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Tetrahedron Letters 49 (2008) 1184–1187
Tetrahedron Letters

A new synthetic route to 3-polyfluoroalkyl-containing pyrroles

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Received 30 October 2007; revised 29 November 2007; accepted 10 December 2007
Available online 15 December 2007

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.

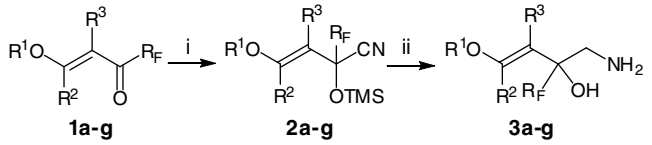
Keywords: Enone; Pyrrole; Cyclization; Hydrolysis; Fluoroalkyl groups; 3-Polyfluoroalkyl pyrroles

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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doi:10.1016/j.tetlet.2007.12.048

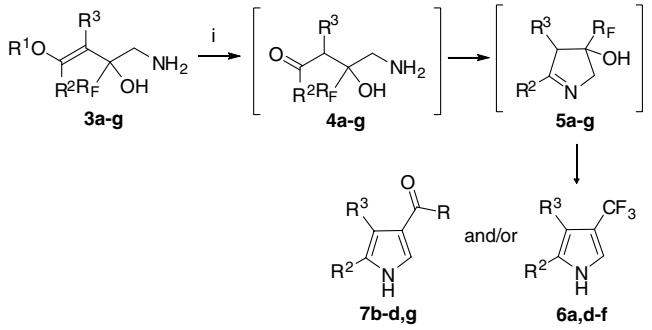
Table 1
Yields of cyanohydrins **2** and amino alcohols **3**

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**

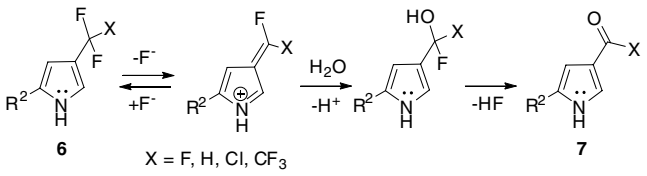
3–7	R^2	R^3	R_F	**6** Yield (%)	R	**7** Yield (%)
a	H	H	CF_3	65[a]	OH	—
b	H	H	CHF_2	—	H	48
c	H	H	CF_2Cl	—	OH	45[b]
d	Me	H	CF_3	55[a]	OH	53[b]
e	H	Br	CF_3	5–10[d]	OH	—
f	Ph	H	CF_3	90[b,c,e]	OH	—
g	H	H	C_2F_5	—	CF_3	55[b,c]

[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**.

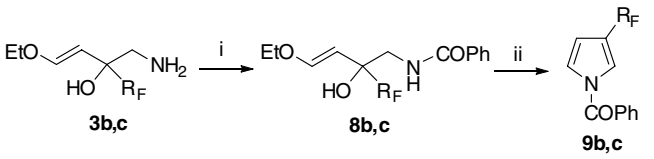
Hydrolysis of amino alcohols **3b**–**g** resulted in both pyrrole ring formation and hydrolysis of the corresponding R_F groups. We suggest that hydrolysis of polyfluoroalkyl groups took place after pyrrole ring formation (Scheme 3), since during the hydrolysis of **3b** (method A) with a catalytic 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.



Scheme 4. Reagents and conditions: (i) PhCOCl, Et_3N, CH_2Cl_2, 0 °C; (ii) H^+, H_2O, MeCN, rt.

the amino alcohol **3f** was converted into trifluoromethyl-containing pyrrole **6f** in high yield. Moreover, in this case the stability of the intermediate Schiff base **5f** was such that it could be isolated and characterized. Hydrolysis of amino alcohol **3g** gave pyrrole **7g** with a trifluoroacetyl group at position 3, its spectral data and mp were consistent with previous reports.[14,21] Pyrrole **6g** was observed by ^1H and ^{19}F NMR spectroscopy only.

Hydrolysis of the polyfluoroalkyl groups at position 3 of the pyrrole ring can be explained by the influence of the high electron density of the heterocycle (Scheme 3). To the best of our knowledge, there are no previous reports on the hydrolytic instability of 3-polyfluoroalkylpyrroles. Only the instability of trifluoro- and difluoromethylimidazoles has been reported.[22,23]

To enhance the stability of the R_F group at position 3 of the pyrrole ring to hydrolysis the electron donor influence of the nitrogen atom was decreased by N-acylation of amino alcohols **3b**,**c** with benzoyl chloride. Vinyl ethers **8b**,**c** were hydrolysed to afford *N*-benzoyl-3-difluoro- and 3-chlorodifluoromethylpyrroles (**9b**,**c**) in good yields under the conditions of method B (Scheme 4).[24] The stability of the R_F groups in *N*-benzoyl pyrroles **9** during work up was consistent with the proposed hydrolysis mechanism of 3-polyfluoroalkyl pyrroles **6**.

In conclusion, the present method provides a new synthetic access to 3-polyfluoroalkyl pyrroles, which are potentially useful precursors for fluorine-containing porphyrins, based on fluorinated enones **1a**–**g**. The hydrolytic instability of some of the 3-polyfluoroalkyl groups in the pyrrole ring was evident and a reasonable pathway for the hydrolysis was proposed. In spite of the hydrolytic instability of difluoro- and chlorodifluoromethyl groups at position 3 of pyrroles **6**, the corresponding *N*-benzoyl derivatives **9** could be synthesized.

Acknowledgements

We are indebted to Dr. B. I. Ugrak (Institute of Organic Chemistry RAN, Moscow, Russia) for presenting us with difluoroacetic acid.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.048.

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18. For a typical procedure for the preparation of 1,2-adducts **2** see: Shaitanova, E. N.; Gerus, I. I.; Belik, M. Yu; Kukhar, V. P. *Tetrahedron: Asymmetry* **2007**, *18*, 192–198.
19. *A typical procedure for the preparation of amino alcohols* **3a**–**g**: To a suspension of $LiAlH_4$ (2.03 g, 53.5 mmol) in dry ether (50 mL) adducts **2a**–**g** (48.6 mmol) was added dropwise with stirring for 30 min at 0–5 °C. The mixture was stirred overnight at room temperature. Excess $LiAlH_4$ was decomposed with 30% aq NaOH (10 mL) with stirring at 0 °C, then precipitated alumina was filtered and washed thoroughly with ether (3 × 50 mL). The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil. The products were purified by vacuum distillation or by crystallization. *Spectral data for (E)-1,1,1-trifluoro-4-ethoxy-2-(aminomethyl)-3-buten-2-ol* (**3a**): Colorless oil, 88%, bp 85–90 °C/0.1 mmHg; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.32 (t, 3H, $J = 7.1$ Hz), 2.7 (d, 1H, $J = 13.0$ Hz), 3.12 (d, 1H, $J = 13.0$ Hz), 3.77 (q, 2H, $J = 7.1$ Hz), 4.7 (d, 1H, $J = 12.5$ Hz), 6.75 (d, 1H, $J = 12.5$ Hz); ^{19}F NMR (470.5 MHz, $CDCl_3$) δ: −81.6 (s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.6, 45.3, 65.4, 72.5 (q, $J_{C-F} = 35.0$ Hz), 99.2, 125.8 (q, $J_{C-F} = 285.0$ Hz), 150.9. IR ($CHCl_3$, cm^{-1}): $\nu = 3424$, 3048, 2984, 2336, 1656, 1424, 1260, 1200, 1158, 1037. Anal. Calcd for $C_7H_{12}F_3NO_2$: C, 42.21; H, 6.07; N, 7.03. Found: C, 42.36; H, 6.25; N, 7.10.

20. *A typical procedure for the preparation of pyrroles* **6** *and/or* **7**: Method A. The amino alcohols **3a**,**d** (1 mmol) were dissolved in a mixture of MeCN (1 mL) and water (0.5 mL), then 5% aq HCl (0.03 mL, 0.1 mmol) was added. The reaction mixture was stirred at room temperature for 1 week (the mixture became light red). The reaction was monitored by TLC and ^{19}F NMR spectroscopy. The reaction mixture was diluted with ether (5 mL) and dried over anhydrous $MgSO_4$. The products were obtained as oils by careful removal of the solvents by distillation at atmospheric pressure. Method B. To a solution of amino alcohols **3b**,**c**,**e**–**g** (2.5 mmol) in a mixture of acetonitrile (3 mL) and water (1.5 mL), 5% aq HCl (0.8 mL, 2.5 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The reaction was monitored by TLC and ^{19}F NMR spectroscopy. The solution was poured into water and 3% $NaHCO_3$ (10 mL) was added, the products were extracted with CH_2Cl_2 (3 × 15 mL) and the combined organics dried over anhydrous $MgSO_4$. Products **6** and/or **7** were purified by silica gel chromatography. *Spectral data for 3-trifluoromethyl-1H-pyrrole* (**6a**): Brown oil, 65%; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.16 (s, 1H), 7.33 (s, 1H), 7.50 (s, 1H), 8.54 (br s, 1H); ^{19}F NMR (470.5 MHz, $CDCl_3$) δ: −57.3 (s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 104.33, 114.92, 113.15 (q, J_{C-F} = 36.4 Hz), 117.33, 122.37 (q, J_{C-F} = 265.7 Hz). IR (CH_2Cl_2, cm^{-1}): ν = 3685, 3464, 3060, 1608, 1578, 1496, 1432, 1400, 1362, 1248, 1202, 1134, 928. Anal. Calcd for $C_5H_4F_3N$: C, 44.46; H, 2.98; N, 10.37. Found: C, 44.27; H, 3.04; N, 10.28.

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24. *A typical procedure for the preparation of N-benzoylated amino alcohols* **8b**,**c**: To a mixture of amino alcohols **3b**,**c** (1.3 mmol) and Et_3N (0.18 mL, 1.3 mmol) in dry methylene chloride (20 mL), benzoyl chloride (0.15 mL, 1.3 mmol) was added at 0 °C with stirring for 5 min. The mixture was stirred for 2 h at room temperature and water (10 mL) was added. The organic phase was washed with 5% $NaHCO_3$ (2 × 5 mL) and water (2 × 25 mL). The aqueous layer was extracted with methylene chloride (2 × 25 mL) and the combined organics were dried ($MgSO_4$) and then evaporated. Products **8b**,**c** were purified by column chromatography on silica gel (eluent—EtOAc/hexane 1:6). *Spectral data for N-(2-difluoromethyl-4-ethoxy-2-hydroxybut-3-enyl)benzamide* (**8b**): Low-melting solid, 65%; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.26 (t, 3H, J = 7.0 Hz), 3.59 (d, 1H, J = 14.7 Hz), 3.76 (q, 2H, J = 7.0 Hz), 3.85 (d, 1H, J = 14.7 Hz), 4.75 (d, 1H, J = 12.6 Hz), 5.63 (t, 1H, J = 56.1 Hz), 6.53 (s, 1H), 6.74 (d, 1H, J = 12.6 Hz), 7.46 (m, 2H), 7.54 (m, 1H), 7.77 (m, 2H); ^{19}F NMR (470.5 MHz, $CDCl_3$) δ: −132.1 (dd, 1F, J_{F-F} = 272.1 Hz, J_{F-H} = 56.1 Hz), −131.0 (dd, 1F, J_{F-F} = 272.1 Hz, J_{F-H} = 56.1 Hz); Anal. Calcd for $C_{14}H_{17}F_2NO_3$: C, 58.94; H, 6.01; N, 4.91. Found: C, 58.90; H, 6.27; N, 4.99. *A typical procedure for the preparation of N-benzoyl pyrroles* **9b**,**c**: Products **9b**,**c** were prepared according to the general procedure as described for pyrroles **6** by method B. *Spectral data for 3-difluoromethyl-1-benzoyl-1H-pyrrole* (**9b**): White solid, 75%, mp 168 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 6.49 (s, 1H), 6.65 (t, 1H, J_{H-H} = 56.1 Hz), 7.33 (m, 1H), 7.48 (m, 1H), 7.54 (m, 2H), 7.65 (m, 1H), 7.75 (m, 2H); ^{19}F NMR ($CDCl_3$) δ: −110.1 (d, J_{F-H} = 56.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 109.9, 111.4 (t, J_{C-F} = 248.5 Hz), 122.4, 123.0 (t, J_{C-F} = 26.2 Hz), 128.6, 129.5, 132.2, 132.7, 167.3; IR (CH_2Cl_2, cm^{-1}): ν = 3152, 3060, 2960, 2928, 2856, 1707, 1599, 1488, 1448, 1392, 1334, 1248, 1224, 1144, 1072, 1022, 960. Anal. Calcd for $C_{12}H_9F_2NO$: C, 65.16; H, 4.10; N, 6.33. Found: C, 65.35; H, 4.15; N, 6.52.