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A new synthetic route to 3-polyfluoroalkyl-containing pyrroles

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Abstract

A novel approach to 3-polyfluoroalkyl pyrroles is reported based on step by step reactions: 1,2-addition of Me_3SiCN to β-alkoxyvinyl polyfluoroalkyl ketones, reduction with $LiAlH_4$ and subsequent hydrolysis with intramolecular cyclization. The hydrolytic instability of various polyfluoroalkyl groups at position 3 of the pyrrole ring was evident and a pathway for the hydrolysis was proposed.

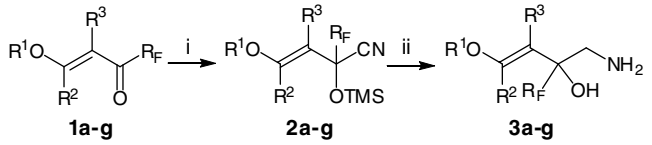
Keywords: Enone; Pyrrole; Cyclization; Hydrolysis; Fluoroalkyl groups; 3-Polyfluoroalkyl pyrroles

Recently, organofluorine compounds have gained considerable interest due to their enhanced biological activity,[1–3] especially polyfluoroalkyl substituted heterocycles. Pyrrole-containing structures are common in syntheses of bioactive compounds. For example, fluoroalkyl-containing pyrroles are good precursors to various herbicides[4] and porphyrins.[5–7]

Synthesis of pyrroles bearing several substituents together with a polyfluoroalkyl group at position 3 has been reported,[8] whereas 3-polyfluoroalkyl pyrroles with few other substituents are less accessible.[9] Thus, attention has been devoted to the synthesis of 3-trifluoromethyl substituted pyrroles mainly as precursors for electron deficient porphyrins.[10] The first synthesis of a 3-trifluoromethyl-containing pyrrole was accomplished using the modified Knorr condensation starting from ethyl trifluoroacetoacetate.[10] A later synthesis of 3-trifluoromethyl pyrroles used α,β-unsaturated ketones.[11] Another approach to 3-trifluoromethyl substituted pyrroles consisted of photochemical trifluoromethylation using CF_2I_2 or CF_3I. A mixture of 2- and 3-trifluoromethyl pyrroles (in very poor yield) was obtained in ratios of isomers which depended on the reaction conditions and the nature of the substituents on the pyrrole ring.[8,12]

In addition, there are reports on the synthesis of 3-trifluoroacetyl pyrroles starting from readily available β-alkoxyvinyl trifluoromethyl ketones **1**.[13,14] Thus, we have developed a new efficient route to the construction of 3-polyfluoroalkyl-containing pyrroles starting from polyfluoroalkyl-containing enones **1a**–**g**.[15]

The addition of trimethylsilylcyanide (TMSCN) to carbonyl compounds is widely used to obtain silylated cyanohydrins, which are used as precursors for β-amino alcohols,[16a] α-hydroxy acids[16b] and α-amino acids.[16c] The first step in the proposed synthetic route is 1,2-addition of TMSCN to the carbonyl group of enones **1a**–**g** in the presence of a catalytic amount of base[17] leading to silylated cyanohydrins **2a**–**g** (Scheme 1).[18] Cyanohydrins **2** were easily reduced with $LiAlH_4$ to amino alcohols **3** in high yields (Table 1).[19]



Scheme 1. Reagents and conditions: (i) TMSCN, Et_3N, 0–10 °C; (ii) $LiAlH_4$, ether, 0–5 °C.

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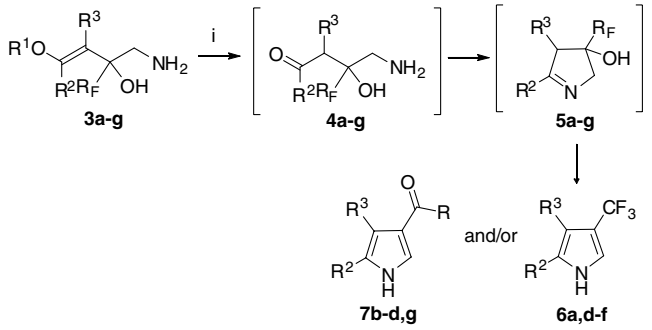
Table 1
Yields of cyanohydrins **2** and amino alcohols **3**

1–3	R^1	R^2	R^3	R_F	Product **2** yield (%)	Product **3** yield (%)
a	Et	H	H	CF_3	80	88
b	Et	H	H	CHF_2	80	80
c	Et	H	H	CF_2Cl	87	75
d	Me	Me	H	CF_3	90	92
e	Et	H	Br	CF_3	82	81
f	Et	Ph	H	CF_3	85	90
g	Et	H	H	C_2F_5	74	78

The amino alcohols **3** are good precursors to biologically active fluorinated compounds, and we have recently used amino alcohols **3a**,**b** for the synthesis of β-R_F-containing analogs of GABA.[18] NMR spectral data of amino alcohols **3c**–**g** are similar to the corresponding data for **3a**,**b**.[19] Amino alcohols **3a**–**g** maintain the starting configuration of the C=C double bond under the reaction conditions. Purification of amino alcohols **3** was dependent on the nature of the substituents R^2 and R^3: products **3a**–**c**,**g** are oils which were purified by vacuum distillation, whereas the crystalline amino alcohols **3d**–**f** were purified by crystallization.

The last step of the 3-polyfluoroalkyl pyrrole synthesis was hydrolysis of the alkoxyvinyl group with the formation of aminocarbonyl compounds **4** which are unstable and cyclized readily to the pyrroles **6** via intramolecular Schiff base **5** formation with subsequent dehydration and proton migration (Scheme 2, Table 2).

The structure of the pyrroles was dependent on the reaction and isolation conditions.[20] It was found that some of the R_F-groups at position 3 of the pyrrole ring were hydrolytically unstable. The main attention was focused on the synthesis of 3-trifluoromethylpyrrole **6a** and we found the optimal reaction conditions for the hydrolysis of amino alcohol **3a** using ^{19}F NMR spectroscopy using the low field shift (20–25 ppm) of the trifluoromethyl group signal after pyrrole ring formation. Thus, method A provides a higher yield compared to method B because of the volatility of product **6a** while its trifluoromethyl group is rather stable (Table 2). The spectral data of product **6a** (3-trifluoromethylpyrrole) were identical to those published by Leroy.[9]



Scheme 2. Reagents and conditions: (i) H^+, H_2O, MeCN, rt.

Table 2
Yields of pyrroles **6** and **7**

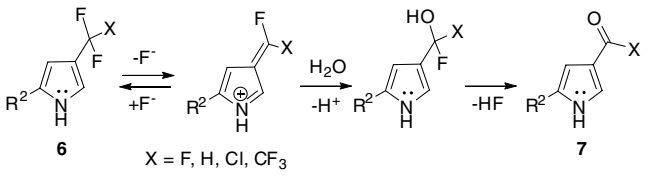
3–7	R^2	R^3	R_F	**6** Yield (%)	R	**7** Yield (%)
a	H	H	CF_3	65[a]	OH	—
b	H	H	CHF_2	—	H	48
c	H	H	CF_2Cl	—	OH	45[b]
d	Me	H	CF_3	55[a]	OH	53[b]
e	H	Br	CF_3	5–10[d]	OH	—
f	Ph	H	CF_3	90[b,c,e]	OH	—
g	H	H	C_2F_5	—	CF_3	55[b,c]

[a] Method A: 0.1 equiv of HCl, rt.
[b] Method B: 1 equiv of HCl, rt.
[c] Reaction temperature ~80 °C.
[d] From ^1H and ^{19}F NMR spectroscopic data of the reaction mixture.
[e] From Schiff base **5f**.

Hydrolysis of amino alcohols **3b**–**g** resulted in both pyrrole ring formation and hydrolysis of the corresponding R_F groups. We suggest that hydrolysis of polyfluoroalkyl groups took place after pyrrole ring formation (Scheme 3), since during the hydrolysis of **3b** (method A) with a catalytic amount of HCl we observed 3-difluoromethylpyrrole (**6b**) formation in the reaction mixture by NMR spectroscopy together with pyrrole-3-carboxaldehyde (**7b**). However, only aldehyde **7b** was obtained after work up and purification by column chromatography; its structure was unambiguously confirmed by IR and NMR spectroscopy. Only product **7b** was obtained using method B.

During the hydrolysis of amino alcohol **3c**, 1*H*-pyrrole-3-carboxylic acid (**7c**) was obtained in a moderate yield, the formation of pyrrole **6c** with a chlorodifluoromethyl group was not detected (^{19}F NMR spectroscopy) due to easier chloride ion elimination. The introduction of the weak electron donating methyl group at position 5 of the pyrrole ring leads to destabilization of the CF_3 group and as a result (method B conditions) a mixture of **6d** and **7d** was observed by NMR but only **7d** was obtained after work up and purification. Using method A, product **6d** was formed in a moderate yield.

The amino alcohols **3e**–**g** were significantly more stable to hydrolysis than the amino alcohols **3a**–**d** and hydrolysis of the ethoxyvinyl group occurred using method B at a higher temperature (~80 °C). In the case of bromo-containing amino alcohol **3e** a complex mixture of reaction products together with pyrrole **6e** (observed only by NMR spectroscopy) was obtained. Under these conditions,



Scheme 3. Assumed mechanism of the hydrolysis of the R_F groups at position 3 of pyrroles.