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First Access to 3,4-Difluoro-1*H*-pyrrole

Jacques Leroy[1] and Claude Wakselman

CNRS-CERCOA, 2, rue H. Dunant, F94320 Thiais, France

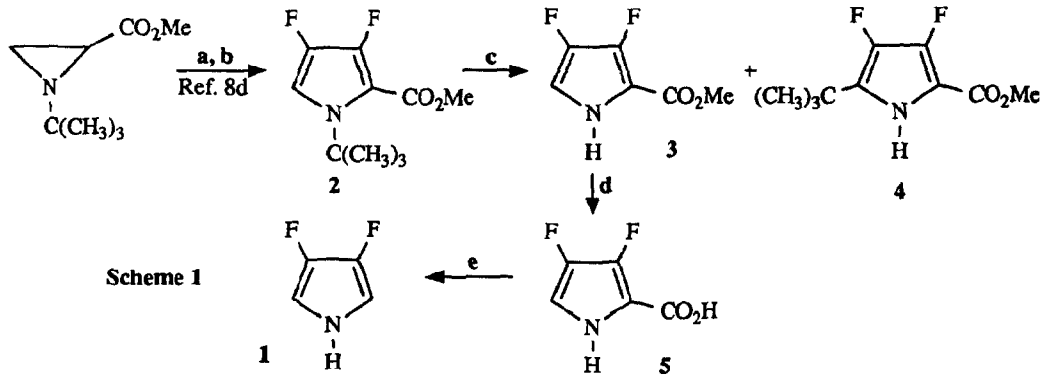
Abstract: *N*-Unsubstituted 3,4-difluoropyrrole is synthesized via a thermal [2+3] cycloaddition reaction of a *N*-tert-butyl 2-alkoxycarbonyl aziridine and chlorotrifluoroethylene. Dealkylation of an intermediate *N*-tert-butylpyrrole is obtained with trifluoromethanesulfonic acid.

Owing to its presence in biologically active natural and unnatural products, the pyrrole nucleus[2] has attracted a continuous attention for new methods of ring elaboration and (or) introduction of various substituents on it.[3] On the other hand, due to the unique effects of fluorine atom, either alone or incorporated into perfluoroalkyl groups, on the physico-chemical properties and biological activities of the receiving molecule,[4] fluoropyrroles appeared to be valuable targets *e.g.* for porphyrins elaboration,[5] polymerisation[6] or preparation of compounds of agricultural and medicinal interest. For example, fluorine-containing porphyrins were designed as potentially useful for diagnosis and phototherapy of cancer[5g] while certain naturally occuring halopyrroles exhibited a strong anti-bacterial activity.[7] Despite this spurring background, known examples of genuine fluoropyrroles *i.e.* bearing at least one fluorine atom directly linked to the nucleus, remained scarce for years.[8] Starting from a preformed pyrrole ring, a β-fluoropyrrole was obtained *via* a modified Schiemann reaction then converted to porphyrins.[5c] Xenon difluoride was employed for direct fluorination at the α position of a 1-methylpyrrole unit included in a drug[9] and was also recently used for fluorination at the α-position of simple *N*-H pyrroles bearing electron-withdrawing groups in the α' position.[10] In view of ^{18}F-labelling, reaction of diluted molecular fluorine with pyrrole itself gave only tars whereas *N*-methylpyrrole led mainly to a mixture of 2 and 3-fluoro-*N*-methylpyrrole.[11] Direct fluorination of a tetrakis(pentafluorophenyl)porphyrin as its Zn complex form, with silver or cobalt fluoride was reported to give the corresponding perfluorinated tetraphenylporphyrin.[12] More recently, Barnes and co-workers performed an electrophilic fluorination at the β-position of 1-(triisopropylsilyl)pyrrole and of a highly functionalized pyrrole with *N*-fluorobenzenesulfonimide, *via* their β-lithio derivatives.[13] In other new approaches, Burton synthesized 2,5-disubstituted-β-fluoropyrroles in high yields from α,α-difluoro-γ-iodo-γ-(electron withdrawing group)-substituted ketones and ammonium hydroxide,[14] while the Michael addition of isocyanomethylide to α-fluoroalkenyl sulfones and sulfoxides led to mixtures containing β-fluoropyrroles in low proportions.[15]

Despite these efforts, no method was available to date for the preparation of N-*unsubstituted* 3,4-difluoropyrrole derivatives, and particularly the parent 3,4-difluoropyrrole **1**.

3,4-Dichloropyrrole itself was obtained by halogenation of ethyl 5-methyl-pyrrole-2-carboxylate with sulfuryl chloride in boiling ethanol, followed by a saponification-decarboxylation of the diethyl 3,4-dichloro-2,5-dicarboxylate thus obtained.[16] Attempted direct chlorine by fluorine exchange performed on the diester, using inorganic fluorides, failed.[17]

Among different approaches we envisioned to reach the desired structure, an attractive one was to use a thermal [2+3] cycloaddition reaction of a suitably *N*-protected activated aziridine with chlorotrifluoroethylene. We already described such a condensation between methyl 1-*tert*-butylaziridine-2-carboxylate and chlorotrifluoroethylene at 200 °C, affording a mixture of diastereoisomeric chlorofluoropyrrolidines we did not separated. Subsequent treatment of this mixture with sodium methylate resulted in aromatization of the pyrrolidines and a single methyl 1-*tert*-butyl-3,4-difluoropyrrole-2-carboxylate **2** was obtained. Saponification of **2** afforded the corresponding acid which was easily decarboxylated by simple heating at 160 °C to give 1-*tert*-butyl-3,4-difluoropyrrole in good yield.[8d] At this stage, we were unable to remove the *tert*-butyl substituent on nitrogen while some other *N*-protective groups for the 2-alkoxycarbonyl aziridine *e.g.* trimethylsilyl,[18] 2-(phenylthio)ethyl, *tert*-butoxycarbonyl or benzyl were used unsuccessfully.



Scheme 1

Reagents and conditions: **a**, CF_2=CFCl, C_6H_6, 200 °C, 2 h 30, 40 %; **b**, MeONa-MeOH, r.t., 2 h, 73 %; **c**, CF_3SO_3H, CH_2Cl_2, r.t., 15-45 min, 59% (**3**); **d**, KOH-EtOH, 85 °C, 3 h, 71 %; **e**, Ba-promoted copper chromite, quinoline, 200 °C, 21 %.

Fortunately, we reported the fortuitous direct formation of the *N*-deprotected methyl 3,4-bis (trifluoromethyl)pyrrole-2-carboxylate in the thermal cycloaddition of methyl 1-*tert*-butyl-aziridine-2-carboxylate and perfluorobutene at 180 °C.[8c] On the basis of our report, La Porta *et al.* proposed the hypothesis that hydrogen fluoride, occuring from direct aromatization of the intermediate pyrrolidines, was responsible for this unexpected cleavage.[19] Similarly to the removal of the *tert*-butyl group of *N*-*tert*-butylcarbamates with trifluoromethanesulfonic acid (triflic acid),[20] they confirmed this interpretation by deprotecting the nitrogen atom of methyl 1-*tert*-butyl-3-aryl-4-trifluoromethylpyrrole-2-carboxylates with triflic acid in dichloromethane at 40 °C. As for carbamates, the alkoxycarbonyl group appeared to be fully involved in the acid-catalyzed deprotection mechanism.

We effectively found that, when treated with triflic acid in dichloromethane at room temperature, methyl 1-*tert*-butyl-3,4-difluoropyrrole-2-carboxylate **2** underwent a rapid dealkylation at nitrogen, affording the expected methyl 3,4-difluoropyrrole-2-carboxylate **3** (59 % yield) as the major product accompanied with the pyrrole **4** (14 % yield), an isomer of the starting material, in an about 4:1 ratio (**Scheme 1**). When treated in the same conditions, 1-*tert*-butyl-3,4-difluoropyrrole[8d] remained unaffected, thus confirming the role of the carboxylate function in the deprotection.

Pyrrole **2** appeared to be far more reactive towards triflic acid than methyl 1-*tert*-butyl-3-(2- or 4-chlorophenyl)-4-trifluoromethyl-pyrrole-2-carboxylates which needed 2 hours heating at 40 °C for deprotection.[19] In our case, TLC monitoring indicated that starting material was no longer present only 15

min after addition of the acid to the pyrrole at room temperature. Another difference was the formation of pyrrole **4**, most likely resulting from the alkylation of pyrrole **3** with the detached *tert*-butyl cation. Such a side reaction was not observed with the trifluoromethylated pyrroles[19] probably as an effect of ring deactivation. Saponification of the ester **3** with ethanolic potassium hydroxide led to the acid **5** which was submitted to decarboxylation. Heating this infusible compound at 160 °C produced only a coal. Moreover, the reluctance to decarboxylation of pyrroles bearing electron-withdrawing substituents was well-established. For example, 3,4-bis-(trifluoromethyl)pyrrole-2-carboxylic[18] and 4-trifluoromethyl-3-carboxylic acids[21] failed to decarboxylate on dry heating even in the presence of copper powder. An efficient method of decarboxylation of such stabilized pyrroles was proposed by Loader *et al.*, involving the use of barium-promoted copper chromite in quinoline and a cautious monitoring of evolved carbon dioxide.[22] This procedure allowed us to prepare 3-trifluoromethylpyrrole.[21] We applied it to the acid **5** and, as expected, we could isolate 3,4-difluoropyrrole **1** in 21 % yield.[23] This low yield resulted, at least in part, from harsch reaction and work-up conditions associated to a high vapour-pressure rendering isolation delicate.

References and Notes

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23. Except for compound **5**, all spectra were recorded in $CDCl_3$ on a Bruker AC 200e NMR apparatus.
Dealkylation procedure: to a stirred solution of pyrrole 2^{8d} (1.0 g, 4.6 mmol) in anhydrous dichloromethane (40 mL) under a dry atmosphere (argon or N_2) at room temperature, was added at once anhydrous triflic acid (0.12 mL, 1.36 mmol). After *ca.* 45 min (TLC, CH_2Cl_2), 5% aqueous NaOH solution (10 mL) was added. After extraction (CH_2Cl_2) and drying ($MgSO_4$), the residual solid was submitted to a flash chromatography (silica gel, CH_2Cl_2) to give *pyrrole* **4** at R_F ~0.6 (0.14 g, 0.65 mmol, 14%): ^1H NMR δ 1.31 (s, 9 H, *t*Bu), 3.84 (s, 3 H, CO_2Me), 8.32 (br s, 1 H, NH); ^{19}F NMR δ -163.47 (dd, 1 F, *J* 12.4, 1.8 Hz, F-3), -175.11 (dm, 1 F, *J* 12.4 Hz, F-4); ^{13}C NMR δ 28.73 (d, *J* 2.0 Hz, $C(\underline{C}H_3)_3$, 31.97 (dd, *J* 3.1, 1.0 Hz, $\underline{C}(CH_3)_3$), 51.66 (s, $CO_2\underline{C}H_3$), 101.70 (d, *J* 16.3 Hz, C-2), 128.39 (d, *J* 16.2 Hz, C-5), 134.74 (dd, *J* 240.0, 10.0 Hz, C-3 or C-4), 140.98 (dd, *J*, 256.3, 10.5 Hz, C-4 or C-3), 160.64 (t, *J* 3.0 Hz, $\underline{C}O_2Me$); m.p. 133.2 °C; EI-MS m/e 217 (M^+, 34), 202 (89), 170 (100). Anal. Calcd for $C_{10}H_{13}F_2NO_2$: C, 55.29; H, 6.03; N, 6.45. Found: C, 55.27; H, 6.02; N, 6.28, then *pyrrole* **3** at R_F ~0.36 (0.44 g, 2.73 mmol, 59%): ^1H NMR δ 3.88 (s, 3 H, Me), 6.65 (td, *J* 3.9, 3.9, 3.0 Hz, 1 H, H-5), ~8.99 (br s, 1 H, NH); ^{19}F NMR δ -165.57 (ddd, 1 F, *J* 11.9, 3.9, 1.6 Hz, F-3), -176.77 (dt, 1 F, *J* 11.9, 2.8, 2.8 Hz, F-4); ^{13}C NMR δ 51.88 (s, Me), 105.40 (d, *J* 16.5 Hz, C-2), 106.35 (d, *J* 23.0 Hz, C-5), 138.43 (dd, *J* 241.9, 10.2 Hz, C-3 or C-4), 140.23 (dd, *J* 255.7, 9.9 Hz, C-4 or C-3), 160.64 (t, *J* 3.0 Hz, $\underline{C}O_2Me$); m.p. 126.7 °C. Anal. Calcd for $C_6H_5F_2NO_2$: C, 44.73; H, 3.13; N, 8.69. Found: C, 44.51; H, 3.17; N, 8.52. Melting points were taken in sealed capillary.
The *acid* **5** was obtained following reference 8c in 71% yield after sublimation at 100 °C/0.06 mmHg. ^1H NMR (CD_3COCD_3) δ 6.95 (td, 1 H, *J* 4.2, 4.2, 2.7 Hz, H-5), ~8.2 (br s, 1 H, NH), ~10.6 (br s, 1 H, CO_2H); ^{19}F NMR (CD_3COCD_3) δ -167.53 (ddd, 1 F, *J* 11.8, 4.1, 2.4 Hz, F-3), -179.09 (dt, 1 F, *J* 11.8, 2.8, 2.8 Hz, F-4); EI-MS m/e 147 (M^+, 88), 129 (100).
Decarboxylation procedure:[21, 22] to a vigourously stirred, pre-heated suspension of Ba-promoted copper chromite (0.15 g) in quinoline (2.5 mL) at 200 °C, the acid **5** (0.24 g, 1.63 mmol) was added at once. Carbon dioxide rapidly evolved then stopped after *ca.* 25 mL (calcd. 36.5 mL). The mixture was cooled, poured onto ice (~30 g) and acidified with concentrated HCl (3 mL) then extracted with ether after filtration through Celite. After drying ($MgSO_4$), the solvent was carefully distilled off, leaving a brown oil as residue. Last traces of ether were removed by sweeping with a slow argon or N_2 stream. By evaporation at r.t. (0.06 mmHg) and trapping in a collector at -70°C, *pyrrole* **1** was obtained as a white solid crystallizing on the wall (0.035 g, 0.34 mmol, 21%). Last traces of quinoline were removed by a new sublimation-trapping sequence, m.p. 44.1 °C: ^1H NMR δ 6.37 (dd, 2 H, *J* 3.5, 0.9 Hz, H-2, 5), ~7.20 (br s, 1 H, NH); ^{19}F NMR δ - 181.67 (m, $W_{1/2}$ 3.8 Hz); ^{13}C NMR δ 100.39 (m, C-2, 5), 139.03 (dd, *J* 237.3, 11.8, C-3, 4); IR (CCl_4) 3460, 1590, 1555, 1320, 1170, 1100 cm^{-1}; EI-MS m/e 103 (M^+, 100).

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