Switchable Reactivity: The Site-Selective Functionalization of Trifluoromethyl-Substituted Pyrazoles

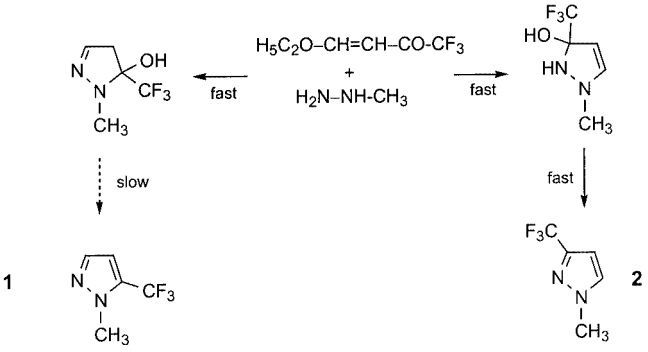
Manfred Schlosser,*[a] Jean-Noël Volle,[a] Frédéric Leroux,[a] and Kurt Schenk[b]

Keywords: Heterocycles / Bromopyrazoles / Carboxylation / Hydrogen/metal exchange / Halogen/metal exchange / Organolithium intermediates

Modern organometallic methods enable the regioflexible conversion of simple heterocyclic starting materials into families of isomers and congeners. Depending on the choice of the reagent, 1-methyl-5-(trifluoromethyl)pyrazole (**1**) undergoes deprotonation and subsequent carboxylation mainly or exclusively at either the 4-position of the heterocycle or at the nitrogen-attached methyl group. Similarly, 1-phenyl-5-(trifluoromethyl)pyrazole (**5**) and 3-methyl-1-phenyl-5-(trifluoromethyl)pyrazole (**8**) are selectively attacked by lithium diisopropylamide at the heterocyclic 4-position and by butyllithium concomitantly at the 4-position and the *ortho* position of the phenyl ring. In contrast, metalation of 1-methyl-3-(trifluoromethyl)pyrazole (**2**) occurs only at the 5-position, whatever the organometallic or metal amide base. Further sites become accessible to functionalization if bromine is introduced into the heterocyclic or aromatic ring. This has been demonstrated with 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole (**3**), 4-bromo-1-methyl-3-(trifluoromethyl)pyrazole (**4**), 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole (**7**) and 1-(2-bromophenyl)-5-(trifluoromethyl)pyrazole (**6**).

Efficacy and versatility make organometallic methods particularly suitable for the functionalization of olefinic, aromatic and heterocyclic core structures.[1−2] The metalation of pyrazole, *N*-alkylpyrazoles and *N*-phenylpyrazole at the 5-position has been repeatedly reported.[3−10] The trapping products qualify as valuable intermediates for the synthesis of pharmaceuticals and agrochemicals. To probe further the intriguing steric and electronic properties of the CF_3 group,[11−12] we have turned our attention to trifluoromethyl-substituted pyrazoles. Previously, 5-methyl-1-phenyl-3-(trifluoromethyl)pyrazole, 3-methyl-1-phenyl-5-(trifluoromethyl)pyrazole and 1-phenyl-3,4-bis(trifluoromethyl)pyrazole have been treated with butyllithium, and metalation at the 4-position of the azole ring has been achieved to the extent of 0%, 11% and 95%, respectively.[13] Under similar conditions, 3-chloro-1-methyl-5-(trifluoromethyl)pyrazole was found to undergo 4-lithiation and subsequent carboxylation in 75% yield.[14]

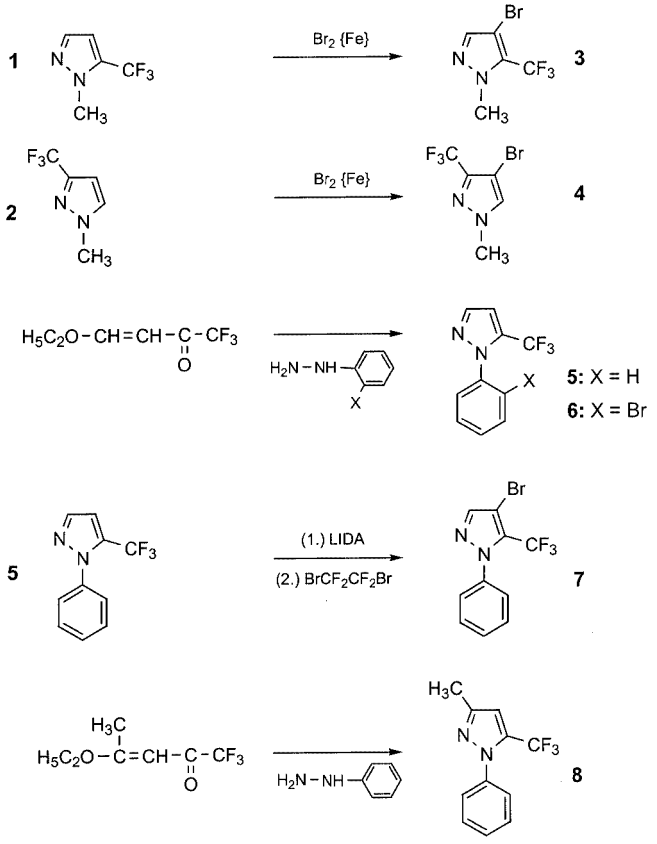
Although (trifluoromethyl)pyrazoles are readily accessible by condensation[15−27] or [3 + 2] cycloaddition[28] reactions, only one out of eight model substrates studied, 3-methyl-1-phenyl-5-(trifluoromethyl)pyrazole,[29] could be prepared according to a literature procedure. The isolation of 1-methyl-5-(trifluoromethyl)pyrazole (**1**) in 76% yield has also been reported. However, these results were not reproducible. In reality, 4-ethoxy-1,1,1-trifluoro-3-butene-2-one and methylhydrazine afforded a 3:7 mixture (up to 98%) of pyrazole **1** and the regioisomeric 1-methyl-3-(trifluoromethyl)pyrazole (**2**). A convenient separation of the two components could be accomplished after short reaction times when 4,5-dihydro-5-hydroxy-1-methyl-5-(trifluoromethyl)pyrazole, the precursor to isomer **1**, was still present, whereas isomer **2** had already formed.



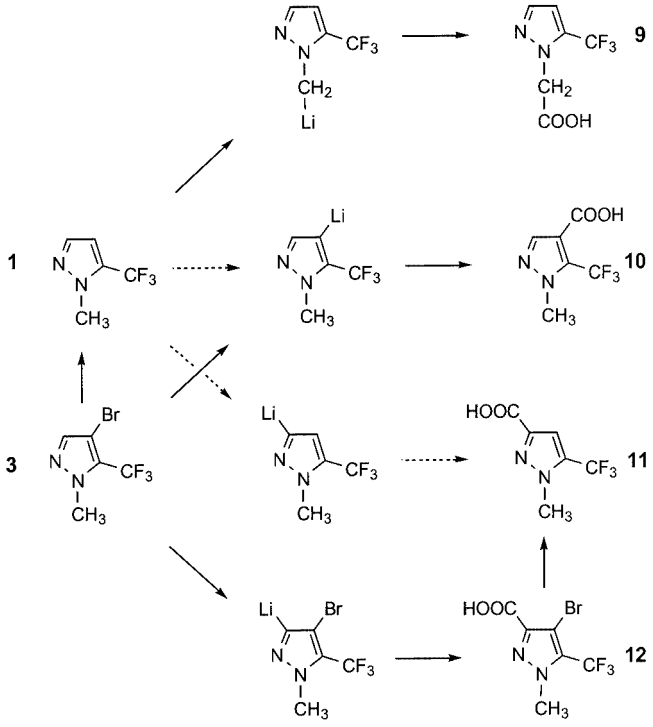
The other model substrates were prepared in a straightforward manner. Treatment of the isomers **1** and **2** with bromine in the presence of iron gave 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole (**3**; 67%) and 4-bromo-1-methyl-3-(trifluoromethyl)pyrazole (**4**; 65%), respectively. Condensation of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one with aniline or 2-bromoaniline gave 1-phenyl-5-(trifluoromethyl)pyrazole (**5**; 78%) and 1-(2-bromophenyl)-5-(trifluoromethyl)pyrazole (**6**; 78%). Compound **5** was converted into 4-bromo-1-phenyl-5-(trifluoromethyl)pyrazole (**7**; 52%) by consecutive reaction with lithium diisopropyl-

[a] Département de Chimie, BCh, Ecole Polytechnique Fédérale 1015 Lausanne, Switzerland
[b] Institut de Cristallographie, BSP, Université 1015 Lausanne, Switzerland

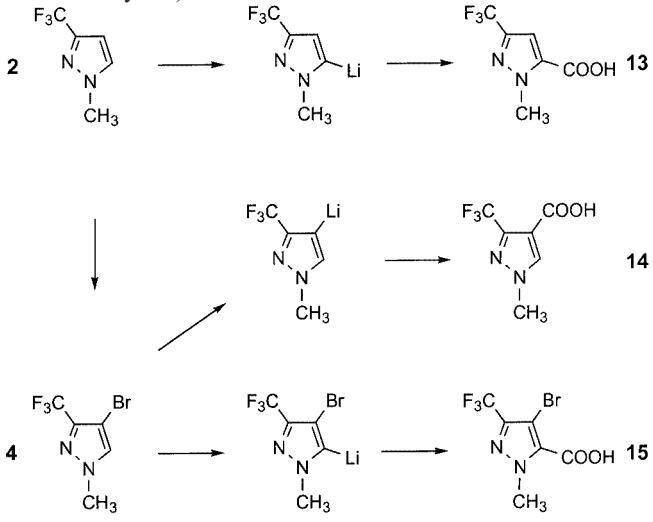
amide (LIDA) and 1,2-dibromo-1,1,2,2-tetrafluoroethane. 3-Methyl-1-phenyl-5-(trifluoromethyl)pyrazole[29] (**8**; 82%) was made by condensation of phenylhydrazine with 4-ethoxy-1,1,1-trifluoro-3-penten-2-one.



1-Methyl-5-(trifluoromethyl)pyrazole (**1**) was found to react with butyllithium in tetrahydrofuran at −75 °C exclusively at the methyl group. After carboxylation and neutralization, the acid **9** present in the crude reaction mixture amounted to 85%. It was isolated in 72% yield. Attack at *N*-methyl groups has previously been observed only as a side reaction when 1-methylpyrazole and 1,3-dimethylpyrazole were treated with butyllithium, the resulting NCH_2Li species being reminiscent of dipole stabilized[30−32] organometallic intermediates. Deprotonation of 1-methyl-5-(trifluoromethyl)pyrazole (**1**) with LIDA followed by carboxylation gave the 1-methyl-5-trifluoromethyl-4-pyrazolecarboxylic acid (**10**) in poor yields (25−33%) and, moreover, contaminated by trace amounts (2−6%) of the isomeric 1-methyl-5-trifluoromethyl-3-pyrazolecarboxylic acid (**11**). Both compounds **10** and **11** could be prepared selectively starting from 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole (**3**). Halogen/metal permutation with *tert*-butyllithium afforded 88% of the acid **10** after carboxylation and 67% of the corresponding aldehyde after trapping with *N*,*N*-dimethylformamide. Alternatively, LIDA-promoted deprotonation and subsequent carboxylation produced the brominated acid **12** in 70% yield. Reduction of the latter compound with zinc gave 1-methyl-5-trifluoromethyl-3-pyrazolecarboxylic acid (**11**) almost quantitatively (93%).

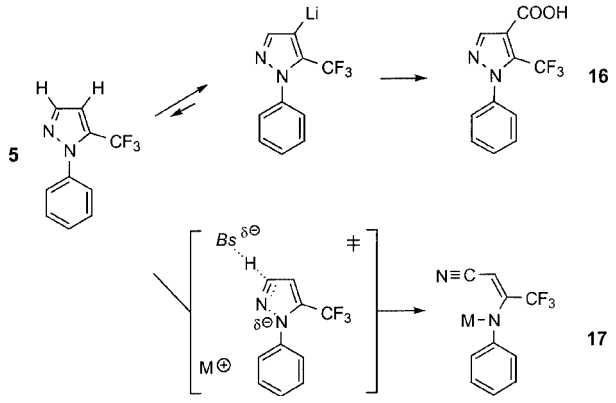


The transformations in the 3-(trifluoromethyl)pyrazole series were not compromised by any regioselectivity problems. Both 1-methyl-3-(trifluoromethyl)pyrazole (**2**) and 4-bromo-1-methyl-3-(trifluoromethyl)pyrazole (**4**) underwent LIDA-promoted deprotonation solely at the 5-position (thus making the acids **13** and **15** accessible in 70% and 90% yield), whereas bromo compound **4** reacted with *tert*-butyllithium by halogen/metal exchange (giving rise to acid **14** in 85% yield).

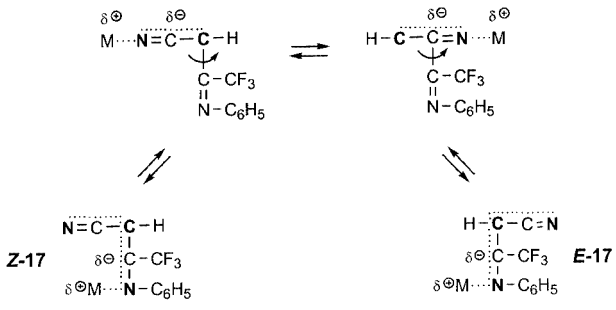


Lithiation and carboxylation were accomplished efficiently (62% of acid **16**, 52% of the corresponding aldehyde and 44% of the 4-iodo derivative) when LIDA was employed in the presence of *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyltriethylenediamine (PMDTA). In the absence of this complexand, large amounts (35−75%) of 3-anilino-4,4,4-trifluoro-2-butenenitrile (**17**; M = H) were formed along with the trapping product **16**. Other examples of basicity-driven ring opening reactions with pyrazoles are documented in

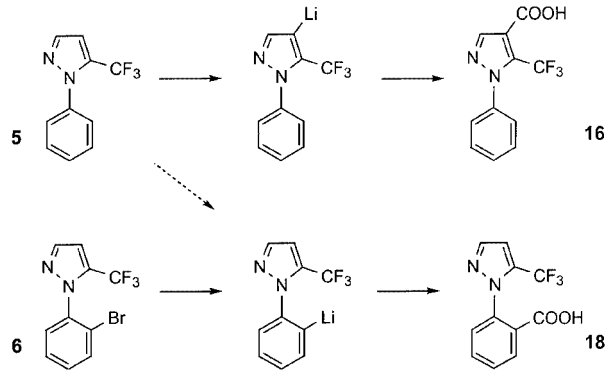
the literature.[33−36] In the present case, the N−N scission was presumably brought about in a concerted E2 process whereby LIDA and the 4-lithiated 1-phenyl-5-(trifluoromethyl)pyrazole may both have acted as bases ("*Bs*"). As a corollary, the product ratio **17/16** was found to increase progressively as a function of the exposure time (from 0.8 through 0.9 and 1.1 to 2.3 after 5, 15, 45 and 120 min at −75 °C).



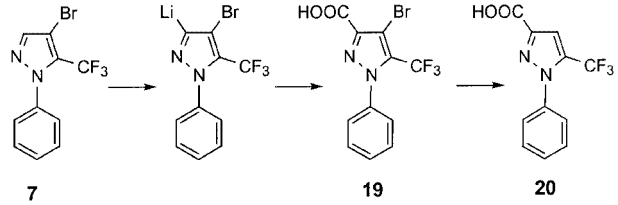
Although metal anilide **17** (M = Li) must have initially emerged in the (*Z*) configuration, the pure (*E*) isomer of the nitrile **17** (M = H) was isolated after neutralization. As previously encountered with monoaza analogs,[37−39] the 1,5-diaza-1,2-didehydropentadienyl intermediate apparently requires little energy to confine the area of delocalization to the 1-azapropargyl anion (nitrilomethanide) subunit and thus to restore free rotation around the CH−C(CF_3) axis.



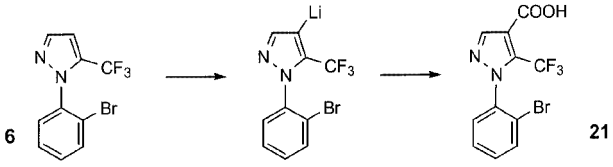
Concomitant deprotonation at the 4-position of the heterocycle and the *ortho* position of the phenyl ring took place when 1-phenyl-5-(trifluoromethyl)pyrazole (**5**) was treated with butyllithium. A mixture of 18% of the pyrazolecarboxylic acid **16** (see above) and 45% of 2-(5-trifluoromethyl-1-pyrazolyl)benzoic acid (**18**) was formed. The latter product was obtained uncontaminated and in 82% yield by the consecutive treatment of 1-(2-bromophenyl)-5-(trifluoromethyl)pyrazole (**6**) with *tert*-butyllithium and dry ice.



Deprotonation of the 4-bromo compound **7** with LIDA followed by carboxylation gave 4-bromo-1-phenyl-5-trifluoromethyl-3-pyrazolecarboxylic acid (**19**; 14%), which could be reduced with zinc to the 1-phenyl-5-trifluoromethyl-3-pyrazolecarboxylic acid (**20**; 32%). Ring opening producing derivatives of the nitrile **17** (see above) as unstable intermediates appears to compromise the success of both the deprotonation and the debromination step.

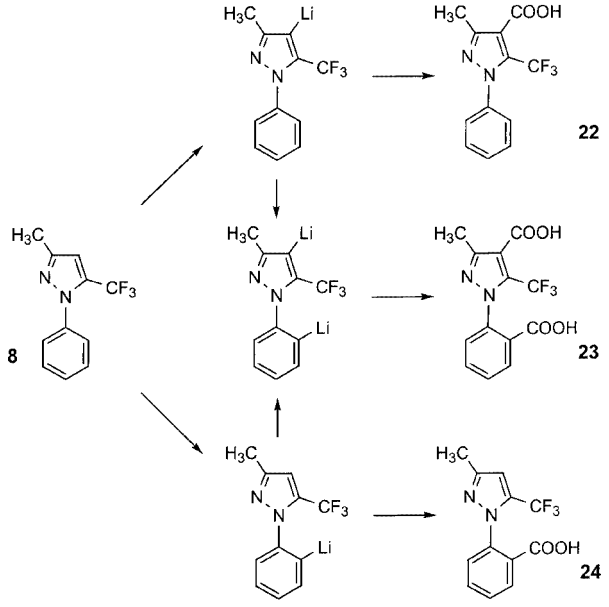


A slightly better result was achieved when 1-(2-bromophenyl)-5-(trifluoromethyl)pyrazole (**6**) was submitted to LIDA-promoted deprotonation and carboxylation. After neutralization, the acid **21** was isolated in still poor yield (24%).



In contrast to all the other substrates, the last one, 3-methyl-1-phenyl-5-(trifluoromethyl)pyrazole (**8**) has only a single vacant heterocyclic position and, therefore, has only a limited choice of regioselectivity. Moreover, the possibility of ring-opening β-eliminations is removed. Nevertheless, a mixture of two carboxylation products, 2-(3-methyl-5-trifluoromethyl-1-pyrazolyl)benzoic acid (**24**; 68%) and 3-methyl-1-phenyl-5-trifluoromethyl-4-pyrazolecarboxylic acid (**22**; 12%), was formed when butyllithium in tetrahydrofuran was used as the metalating agent. In addition, trace amounts (3%) of 1-(2-carboxylphenyl)-3-methyl-5-trifluoromethyl-4-pyrazolecarboxylic acid[13] (**23**) were present. The diacid **23** became the sole product (isolated in 65% yield) when a fourfold excess of butyllithium was employed. Clean *ortho* metalation of the pyrazole **8** was achieved with a stoichiometric quantity of butyllithium in diethyl ether, affording the acid **24** in 82% yield. On the other hand, lithium 2,2,6,6-tetramethylpiperidide was found

to abstract protons exclusively from the heterocyclic 4-position, thus opening an easy access to the acid **22** (68%) and the corresponding aldehyde (57%) and iodide (65%) as well.



Experimental Section

Details regarding standard operations and abbreviations can be found in previous publications from this laboratory.[40−42] ^{1}H and ^{19}F NMR spectra were recorded at 400 and 376 MHz, the chemical shifts listed referring to the internal standards (δ = 0.00 ppm) tetramethylsilane and trichlorofluoromethane, respectively. Samples were dissolved in deuterochloroform unless stated otherwise. Mass spectra were produced by chemical ionization (c.i.) in an ammonia atmosphere at 96 eV ionization potential and 100 °C source temperature.

1. Starting Materials

1-Methyl-5-(trifluoromethyl)pyrazole (1): At 0 °C, methylhydrazine (26 mL, 23 g, 0.50 mol) was slowly added to 4-ethoxy-1,1,1-trifluoro-3-buten-2-one[43] (84 g, 0.50 mol) in ethanol (0.25 L). The mixture was heated to 50 °C for 15 min before the solvents were evaporated. The oily residue became solid upon exhaustive trituration with pentanes (3 × 0.10 L). It was then taken up in diethyl ether (50 mL), treated with concentrated hydrochloric acid (1 mL) and heated under reflux for 1 h before being poured into water (50 mL). Extraction with diethyl ether (3 × 25 mL), washing of the combined organic layers with brine (2 × 25 mL), drying and evaporation of the solvents gave a colorless liquid which was distilled; b.p. 97−99 °C (ref.:[20] m.p. 68−70 °C); n_D^{20} = 1.3923; yield: 19.5 g (26%). ^{1}H NMR: δ = 7.47 (s, 1 H), 6.60 (s, 1 H), 4.00 (s, 3 H) ppm. ^{19}F NMR: δ = −60.9 (s) ppm. MS (c.i.): *m/z* (%) = 152 (7) [M + 2], 151 (100) [M + 1], 150 (44) [M$^+$], 149 (21), 131 (12). $C_5H_5F_3N_2$ (150.10): calcd. C 40.01, H 3.36; found C 40.04, H 3.43.

4,5-Dihydro-5-hydroxy-1-methyl-5-(trifluoromethyl)pyrazole: An analogous reaction performed on a 25 mmol scale was stopped before the acid treatment. The solid material obtained after thorough trituration was rapidly dried; yield: 1.3 g (31%). ^{1}H NMR: δ = 6.74 (s, 1 H), 3.61 (br. s, 1 H), 3.24 (d, *J* = 18.5 Hz, 1 H), 2.98 (s, 3 H), 2.90 (d, *J* = 18.5 Hz, 1 H). Due to slow spontaneous dehydration the material was too fragile to be sent for microanalysis.

1-Methyl-3-(trifluoromethyl)pyrazole (2): A solution of methylhydrazine (16 mL, 14 g, 0.30 mol) and 4-ethoxy-1,1,1-trifluoro-3-buten-2-one[43] (50 g, 0.30 mol) in methanol (0.15 L) was heated under reflux for 4 h before being poured into water (0.50 L). Extraction of the aqueous phase with diethyl ether (3 × 0.10 L), washing of the combined organic layers with water (3 × 50 mL) and brine (2 × 50 mL), drying, evaporation of the solvents and fractional distillation afforded a colorless liquid; b.p. 66−68 °C/18 Torr; $[n]_D^{20}$ = 1.4000; yield: 22.0 g (49%). ^{1}H NMR: δ = 7.41 (d, *J* = 1.1 Hz, 1 H), 6.51 (d, *J* = 2.4 Hz, 1 H), 3.97 (s, 3 H) ppm. ^{19}F NMR: δ = −62.4 (s) ppm. MS (c.i.): *m/z* (%) = 152 (6) [M$^+$ +2], 151 (100) [M + 1], 150 (36) [M$^+$], 149 (12), 131 (14). $C_5H_5F_3N_2$ (150.10): calcd. C 40.01, H 3.36; found C 39.91, H 3.33.

1-Bromo-1-methyl-5-(trifluoromethyl)pyrazole (3): 1-Methyl-5-(trifluoromethyl)pyrazole (**1**; 11 g, 75 mmol), bromine (10 mL, 32 g, 0.20 mol) and iron powder (2.2 g, 40 mmol) were mixed at 0 °C and heated to 100 °C for 1 h before being treated with a solution of sodium thiosulfate (40 g, 0.25 mol) in water (0.25 L). The aqueous phase was extracted with diethyl ether (3 × 0.10 L). The combined organic layers were washed with water (2 × 50 mL) and brine (50 mL), dried and the solvents evaporated. Upon distillation a colorless liquid was collected; b.p. 65−66 °C/70 Torr; $[n]_D^{20}$ = 1.4519; yield: 11.5 g (67%). ^{1}H NMR: δ = 7.48 (s, 1 H), 4.01 (q, *J* = 1.1 Hz, 3 H) ppm. ^{19}F NMR: δ = −59.0 (s) ppm. MS (c.i.): *m/z* (%) = 231 (7) [M$^+$ + 1], 230 (94) [M$^+$], 228 (100), 227 (23), 211 (14). $C_5H_4BrF_3N_2$ (229.00): calcd. C 26.22, H 1.76; found C 26.16, H 1.80.

4-Bromo-1-methyl-3-(trifluoromethyl)pyrazole (4): 1-Methyl-3-(trifluoromethyl)pyrazole (**2**; 11 g, 75 mmol) was submitted to the same treatment as described in the preceding paragraph except that the mixture was heated to 100 °C for 4 h. After distillation, the product crystallized from pentanes (at −25 °C) as colorless platelets; m.p. 28−30 °C; b.p. 84−85 °C/14 Torr; yield: 11.2 g (65%). ^{1}H NMR: δ = 7.47 (s, 1 H), 3.95 (s, 3 H) ppm. ^{19}F NMR: δ = −62.5 (s) ppm. MS (c.i.): *m/z* (%) = 231 (22) [M + 1], 230 (96) [M$^+$], 228 (100). $C_5H_4BrF_3N_2$ (229.00): calcd. C 26.22, H 1.76; found C 26.58, H 1.72.

Pyrazole **4** was also prepared by condensation of 3-bromo-4-ethoxy-1,1,1-trifluoro-3-buten-2-one[44] (50 mmol) with methylhydrazone (50 mmol). However, due to the extensive formation of by-products, the expected compound **4** could be isolated in a yield of only 11%.

1-Phenyl-5-(trifluoromethyl)pyrazole (5): A solution of 4-ethoxy-1,1,1-trifluoro-3-buten-one[43] (25 g, 0.15 mol) and phenylhydrazine (15 mL, 16 g, 0.15 mol) in ethanol (75 mL) was heated for 2 h under reflux and then the volatiles were evaporated. The residue was taken up in dichloromethane (0.10 L) and concentrated hydrochloric acid (5.0 mL) was added. The mixture was stirred at 25 °C for 1 h. After washing of the organic layer with a saturated aqueous solution (2 × 25 mL) of sodium hydrogen carbonate, distillation under reduced pressure gave a colorless liquid; m.p. −12 to −9 °C; b.p. 81−82 °C/14 Torr; $[n]_D^{20}$ = 1.5010; yield: 24.8 g (78%). ^{1}H NMR: δ = 7.70 (d, *J* = 1.1 Hz, 1 H), 7.48 (s, 5 H), 6.81 (d, *J* = 1.6 Hz, 1 H) ppm. ^{19}F NMR: δ = −57.9 (s) ppm. MS (c.i.): *m/z* (%) = 230 (4) [M$^+$ + NH$_4$], 214 (8) [M$^+$ + 2], 213 (100) [M$^+$ + 1], 212 (27) [M$^+$]. $C_{10}H_7F_3N_2$ (212.17): calcd. C 56.61, H 3.33; found C 56.79, H 3.24.

1-(2-Bromophenyl)-5-(trifluoromethyl)pyrazole (6): Prepared from 2-bromophenylhydrazine[45] (28 g, 0.15 mol) as described in the pre-

ceding paragraph; colorless cubes; m.p. 26−28 °C (from pentanes); b.p. 115−117 °C/13 Torr; yield: 34.1 g (78%). ^{1}H NMR: δ = 7.76 (d, *J* = 1.1 Hz, 1 H), 7.73 (dt, *J* = 7.7, 1.1 Hz,), 7.4 (m, 3 H), 6.82 (d, *J* = 1.1 Hz, 1 H) ppm. ^{19}F NMR: δ = −59.6 (s) ppm. MS (c.i.): *m/z* (%) = 310 (5) [M^+ + NH_4], 294 (17), 293 (95) [M^+ + 1], 292 (38) [M^+], 291 (100), 290 (21). $C_{10}H_6BrF_3N_2$ (291.07): calcd. C 41.26, H 2.08; found C 41.28, H 2.25.

4-Bromo-1-phenyl-5-(trifluoromethyl)pyrazole (7): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (5.2 mL, 4.3 g, 25 mmol) and 1-phenyl-5-(trifluoromethyl)pyrazole (**5**; 5.3 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL) kept in a dry ice bath. After 5 min at −75 °C, the mixture was treated with 1,2-dibromotetrafluoroethane (3.0 mL, 6.5 g, 25 mmol), the volatiles were evaporated, the residue dissolved in hexanes (0.10 L) and filtered through a pad of silica gel (40 mL). Upon distillation under reduced pressure, a faintly yellow liquid was collected; b.p. 79−81 °C/1 Torr; yield: 3.8 g (52%). ^{1}H NMR: δ = 7.71 (s, 1 H), 7.5 (m, 3 H), 7.4 (m, 2 H) ppm. ^{19}F NMR: δ = −56.6 (s) ppm. MS (c.i.): *m/z* (%) = 310 (2) [M^+ + NH_4], 293 (93) [M^+ + 1], 292 (41) [M^+], 291 (100), 290 (32). $C_{10}H_6BrF_3N_2$ (291.07): calcd. C 41.26, H 2.08; found C 41.20, H 2.07.

2. Transformations of Trifluoromethyl-Substituted 1-Methylpyrazoles

(5-Trifluoromethyl-1-pyrazolyl)acetic Acid (9): A solution containing 1-methyl-5-(trifluoromethyl)pyrazole (**1**; 3.0 g, 20 mmol) and butyllithium (20 mmol) in tetrahydrofuran (50 mL) and hexanes (12 mL) was stored for 45 min at −75 °C before being poured onto an excess of freshly crushed dry ice. After evaporation of the volatiles, the residue was dissolved in 1.0 M aqueous sodium hydroxide (0.10 L). A small sample was withdrawn, acidified and treated exhaustively with diazomethane. According to gas chromatography (30 m, DB-FFAP, 90 °C; 30 m, DB-1701, 120 °C; pentadecane as a calibrated internal standard) the mixture contained 85% of acid **9** (or its methyl ester). The bulk of the aqueous phase was washed with diethyl ether (2 × 25 mL), acidified with concentrated hydrochloric acid to pH 2, saturated with sodium chloride and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (25 mL), dried and the solvents evaporated. The solid left behind was crystallized from an ethyl acetate/hexanes mixture; m.p. 83−85 °C; yield: 2.8 g (72%). ^{1}H NMR: δ = 7.62 (d, *J* = 1.3 Hz, 1 H), 6.71 (d, *J* = 1.3 Hz, 1 H), 5.14 (s, 2 H) ppm. ^{19}F NMR: δ = −60.3 (s) ppm. MS (c.i.): *m/z* (%) = 212 (6) [M^+ + NH_4], 196 (33) [M^+ + 2], 195 (100) [M^+ + 1], 194 (1) [M^+], 150 (7). $C_6H_5F_3N_2O_2$ (194.11): calcd. C 37.13, H 2.60; found C 37.08, H 2.44.

1-Methyl-5-trifluoromethyl-4-pyrazolecarboxylic Acid (10): With gentle shaking, a precooled solution of *tert*-butyllithium (40 mmol) in pentanes (25 mL) was added to 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole (**3**; 4.6 g, 20 mmol) in diethyl ether (50 mL) kept in a dry ice bath. After 5 min at −75 °C, the mixture was treated with carbon dioxide and worked up as described in the preceding paragraph. The product was isolated as small, colorless cubes; m.p. 122−124 °C (from chloroform and hexanes); yield: 3.4 g (88%). ^{1}H NMR: δ = 8.01 (s, 1 H), 4.11 (q, *J* = 1.9 Hz, 3 H) ppm. ^{19}F NMR: δ = −57.7 (s) ppm. MS (c.i.): *m/z* (%) = 213 (17), 212 (82) [M^+ + NH_4], 196 (16) [M^+ + 2], 195 (97) [M^+ + 1], 194 (23) [M^+], 178 (10), 177 (100). $C_6H_5F_3N_2O_2$ (194.11): calcd. 37.13, H 2.60; found C 37.09, H 2.70.

When 1-methyl-5-(trifluoromethyl)pyrazole (**1**; 3.0 g, 20 mmol) was added to a solution of lithium diisopropylamide (20 or 40 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL) and, after 45 min or 2 h at −75 °C, the mixture was allowed to react with dry ice, 25−33% of acid **10** and 2−6% of acid **11** (see below) were present. They were identified and quantified by gas chromatography (30 m, DB-FFAP, 90 °C; 30 m, DB 1701, 120 °C; pentadecane as a calibrated internal standard) after prior alkaline extraction, neutralization and treatment with diazomethane until the yellow color persisted.

When *tert*-butyllithium in diethyl ether was again used as the metalating reagent (see above), but *N*,*N*-dimethylformamide (1.5 mL, 1.4 g, 20 mmol) was employed instead of carbon dioxide, **1-methyl-5-trifluoromethyl-4-pyrazolecarbaldehyde** was obtained after hydrolysis, ethereal extraction and crystallization as tiny needles; m.p. 56−58 °C (from hexanes); yield: 2.4 g (67%). ^{1}H NMR: δ = 10.03 (s, 1 H), 8.00 (s, 1 H), 4.07 (q, *J* = 1.1 Hz, 3 H) ppm. ^{19}F NMR: δ = −58.3 (s) ppm. MS (c.i.): *m/z* (%) = 196 (3) [M^+ + NH_4], 179 (23) [M^+ + 1], 178 (19) [M^+], 177 (100), 159 (11). $C_6H_5F_3N_2O$ (178.11): calcd. C 40.46, H 2.83; found C 40.42, H 2.91.

1-Methyl-5-trifluoromethyl-3-pyrazolecarboxylic Acid (11): A slurry containing 4-bromo-1-methyl-5-trifluoromethyl-3-pyrazolecarboxylic acid (**12**; 2.7 g, 10 mmol; see below) and zinc (3.3 g, 50 mmol) in 10% aqueous sodium hydroxide (50 mL) was vigorously stirred at 25 °C for 1 h. The mixture was filtered and worked up as described above (see acid **9**). Colorless platelets were collected; m.p. 127−129 °C (after sublimation); yield: 1.8 g (93%). ^{1}H NMR: δ = 7.23 (s, 1 H), 4.11 (s, 3 H) ppm. ^{19}F NMR: δ = −61.4 (s) ppm. MS (c.i.): *m/z* (%) = 213 (31), 212 (100) [M^+ + NH_4], 196 (20) [M^+ + 2], 195 (79) [M^+ + 1], 194 (17) [M^+], 177 (38). $C_6H_5F_3N_2O_2$ (194.11): calcd. C 37.13, H 2.60; found C 37.06, H 2.66.

4-Bromo-1-methyl-5-trifluoromethyl-3-pyrazolecarboxylic Acid (12): At −75 °C, diisopropylamine (2.8 mL, 2.0 g, 20 mmol) and 4-bromo-1-methyl-5-(trifluoromethyl)pyrazole (**3**; 4.6 g, 20 mmol) were added consecutively to butyllithium (20 mmol) in tetrahydrofuran (40 mL) and hexanes (15 mL). After 5 min, the mixture was poured onto an excess of freshly crushed dry ice and treated further as described above (see acid **9**) to afford colorless cubes; m.p. 143−145 °C (from ethyl acetate and hexanes); yield: 3.8 g (70%). ^{1}H NMR: δ = 4.15 (s, 3 H) ppm. ^{19}F NMR: δ = −59.3 ppm. MS (c.i.): *m/z* (%) = 275 (16) [M^+ + 1], 274 (100) [M^+], 273 (23), 272 (100), 271 (6), 257 (49), 255 (48). $C_6H_4BrF_3N_2O_2$ (273.01): calcd. C 26.40, H 1.48; found C 26.04, H 1.59.

1-Methyl-3-trifluoromethyl-5-pyrazolecarboxylic Acid (13): Diisopropylamine (2.8 mL, 2.0 g, 20 mmol) and 1-methyl-3-(trifluoromethyl)pyrazole (**2**; 3.0 g 20 mmol) were added consecutively to a solution of butyllithium (20 mmol) in tetrahydrofuran (40 mL) and hexanes (15 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed, solid carbon dioxide. The workup procedure followed the example described above (see acid **9**). The product was collected as colorless needles; m.p. 130−131 °C (after sublimation); yield: 3.2 g (70%). ^{1}H NMR: δ = 7.24 (s, 1 H), 4.27 (s, 3 H) ppm. ^{19}F NMR: δ = −62.8 (s) ppm. MS (c.i.): *m/z* (%) = 212 (2) [M^+ + NH_4], 195 (89) [M^+ + 1], 194 (69) [M^+], 172 (34). $C_6H_5F_3N_2O_2$ (194.11): calcd. C 37.13, H 2.62; found C 37.21, H 2.60.

1-Methyl-3-trifluoromethyl-4-pyrazolecarboxylic Acid (14): Obtained from 4-bromo-1-methyl-3-(trifluoromethyl)pyrazole (**4**; 4.6 g, 20 mmol) and *tert*-butyllithium (40 mmol) as described above (see acid **10**); colorless prisms; m.p. 200−201 °C (from ethyl acetate and hexanes; ref.:[46] m.p. 199−200 °C); yield: 3.3 g (85%) ppm. MS

(c.i.): *m/z* (%) = 195 (21) [M^+ + 1], 194 (37) [M^+], 178 (7), 177 (100), 155 (23).

4-Bromo-1-methyl-3-trifluoromethyl-5-pyrazolecarboxylic Acid (15): Prepared from 4-bromo-1-methyl-3-(trifluoromethyl)pyrazole (**4**; 4.6 g, 20 mmol) and lithium diisopropylamide (20 mmol) as described above (see acid **12**); colorless prisms; m.p. 194−196 °C (from ethyl acetate and hexanes); yield: 4.9 g (90%). ^{1}H NMR: δ = 4.27 (s, 3 H) ppm. ^{19}F NMR: δ = −62.9 ppm. MS (c.i.): *m/z* (%) = 275 (13) [M^+ + 1], 274 (100) [M^+], 273 (18), 272 (97), 271 (6), 255 (21). $C_6H_4BrF_3N_2O_2$ (273.01): calcd. C 26.40, H 1.48; found C 26.15, H 1.08.

3. Transformation of Trifluoromethyl-Substituted 1-Arylpyrazoles

(*E*)-4,4,4-Trifluoro-2-phenylamino-2-butenenitrile (17): Diisopropylamine (2.8 mL, 2.0 g, 20 mmol) and 1-phenyl-5-(trifluoromethyl)-pyrazole (**5**; 4.2 g, 20 mmol) were added consecutively to a solution of butyllithium (20 mmol) in tetrahydrofuran (25 mL) and hexanes (15 mL) kept in a dry ice bath. After 6 h at −75 °C, the mixture was allowed to reach 0 °C. It was concentrated, poured into water (0.10 L) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (2 × 25 mL), dried and the solvents evaporated. The residue was crystallized; yellow stars; m.p. 97−99 °C (from chloroform and hexanes; yield: 3.2 g (75%). ^{1}H NMR: δ = 7.45 (t, *J* = 7.9 Hz, 2 H), 7.30 (t, *J* = 7.5 Hz, 1 H), 7.20 (d, *J* = 7.5 Hz, 2 H), 6.21 (br. s, 1 H), 4.76 (s, 1 H) ppm. ^{19}F NMR: δ = −67.9 ppm. MS (c.i.): *m/z* (%) = 231 (13), 230 (100) [M^+ + NH_4], 214 (11) [M^+ + 2], 2 13 (83) [M^+ + 1], 212 (47) [M^+]. $C_{10}H_7F_3N_2$ (212.17): calcd. C 56.61, H 3.33; found C 56.46, H 3.40.

Crystal Structure of Nitrile 17: The compound crystallized from a chloroform/hexanes mixture in the orthorhombic space group $Pbn2_1$. At $Z = 4$, $a = 7.2381(14)$, $b = 7.525(2)$, $c = 17.556(4)$ Å and $M_r = 212.18$, the calculated density, ρ_{calc}, became 1.474 g·cm^{-1}. The structure was solved by direct methods as implemented in the program SIR97.[47] A total of 5393 reflections were collected on a *Stoe IPDS* diffractometer using Mo-K_α radiation (λ = 0.71073 Å), μ = 0.131 mm^{-1}, no absorption correction being made. Using 2128 reflections with $I \geq 2\sigma(I)$, the final full-matrix least-squares refinement[48] of 136 variables converged to R_1 = 0.0563 {$wR_2 = 0.0818$, $w = [\sigma^2(F_o^2)]^{-1}$}. The residual electron density fell in the range $\Delta\rho = [-0.351, +0.238]$ e·Å^{-3}. Hydrogen atoms were located and refined isotropically, whereas the remainder of the atoms were optimized anisotropically. CCDC-179870 contains the supplementary crystallographic data for this work. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

1-Phenyl-5-trifluoromethyl-4-pyrazolecarboxylic Acid (16): Diisopropylamine (2.8 mL, 2.0 g, 20 mmol), *N*,*N*,*N*′,*N*′′,*N*′′′-pentamethyldiethylenetriamine (4.2 mL, 3.5 g, 20 mmol) and 1-phenyl-5-(trifluoromethyl)pyrazole (**5**; 4.2 g, 20 mmol) were added consecutively to a solution of butyllithium (20 mmol) in tetrahydrofuran (25 mL) and hexanes (10 mL) kept in a dry ice bath. After 5 min at −75 °C, the mixture was poured onto an excess of freshly crushed carbon dioxide, before being worked up as described above (see acid **9**). The product was purified by recrystallization; colorless cubes; m.p. 132−134 °C (from chloroform and hexanes; ref.:[46] m.p. 129−131 °C); yield: 3.2 g (62%). ^{1}H NMR: δ = 8.22 (s, 1 H), 7.5 (m, 3 H), 7.4 (m, 2 H) ppm. ^{19}F NMR: δ = −55.9 ppm. MS (c.i.): *m/z* (%) = 257 (73) [M^+ + 1], 256 (100) [M^+], 239 (33).

Treatment of the acid **16** (10 mmol) with ethereal diazomethane gave the **methyl ester** as a colorless viscous oil; m.p. 21−23 °C; b.p. 60−61 °C/0.1 Torr; yield: 2.5 g (93%). ^{1}H NMR: δ = 8.12 (s, 1 H), 7.5 (m, 3 H), 7.4 (m, 2 H), 3.92 (s, 3 H) ppm. ^{19}F NMR: δ = −56.0 ppm. MS (c.i.): *m/z* (%) = 288 (4) [M^+ + NH_4], 272 (19) [M^+ + 2], 2 71 (100) [M^+ + 1], 270 (23) [M^+], 239 (15). $C_{12}H_9F_3N_2$ (270.21): calcd. C 53.34, H 3.36; found C 53.41, H 3.15.

1-Phenyl-5-trifluoromethyl-4-pyrazolecarbaldehyde: 1-Phenyl-5-(trifluoromethyl)pyrazole (**5**; 4.2 g, 20 mmol) was treated as described in the preceding paragraph (see acid **16**) but at the end *N*,*N*-dimethylformamide (3.1 mL, 2.9 g, 40 mmol) was added rather than carbon dioxide. At 25 °C, the mixture was poured into water (0.10 L) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were concentrated, absorbed on silica gel (20 mL) and eluted with a 1:9 (v/v) mixture of ethyl acetate and hexanes from a column filled with more silica (0.20 L). Crystallization afforded small yellow cubes; m.p. 93−95 °C (from chloroform and hexanes); yield: 2.5 g (52%). ^{1}H NMR: δ = 10.15 (s, 1 H), 8.21 (s, 1 H), 7.5 (m, 5 H) ppm. ^{19}F NMR: δ = −55.2 ppm. MS (c.i.): *m/z* (%) = 241 (36) [M^+ + 1], 2 40 (100) [M^+], 239 (93) [M^+], 238 (14). $C_{11}H_7F_3N_2O$ (240.18): calcd. C 55.01, H 2.94; found C 55.21, H 2.62.

4-Iodo-1-phenyl-5-(trifluoromethyl)pyrazole: The iodo derivative was prepared from 1-phenyl-5-(trifluoromethyl)pyrazole (**5**; 4.2 g, 20 mmol) using iodine (2.6 g, 20 mmol) instead of carbon dioxide (see acid **16**) or *N*,*N*-dimethylformamide (see preceding paragraph) to intercept the organometallic intermediate. The product was isolated by column chromatography (under identical conditions to those reported in the preceding paragraph) as a colorless viscous oil (after distillation); b.p. 73−75 °C/0.2 Torr; yield: 3.0 g (44%). ^{1}H NMR: δ = 7.75 (s, 1 H), 7.5 (m, 3 H), 7.4 (m, 2 H) ppm. ^{19}F NMR: δ = −55.8 (s) ppm. MS (c.i.): *m/z* (%) = 340 (15) [M^+ + 2], 339 (65) [M^+ +1], 338 (46) [M^+], 213 (29). $C_{10}H_6F_3IN_2$ (338.07): calcd. C 35.53, H 1.79; found C 35.28, H 1.65.

2-(5-Trifluoromethyl-1-pyrazolyl)benzoic Acid (18): At −75 °C, *tert*-butyllithium (40 mmol) in pentanes (25 mL) was added to 1-(2-bromophenyl)-5-(trifluoromethyl)pyrazole (**6**; 5.8 g, 20 mmol) in diethyl ether (50 mL). After 5 min, the mixture was poured onto an excess of freshly crushed dry ice. The product was isolated as described above (see acid **9**); colorless stars; m.p. 121−123 °C (from ethyl acetate and hexanes); yield: 4.2 g (82%). ^{1}H NMR: δ = 8.14 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.7 (m, 2 H), 7.63 (td, *J* = 7.8, 1.4 Hz, 1 H), 7.48 (d, *J* = 7.8 Hz, 1 H), 6.8 (m, 1 H) ppm. ^{19}F NMR: δ = −59.2 (s) ppm. MS (c.i.): *m/z* (%) = 270 (12) [M^+ + NH_4], 257 (5) [M^+ + 1], 239 (22), 212 (93), 84 (100). $C_{11}H_7F_3N_2O_2$ (256.18): calcd. C 51.57, H 2.75; found C 51.48, H 3.01.

The acid **18** (2.6 g, 10 mmol) was converted into the **methyl ester** using ethereal diazomethane; white waxy mass; m.p. 29−31 °C; b.p. 76−78 g/0.1 Torr; yield: 2.5 g (93%). ^{1}H NMR: δ = 8.09 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.71 (td, *J* = 7.8, 1.5 Hz, 1 H), 7.67 (td, *J* = 7.8, 1.8 Hz, 1 H), 7.48 (d, *J* = 7.8 Hz, 1 H), 6.81 (d, *J* = 1.8 Hz, 1 H), 3.68 (s, 3 H) ppm. ^{19}F NMR: δ = −59.3 (s) ppm. MS (c.i.): *m/z* (%) = 271 (24) [M^+ + 1], 270 (69) [M^+], 240 (27), 239 (100), 212 (20). $C_{12}H_9F_3N_2O_2$ (270.21): calcd. C 53.34, H 3.36; found C 53.61, H 3.13.

4-Bromo-1-phenyl-5-trifluoromethyl-3-pyrazolecarboxylic Acid (19): Diisopropylamine (1.4 mL, 1.0 g, 10 mmol), *N*,*N*,*N*′,*N*′′,*N*′′′-pentamethyldiethylenetriamine (2.1 mL, 1.7 g, 10 mmol) and 4-bromo-1-phenyl-5-(trifluoromethyl)pyrazole (**7**; 3.0 g, 10 mmol) were added consecutively to a solution of butyllithium (10 mmol) in tetrahydrofuran (20 mL) and hexanes (5 mL) kept in a dry ice bath. After

5 min at −75 °C, carboxylation, neutralization and crystallization were carried out as described above (see acid **9**); colorless needles; m.p. 163−164 °C (after sublimation); yield: 0.47 g (14%). ^{1}H NMR: δ = 7.5 (m, 3 H), 7.44 (d, *J* = 7.8 Hz, 2 H) ppm. ^{19}F NMR: δ = −56.5 ppm. MS (c.i.): *m/z* (%) = 356 (4), 355 (27), 354 (72) [$M^+ + NH_4$], 353 (30), 352 (79), 339 (5), 338 (37), 337 (99) [$M^+ + 1$], 336 (80) [M^+], 335 (100), 334 (68). $C_{11}H_6BrF_3N_2O_2$ (335.08): calcd. C 39.43, H 1.80; found C 39.42, H 1.90.

1-Phenyl-5-trifluoromethyl-3-pyrazolecarboxylic Acid (20): Zinc powder (0.14 g, 2.0 mmol) was added to a solution of 4-bromo-1-phenyl-5-trifluoromethyl-3-pyrazolecarboxylic acid (**19**; 0.35 g, 1.0 mmol) in 10% aqueous sodium hydroxide (5.0 mL). After 6 h of vigorous stirring at 25 °C, the reaction mixture was filtered to remove unconsumed zinc, acidified to pH 2, saturated with sodium chloride and extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried and the solvents evaporated. Colorless platelets were obtained upon crystallization; m.p. 132−133 °C (from ethyl acetate and hexanes); yield: 82 mg (32%). ^{1}H NMR: δ = 8.21 (s, 1 H), 7.5 (m, 3 H), 7.4 (m, 2 H) ppm. ^{19}F NMR: δ = −55.9 (s) ppm. MS (c.i.): *m/z* (%) = 275 (28), 274 (47) [$M^+ + NH_4$], 273 (24), 259 (21), 258 (49), 257 (100) [$M^+ + 1$], 256 (86), 255 (31). $C_{11}H_7F_3N_2O_2$ (256.18): calcd. C 51.57, H 2.75; found C 51.55, H 2.72.

1-(2-Bromophenyl)-5-trifluoromethyl-4-pyrazolecarboxylic Acid (21): The procedure specified above (see acid **16**), applied to 1-(2-bromophenyl)-5-trifluoromethyl)pyrazole (**6**; 5.8 g, 20 mmol), afforded the expected product; colorless prisms; m.p. 130−132 °C (from diethyl ether and pentanes); yield: 1.6 g (24%). ^{1}H NMR: δ = 8.29 (s, 1 H), 7.7 (m, 1 H), 7.4 (m, 3 H) ppm. ^{19}F NMR: δ = −57.6 (s) ppm. MS (c.i.): *m/z* (%) = 338 (28), 337 (91), 336 (42) [M^+], 335 (92), 334 (17), 272 (23), 76 (100). $C_{10}H_6BrF_3N_2O_2$ (335.08): calcd. C 39.43, H 1.80; found C 39.26, H 1.81.

3-Methyl-1-phenyl-5-trifluoromethyl-4-pyrazolecarboxylic Acid (22): 2,2,6,6-Tetramethylpiperidine (5.6 mL, 4.0 g, 40 mmol) and 3-methyl-1-phenyl-5-(trifluoromethyl)pyrazole[29] (**8**; 9.0 g, 40 mmol) were added consecutively to a solution of butyllithium (40 mmol) in tetrahydrofuran (75 mL) and hexanes (25 mL) cooled to −25 °C. After 2 h at −25 °C, the mixture was poured onto an excess of freshly crushed dry ice and was worked up as described above (see acid **9**) to afford colorless needles; m.p. 149−151 °C; yield: 7.4 g (68%). ^{1}H NMR: δ = 7.5 (m, 3 H), 7.4 (m, 2 H), 2.57 (s, 3 H) ppm. ^{19}F NMR: δ = −59.2 (s) ppm. MS (c.i.): *m/z* (%) = 288 (12) [$M^+ + NH_4$], 272 (32) [$M^+ + 2$], 271 (45) [$M^+ + 1$], 270 (100) [M^+]. $C_{12}H_9F_3N_2O_2$ (270.21): calcd. 53.34, H 3.36; found C 53.66, H 3.13.

The acid (**22**; 10 mmol) was converted into the **methyl ester** using diazomethane; colorless needles; m.p. 81−83 °C; yield: 2.0 g (70%). ^{1}H NMR: δ = 7.5 (m, 3 H), 7.4 (m, 2 H), 3.91 (s, 3 H), 2.50 (s, 3 H) ppm. ^{19}F NMR: δ = −56.3 (s) ppm. MS (c.i.): *m/z* (%) = 285 (39), 284 (100) [M^+], 253 (58). $C_{13}H_{11}F_3N_2O_2$ (284.24): calcd. C 54.93, H 3.90; found C 55.30, H 4.31.

3-Methyl-1-phenyl-5-trifluoromethyl-4-pyrazolecarbaldehyde: This compound was prepared from 3-methyl-1-phenyl-5-(trifluoromethyl)pyrazole [29] (**8**; 40 mmol) as described above (see the acid **22**), only with carbon dioxide being replaced by *N*,*N*-dimethylformamide (3.9 mL, 3.7 g, 50 mmol). Partitioning between water and diethyl ether followed by distillation gave a colorless liquid which crystallized as small prisms; m.p. 46−47 °C (from pentanes at 0 °C); b.p. 87−89 °C/1 Torr; yield: 5.8 g (57%). ^{1}H NMR: δ = 10.2 (m, 1 H), 7.5 (m, 3 H), 7.4 (m, 2 H), 2.56 (s, 3 H) ppm. ^{19}F NMR: δ = −54.7 (s) ppm. MS (c.i.): *m/z* (%) = 255 (22) [$M^+ + 1$], 254 (100) [M^+], 253 (72). $C_{12}H_9F_3N_2O_2$ (254.21): calcd. C 56.70, H 3.57; found C 56.69, H 3.59.

4-Iodo-3-methyl-1-phenyl-5-(trifluoromethyl)pyrazole: This compound was prepared from 3-methyl-1-phenyl-5-(trifluoromethyl)-pyrazole [29] (**8**; 9.0 g, 40 mmol) as described above (see the acid **22**), only with carbon dioxide being replaced by iodine (5.1 g, 40 mmol). The product was purified by distillation and crystallization after washing with a saturated aqueous solution of sodium thiosulfate and extraction with diethyl ether (3 × 50 mL); colorless needles; m.p. 51−53 °C (from pentanes at 0 °C); b.p. 93−95 °C/0.2 Torr; yield: 9.1 g, (65%). ^{1}H NMR: δ = 7.5 (m, 3 H), 7.4 (m, 2 H), 2.36 (s, 3 H) ppm. ^{19}F NMR: δ = −56.4 (s) ppm. MS (c.i.): *m/z* (%) = 371 (5), 370 (21) [$M^+ + NH_4$], 355 (11), 354 (51), 353 (100) [$M^+ + 1$], 352 (58) [M^+], 351 (24). $C_{11}H_8F_3IN_2$ (352.09): calcd. C 37.52, H 2.29; found C 37.53, H 2.54.

1-(2′-Carboxyphenyl)-3-methyl-5-trifluoromethyl-4-pyrazolecarboxylic Acid (23): 3-Methyl-1-phenyl-5-(trifluoromethyl)pyrazole[29] (**8**; 4.5 g, 20 mmol) was added to an ice-cold solution of butyllithium (80 mmol) in tetrahydrofuran (50 mL) and hexanes (50 mL). After 2 h at 0 °C, the mixture was poured onto an excess of freshly crushed dry ice and was worked up as described above (see the acid **9**). Colorless stars were obtained; m.p. 205−207 °C; yield: 4.1 g (65%). ^{1}H NMR (D_3CSOCD_3): δ = 8.16 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.82 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.76 (td, *J* = 7.6, 1.0 Hz, 1 H), 7.59 (dd, *J* = 7.6, 1.0 Hz, 1 H), 2.44 (s, 3 H) ppm. ^{19}F NMR (D_3CSOCD_3): δ = −55.5 (s) ppm. MS (c.i.): *m/z* (%) = 332 (4) [$M^+ + NH_4$], 316 (26), 315 (100) [$M^+ + 1$], 314 (9) [M^+], 297 (34), 271 (12). $C_{13}H_9F_3N_2O_4$ (314.22): calcd. C 49.69, H 2.89; found C 49.79, H 2.89.

2-(3-Methyl-5-trifluoromethyl-1-pyrazolyl)benzoic Acid (24): 3-Methyl-1-phenyl-5-(trifluoromethyl)pyrazole[29] (**8**; 4.5 g, 20 mmol) was added to an ice-cold solution of butyllithium (20 mmol) in diethyl ether (35 mL) and hexanes (15 mL). After 6 h at 0 °C, the mixture was poured onto an excess of freshly crushed dry ice and worked up as described above (see the acid **9**) to afford colorless needles; m.p. 117−119 °C (from ethyl acetate and hexanes); yield: 4.4 g (81%). ^{1}H NMR: δ = 8.11 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.67 (td, *J* = 7.8, 1.6 Hz, 1 H), 7.59 (td, *J* = 7.8, 1.3 Hz, 1 H), 7.46 (d, *J* = 7.8 Hz, 1 H), 6.56 (s, 1 H), 2.34 (s, 3 H) ppm. ^{19}F NMR: δ = −59.4 (s) ppm. MS (c.i.): *m/z* (%) = 271 (6) [$M^+ + 1$], 270 (6) [M^+], 253 (14), 227 (15), 226 (100). $C_{12}H_9F_3N_2O_2$ (270.21): calcd. C 53.34, H 3.36; found C 53.65, H 3.18.

Treatment of the acid **24** (10 mmol) with ethereal diazomethane gave the **methyl ester**, which was collected as a colorless oil after distillation; b.p. 90−92 °C/0.5 Torr; $[n]_D^{20}$ = 1.5033; yield: 2.3 g (81%). ^{1}H NMR: δ = 8.06 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.64 (td, *J* = 7.8, 1.8 Hz, 1 H), 7.58 (td, *J* = 7.8, 1.4 Hz, 1 H), 7.46 (d, *J* = 7.8 Hz, 1 H), 6.59 (s, 1 H), 3.69 (s, 3 H), 2.36 (s, 3 H) ppm. ^{19}F NMR: δ = −59.4 (s) ppm. MS (c.i.): *m/z* (%) = 285 (46), 284 (77) [M^+], 253 (100). $C_{13}H_{11}F_3N_2O_2$ (284.24): calcd. C 54.93, H 3.90; found C 54.93, H 3.79.

Acknowledgments

This work was financially supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Bern (grant 20-55′303-98), and the Bundesamt für Bildung und Wissenschaft, Bern (grant 97.0083 linked to the TMR project FMRXCT-970129).

[1] M. Schlosser, *Eur. J. Org. Chem.* **2001**, 3975−3984.
[2] M. Schlosser, in *Organometallics in Synthesis: A Manual* (Ed.: M. Schlosser), second edition, Wiley, Chichester, **2002**, pp. 1−352.
[3] H. R. Snyder, F. Verbanac, D. B. Bright, *J. Am. Chem. Soc.* **1952**, *74*, 3243−3246.
[4] P. W. Alley, D. A. Shirley, *J. Am. Chem. Soc.* **1958**, *80*, 6271−6274.
[5] R. Hüttel, M. E. Schön, *Justus Liebigs Ann. Chem.* **1959**, *625*, 55−65.
[6] D. E. Butler, S. M. Alexander, *J. Org. Chem.* **1972**, *37*, 215−220.
[7] A. Marxer, M. Siegrist, *Helv. Chim. Acta* **1974**, *57*, 1988−2000.
[8] A. R. Katritzky, P. Lue, K. Akutagawa, *Tetrahedron* **1989**, *45*, 4253−4262.
[9] G. W. Rewcastle, A. R. Katritzky, *Adv. Heterocycl. Chem.* **1993**, *56*, 155−302.
[10] M. R. Grimmett, B. Iddon, *Heterocycles* **1994**, *37*, 2087−2147; *Chem. Abstr.* **1994**, *121*, 230680t.
[11] M. Schlosser, F. Mongin, J. Porwisiak, W. Dmowski, H. H. Büker, N. M. M. Nibbering, *Chem. Eur. J.* **1998**, *4*, 1281−1286.
[12] M. Schlosser, in *Enantiocontrolled Synthesis of Fluoroorganic Compounds: Stereochemical Challenges and Biomedicinal Targets* (Ed.: V. A. Soloshonok), Wiley, Chichester, **1999**, 613−659.
[13] S. Iwata, C.-P. Qian, K. Tanaka, *Chem. Lett.* **1992**, 357−360.
[14] J. P. Chupp, *J. Heterocycl. Chem.* **1994**, *31*, 1377−1380.
[15] J. B. Wright, W. E. Dullin, J. H. Markillie, *J. Med. Chem.* **1964**, *7*, 102−105.
[16] S. Portnoy, *J. Heterocycl. Chem.* **1969**, *6*, 223−228.
[17] K. Tanaka, T. Suzuki, S. Maeno, K. Mitsuhashi, *J. Heterocycl. Chem.* **1986**, *23*, 1535−1538.
[18] I. I. Gerus, S. I. Vdovenko, M. G. Gorbunova, V. P. Kukhar, *Khim. Geterots. Soedin.* **1991**, *4*, 502−511; *Chem. Abstr.* **1991**, *115*, 183234q.
[19] E. Okada, R. Masuda, M. Hojo, *Heterocycles* **1992**, *34*, 791−798; *Chem. Abstr.* **1992**, *117*, 90199 h.
[20] M. E. F. Braibante, G. Clar, M. A. P. Martins, *J. Heterocycl. Chem.* **1993**, *30*, 1159−1160.
[21] M. Soufyane, C. Mirand, J. Levy, *Tetrahedron Lett.* **1993**, *34*, 7737−7740.
[22] I. I. Gerus, M. G. Gorbunova, V. P. Kukhar, *J. Fluorine Chem.* **1994**, *69*, 195−198.
[23] B. Jiang, Y.-Y. Xu, J. Yang, *J. Fluorine Chem.* **1994**, *67*, 83−85.
[24] B. G. Jones, S. K. Branch, A. S. Thompson, M. D. Threadgill, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2685−2691.
[25] S.-Z. Zhu, G.-L. Xu, C.-Y. Qin, Q.-L. Chu, Y. Xu, *Monatsh. Chem.* **1999**, 671−680.
[26] L.-P. Song, Q.-L. Chu, S.-Z. Zhu, *J. Fluorine Chem.* **2001**, *107*, 107−112.
[27] L.-P. Song, S.-Z. Zhu, *J. Fluorine Chem.* **2001**, *111*, 201−205.
[28] J.-H. Zheng, Z.-B. Wang, Y.-C. Shen, *J. Fluorine Chem.* **1993**, *61*, 17−21.
[29] J. W. Lyga, R. M. Patera, *J. Heterocycl. Chem.* **1990**, *27*, 919−921.
[30] R. R. Fraser, P. R. Hubert, *Can. J. Chem.* **1974**, *52*, 185−187.
[31] D. Enders, D. Seebach, *Angew. Chem.* **1973**, *85*, 1104−1104; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 1014−1015.
[32] P. Beak, W. J. Zajdel, D. B. Reitz, *Chem. Rev.* **1984**, *84*, 471−523, espec. 515−516.
[33] I. I. Grandberg, N. I. Bobrova, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR* **1965**, *4*, 566−570; *Chem. Abstr.* **1965**, *64*, 3516g.
[34] B. A. Tertov, V. V. Bessonov, P. P. Onishchenko, *Zh. Org. Khim.* **1974**, *10*, 2634; *Chem. Abstr.* **1975**, *82*, 72867d.
[35] M. Takahashi, T. Mamiya, H. Hasegawa, T. Nagai, H. Wakita, *J. Heterocycl. Chem.* **1986**, *23*, 1363−1366.
[36] M. K. Bernard, M. Mąkosza, B. Szafran, U. Wrzeciono, *Liebigs Ann. Chem.* **1989**, 545−549.
[37] T. M. T. Truong-Nguyen, H. Togo, M. Schlosser, *Tetrahedron* **1994**, *50*, 7827−7836.
[38] H. Stakemeier, E.-U. Würthwein, *Liebigs Ann.* **1996**, 1833−1843.
[39] M. Könemann, G. Erker, R. Fröhlich, E.-U. Würthwein, *J. Am. Chem. Soc.* **1997**, *119*, 11155−11164.
[40] M. Schlosser, J. Porwisiak, F. Mongin, *Tetrahedron* **1998**, *54*, 895−900.
[41] Q. Wang, H.-X. Wei, M. Schlosser, *Eur. J. Org. Chem.* **1999**, 3263−3268.
[42] C. Bobbio, M. Schlosser, *Eur. J. Org. Chem.* **2001**, 4533−4536.
[43] A. Colla, M. A. P. Martins, G. Clar, S. Krimmer, P. Fisher, *Synthesis* **1991**, 483−486.
[44] J.-N. Volle, M. Schlosser, *Eur. J. Org. Chem.* **2002**, 1490−1492.
[45] F. I. Harden, R. J. Quinn, P. J. Scammells, *J. Med. Chem.* **1991**, *34*, 2892−2898.
[46] J. R. Beck, F. L. Wright, *J. Heterocycl. Chem.* **1987**, *24*, 739−740.
[47] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, M. C. Burla, G. Polidori, M. Camalli, R. Spagna, *Package for Crystal Structure Solution by Direct Methods and Refinement*, SIR97.
[48] G. M. Sheldrick, *Bruker Analytical X-ray Instruments Program*, WI (1996) SHELXTL 5.05.

Received March 5, 2002
[O022327]