# A Straightforward Synthesis of 3,4-Difluoropyrrole

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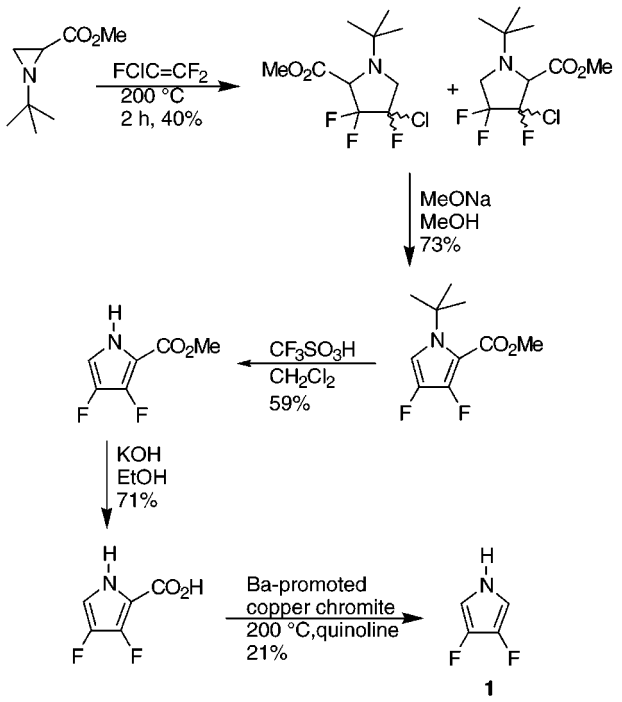
Halogenated pyrroles have been synthetic targets for over a century. 2,3,4,5-Tetrahalopyrroles were first reported in the 1880s;[1−3] by 1934 Fischer had catalogued more than 60 simple ring-halogenated derivatives in *Die Chemie des Pyrrols*.[4] The first definitive preparation of an otherwise unsubstituted 3,4-dihalopyrrole was due to Fischer, who synthesized 3,4-dichloropyrrole by saponification and double decarboxylation of 3,4-dichloro-2,5-dicarbethoxypyrrole.[5] 3,4-Dibromopyrrole has been prepared by two routes: bromination and decarboxylation of 2-pyrrole carboxylic acid[6] and bromination and deprotection of *N*-(triisopropylsilyl)pyrrole.[7] 3,4-Diiodopyrrole has been obtained from the *N*-(triisopropylsilyl)pyrrole method and by a dissolving metal reduction (Zn, HOAc) of 2,3,4,5-tetraiiodopyrrole[8]

3,4-Dihalopyrroles have been employed as Diels−Alder dienes,[9−11] and as precursors for poly(3,4-dihalopyrroles).[6,12,13] In addition, these compounds have been recognized as potential starting materials for selectively or heavily halogenated azamacrocycles.[14] The recently reported class of highly electron deficient $\beta$-octachloro- and $\beta$-octabromoporphyrins could, in principle, be prepared from the corresponding 3,4-dihalopyrroles, but this approach has been supplanted by the development of efficient methods to chlorinate and brominate the macrocycle periphery.[15−22] In contrast, 2,3,7,8,12,13,17,18-octafluoro-5,10,15,20-tetraarylporphyrins have only been successfully synthesized from the condensation of 3,4-difluoropyrrole, **1**, with aryl aldehydes.[23,24] Direct fluorination of tetraarylporphyrins gave pigments of a still undetermined structure.[25] Despite the long-standing interest in halogenated pyrroles, the diverse potential synthetic routes into the 3,4-dihalogenated derivatives, and the foreseeable and demonstrated synthetic utility of 3,4-difluoropyrrole, **1**, remains a remarkably uncommon halogenated heterocycle.

**Scheme 1**




**1**

The only reported preparation of **1** is outlined in Scheme 1.[26] The relatively elaborate isolation and purification protocol required after the final copper-catalyzed decarboxylation is a severe obstacle to scaling up this procedure; the initial report described the preparation of 35 mg of **1**. Since small quantities of **1** are clearly inadequate to explore the utility of this building block in materials or macrocycle chemistry, an efficient, scalable preparation providing gram quantities from relatively inexpensive precursors is highly desirable.

After variants of traditional 3,4-dihalopyrrole syntheses proved fruitless, the double H−X elimination route originally employed by Leroy and Wakselman (Scheme 1) was revisited. Modifications of this strategy that

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eliminated the cumbersome deprotection and decarboxylation procedures seemed attractive. A search of the literature for suitable starting materials yielded 3,3,4,4-tetrafluoropyrrolidine, first synthesized by reduction of 3,3,4,4-tetrafluorosuccinimide with $LiAlH_4$.[27] Later, an improved synthesis of this intermediate was reported by Roberts and Spencer, who employed borane in THF in the final reduction step.[28] In both tetrafluoropyrrolidine preparations, the precursor 3,3,4,4-tetrafluorosuccinimide was obtained by the method of Henne and Zimmer.[29] Because of its volatility 3,3,4,4-tetrafluoropyrrolidine is most conveniently isolated and handled as its hydrochloride salt, **2**. Compound **2** is readily prepared in large quantities (10−40 g) and is sufficiently stable to be stored for months under ambient conditions.

Many conditions were surveyed to effect the double elimination of H−F from **2** to form **1**. Nonnucleophilic neutral amines such as triethylamine, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), or 1,4-diazabicyclo[2.2.2]octane (DABCO) were insufficiently basic to abstract a proton from the 2-position of the pyrrolidine. Alkoxides in alcohol solvents were also ineffectual. The poor leaving group ability of fluoride most likely dictates an $E_{1cb}$-like mechanism, in which proton abstraction precedes departure of $F^-$.[30] Thus, strongly basic conditions are expected to be required to eliminate H−F. Treatment of **2** with lithium bis(trimethylsilyl)amide ($Li(TMS)_2N$) gave moderate yields of **1**, but separation of the volatile 3,4-difluoropyrrole from the ethereal solvent and amine base proved difficult. A survey of strong bases indicated that good to excellent crude yields of **1** could be obtained from **2** without difficulty (as determined by GC-MS analyses of the reaction mixtures), but recovery of significant quantities of pure **1** was problematic.

Once it was recognized that isolation and purification of **1** were the major obstacles to a successful synthesis, the search for optimal reagents was confined to bases and solvents that were sufficiently water soluble to be washed from the pyrrole. A mixture of *t*-BuOK in DMSO was most satisfactory in terms of yield and ease of handling.


**2** **1**

For a typical gram scale preparation of **1**, tetrafluoropyrrolidinium chloride dissolved in a minimal amount of dry, chilled DMSO underwent efficient double dehydrohalogenation within 30 min after addition of *t*-BuOK (4 equiv). Aqueous workup and extraction with $CH_2Cl_2$ followed by concentration and crystallization gave large (typically 2 × 0.3 × 0.2 cm) prismatic crystals of pure **1**. Typical isolated yields were greater than 50%. Interestingly, NMR tube reactions showed quantitative conversion of **2** to **1** with *t*-BuOK and a number of other bases. Clearly, efficient isolation of **1** remains the chief challenge for development of an improved synthesis.

In conclusion, a simple method to prepare **1** is reported. The route is one step from the previously reported compound **2** and three steps from a commercially available precursor, 2,2,3,3-tetrafluorosuccinamide.

## Experimental Section

**General.** Dimethyl tetrafluorosuccinate was purchased from Oakwood Research or PCR and used without purification. DMSO was vacuum distilled from calcium hydride. THF was distilled from a sodium mirror. Tetrafluorosuccinamide, tetrafluorosuccinimide and tetrafluoropyrrolidinium chloride were prepared according to literature methods.[28,29] All other reagents were obtained from commercial sources and used as received.

**3,4-Difluoropyrrole (1).** In a 250 mL round-bottom Schlenk flask equipped with a magnetic stir bar, 3,3,4,4-tetrafluoropyrrolidinium chloride, **2** (5.106 g, 28 mmol), was dissolved in dry DMSO (40 mL). The reaction flask was cooled in an ice bath, and *t*-BuOK (12.779 g, 114 mmol) was introduced under $N_2$ with a powder addition funnel equipped with an auger. After addition of the base was complete (10 min), the mixture was stirred at room temperature for 30 min, cooled to 0 °C, and quenched with ice water (50 mL). After the solids dissolved, the mixture was diluted to 600 mL with water, neutralized to pH 7 with aqueous HCl, and extracted (6 × 50 mL) with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were combined and washed with water (4 × 50 mL) and brine (2 × 50 mL), dried with $Mg_2SO_4$, and filtered. The $CH_2Cl_2$ was removed by rotary evaporation at −10 °C. The resulting yellowish oil was crystallized from pentane (30 mL) at −20 °C to give 1.553 g of colorless crystalline product (53% yield). (Occasionally, oils are obtained from pentane recrystallization if the pyrrole is insufficiently pure. In this case, crystallization can be induced by adding a seed crystal. Large seed crystals are grown from concentrated $CH_2Cl_2$ solutions cooled to −20 °C.) Crystalline **1** (sealed tube mp 44.5−45.5 °C, lit.[26] mp 44.1 °C) was stable for months at −20 °C; slight discoloration occurred upon extended storage. Repurification of discolored samples was readily achieved by vacuum (5 $\mu$m) transfer of **1** at room temperature into a cold (−78 °C) receiver (sealed tube mp 45−46 °C): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.23 (br t, 1 H, $J^{14}_{N-H}$ = 50 Hz), 6.35 (dd 2 H, $J_1$ = 3.5, $J_2$ = 1.2 Hz, H-2, 5); $^{13}$C NMR (125 MHz, $^1$H dec, $CDCl_3$) $\delta$ 139.1 (dd, $J_1$ = 238 Hz, $J_2$ = 12 Hz), 100.4 (dd, $J_1$ = 21 Hz, J2 = 3.5 Hz); $^{19}$F NMR (470 MHz, $CFCl_3$ internal standard, $CDCl_3$) $\delta$ −181.54 (dd, $J_1$ = 2 Hz, $J_2$ = 1 Hz); EI-MS *m/e* 103 ($M^+$).

**p$K_a$ Determination of 1.** The strong $\sigma$-electron withdrawing effect of the two fluorine substituents is manifest in the increased ion pair acidity of **1** in THF. We used the single indicator method of Streitwieser (lithium carbazole as an indicator and base, $pK_{Li/THF}$ = 13.48).[31] The p$K_a$ of **1** was determined to be 11.8 ± 0.1. In contrast, pyrrole has been found to be less acidic than carbazole (by approximately 3 p$K_a$ units) in DMSO[32] and water.[33] Thus, the two fluorine substituents result in a roughly 50000-fold increase in N−H acidity for **1**.

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