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METALATED FLUOROPYRIDINES AND FLUOROQUINOLINES AS REACTIVE INTERMEDIATES : NEW WAYS FOR THEIR REGIOSELECTIVE GENERATION

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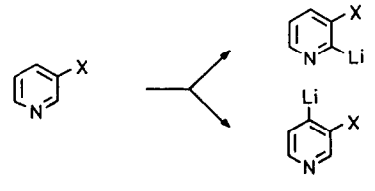
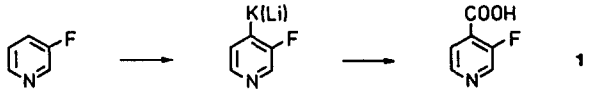
Abstract : The mixture of lithium diisopropylamide and potassium *tert*-butoxide ("LIDA-KOR reagent") is a powerful base which can be advantageously employed for the regioselective deprotonation of fluoropyridines and, in particular, 3-fluoroquinoline. A novel cyclization process was elaborated for the preparation of the latter product.

In general, organometallic reagents tend to add nucleophilically onto the latent imino function of the pyridine ring rather than to promote metalation of the heterocycle [1]. Just the LIC-KOR mixture [2] (butyllithium activated by potassium *tert*-butoxide) is powerful and protophilic enough to bring about a hydrogen/metal exchange, although deprotonation occurs competitively at the 2- and 4-positions. Moreover, the resulting intermediates apparently do not react with ordinary electrophiles but can only be identified through deuterolysis [3]. Electron withdrawing or metal complexing substituents enhance the hydrocarbon reactivity [4]. As a consequence, 2- or 4-(α-lithiooxyalkylidene)amino [5], -alkoxy [6], -*N*,*N*-diethylcarbamoyloxy [7] or -halo [8] substituted pyridines do undergo rapid deprotonation at the heteroadjacent 3-position even with relatively weak bases such as lithium diisopropylamide. Some regiochemical ambiguity arises if the heterosubstituent occupies the 3-position. The (α-lithiooxyalkylidene)amino [4] and *N*,*N*-dialkylsulfamoyl [9] moieties appear to direct the metal invariably to the 4-position. With 3-pyridyl ethers as substrates, both the alkoxy moiety and the reaction conditions play a crucial role. Thus it is possible to produce selectively 3-benzyloxy-, 3-ethoxy- and other 3-alkoxy-2-lithiopyridines [6, 10] or, on the other hand, 4-lithio-3-(methoxymethoxy)pyridine [11]. While lithium diisopropylamide allows to introduce a metal cleanly into the 4-position of 3-fluoropyridine [12] and 3-chloropyridine [13], both halo compounds are concomitantly attacked at the 2- and 4-position when standard organolithium reagents are employed [12, 13]. However, under optimized conditions the almost selective generation of 3-fluoro-2-lithiopyridine becomes again possible [14].



X = N=C(OLi)R, SO_2NR_2, OR, Cl, F

We expected the LIC-KOR mixture to behave differently. This "superbasic" reagent is fairly insensitive to neighboring group assistance as provided by electron donor substituents but systematically favors the proton abstraction from the most acidic aromatic positions [15]. Exchange kinetics suggest that the acidity of the various sites in pyridine increases with their distance from the nitrogen atom [16]. The outcome of the reaction between 3-fluoropyridine and LIC-KOR is in agreement with this assumption : metalation occurred exclusively at the 4-position. After carboxylation 3-fluoro-4-pyridinecarboxylic acid (1) was isolated as the sole product. The yield of 51% (after recrystallization) is somewhat lower than that reported for the deprotonation with lithium diisopropylamide. On the other hand, our method offers the advantage to avoid the presence of other reactive components, especially diisopropylamine, in the reaction mixture. In the same way, 2-fluoropyridine was metalated and afforded 57% of 2-fluoro-3-pyridinecarboxylic acid (2) upon carboxylation and neutralization.



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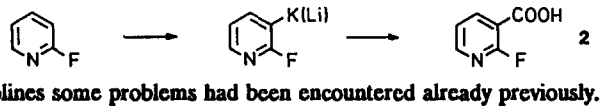
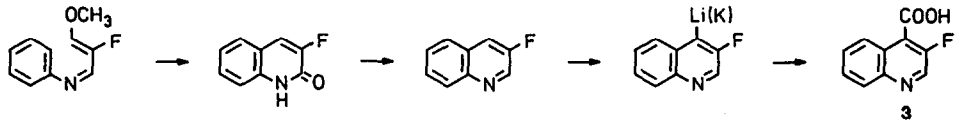


2

With 2- and 3-fluoroquinolines some problems had been encountered already previously. Butyllithium, activated by *N,N,N',N'*-tetramethylethylenediamine, reacts with both isomers under nucleophilic addition onto the imine center (positions 2 and 1) rather than under proton abstraction. [17] We have found *tert*-butyllithium or the LIC-KOR mixture to behave in the same manner. Deprotonation does occur when lithium diisopropylamide in the presence of hexamethylphosphoric triamide is employed as the base. Yields in the order of 60% have been reported for reactions quenched with chlorotrimethylsilane [17]. With carbon dioxide as the trapping reagent, however, we have obtained only moderate results. As we have subsequently recognized, the yields improve (*e.g.*, 64% of acid 3) if the metalation is performed with lithium diisopropylamide activated by potassium *tert*-butoxide ("LIDA-KOR reagent" [18]) in a tetrahydrofuran/hexane mixture.

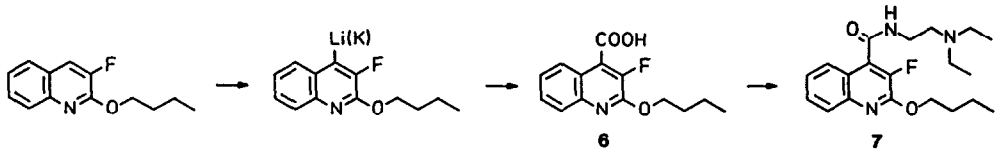


3

3-Fluoroquinoline can be prepared according to the Schiemann-Balz method [19]. We have opened a quite attractive novel entry to this compound by submitting 2-fluoro-3-methoxyacrylanilide (from methyl 2-fluoro-3-methoxyacrylate and lithium anilide) to an acid catalyzed cyclization. The 3-fluoro-2-quinolone (4) thus formed could be easily reduced to 3-fluoroquinoline *via* the 2-chloro-3-fluoroquinoline (5).

4 5

Selective *O*-alkylation of the amide **4** gave to 2-butoxy-3-fluoroquinoline. After consecutive treatment with lithium diisopropylamide and dry ice, 2-butoxy-3-fluoro-4-quinolinecarboxylic acid (**6**) was isolated with 82% yield. The latter compound was cleanly converted into its 2-(*N,N*-diethylaminoethyl)amide **7** which is a fluorine bearing analogue of the prominent local anesthetic Cinchocain (Dibucain, Percain) [20].



6 **7**

EXPERIMENTAL PART

1. Generalities

Starting materials have been purchased from Fluka AG (Buchs), Aldrich-Chemie (Steinheim), or Merck-Schuchardt (Darmstadt), unless literature sources or details of the preparation are given. *Butyllithium* and *potassium tert-butoxide* were supplied by CheMetall, Frankfurt, and Hüls, Troisdorf. All commercial reagents were used without further purification.

Air and moisture sensitive compounds were stored in Schlenk tubes or Schlenk burettes. They were protected by and handled under an atmosphere of 99.995% pure nitrogen.

Pentane, hexane, benzene and *toluene* were obtained anhydrous by careful azeotropic distillation, *tetrahydrofuran* and *diethyl ether* by distillation from sodium wire after the characteristic blue color of *in situ* general sodium diphenyl ketyl [21] was found to persist.

Ethereal extracts were dried with sodium sulfate. Before distillation of compounds prone to radical polymerization or sensitive to acids a spatula tip of *hydroquinone* or, respectively, *potassium carbonate* was added.

The temperature of dry ice methanol baths is consistently indicated as -75°C and "room temperature" (22 - 26°C) as 25°C. *Melting ranges* (mp) are reproducible after resolidification, unless otherwise stated ("dec."), and are corrected using a calibration curve which was established with authentic standards. If no melting points are given, it means that all attempts to crystallize the liquid product have failed even at temperatures as low as -75°C. If reduced pressure is not specified, *boiling ranges* were determined under ordinary atmospheric conditions (720 ± 25 mmHg).

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 hexane and, when all air bubbles had escaped, was sluiced into the column. When the level of the liquid was still some 3 - 5 cm above the silica layer, the dry powder obtained by absorption of the crude product mixture on 15 - 20 g silica gel and subsequent evaporation of the solvent was poured on top of the column.

Whenever reaction products were not isolated, their yields were determined by *gas chromatography* comparing their peak areas with that of an internal standard and correcting the ratios by calibration factors. The purity of distilled compounds was checked on at least two columns loaded with stationary phases of different polarity. Chromosorb G-AW of 80 - 100 and 60 - 80 mesh particle size was chosen as the support for packed analytical or preparative columns (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 chosen as the material for coated, Grob type capillary columns (≥ 10 m long). The type of the stationary phase used is abbriviated as SP-2340 (cyanopropylsilicone) and SPB-5 (methylphenylsilicone). In the case of programmed temperature increase a rate of 10 °C/min was maintained.

Nuclear magnetic resonance spectra of hydrogen-1-nuclei in deuterochloroform solution were recorded at 250 MHz and of fluorine-19 nuclei at 376 MHz. Chemical shifts δ refer to the signal of tetramethylsilane in the case of ^{1}H spectra and to α,α,α-trifluorotoluene in the case of ^{19}F spectra. Coupling constants (J) are measured in Hz. Abbreviations of coupling patterns : s (singlet), d (doublet), t (triplet), q (quadruplet), td (triplet of doublets) and m (multiplet).

Mass spectra were obtained at a 70 eV ionization potential maintaining a source temperature of 200 °C. Whenever no molecular peak was observed under standard conditions, chemical ionization ("c.i.") in an ammonia atmosphere at 100 °C source temperature was applied. The molecular peaks (M^+) listed of chlorides refer to the ^{37}Cl isotope.

2. Starting Materials

Methyl 2-fluoro-3-methoxy-2-butenoate : Dichlorofluoromethane (44 mL, 62 g, 0.60 mol) was added dropwise, over a period of 30 min, to the vigorously stirred mixture of 1,2-dimethoxy-1-(trimethylsilyloxy)ethene (88 g, 0.50 mol; from methyl methoxyacetate by consecutive treatment with lithium diisopropylamide in tetrahydrofuran and chlorotrimethylsilane) and potassium *tert*-butoxide (62 g, 0.55 mol) in hexane (0.40 L) at -75 °C. After 30 min at -75 °C and under continuous stirring, the mixture was allowed to gradually reach 25 °C. The solution was filtered through a Celite pad which was washed with diethyl ether. Evaporation and distillation afforded methyl 2-fluoro-3-methoxy-2-butenoate as a 1 : 1 (*Z/E*) isomeric mixture which could be separated by column chromatography (silica gel as the support, a 1 : 4 mixture of ethyl acetate and hexane as the eluent); 52 g (78%); bp 82 - 83 °C/10 mmHg. - (*Z*) **isomer** : mp 8 - 10 °C; n_D^{20} 1.4930. - ^{1}H-NMR : δ 6.89 (1 H, d, J 19.1), 3.89 (3 H, s), 3.78 (3 H, s). - MS : 134 (57%, M^+), 119 (38%), 103 (100%). - Analysis : calc. for $C_5H_7FO_3$ (134.11) C 44.78, H 5.26; found C 45.02, H 5.26%. - (*E*) **isomer** : mp 45 - 46 °C. - ^{1}H-NMR : δ 6.98 (1 H, d, J 9.6), 3.87 (3 H, s), 3.85 (3 H, s). - MS : 134 (32%, M^+), 119 (31%), 103 (100%). - Analysis : calc. for $C_5H_7FO_3$ (134.11) C 44.78, H 5.26; found C 44.62, H 5.38%.

3-Fluoro-2-quinolone (4) : Under gentle shaking, methyl 2-fluoro-3-methoxy-2-butenoate (10.0 g, 75 mmol, *Z/E* mixture) was added to an ice cooled solution of lithium anilide (0.15 mol, from equivalent amounts of aniline and butyllithium) in a 2 : 1 (v/v) mixture (30 mL) of tetrahydrofuran and hexane. A precipitate deposited. After 30 min at 0 °C, the reaction mixture was poured into ice-cold 1 M hydrochloric acid (0.2 L) and was extracted with diethyl ether (3 × 0.1 L). Upon evaporation of the volatile components, a colorless waxy material remained, which presumably was the anilide 4. This raw material was heated together with 70 % aqueous sulfuric acid (50 mL) 2 h to 60 °C. The mixture was then poured on crushed ice. 3-Fluoro-2-quinolone was collected by filtration and was washed with water (4 × 20 mL) and ice-cold diethyl ether (2 × 10 mL); 11.0 g (87%); mp 239 - 241 °C (from acetone). - ^{1}H-NMR (D_3CCOCD_3) : δ 11.25 (1 H, s, broad), 7.73 (1 H, d, J 11.0), 7.68 (1 H, dd, J 8.0, 1.0), 7.53 (1 H, ddd, J 8.0, 6.1, 1.3), 7.45 (1 H, dd, J 8.2, 1.3), 7.27 (1 H, ddd, J 8.2, 6.1, 1.0). - MS : 163 (100%, M^+), 135 (82%). - Analysis : calc. for C_9H_6FNO (163.15) C 66.26, H 3.71; found C 66.34, H 3.87%.

2-Chloro-3-fluoroquinoline [22] **(5)** : A suspension of 3-fluoro-2-quinolone (8.2 g, 50 mmol) in phosphoryl trichloride (30 mL) was heated under stirring until, after approximately 30 min, a clear solution had formed. The brownish mixture was cautiously poured on crushed ice and was neutralized with a 2 M aqueous solution of sodium hydroxide. Extraction with hexane (3 × 0.1 L) and evaporation of the solvent gave a light-yellow solid which was purified by sublimation (50 °C/0.05 mmHg); 8.1 g (89%) of white crystals: mp 85 - 86 °C. - ^{1}H-NMR : δ 8.05 (1 H, d, broad, J 8.5), 7.87 (1 H, d, J 8.2), 7.81 (1 H, dd, J 8.1, 1.5), 7.73 (1 H, ddd, J 8.5, 7.0, 1.5), 7.61 (1 H, ddt, J 8.1, 7.0, 1.0). - MS : 181 (100%, M^+), 149 (35%), 146 (42%). - Analysis : calc. for C_9H_5ClFN (181.60) C 59.53, H 2.78; found C 59.43, H 2.90%.

3-Fluoroquinoline : Palladium (10% on charcoal, 0.2 g) was added to a solution of 2-chloro-3-fluoroquinoline (5; 7.3 g, 40 mmol) and triethylamine (11.0 mL, 8.1 g, 80 mmol) in ethanol (0.10 L), which was stirred under an atmosphere of hydrogen (1 atm) at 25 °C. After approximately 4 h, the required amount of hydrogen had been taken up. The reaction mixture was filtrered, concentrated and distilled to afford pure 3-fluoroquoinoline [19]; 5.0 g (84%); mp 7 - 9 °C; bp 68 - 70 °C/1 mmHg; n_D^{20} 1.4762. - ^{1}H-NMR : δ 8.83 (1 H, d, J 2.9), 8.13 (1 H, dd, J 8.5, 0.9), 7.80 (1 H, dd, J 8.0, 1.5), 7.78 (1 H, dd, J 8.7, 2.9), 7.70 (1 H, ddd, J 8.5, 7.0, 1.5), 7.59 (1 H, ddt, J 8.0, 7.0, 0.9).

2-Butoxy-3-fluoroquinoline : The heterogeneous mixture of 3-fluoro-2-quinolone (4.1 g, 25 mmol), butyl iodide (5.7 mL, 9.2 g, 50 mmol), silver carbonate (3.5 g, 13 mmol) and toluene (0.10 L) was stirred 48 h at 25 °C in the dark. Elution with hexane from a chromatography column filled with silica gel (50 g, for details see "generalities", Section 1) gave 2-butoxy-3-fluoroquinoline as a colorless viscous oil which solidified in the refrigerator; 5.2 g (95%); mp 16 - 18 °C. - ^{1}H-NMR : δ 7.85 (1 H, dm, J 8.5), 7.67 (1 H, dd, J 7.5, 1.0), 7.63 (1 H, d, J 10.2), 7.58 (1 H, symm. m), 7.41 (1 H, ddt, J 8.5, 7.5, 1.0), 4.58 (2 H, t, J 6.7), 1.90 (2 H, symm. m), 1.56 (2 H, symm. m) 1.03 (3 H, t, J 7.2). - MS : 219 (14%, M^+) 163 (100%). - Analysis : calc. for $C_{13}H_{14}FNO$ (219.26) C 71.21, H 6.44; found C 71.28, H 6.58%.

3. Metalation Reactions

3-Fluoro-4-pyridinecarboxylic acid (1) [23] : Under reduced pressure, the volatile components were stripped off from the solution of butyllithium (10 mL) in hexane (7 mL). At -75 °C, precooled tetrahydrofuran (20 mL), potassium *tert*-butoxide (1.1 g, 10 mmol) and 3-fluoropyridine (0.87 mL, 1.0 g, 10 mmol) were consecutively added to the residue under stirring until the alcoholate had dissolved. After 3 h at -75 °C, the reaction mixture was poured on dry ice. After evaporation to dryness, the solid salt was treated with a small excess of hydrogen chloride in diethyl ether and the acid 1 was recrystallized from cyclohexane; 0.72 g (51%); mp 253 - 256 °C (dec.). - ^{1}H-NMR : δ 8.60 (1 H, d, J 2.6), 8.52 (1 H, d, J 5.0), 7.85 (1 H, dd, J 6.0, 5.0). - MS : 142 (100%), 141 (95%), 124 (82%). - Analysis : calc. for $C_6H_4FNO_2$ (141.10) C 51.07, H 2.86; found C 51.36, H 3.28%.

2-Fluoro-3-pyridinecarboxylic acid (2) [24] : In an analogous manner, acid 2 was prepared and isolated; 0.80 g (57%); mp 162 - 165 °C (dec.). - ^{1}H-NMR : δ 8.46 (1 H, ddd, J 9.4, 7.5, 2.1), 8.39 (1 H, ddd, J 5.0, 2.0, 1.0), 7.44 (1 H, ddd, J 7.5, 5.0, 1.7). - MS : 142 (100%), 124 (74%). - Analysis : calc. for $C_6H_4FNO_2$ (141.10) C 51.07, H 2.86; found C 52.32, H 3.28%.

3-Fluoro-4-quinolinecarboxylic acid (3) : At -75 °C, 3-fluoroquinoline (2.9 g, 20 mmol) in tetrahydrofuran (10 mL) was slowly added to a solution containing lithium diisopropylamide (20 mmol; from diisopropylamine and butyllithium) and potassium *tert*-butylalcoholate (2.5 g, 22 mmol) in tetrahydrofuran (40 mL) and hexane (15 mL). After 15 min at -75 °C, the greenish solution formed was poured on crushed dry ice. Upon evaporation to dryness a solid residue remained. It was acidified with 2 M hydrochloric acid to pH 3. The aqueous phase was extracted with diethyl ether (5 × 20 mL). The combined organic layers were washed with brine (2 × 25 mL), dried and evaporated. Crystallization from acetone afforded the acid 3 as colorless needles; 2.5g (64%); mp 233 - 235 °C (dec.). - ^{1}H-NMR : δ 9.00 (1 H, d, J 1.5), 8.28 (1 H, ddd, J 8.0, 1.8, 0.8), 8.15 (ddd, J 8.0, 1.5, 0.8), 7.83 (1 H, ddd, J 8.0, 6.5, 1.8), 7.75 (1 H, ddd, J 8.0, 6.5, 1.5). - MS : 191 (100%, M^+), 174 (11%). - Analysis : calc. for $C_{10}H_6FNO_2$ (191.16) C 62.83, H 3.16; found C 63.04, H 3.33%.

2-Butoxy-3-fluoro-4-quinolinecarboxylic acid (6) : From a similar reaction, although without adding potassium *tert*-butylalcoholate, acid 6 was isolated; 4.4 g (82%); mp 143 - 145 °C (crystallized from a 1 : 4 mixture of diethyl ether and hexane). - ^{1}H-NMR : δ 8.12 (1 H, d, broad, J 8.2), 7.89 (1 H, dd, J 8.2, 1.0), 7.66 (1 H, t, broad, J 8.2), 7.51 (1 H, t, broad, J 8.2), 6.6 (1 H, s, broad), 4.59 (2 H, t, J 6.6), 1.90 (2 H, symm. m), 1.56 (2 H, symm. m), 1.03 (3 H, t, J 7.2). - MS : 263 (7%), M^+), 218 (16%), 207 (100%). - Analysis : calc. for $C_{14}H_{14}FNO_2$ (263.27) C 63.87, H 5.36; found C 64.01, H 5.37%.

2-Butoxy-*N*-(2-diethylaminoethyl)-3-fluoro-4-quinolinecarboxamide (7) : Acid 6 (2.6 g, 10 mmol) and oxalyl chloride (5 mL) were heated under stirring to 50 °C until (after approx. 1 h) a homogeneous mixture was obtained. Then all volatile materials were evaporated under reduced pressure. The residue was dissolved in diethyl ether (20 mL) and was treated with 2-(diethylamino)ethylamine (3.1 mL, 2.3 g, 20 mmol). The ethereal solution was filtered through a layer of silica gel before being evaporated. The remaining syrup solidified when triturated with hexane; 3.5 g (96%); mp 55 - 57 °C. - ^{1}H-NMR : δ 7.95 (1 H, dd, J 8.5, 1.0), 7.83 (1 H, d, broad, J 8.5), 7.61 (1 H, ddd, J 8.5, 7.0, 1.0), 7.43 (1 H, dd, broad, J 8.5, 7.0), 6.85 (1 H, s, broad), 4.57 (2 H, t, J 6.5), 3.62 (2 H, q, J 6.0), 2.70 (2 H, t, J 6.0), 2.55 (4 H, q, J 7.0), 1.78 (2 H, symm. m), 1.55 (2 H, symm. m), 1.01 (3 H, t, J 7.1), 1.00 (6 H, t, J 7.0). - MS : (c.i.) 362 (1%, M^+ + 1), 289 (1%), 134 (16%), 86 (100%). - Analysis : calc. for $C_{20}H_{28}FN_3O_2$ (361.46) C 66.46, H 7.81; found C 66.22, H 7.83%.

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