Fluoro-decarboxylation of Pyrrolecarboxylic Acids by F–TEDA–BF_4– A Convenient General Synthesis of Fluoropyrroles

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Reaction of a range of α-pyrrolecarboxylic acids, in which the ring is highly substituted by electron-withdrawing or -donating groups, with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis (tetrafluoroborate) (F–TEDA–BF_4) gives the corresponding α-fluoropyrroles in 32-47% yields; 2-fluoroporphobilinogen (F–PBG), of potential use as an inhibitor of the enzyme porphobilinogen (PBG) deaminase, has been synthesized by this method.

Replacement of hydrogen by fluorine in biologically active molecules to yield analogues with improved reactivity and selectivity has led to the development of methodologies for the selective formation of carbon–fluorine bonds within complex molecular arrays.[1] Certain naturally occuring halopyrroles exhibit a strong anti-bacterial activity,[2] while fluoropyrroles have been shown to be valuable targets for elaboration to porphyrins[3] and for preparation of compounds of agricultural and medicinal interest. However, a general synthetic route to fluoropyrroles, particularly those containing additional functionality appropriate for subsequent formation of biologically interesting molecules, is still not available, due to the high reactivity of pyrroles towards electrophiles and to the oxidizing power of electrophilic fluorinating reagents. There have been several reports on the synthesis of fluoropyrroles,[4] but these methods still suffer from the disadvantage of multi-step preparation or from limited application. Here we report a convenient general method (Scheme 1) for the synthesis of α-fluoropyrroles by fluoro-decarboxylation of the corresponding α-pyrrolecarboxylic acids with F–TEDA–BF_4, a new fluorinating reagent which has been used extensively for the synthesis of selective fluorinated compounds of biological interest.[5] The method has also been applied to synthesize F–PBG, a potential suicide inhibitor of the enzyme PBG deaminase.

Treatment of α-pyrrolecarboxylic acids substituted with electron-withdrawing substituents (Table 1; entries 1–4) with 1 equiv. of F–TEDA–BF_4 in a two phase CH_2Cl_2–aq. $NaHCO_3$ (2 equiv.) system, according to Scheme 1, gave the corresponding fluoropyrroles in acceptable yields (32–47%). The reaction is performed at room temperature and usually requires 0.5–1 h for completion. In the case of entry 2, although small amounts of oxidized by-products were observed, F–TEDA–BF_4 tolerated the aldehyde function during fluoro-decarboxylation. α-Pyrrolecarboxylic acids bearing electron-donating substituents were smoothly fluoro- decarboxylated as seen in entries 5–7, but the reactions were much faster than with those pyrroles substituted with electron-withdrawing groups (entries 1–4) and the reaction time had to be limited to 20 min. Although optimum reaction conditions remain to be established, the results presented in Table 1 clearly show the feasibility of this method for the synthesis of fluoropyrroles substituted with both electron-withdrawing and -donating groups.

The major advantages of this method are readily available substrates, mild reaction conditions, ease of isolation of the product and toleration of a variety of functional groups during the fluoro-decarboxylation. Moreover, the method allows the synthesis of fluoropyrroles, not bearing electron-withdrawing substituents, which have been difficult to obtain by reported methods.[4]

The above results prompted us to use the method for the synthesis of F–PBG, a new, potential suicide inhibitor of porphobilinogen deaminase, a key enzyme in the biosynthesis of heme, chlorophylls, vitamin B_{12} and related macrocycles.[6] When substrate **3**[7] was treated with F–TEDA–BF_4 under the above conditions (Scheme 2), the corresponding fluoro-decarboxylation product, 2-fluoroporphobilinogen lactam methyl ester **4**, was produced in 37% yield. Hydrolysis of **6** with 2 mol dm^{-3} aq KOH gave F–PBG **5**.

The mechanism of the process has not been established, but the procedure described above constitutes a very useful improvement in current methodology.

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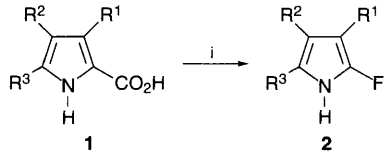
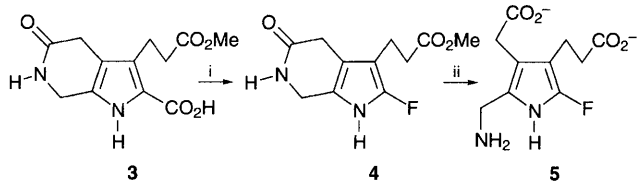


Scheme 1 *Reagents and conditions*: i, F–TEDA–BF_4, $NaHCO_3$, room temp.



Scheme 2 *Reagents and conditions*: i, F–TEDA–BF_4, $NaHCO_3$, room temp., 37%; ii, KOH (2 mol dm^{-3})

Table 1 Fluoro-decarboxylation of α-pyrrolecarboxylic acids by F–TEDA–BF_4

Entry	R^1	R^2	R^3	Reaction time[b]	Yield (%)
1	Me	Me	CBZ[a]	1 h	42
2	$CH_2CH_2CO_2Me$	CH_2CO_2Me	CHO	40 min	32
3	$CH_2CH_2CO_2Me$	CH_2CO_2Me	CBZ	45 min	35
4	CH_2CO_2Me	$CH_2CH_2CO_2Me$	CBZ	45 min	47
5	$CH_2CH_2CO_2Me$	CH_2CO_2Me	Me	20 min	37
6	Me	H	Me	20 min	34
7	Me	Me	Me	20 min	32

[a] CBZ = CO_2CH_2Ph. [b] All reactions were carried at room temp.

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