The Direct Metalation and Subsequent Functionalization of Trifluoromethyl-Substituted Pyridines and Quinolines

Manfred Schlosser*[a,b] and Marc Marull[a]

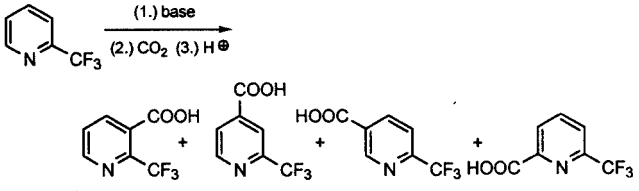
Keywords: Carboxylation / Caubère's base / Dialkylamides / Fluorinated building blocks / Heterocycles / Lithium / Optional site selectivity / Regioisomers

Depending on the choice of the reagent, 2-(trifluoromethyl)-pyridine can be selectively metalated and subsequently carboxylated or otherwise functionalized either at the 3- or at the 6-position. "Optional site selectivity" can also be achieved with 4-(trifluoromethyl)pyridine, which may be deprotonated either at the 2- or at the 3-position. In contrast, 3-(trifluoromethyl)pyridine undergoes nucleophilic addition and ensuing decomposition whatever the base. Depending on the reaction conditions, 2-(trifluoromethyl)quinoline displays reactivity toward lithium reagents at its 3-, 4-, or 8-positions, 3-(trifluoromethyl)quinolines at the 2- or 4-positions, and 4-(trifluoromethyl)quinoline at the 2- or 3-positions. It was therefore possible to prepare four trifluoromethyl-substituted pyridinecarboxylic acids (**1**, **4**, **9**, and **10**) and six trifluoromethyl-substituted quinolinecarboxylic acids (**11**, **13**, **14**, **15**, **17**, and **18**) regioisomerically uncontaminated and in a most straightforward way.

According to gas-phase studies of arenes, the trifluoromethyl group has a stronger acidifying effect than any other halogen substituent, including chlorine, fluorine, and trifluoromethoxy.[1–3] On the other hand, (trifluoromethyl)-benzene (α,α,α-trifluorotoluene, benzotrifluoride) reacts with butyllithium[4] or *sec*-butyllithium in the presence of *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PMDTA)[2] sluggishly and non-regioselectively, clean and expedient *ortho*-metalation only being achieved with the superbasic mixtures of butyllithium or methyllithium with potassium *tert*-butoxide.[2,5]

We wondered whether similar deprotonation/electrophilic trapping procedures could successfully be elaborated for trifluoromethyl-substituted pyridines and quinolines. This would open a very short route to functionalized derivatives, potentially valuable building blocks for pharmaceutical research. Carbon dioxide was once again selected as the standard electrophile.

Depending on the reagent and the reaction conditions, the first substrate investigated provided access to any of the four possible derivatives and thus set an unprecedented example of maximum optional site selectivity.[6,7] When the metalation was performed with an excess of lithium 2-(dimethylamino)ethoxide-activated butyllithium ("Caubère's base"),[8,9] metalation occurred at the 6-position, and subsequent carboxylation thus afforded the acid **4** (71%) exclusively. The amide base lithium 2,2,6,6-tetramethylpiperidide (LITMP) deprotonated the 5- and the 6-positions concomitantly, as evidenced by the formation of acids **3** and **4** in a 4:3 ratio when the reaction was carried out in diethyl ether (DEE). When employed in tetrahydrofuran, though, the same base was found to abstract protons most rapidly from the 4-position, thus producing predominantly the acid **2** after early quenching (≤ 15 min). However, the acid **1** (73%) was isolated as the sole product, when the reaction time was extended to 6 h.



	1	2	3	4
[a]	27%	41%	–	–
[b]	73%	–	–	–
[c]	–	–	23%	18%
[d]	–	–	–	71%

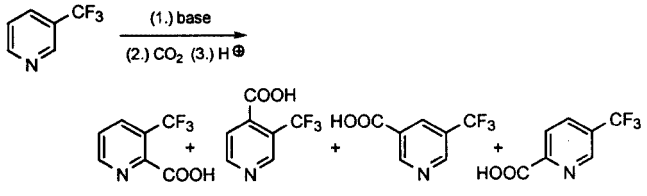
[a] Metalation conditions : [a] LITMP in THF at -75 °C for 15 min. [b] LITMP in THF at -75 °C for 6 h. [c] LITMP (2.0 equiv.) in DEE at -75 °C for 2 h. [d] Butyllithium in the presence of lithium 2-(dimethylamino)ethoxide in DEE at -75 °C for 2 h.

To explain this divergence in reaction outcomes, one has to invoke the interplay of inductive, coordinative, and steric effects. According to base-catalyzed hydrogen/deuterium exchange experiments,[10,11] proton mobility in the unsubsti-

[a] Institut de Chimie moléculaire et biologique,
Ecole Polytechnique Fédérale, BCh
1015 Lausanne, Switzerland
E-mail: manfred.schlosser@epfl.ch
[b] Faculté des Sciences, Université, BCh
1015 Lausanne, Switzerland

tuted pyridine is highest at the 4-position and lowest at the 2-position. Although counterintuitive at first sight, this order of kinetic acidities is corroborated by the sharply decreasing basicity[12] in the diazene series on going from pyridazine (pK_a = 2.6), through pyrimidine (pK_a = 1.3) to pyrazine (pK_a = 0.7), the three azapyridines being isoelectronic species with respect to the three pyridinides (pyridine anions). The introduction of the strongly electron-withdrawing trifluoromethyl group[2] next to the nitrogen increases local acidities everywhere, but most markedly at the neighboring 3-position, which thus becomes the most acidic site. However, this inductive activation is counterbalanced by the steric hindrance caused by the fairly bulky substituent. Therefore, lithiation initially occurs at the 4-position. Despite its lower basicity, the 3-lithiated species prevails only later, as a consequence of equilibration due to the reversibility of deprotonation. A change of the medium from THF to DEE deprives the reagent of adequate solvation. Complexation of the metal to the heterocyclic nitrogen now becomes crucial and directs the attack of the base to the 6-position or, through aggregate-mediated, long-range coordination, to the 5-position.

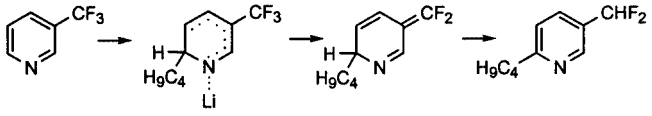
The successful metalation of 3-(trifluoromethyl)pyridine at the 2-position with butyllithium in diethyl ether has already been reported by W. Dmowski et al.[13] However, despite numerous attempts undertaken independently by several collaborators, we were unable to reproduce these findings. A variety of other bases was examined next, but these also failed to produce any practically useful result. The crude reaction mixtures, analyzed by gas chromatography after esterification with diazomethane, contained trace amounts of acid **5** at best and no isomers **6**, **7**, or **8** at all. The first compound was unequivocally identified by the comparison of its retention times with those of an authentic sample.[14]



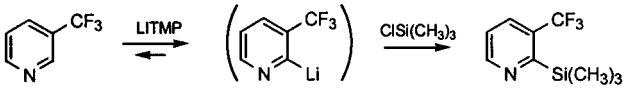
	5	6	7	8
[a]	–	–	–	–
[b]	1.5%	–	–	–
[c]	1.0%	–	–	–

[a] Metalation conditions : [a] Butyllithium in DEE at -75 °C and -60 °C, each time for 1 h. [b] LIDA in THF at -75 °C for 2 h. [c] LITMP + PMDTA + $KOC(CH_3)_3$ in THF at -100 °C for 6 h.

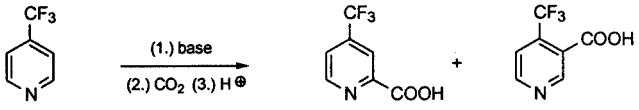
Nucleophilic addition of the reagent to the nitrogen-adjacent 2-position,[15–17] a menace anyhow, appears to outperform the competing deprotonation mode completely when it is assisted by the strongly electron-withdrawing trifluoromethyl group attached to the antinodal 5-position across the ring. The resulting dihydropyridylmetal intermediate then is rapidly destroyed by consecutive fluoride elimination and further nucleophilic addition of the reagent.[18–20] The isolation of 2-butyl-5-(difluoromethyl)pyridine as a by-product (14%) provided evidence in support of the postulated addition/elimination mode.



That competitive, though reversible, deprotonation at the 2-position nevertheless does occur was demonstrated by an in situ trapping experiment. When 3-(trifluoromethyl)pyridine was simultaneously treated in THF at −100 °C with chlorotrimethylsilane and a mixture ("Faigl mix") of LITMP, potassium *tert*-butoxide, and *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PMDTA), trimethyl-2-[(3-trifluoromethyl)pyridyl]silane was obtained in 30% yield.



Clean and again optionally site-selective hydrogen/metal interconversion reactions could be performed with 4-(trifluoromethyl)pyridine as the substrate. Whereas both lithium diisopropylamide (LIDA) and lithium 2,2,6,6-tetramethylpiperidide (LITMP) abstracted protons exclusively from the 3-position, thus paving the way towards the acid **10**, Caubère's base once more proved perfectly specific in favor of the nitrogen-adjacent 2-position, as evidenced by the formation of acid **9**. Both acids **9** and **10** were independently prepared from 2- and 3-iodo-4-(trifluoromethyl)pyridine, respectively, by halogen/metal permutation followed by carboxylation.

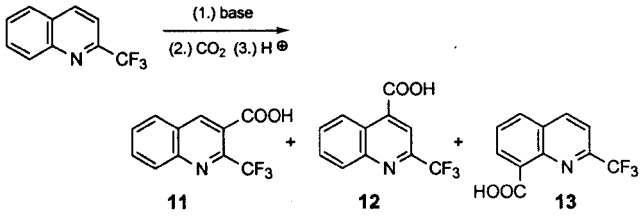


	9	10
[a]	–	80%
[b]	–	84%
[c]	41%	–

[a] Metalation conditions : [a] LIDA in THF at -75 °C for 2 h. [b] LITMP in THF at -75 °C for 2 h. [c] Butyllithium in the presence of lithium 2-(dimethylamino)ethoxide in DEE at -75 °C for 2 h.

Depending on the reagent and the reaction conditions, 2-(trifluoromethyl)quinoline can be converted into three different quinolinecarboxylic acids by metalation and subsequent carboxylation. LIDA as the base in tetrahydrofuran promoted deprotonation at the 3-position, thus giving the acid **11** as the final product. The bulkier LITMP in THF concomitantly attacked the 3-position and the sterically less hindered 4-position to afford a 3:2 mixture of acids **11** and

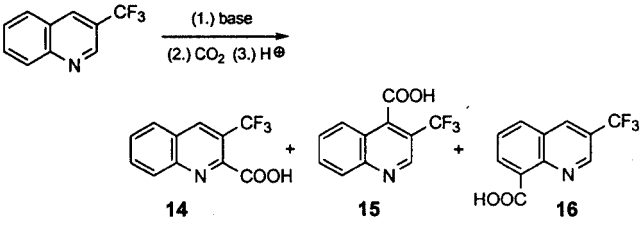
12. When diethyl ether was used as the solvent, however, coordination of the reagent by the nitrogen lone pair became a crucial factor and the metalation was rerouted to the 8-position. After carboxylation, the acid **13** was isolated without any regioisomeric contamination.



	11	12	13
[a]	31%	–	–
[b]	43%	27%	–
[c]		–	20%

[a] Metalation conditions : [a] LIDA in THF at -75 °C for 2 h. [b] LITMP in THF at -75 °C for 2 h. [c] LITMP in DEE at -75 °C for 6 h.

3-(Trifluoromethyl)quinoline offered another noteworthy and unprecedented case of optional site selectivity. LIDA neatly deprotonated the 4-position (giving the acid 32%), thus exploiting the presumably higher acidity of the latter in comparison with the 2-position.[11,21,22] Conversely, LITMP preferred to avoid the congestion caused by the *peri*-hydrogen atom and exclusively attacked the 2-position (to produce, after carboxylation, the same carboxylic acid **14** that could also be obtained after treatment with Caubère's base, although in only 12% yield).

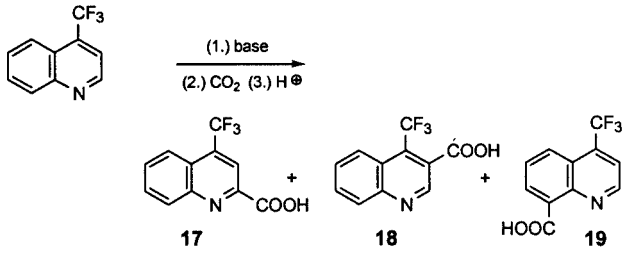


	14	15	16
[a]	–	32%	–
[b]	41%	–	–
[c]	12%	–	–

[a] Metalation conditions : [a] LIDA in THF at -75 °C for 2 h. [b] LITMP in THF at -75 °C for 2 h. [c] Butyllithium in the presence of lithium 2-(dimethylamino)ethoxide in DEE at -75 °C for 2 h.

4-(Trifluoromethyl)quinoline was converted solely into the acid **18** regardless of whether LIDA or LITMP was employed as the base. Caubère's base, however, once again took advantage of the neighboring group assistance provided by the ring-incorporated nitrogen atom and oriented the hydrogen/metal interconversion and the subsequent carboxylation to the 2-position (providing acid **17**).

(Trifluoromethyl)pyridines[23–25] and 2-, 3-, and 4-(trifluoromethyl)quinolines[26–32] are readily accessible. Thus, the metalation/functionalization sequence disclosed above currently offers the most straightforward route to the trifluoromethyl-substituted pyridinecarboxylic acids **1**, **4**,



	17	18	19
[a]	–	54%	–
[b]	–	76%	–
[c]	36%	–	–

[a] Metalation conditions : [a] LIDA in THF at -75 °C for 2 h. [b] LITMP in THF at -75 °C for 2 h. [c] Butyllithium in the presence of lithium 2-(dimethylamino)ethoxide in DEE at -75 °C for 2 h.

and **10** and the quinolinecarboxylic acids **11**, **12**, **13**, **14**, **15**, and **18**. The fact that some of these products were isolated only in moderate yield does not matter very much, as the unconsumed starting material can be integrally recovered at the end of the reaction.

To identify regioisomeric by-products or to rule out their presence, authentic samples of the acids **2**–**3**, **5**–**8**, **16**, and **19** were required. Their preparation is described in the preceding publication.[14]

Experimental Section

1. Generalities

Starting materials, if commercially available, were purchased from Aldrich-Fluka (9479 Buchs, Switzerland), Acros Organics (2440 Geel, Belgium) and Apollo (Stockport SK6 2QR, United Kingdom) and used as such, provided that adequate checks (melting ranges, n_D^{20}, gas chromatography) had confirmed the claimed purity. Solutions of butyllithium, *sec*-butyllithium, and *tert*-butyllithium in pentanes, hexanes, or cyclohexane were supplied by Chemetall (60487 Frankfurt, Germany) and potassium *tert*-butoxide by Callery (Pittsburgh, PA 15230, USA). When known compounds had to be prepared by literature procedures, pertinent references are given.

Air- and moisture-sensitive materials were stored in Schlenk tubes or Schlenk burettes. They were protected by and handled under an atmosphere of 99.995% pure nitrogen, using appropriate glassware (Glasgerätebau Pfeifer, 98711 Frauenfeld, Germany).

Paraffinic or aromatic hydrocarbons (hexanes, toluene) were submitted to azeotropic distillation. Diethyl ether and tetrahydrofuran were dried by distillation over sodium wire after the characteristic blue color of sodium diphenyl ketyl (benzophenone–sodium "radical anion") generated in situ had been observed to persist.[33–34]

Ethereal or other organic extracts were dried by washing with brine and then by storage over sodium sulfate. Prior to distillation, a spatula tip of hydroquinone or potassium carbonate was added to compounds prone to radical polymerization or sensitive to acids. If no reduced pressure is specified, boiling ranges (b.p.) refer to ordinary atmospheric conditions (725 ± 25 Torr).

Melting ranges (m.p.) given were found to be reproducible after resolidification, unless stated otherwise ("decomp."), and were corrected by use of a calibration curve established with authentic

standards. If melting points are absent, this means all attempts failed to crystallize the liquid at temperatures down to −75 °C. The temperature of dry ice/methanol baths is consistently indicated as −75 °C and "room temperature" (22−26 °C) as 25 °C.

Silica gel (Merck Kieselgel 60) of 70−230 mesh (0.06−0.20 mm) particle size was used for column chromatography. The solid support was suspended in hexanes and, when all air bubbles had escaped, was washed into the column. When the level of the liquid was still 3−5 cm above the support layer, the dry powder obtained by adsorption of the crude mixture onto some 25 mL of silica and subsequent evaporation of the solvent was poured on top of the column.

Whenever possible and appropriate, yields of products were determined, prior to isolation, by gas chromatographic comparison of their peak areas with those of known amounts of reference substances ("internal standards") and correction of the ratios obtained by means of separately established calibration factors. The purity of distilled compounds was checked on at least two columns loaded with stationary phases of contrasting polarity. Chromosorb G-AW of 80−100 and 60−80 mesh particle size was used as the support for packed columns for the analytical and preparative scales (2 or 3 m long, 2 mm inner diameter and 3 or 6 m long, 1 cm inner diameter, respectively). Packed columns were made of glass, while quartz was the material selected for capillary columns (> 10 m long). For programmed temperature increase, a constant rate of 10 °C per minute was applied. The stationary phases employed are encoded as DB-1, OV-17, or SE-30 (of the silicone type), DEGS or DBS (both of the polyester type), AP-L (Apiezon-L hydrocarbon), and C-20M, DB-WAX, or DB-FFAP (all belonging to the polyethylene glycol family).

^{1}H, ^{13}C, and ^{19}F nuclear resonance (NMR) spectra were recorded at 400, 101, and 376 MHz, respectively, of samples dissolved in deuteriochloroform or, if marked by an asterisk (*), in perdeuterioacetone. Chemical shifts δ refer to the signal of tetramethylsilane (δ = 0.00 ppm) and coupling constants *J* are given in Hz. Coupling patterns are abbreviated as, for example, s (singlet), d (doublet), t (triplet), qr (quartet), qn (quintet), hx (hextet), hp (heptet), oct (octet), non (nonet), td (triplet of doublets) and m (multiplet).

A few of the mass spectra could be obtained by electron impact fragmentation at 70 eV ionization potential and 200 °C source temperature. In general, however, no molecular peak was observed under such standard conditions, so chemical ionization ("c.i.") in an ammonia atmosphere at a potential of 95 eV and a source temperature of 100 °C was routinely applied.

Elementary analyses were performed by the laboratory of I. Beetz (96301 Kronach, Germany). The expected percentages were calculated by use of the atomic weight numbers listed in the 1999 IUPAC recommendations.

2. Starting Materials

All three (trifluoromethyl)pyridines have been made by fluorinative deoxygenation of the respective pyridinecarboxylic acids with sulfur tetrafluoride[23] and by halogen displacement with trifluoromethylcopper generated in situ.[25,27,28] The latter method has the advantage of not requiring special pressure equipment and gives high yields, at least in the case of the 2-isomer. 3-(Trifluoromethyl)pyridine is commercially available, though expensive (approx. 2200 EUR/mol). It can be advantageously prepared by catalytic hydrogenolysis of 2-chloro-5-(trifluoromethyl)pyridine[14] (approx. 100 EUR/mol). In principle, 2-chloro-6-(trifluoromethyl)pyridine and 2-chloro-4-(trifluoromethyl)pyridine could be reduced analogously to afford 2- and 4-(trifluoromethyl)pyridine, respectively. However, the prices of the precursors (approx. 70000 and 15000 EUR/mol) are prohibitive.

The 2- and 4-isomers of (trifluoromethyl)quinoline can readily be obtained by the regiocontrolled condensation and cyclization of aniline with ethyl 4,4,4-trifluoroacetylacetate, treatment of the resulting 2- or 4-quinolinone with phosphorus oxybromide and final debromination of the obtained 2- or 4-bromo-(trifluoromethyl)quinoline.[31,32] The isomer bearing the trifluoromethyl group at the 3-position has to be prepared by means either of the reaction between 3-quinolinecarboxylic acid and sulfur tetrafluoride[26] or of that between 3-bromoquinoline and trifluoroiodomethane[27] or bromotrifluoromethane[28] in the presence of copper powder.

3. Trifluoromethyl-Substituted Pyridinecarboxylic Acids

2-Trifluoromethyl-3-pyridinecarboxylic Acid (1): 2,2,6,6-Tetramethylpiperidine (2.5 mL, 2.1 g, 15 mmol) and 2-(trifluoromethyl)pyridine (1.7 mL, 2.2 g, 15 mmol) were consecutively added to a solution of butyllithium (15 mmol) in tetrahydrofuran (15 mL) and hexanes (10 mL), kept in a dry ice/methanol bath. After 6 h at −75 °C, the mixture was poured onto an excess of freshly crushed lumps of solid carbon dioxide. The volatiles were evaporated and the residue was dissolved in water (50 mL). The aqueous phase was washed with diethyl ether (2 × 25 mL), acidified to pH 1 with 3.0 M hydrochloric acid, and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried, and the solvents were evaporated to afford colorless prisms; m.p. 175−176 °C (from a mixture of chloroform and methanol); yield: 2.09 g (73%). ^{1}H NMR*: δ = 8.87 (dd, *J* = 4.7, 0.8 Hz, 1 H), 8.32 (dd, *J* = 7.9, 0.8 Hz, 1 H), 7.86 (dd, *J* = 7.9, 4.8 Hz, 1 H) ppm. ^{13}C NMR*: δ = 166.6, 151.6, 145.1 (qr, *J* = 34.5 Hz), 139.1, 129.5, 127.5, 122.4 (qr, *J* = 273.5 Hz) ppm. ^{19}F NMR*: δ = −63.7 (s) ppm. MS (c.i): *m/z* (%) = 192 (100) [M^+ + 1], 191 (41.7) [M^+], 174 (56.9), 146 (53.5), 127 (60.7), 78 (47.3), 77 (8.8). $C_7H_4F_3NO_2$ (191.11): calcd. C 43.99, H 2.11; found C 44.13, H 2.23.

2-Trifluoromethyl-4-pyridinecarboxylic Acid (2): An analogous reaction was performed, the only difference being that it was stopped by carboxylation after only 15 min. After alkaline extraction and acidification to pH 1, the products were treated with an ethereal solution of diazomethane until persistence of the yellow color. After addition of a know amount of nonane as internal standard, the mixture was analyzed by gas chromatography (30 m, DB-1701, 120 °C; 30 m, DB-FFAP, 100 °C). Retention time comparison with authentic samples[14] revealed the presence of 27% of methyl 2-trifluoromethyl-3-pyridinecarboxylate and 41% of methyl 2-trifluoromethyl-4-pyridinecarboxylate.

6-Trifluoromethyl-3-pyridinecarboxylic Acid (3): An analogous reaction was performed on a fivefold smaller scale (3.0 mmol), the only other difference being that the solvent mixture of tetrahydrofuran and hexanes was replaced by diethyl ether (3.0 mL) and hexanes (2.0 mL). After alkaline extraction and acidification to pH 1, the products were treated with an ethereal solution of diazomethane until persistence of the yellow color. After addition of a known amount of nonane as an internal standard, the mixture was analyzed by gas chromatography (30 m, DB-1701, 120 °C; 30 m, DB-FFAP, 100 °C). Retention time comparison with authentic samples[14] showed the presence of 18% of methyl 6-trifluoromethyl-3-pyridinecarboxylate and 23% of methyl 6-trifluoromethyl-2-pyridinecarboxylate.

6-Trifluoromethyl-2-pyridinecarboxylic Acid (4): 2-(Dimethylamino)ethanol (6.5 mL, 5.4 g, 60 mmol) and 2-(trifluoromethyl)pyridine (1.7 mL, 2.2 g, 15 mmol) were added consecutively to a solution of butyllithium (120 mmol) in diethyl ether (50 mL) and hexanes (75 mL), kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed lumps of solid carbon dioxide and worked up as described above (see acid **1**). The product was collected as colorless needles; m.p. 156−157 °C (from a mixture of chloroform and hexanes); yield: 2.03 g (71%). ^{1}H NMR*: δ = 8.36 (m, 2 H), 8.13 (dd, *J* = 7.6, 1.2 Hz, 1 H) ppm. ^{13}C NMR*: δ = 166.0, 150.4, 149.0 (qr, *J* = 35 Hz), 141.8, 129.3, 125.8, 122.8 (qr, *J* = 275 Hz) ppm. ^{19}F NMR* : δ = −67.1 (s) ppm. MS (c.i.): *m*/*z* (%) = 192 (100) [M$^+$ + 1], 191 (4) [M$^+$], 174 (33.2), 146 (8), 127 (6). $C_7H_4F_3NO_2$ (191.11): calcd. C 43.99, H 2.11; found C 44.07, H 2.23.

2-Trimethylsilyl-3-(trifluoromethyl)pyridine: 2,2,6,6-Tetramethylpiperidine (2.8 g, 3.4 mL, 20 mmol), potassium *tert*-butoxide (2.2 g, 20 mmol) and *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (4.2 mL, 3.5 g, 20 mmol), chlorotrimethylsilane (2.5 mL, 2.1 g, 20 mmol), and (trifluoromethyl)pyridine (2.2 mL, 2.9 g, 20 mmol) were added consecutively at −100 °C to butyllithium (20 mmol) in tetrahydrofuran (20 mL) and hexanes (13 mL). After the mixture had been kept for 6 h at −100 °C, methanol (2.0 mL, 1.6 g, 50 mmol) was injected. Trimethyl-2-[3-(trifluoromethyl)pyridyl]silane (30%) was detected and quantified by gas chromatographic analysis (30 m, DB-1701, 30 °C [5 min] → 110 °C; 30 m, DB-FFAP, 50 °C [5 min] → 100 °C; nonane as an internal standard). The bulk of the solution was evaporated and concentrated, and the crude residue was purified by preparative gas chromatography (5 m, 2% C-20M, 150 °C); colorless liquid; b.p. 54−55 °C/11 Torr; n_D^{20} = 1.6385. ^{1}H NMR: δ = 8.99 (d, *J* = 4.6 Hz, 1 H), 7.49 (d, *J* = 8.1 Hz, 1 H), 7.31 (dd, *J* = 8.1, 4.8 Hz, 1 H), 0.38 (s, 9 H) ppm. ^{13}C NMR: δ = 167.5, 151.5, 131.8 (m, 2 C), 124.5 (qr, *J* = 273 Hz), 121.7, 0.4 (3 C) ppm. ^{19}F NMR: −59.1 (s) ppm. MS (c.i.): *m*/*z* (%) = 220 (24) [M$^+$ + 1], 219 (42) [M$^+$], 168 (81), 104 (53), 77 (100). $C_9H_{12}F_3NSi$ (219.28): calcd. C 49.30, H 5.52; found C 49.20, H 5.44.

3-Trifluoromethyl-2-pyridinecarboxylic Acid (5): Diisopropylamine (0.42 mL, 0.30 g, 3.0 mmol) and 3-(trifluoromethyl)pyridine (0.34 mL, 0.44 g, 3.0 mmol) were added consecutively to a solution of butyllithium (3.0 mmol) in tetrahydrofuran (13 mL) and hexanes (2.0 mL), kept in a methanol/dry ice bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed lumps of solid carbon dioxide. The product was extracted and esterified as described above (see acid **3**). The presence of 1.5% of methyl 3-trifluoro-2-pyridinecarboxylate was detected by gas chromatographic analysis (30 m, DB-1701, 30 °C [5 min] → 110 °C; 30 m, DB-FFAP, 50 °C [5 min] → 100 °C) in comparison with authentic samples[14] of the methyl esters of all possible acids **5**−**8** and nonane as an internal standard for quantification.

2-Butyl-5-(difluoromethyl)pyridine: 3-(Trifluoromethyl)pyridine (2.9 g, 2.2 mL, 20 mmol) was added to a solution of butyllithium (40 mmol) in diethyl ether (50 mL) and hexanes (26 mL), kept in a methanol dry ice bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed lumps of solid carbon dioxide. The mixture was neutralized with hydrochloric acid (2.0 M, 20 mL) and the product was extracted with diethyl ether (3 × 20 mL). The presence of 14% of 2-butyl-5-(difluoromethyl)pyridine was detected by gas chromatographic analysis (30 m, DB-1701, 30 °C [5 min] → 110 °C; 30 m, DB-FFAP, 50 °C [5 min] → 100 °C). The remaining ethereal solution was evaporated, and the crude material was purified by preparative gas chromatography (5 m, 5% SE-30, 140 °C) to afford a colorless liquid, which became yellow and brown after a few days even if stored in the dark. ^{1}H NMR: δ = 8.65 (s, 1 H), 7.75 (dm, *J* = 8.3 Hz, 1 H), 7.25 (d, *J* = 8.1 Hz, 1 H), 6.69 (t, *J* = 55.9 Hz, 1 H), 2.85 (dd, *J* = 7.8, 7.5 Hz, 2 H), 1.7 (m, 2 H), 1.40 (hx, *J* = 7.5 Hz, 2 H), 0.95 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 165.3, 146.5, 133.5, 127.4 (t, *J* = 24 Hz), 122.6, 113.6 (t, *J* = 239 Hz), 38.0, 31.9, 22.5, 14.0 ppm. ^{19}F NMR: −111.9 (d, *J* = 56 Hz) ppm. MS (c.i.): *m*/*z* (%) = 203 (2) [M$^+$ + NH$_4$], 186 (72) [M$^+$ + 1], 185 (7) [M$^+$], 161 (24), 143 (100), 124 (47). $C_{10}H_{13}F_2N$ (185.22): calcd. C 64.85, H 7.07; found C 64.05, H 7.22.

4-Trifluoromethyl-2-pyridinecarboxylic Acid (9): 4-(Trifluoromethyl)pyridine (1.7 mL, 2.2 g, 15 mmol) was treated with butyllithium (60 mmol) in the presence of lithium 2-(dimethylamino)ethoxide (60 mmol) as described above (see acid **3**). The product was isolated in the same way; colorless prisms (from chloroform); m.p. 156−158 °C; yield: 1.18 g (41%). ^{1}H NMR: δ = 9.82 (br. s, 1 H), 9.05 (d, *J* = 5.0 Hz, 1 H), 8.51 (s, 1 H), 7.89 (d, *J* = 5.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 165.0, 150.4, 149.5, 139.7 (qr, *J* = 35 Hz), 122.4 (qr, *J* = 3 Hz), 122.2 (qr, *J* = 273 Hz), 121.0 (qr, *J* = 3 Hz) ppm. ^{19}F NMR: −65.3 (s) ppm. MS (c.i.): *m*/*z* (%) = 192 (73) [M$^+$ + 1], 191 (12) [M$^+$], 174 (37), 147 (100), 127 (19). $C_7H_4F_3NO_2$ (191.11): calcd. C 43.99, H 2.11; found C 43.71, H 1.99.

4-Trifluoromethyl-2-pyridinecarboxylic acid (**9**) was also prepared by addition, at −75 °C, of 2-iodo-4-(trifluoromethyl)pyridine (1.2 mL, 2.7 g, 10 mmol; see below) to butyllithium (10 mmol) in tetrahydrofuran (14 mL) and hexanes (6.0 mL), pouring the mixture onto freshly crushed dry ice after 2 min and working it up as described (see the preparation of acid **1**); m.p. 156−158 °C; yield: 1.47 g (77%).

2-Iodo-4-(trifluoromethyl)pyridine: Diisopropylamine (4.3 mL, 3.0 g, 30 mmol) and 3-iodo-4-(trifluoromethyl)pyridine (3.7 mL, 8.2 g, 30 mmol; see below) were added consecutively to a solution of butyllithium (30 mmol) in tetrahydrofuran (40 mL) and hexanes (20 mL), kept in a methanol/dry ice bath. After 2 h at −75 °C, the mixture was neutralized with hydrochloric acid (2.0 M, 30 mL). Steam distillation followed by distillation under reduced pressure afforded a colorless liquid; m.p. −10 to −8 °C; b.p. 35−37 °C/6 Torr; n_D^{20} = 1.5325; yield: 2.5 g (44%). ^{1}H NMR: δ = 8.57 (d, *J* = 5.1 Hz, 1 H), 7.96 (s, 1 H), 7.61 (d, *J* = 5.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 151.6, 139.5 (qr, *J* = 34 Hz), 130.7 (qr, *J* = 3 Hz), 121.6 (qr, *J* = 273 Hz), 118.5 (qr, *J* = 3 Hz), 118.0 ppm. ^{19}F NMR: −65.5 (s) ppm. MS (c.i.): *m*/*z* (%) = 291 (100) [M$^+$ + NH$_4$], 274 (44) [M$^+$ + 1], 273 (6) [M$^+$], 247 (7), 116 (53), 99 (60), 75 (100). $C_6H_3F_3IN$ (272.99): calcd. C 26.40, H 1.11, N 5.13; found C 26.32, H 1.10, N 5.12.

3-Iodo-4-(trifluoromethyl)pyridine: 2,2,6,6-Tetramethylpiperidine (8.5 mL, 7.1 g, 50 mmol) and 4-(trifluoromethyl)pyridine (5.7 mL, 7.4 g, 50 mmol) were added consecutively to butyllithium (50 mmol) in tetrahydrofuran (70 mL) and hexanes (30 mL), cooled in a methanol/dry ice bath. After the mixture had been kept at −75 °C for 2 h, iodine (25 g, 0.10 mol) was added with vigorous stirring. The solvents were evaporated and the residue, in the presence of sodium thiosulfate (10 g, 63 mmol), was subjected to steam distillation followed by distillation under reduced pressure to give a colorless liquid; m.p. −5 to −3 °C; b.p. 41−43 °C/5 Torr; n_D^{20} = 1.5415; yield: 10.8 g (79%). ^{1}H NMR: δ = 9.14 (s, 1 H), 8.69 (d, *J* = 5.1 Hz, 1 H), 7.55 (d, *J* = 5.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 160.0, 149.4, 140.4 (qr, *J* = 33 Hz), 121.5 (qr, *J* = 6 Hz), 121.4 (qr, *J* = 275 Hz), 89.8 ppm. ^{19}F NMR: −65.8 (s) ppm. MS (c.i.): *m*/*z* (%) = 291 (100) [M$^+$ + NH$_4$], 274 (11) [M$^+$ + 1], 273 (2) [M$^+$], 225 (9), 116 (14). $C_6H_3F_3IN$ (272.99): calcd. C 26.40, H 1.11, N 5.13; found C 26.31, H 1.07, N 5.12.

4-Trifluoromethyl-3-pyridinecarboxylic Acid (10): When lithium 2,2,6,6-tetramethylpiperidide (15 mmol) was employed in tetrahydrofuran (15 mL) and hexanes (10 mL) as described above (see acid **1**), 4-(trifluoromethyl)pyridine (1.7 mL, 2.2 g, 15 mmol) gave an isomeric product; m.p. 146−147 °C (from chloroform and methanol); yield: 2.41 g (84%). ^{1}H NMR*: δ = 9.17 (s, 1 H), 9.04 (d, *J* = 5.2 Hz, 1 H), 7.88 (d, *J* = 5.2 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.9, 154.1, 152.0, 136.9 (qr, *J* = 35 Hz), 126.8, 128.4 (qr, *J* = 275 Hz), 121.3 (qr, *J* = 5 Hz) ppm. ^{19}F NMR*: δ = −61.2 (s) ppm. MS (c.i.): *m/z* (%) = 192 (100) [M$^+$ + 1], 191 (43.6) [M$^+$], 174 (49.5), 146 (79.4), 127 (28), 99 (20.7). $C_7H_4F_3NO_2$ (191.11): calcd. C 43.99, H 2.11; found C 44.12, H 2.30. The yield was decreased slightly (to 80%) when lithium 2,2,6,6-tetramethylpiperidide was replaced by lithium diisopropylamide in tetrahydrofuran. The acid **10** was independently prepared by addition, at −75 °C, of 3-iodo-4-(trifluoromethyl)pyridine (1.2 mL, 2.7 g, 10 mmol; see above) to butyllithium (10 mmol) in tetrahydrofuran (14 mL) and hexanes (6.0 mL), the mixture being poured onto freshly crushed dry ice after 2 min and worked up as described (see acid **1**); m.p. 146−147 °C; yield: 1.55 g (81%).

4. Trifluoromethyl-Substituted Quinolinecarboxylic Acids

2-Trifluoromethyl-3-quinolinecarboxylic Acid (11): Diisopropylamine (2.1 mL, 1.5 g, 15 mmol) and 2-(trifluoromethyl)quinoline (3.0 g, 15 mmol) were consecutively added to a solution of butyllithium (15 mmol) in tetrahydrofuran (65 mL) and hexanes (10 mL), kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed lumps of solid carbon dioxide and extracted as described above (see acid **1**). The product was collected as colorless prisms; m.p. 207−209 °C (reprod.; from chloroform); yield: 1.12 g (31%). ^{1}H NMR*: δ = 9.01 (s, 1 H), 8.25 (m, 2 H), 8.05 (t, *J* = 7.8 Hz, 1 H), 7.89 (t, *J* = 7.6 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.4, 148.4, 145.9 (qr, *J* = 35 Hz), 142.2, 134.5, 131.5 (2 C), 130.5, 128.5, 126.0, 123.2 (qr, *J* = 275 Hz) ppm. ^{19}F NMR*: −63.5 (s) ppm. MS (c.i.): *m/z* (%) = 214 (100) [M$^+$ + 1], 213 (89) [M$^+$], 185 (13), 165 (19), 144 (17). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51; found C 54.78, H 2.99.

2-Trifluoromethyl-4-quinolinecarboxylic Acid (12): When lithium diisopropylamide was replaced by lithium 2,2,6,6-tetramethylpiperidide (from 2,2,6,6-tetramethylpiperidine, 2.5 mL, 2.1 g, 15 mmol) under otherwise identical conditions, a mixture of products was obtained. After alkaline extraction, acidification, and exhaustive esterification with diazomethane, methyl 2-trifluoromethyl-3-quinolinecarboxylate (ester of **11**; 54%) and methyl 2-trifluoromethyl-4-quinolinecarboxylate (ester of **12**; 5%) were identified by gas chromatography (30 m, DB-1701, 180 °C; 30 m, DB-FFAP, 200 °C) with the use of authentic samples[14] for retention time comparison and an internal standard for quantification.

The same reaction carried out at 0.50 M concentration (20 mL rather than 65 mL of tetrahydrofuran, still 10 mL of hexanes) afforded the esters derived from **11** and **12** in 43% and 27% yield, respectively.

2-Trifluoromethyl-8-quinolinecarboxylic Acid (13): When 2-(trifluoromethyl)quinoline (3.0 g, 15 mmol) was treated at −75 °C with two equivalents of lithium 2,2,6,6-tetramethylpiperidide (30 mmol) in diethyl ether (55 mL) and hexanes (20 mL) for 6 h, subsequent carboxylation afforded a regioisomerically pure product as tiny colorless needles; m.p. 177−178 °C (from chloroform); yield: 0.72 g (20%). ^{1}H NMR: δ = 8.94 (dd, *J* = 7.3, 1.4 Hz, 1 H), 8.69 (d, *J* = 8.6 Hz, 1 H), 8.25 (dd, *J* = 8.2, 1.4 Hz, 1 H), 7.96 (d, *J* = 8.6 Hz, 1 H), 7.93 (t, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 165.8, 147.0 (qr, *J* = 36 Hz), 144.1, 141.1, 137.3, 133.1, 129.4 (2 C), 125.5, 119.5 (qr, *J* = 276 Hz), 117.8 ppm. ^{19}F NMR: −68.0 (s) ppm. MS (c.i.): *m/z* (%) = 214 (100) [M$^+$ + 1], 213 (89) [M$^+$], 185 (13), 165 (19), 144 (17). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51; found C 55.16, H 2.18.

3-Trifluoromethyl-2-quinolinecarboxylic Acid (14): 2,2,6,6-Tetramethylpiperidine (2.5 mL, 2.1 g, 15 mmol) and 3-(trifluoromethyl)quinoline (3.0 g, 15 mmol) were added consecutively to a solution of butyllithium (15 mmol) in tetrahydrofuran (15 mL) and hexanes (10 mL), kept in a dry ice/methanol bath. After the mixture had been kept at −75 °C for 2 h, the usual carboxylation and workup procedure (see Section 2, acid **1**) gave the product as colorless prisms; m.p. 125−127 °C (from chloroform); yield: 1.48 g (41%). ^{1}H NMR: δ = 8.77 (s, 1 H), 8.26 (d, *J* = 8.6 Hz, 1 H), 8.07 (d, *J* = 8.3 Hz, 1 H), 8.01 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1 H), 7.86 (ddd, *J* = 8.1, 7.0, 1.1 Hz) ppm. ^{13}C NMR: δ = 161.8, 146.1, 143.6, 138.5 (qr, *J* = 6 Hz), 133.5, 130.6, 129.3, 128.5, 128.0, 122.8 (qr, *J* = 35 Hz), 122.6 (qr, *J* = 272 Hz) ppm. ^{19}F NMR: −60.4 (s) ppm. MS (c.i.): *m/z* (%) = 242 (31) [M$^+$ + 1], 241 (3) [M$^+$], 197 (100), 176 (14), 147 (3). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51, N 5.81; found C 54.63, H 2.41, N 5.77.

3-Trifluoromethyl-4-quinolinecarboxylic Acid (15): When exactly the same reaction as described in the preceding paragraph was conducted with lithium diisopropylamide (15 mmol), a different regioisomer was obtained; colorless prisms; m.p. 259−261 °C (dec.; from chloroform); yield: 1.16 g (32%). ^{1}H NMR*: δ = 9.24 (s, 1 H), 8.24 (d, *J* = 8.5 Hz, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H), 8.04 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1 H), 7.88 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H) ppm. ^{13}C NMR*: δ = 168.0, 151.0, 147.5, 142.3, 134.0, 131.5, 130.6, 127.6, 125.4 (qr, *J* = 273 Hz), 123.8, 119.1 (qr, *J* = 32 Hz) ppm. ^{19}F NMR*: δ = −58.3 (s) ppm. MS (c.i.): *m/z* (%) = 242 (94) [M$^+$ + 1], 241 (100) [M$^+$], 224 (10), 197 (57), 185 (16). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51, N 5.81; found C 54.73, H 2.48, N 5.92.

4-Trifluoromethyl-2-quinolinecarboxylic Acid (17): 4-(Trifluoromethyl)quinoline (3.0 g, 15 mmol) was treated with butyllithium (60 mmol) in the presence of lithium 2-(dimethylamino)ethoxide (60 mmol) as described in the preceding Section (see acid **3**). After carboxylation, the product was isolated by extraction, neutralization, and crystallization; colorless prisms; m.p. 142−143 °C (from chloroform and methanol); yield: 1.30 g (36%). ^{1}H NMR*: δ = 8.47 (s, 1 H), 8.37 (ddd, *J* = 8.4, 1.4, 0.7 Hz, 1 H), 8.27 (d, *J* = 8.5 Hz, 1 H), 8.06 (td, *J* = 6.9, 1.4 Hz, 1 H), 7.99 (td, *J* = 7.0, 1.5 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.0, 158.5 (2 C), 139.0, 136.0 (qr, *J* = 35 Hz), 132.5, 131.8 (2 C), 124.7, 124.5 (qr, *J* = 274 Hz), 118.3 ppm. ^{19}F NMR*: δ = −69.0 (s) ppm. MS (c.i.): *m/z* (%) = 242 (23) [M$^+$ + 1], 241 (22) [M$^+$], 197 (100), 176 (16) 147 (4), 128 (12). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51, found C 54.52, H 2.48.

4-Trifluoromethyl-3-quinolinecarboxylic Acid (18): When 4-(trifluoromethyl)quinoline (3.0 g, 15 mmol) was treated with lithium 2,2,6,6-tetramethylpiperidide (15 mmol) in tetrahydrofuran (15 mL) and hexanes (10 mL) for 2 h at −75 °C and then with carbon dioxide, a regioisomerically pure product was isolated in the usual way (see Section 2, acid **1**); colorless prisms; m.p. 210−212 °C (reprod.; from chloroform); yield: 2.75 g (76%). ^{1}H NMR*: δ = 9.14 (s, 1 H), 8.27 (d, *J* = 8.1 Hz, 1 H), 8.26 (d, *J* = 8.7 Hz, 1 H), 8.00 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1 H), 7.90 (ddd, *J* = 8.9, 7.0, 1.6 Hz, 1 H) ppm. ^{13}C NMR*: δ = 167.9, 150.0, 148.8, 132.3, 131.3 (2 C), 130.4, 127.3, 125.4 (qr, *J* = 3 Hz), 124.6 (qr, *J* = 276 Hz), 122.7 ppm. ^{19}F NMR*: δ = −57.0 (s) ppm. MS (c.i.): *m/z* (%) = 242 (100) [M$^+$ + 1], 241 (17) [M$^+$], 224 (9). $C_{11}H_6F_3NO_2$ (241.17): calcd. C 54.78, H 2.51, N 5.81; found C 54.81, H 2.45, N 5.76.

Acknowledgments

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

[1] H. H. Büker, N. M. M. Nibbering, D. Espinosa, F. Mongin, M. Schlosser, *Tetrahedron Lett.* **1997**, *38*, 8519−8522.
[2] M. Schlosser, F. Mongin, J. Porwisiak, W. Dmowski, H. H. Büker, N. M. M. Nibbering, *Chem. Eur. J.* **1998**, *4*, 1281−1286.
[3] M. Schlosser, E. Marzi, F. Cottet, H. H. Büker, N. M. M. Nibbering, *Chem. Eur. J.* **2001**, *7*, 3511−3516.
[4] J. D. Roberts, D. Y. Curtin, *J. Am. Chem. Soc.* **1946**, *68*, 1658−1660.
[5] M. Schlosser, G. Katsoulos, S. Takagishi, *Synlett* **1990**, 747−748.
[6] M. Schlosser, *Eur. J. Org. Chem.* **2001**, 3975−3984.
[7] M. Schlosser, in, *Organometallics in Synthesis: A Manual* (Ed.: M. Schlosser), 2nd ed., Wiley, Chichester, **2002**, pp. 1−352, spec. 253−257.
[8] P. Gros, Y. Fort, G. Quéguiner, P. Caubère, *Tetrahedron Lett.* **1995**, *36*, 4791−4794.
[9] P. Gros, Y. Fort, P. Caubère, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1685−1689.
[10] I. F. Tupitsyn, N. N. Zatsepina, A. V. Kirova, Y. L. Kaminskii, A. G. Ivanenko, *Reakts. Sposobnost Org. Soedin.* **1973**, *10*, 143−162; *Chem. Abstr.* **1973**, *79*, 114928v.
[11] O. A. Reutov, I. P. Beletskaya, K. P. Butin, *CH-Acids*, Pergamon Press, Oxford, **1978**, pp. 111−114.
[12] D. D. Perrin, *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworth, London, **1965**.
[13] J. Porwisiak, W. Dmowski, *Tetrahedron* **1994**, *50*, 12259−12266.
[14] F. Cottet, M. Marull, O. Lefebvre, M. Schlosser, *Eur. J. Org. Chem.* **2003**, 1559−1568, preceding article.
[15] A. E. Tschitschibabin, *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 1810−1819.
[16] K. Ziegler, H. Zeiser, *Justus Liebigs Ann. Chem.* **1931**, *485*, 174 −192.
[17] J. C. W. Evans, C. P. H. Allen, *Org. Synth., Coll. Vol.* **1943**, *2*, 517−518.
[18] W. Dmowski, J. Porwisiak, *J. Fluorine Chem.* **1992**, *59*, 321−331.
[19] A. A. Kolomeitsev, V. N. Movchun, Y. L. Yagupolskii, J. Porwisiak, W. Dmowski, *Tetrahedron Lett.* **1992**, *33*, 6191−6192.
[20] H. Koroniak, P. Fiedorow, W. Dmowski, J. Porwisiak, *J. Mol. Struct.* **1995**, *351*, 187−195.
[21] I. F. Tupitsyn, N. N. Zatsepina, A. V. Kirova, Y. M. Kapustin, *Org. React.* **1968**, *5*, 601−612; *Chem. Abstr.* **1969**, *70*, 76940x.
[22] J. A. Zoltewicz, A. A. Sale, *J. Am. Chem. Soc.* **1973**, *95*, 3928−3931.
[23] M. S. Raasch, *J. Org. Chem.* **1962**, *27*, 1406−1409.
[24] A. S. Dey, M. M. Joullié, *J. Heterocycl. Chem.* **1965**, *2*, 113−119.
[25] F. Cottet, M. Schlosser, *Eur. J. Org. Chem.* **2002**, 327−330.
[26] Y. Kobayashi, I. Kumadaki, S. Taguchi, *Chem. Pharm. Bull.* **1969**, *17*, 2335−2339.
[27] Y. Kobayashi, I. Kumadaki, S. Sato, N. Hara, E. Chikami, *Chem. Pharm. Bull.* **1970**, *18*, 2334−2339.
[28] Y. Kobayashi, I. Kumadaki, A. Ohsawa, T. Yamada, *Chem. Pharm. Bull.* **1972**, *20*, 1839−1839.
[29] J. M. Paratian, S. Sibille, J. Perichon, *J. Chem. Soc., Chem. Commun.* **1992**, 53−54.
[30] H. Keller, M. Schlosser, *Tetrahedron* **1996**, *52*, 4637−4644.
[31] M. Marull, M. Schlosser, *Eur. J. Org. Chem.* **2003**, 1576−1588, following article.
[32] O. Lefebvre, M. Marull, M. Schlosser, manuscript in preparation [title: 4-(Trifluoromethyl)quinoline Derivatives].
[33] K. Ziegler, F. Crössmann, H. Kleinert, O. Schäfer, *Justus Liebigs Ann. Chem.* **1929**, *473*, 1−35, spec. 20.
[34] H. Metzger, E. Müller, in *Houben-Weyl: Methoden der organischen Chemie* (Ed.: E. Müller), Thieme, Stuttgart, **1959**, *Vol. 1/2*, pp. 321−384, spec. 337−338.

Received October 7, 2002
[O02552]