) and ultimately biphenyl and 4,4′-bipyridyl (Scheme 14). Analogously, electronegatively substituted pyrimidines may readily act as "electron sinks" and, after single electron transfer,[30] get lost by dimerization or, in particular if CF_3 groups are present, by halide ejection.



Scheme 14. The metal-mediated dehydrogenating dimerization of benzene and pyridine. Reaction conditions: *a* "Radical anion" formation by metal addition to the (het)arene; *b* spontaneous dimerization of the radical anions; *c* metal hydride elimination.

What can be done to make pyrimidylmetals chemically more stable without changing a given substituent pattern? "Metal tuning" should offer a valid solution. If lithiated species prove to be too reactive, one may try magnesium or zinc derivatives (set free from bromo- or iodopyrimidines by treatment with lithium tributylmagnesate[31,32] or diethylzinc, respectively). The heavy halogen-bearing precursor should be readily accessible by bromodesilylation[33–36] or iododesilylation[33–35] of silanes prepared by in situ trapping of lithiated pyrimidines with chlorotrimethylsilane or chlorotriethylsilane.

Experimental Section

1. Generalities

Details concerning standard operations and abbreviations have been given in previous publications from this laboratory.[37–39] ^1H and (^1H-decoupled) ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively. If not specified otherwise, samples have been dissolved in deuteriochloroform or, if marked by an asterisk, in hexadeuterioacetone. Mass spectra were obtained at 70 eV ionization potential while a source temperature of 200 °C was maintained. Whenever no molecular peak was observed under such 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] nor [^{81}Br] isotopomers are listed.

2. Starting Materials

2-Bromo- and 5-bromo-4-(trifluoromethyl)pyrimidine, 4-bromo-6-(trifluoromethyl)pyrimidine, 2,4- and 4,5-dibromo-6-(trifluoromethyl)pyrimidine and 2-chloro-5-iodo-4-(trifluoromethyl)pyrimidine have been reported previously.[17] They were prepared following the same protocols.

5-Bromo-4-chloro-6-(trifluoromethyl)pyrimidine: 5-Bromo-6-(trifluoromethyl)pyrimidin-4(3*H*)-one[17] (12 g, 50 mmol) and phosphoric trichloride (25 mL, 40 g, 0.25 mol) were heated for 2 h under reflux before the excess of the reagent was stripped off under reduced pressure. Ice (50 g) was added and the mixture was extracted with hexanes (3 × 50 mL). The combined organic layers were washed with brine (25 mL). Distillation gave a colorless oil; b.p. 44–45 °C/5 Torr; m.p. –2 to 0 °C; n_D^{20} 1.500; d_4^{20} 1.920; yield: 11.0 g (84%). ^1H NMR: δ = 9.02 (s, 1 H) ppm. ^{13}C NMR: δ = 164.4 (s), 156.0 (s), 155.5 (q, J = 36 Hz), 120.1 (q, J = 277 Hz), 118.3 (s) ppm. MS: *m*/*z* (%) = 262 (100), 261 (15) [M^+ + 1], 260 (57) [M^+], 259 (46), 243 (16), 225 (20), 100 (48), 85 (56). $C_5HBrClF_3N_2$ (261.43): calcd. C 22.97, H 0.39; found C 22.73, H 0.20.

4-Chloro-6-(trifluoromethyl)pyrimidine: Analogously, 6-(trifluoromethyl)pyrimidin-4(3*H*)-one[17] (13 g, 80 mmol) was treated with phosphoric trichloride (40 mL, 67 g, 0.44 mol); colorless oil; b.p. 35–36 °C/22 Torr; m.p. –53 to –52 °C; n_D^{20} 1.4419; d_4^{20} 1.429; yield: 10.7 g (73%). ^1H NMR: δ = 9.18 (s, 1 H), 7.73 (s, 1 H) ppm. ^{13}C NMR: δ = 163.8, 159.8, 157.2 (q, J = 37 Hz), 120.2 (q, J = 275 Hz), 118.7 ppm. MS: *m*/*z* (%) = 182 (20) [M^+ + 2], 183 (4) [M^+ + 1], 182 (54) [M^+], 163 (15), 147 (25), 123 (33) 81 (100). $C_5H_2ClF_3N_2$ (182.53): calcd. C 32.90, H 1.10; found C 32.71, H 1.05.

2,4-Dichloro-6-(trifluoromethyl)pyrimidine: Analogously, 6-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione[40] (7.2 g, 40 mmol) was treated with phosphoric trichloride (30 mL, 50 g, 0.32 mol); colorless oil; b.p. 37–38 °C/0.7 Torr; m.p. –48 to –46 °C. n_D^{20} = 1.4656. d_D^{20} = 1.589; yield: 7.12 g (82%). ^1H NMR: δ = 7.66 (s, 1 H) ppm. ^{13}C NMR: δ = 165.2 (s), 162.2 (s), 159.0 (q, J = 38 Hz), 119.4 (q, J = 276 Hz), 116.9 (s) ppm. MS: *m*/*z* (%) = 219 (89), 216 (100) [M^+], 197 (55), 181 (27), 166 (11), 133 (11), 92 (52). $C_5HCl_2F_3N_2$ (216.98): calcd. C 27.68, H 0.46; found C 27.60, H 0.39.

3. Pyrimidinecarboxylic Acids and Esters

Methyl 4-(Trifluoromethyl)pyrimidine-2-carboxylate (1): A solution of 2-bromo-4-(trifluoromethyl)pyrimidine[17] (2.3 g, 10 mmol) and butyllithium (10 mmol) in hexanes (6.5 mL) and toluene (90 mL) was kept 15 min at –90 °C before being poured onto an excess of freshly crushed dry ice. After addition of water (50 mL), the aqueous layer was washed with diethyl ether (2 × 20 mL), acidified with 2.0 M hydrochloric acid (6 mL) to pH 1 and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (10 mL) and the solvents evaporated. The light orange solid residue was treated with an excess of diazomethane in diethyl ether. After 1 h, the clear yellow solution was adsorbed on silica gel (2.0 g), poured onto the top of a column filled with silica (50 mL) and eluted with ethyl acetate; light yellow prisms; m.p. 87–89 °C; yield: 0.74 g (36%). ^1H NMR: δ = 9.22 (d, J = 4.8 Hz, 1 H), 7.84

(d, J = 5.1 Hz, 1 H), 4.11 (s, 3 H) ppm. ^{13}C NMR: δ = 162.9, 160.9, 157.3, 156.7 (q, J = 37 Hz), 120.2 (q, J = 275 Hz), 119.3, 54.0 ppm. MS: m/z (%) = 206 (2) [M$^+$], 175 (10), 148 (100), 121 (9), 97 (12). $C_7H_5F_3N_2O_2$ (206.12): calcd. C 40.79, H 2.45; found C 40.76, H 2.32.

4-Bromo-6-(trifluoromethyl)pyrimidine-5-carboxylic Acid (3): A solution of 4,5-dibromo-6-(trifluoromethyl)pyrimidine[17] (7.6 g, 25 mmol) and isopropylmagnesium chloride (25 mmol) in tetrahydrofuran (15 mL) and diethyl ether (0.10 L) was kept for 2 h at –10 °C before being poured onto an excess of freshly crushed dry ice. After addition of water (0.12 L), the aqueous layer was washed with diethyl ether (2 × 25 mL), acidified with 2.0 M hydrochloric acid (15 mL) to pH 1 and extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine (25 mL) and the solvents evaporated. A yellow oil was collected which slowly crystallized; colorless prisms (from chloroform); m.p. 126–127 °C (reprod.); yield: 3.66 g (54%). ^{1}H NMR: δ = 10.76 (s, broad, 1 H), 9.20 (s, 1 H) ppm. ^{13}C NMR: δ = 164.0, 159.5, 152.3, 151.8 (q, J = 36 Hz), 130.3, 120.8 (q, J = 275 Hz) ppm. MS: m/z (%) = 273 (9), 272 (54), 271 (10), 270 (60) [M$^+$], 253 (11), 191 (29), 119 (27), 100 (100). $C_6H_2BrF_3N_2O_2$ (270.99): calcd. C 26.59, H 0.74; found C 26.54, H 0.71.

4-Chloro-6-(trifluoromethyl)pyrimidine-5-carboxylic Acid (4): A solution of 5-bromo-4-chloro-6-(trifluoromethyl)pyrimidine[17] (9.9 g, 38 mmol) and butyllithium (38 mmol) in hexanes (25 mL) and toluene (0.15 L) was kept 45 min at –75 °C before being poured onto an excess of freshly crushed dry ice. After addition of water (0.20 L), the aqueous layer was washed with diethyl ether (2 × 40 mL), acidified with 2.0 M hydrochloric acid (20 mL) to pH 1 and extracted with diethyl ether (3 × 40 mL). The combined organic layers were washed with brine (25 mL) and the solvents evaporated. The pale yellow oil left behind slowly crystallized; colorless prisms (from ethyl acetate/pentane); m.p. 119–121 °C (reprod.); yield: 6.28 g (73%). ^{1}H NMR: δ = 9.98 (s, broad, 1 H), 9.26 (s, 1 H) ppm. ^{13}C NMR: δ = 162.2, 160.2, 159.1, 153.2 (q, J = 37 Hz), 125.2, 119.6 (q, J = 277 Hz) ppm. MS: m/z (%) = 228 (32), 227 (11) [M$^+$ + 1], 226 (100) [M$^+$], 209 (74), 187 (9), 147 (22), 119 (26), 100 (51), 86 (51). $C_6H_2ClF_3N_2O_2$ (226.54): calcd. C 31.81, H 0.89; found C 31.52, H 0.91.

The same acid **4** was obtained in 31% yield when diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 4-chloro-6-(trifluoromethyl)pyrimidine (3.2 mL, 4.6 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in hexanes (16 mL) and tetrahydrofuran (0.11 L) cooled in a dry ice/methanol bath. After 45 min at –75 °C, the mixture was poured onto an excess of freshly crushed solid carbon dioxide. After evaporation of the volatiles, the residue was taken up in water (75 mL) and washed with diethyl ether (2 × 25 mL). The aqueous layer was acidified with 2.0 M hydrochloric acid (12 mL) to pH 2 and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (1 × 20 mL). The solvent was evaporated and the residue recrystallized from ethyl acetate/hexanes.

6-(Trifluoromethyl)pyrimidine-5-carboxylic Acid (5): Palladium (10% on charcoal, 0.20 g) was added to a solution of 4-chloro-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (**4**, 5.7 g, 25 mmol) and triethylamine (7.0 mL, 5.1 g, 50 mmol) in methanol (50 mL). After 2 h of stirring under an atmosphere of hydrogen (1 atm) at 25 °C, the required amount of hydrogen had been taken up. The reaction mixture was filtered, concentrated and acidified with 1.0 M hydrochloric acid (25 mL) before being extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine (25 mL) and concentrated; colorless prisms (from chloroform); m.p. 146–148 °C (reprod.); yield: 4.01 g (83%). ^{1}H NMR: δ = 9.54 (s, 1 H), 9.42 (s, 1 H) ppm. ^{13}C NMR: δ = 164.6, 160.8, 160.7, 153.1 (q, J = 37 Hz), 125.9, 121.4 (q, J = 275 Hz) ppm. MS: m/z (%) = 193 (6) M$^+$ + 1], 192 (100) [M$^+$], 174 (16), 165 (10), 123 (22), 101 (46). $C_6H_3F_3N_2O_2$ (192.10): calcd. C 37.51, H 1.57; found C 37.51, H 1.70. The acid **5** was obtained in 72% yield when 4-bromo-6-(trifluoromethyl)pyrimidine-5-carboxylic acid (**3**; 2.7 g 10 mmol) was subjected to the same protocol.

2,4-Dibromo-6-(trifluoromethyl)pyrimidine-5-carboxylic Acid (6): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 2,4-dibromo-6-(trifluoromethyl)pyrimidine[17] (7.7 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in hexanes (16 mL) and tetrahydrofuran (0.10 L) cooled in a dry ice/methanol bath. After 45 min at –75 °C, the mixture was poured onto an excess of freshly crushed solid carbon dioxide. The solvents were removed under reduced pressure. The residue was taken up in water (75 mL) and washed with diethyl ether (2 × 25 mL). The aqueous layer was acidified with 2.0 M hydrochloric acid (12 mL) to pH 2 and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (1 × 20 mL). Evaporation of the solvent and subsequent recrystallization of the residue from ethyl acetate/hexanes gave colorless prisms; m.p. 168–170 °C (reprod.); yield: 7.80 g (89%). ^{13}C NMR*: δ = 163.6, 153.4, 153.2 (q, J = 37 Hz), 151.6, 129.4, 120.2 (q, J = 277 Hz) ppm. MS: m/z (%) = 354 (60), 353 (55), 352 (68) 351 (100) [M$^+$ + 1], 350 (75) [M$^+$], 349 (77), 333 (69), 155 (63), 133 (30), 100 (46). $C_6HBr_2F_3N_2O_2$ (349.89): calcd. C 20.60, H 0.29; found C 20.40, H 0.39.

2,4-Dichloro-6-(trifluoromethyl)pyrimidine-5-carboxylic Acid (7): Prepared as described for pyrimidine **3** from 2,4-dichloro-6-(trifluoromethyl)pyrimidine[17] (5.4 g, 3.4 mL, 25 mmol); colorless prisms (from ethyl acetate/hexane); m.p. 101–104 °C (reprod.); yield: 5.15 g (79%). ^{13}C NMR*: δ = 162.9, 162.1, 160.8, 154.8 (q, J = 38 Hz), 126.4, 120.4 (q, J = 277 Hz) ppm. MS: m/z (%) = 264 (24), 262 (100), 261 (52), 260 (14) [M$^+$], 246 (41), 245 (67%), 244 (49), 243 (98), 321 (38), 182 (35). $C_6HCl_2F_3N_2O_2$ (260.99): calcd. C 27.61, H 0.39; found C 27.27, H 0.59.

2,2′-Dibromo-6,6′-bis(trifluoromethyl)-4,4′-bipyrimidyl (10): 2,2,6,6-Tetramethylpiperidine (10 mL, 8.5 g, 60 mmol) and a mixture of 2-bromo-4-(trifluoromethyl)pyrimidine[17] (4.5 g, 20 mmol) and chlorotrimethylsilane (7.7 m, 6.5 g, 60 mmol) in tetrahydrofuran (80 mL) were added consecutively to a solution of butyllithium (60 mmol) in hexanes (36 mL) and tetrahydrofuran (80 mL) at –100 °C over a period of 2 h. The reaction mixture was kept at –100 °C for a further 15 min before precooled methanol (8 mL) and water (0.10 L) were added. The mixture was extracted with hexanes (3 × 25 mL). The combined organic layers were washed with water (2 × 10 mL) and brine 10 mL), dried with sodium sulfate and the solvents evaporated. Sublimation of the residue afforded colorless needles; m.p. 163–164 °C; 0.86 g (19%). ^{1}H NMR: δ = 8.72 (s, 2 H) ppm. ^{13}C NMR: δ = 163.5, 160.1 (q, J = 38 Hz), 153.9, 119.4 (q, J = 276 Hz), 119.1 ppm. MS: m/z (%) = 455 (16), 454 (15), 453 (32), 452 (25), 451 (19) [M$^+$], 383 (21), 382 (11), 381 (10), 16 (27). $C_{10}H_2Br_2F_6N_4$ (451.95): calcd. C 26.58, H 0.45; found C 26.78, H 0.35.

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