Synthesis of Polyfluorinated 5-Hydroxypyrazolidin-3-ones

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4-Fluoro-5-hydroxy-5-perfluoroalkylpyrazolidin-3-ones **3** were synthesized in a convenient two-step procedure from alkyl α-hydroperfluoroalkanoates **1**.

β-Keto esters are versatile synthetic intermediates for the preparation of heterocyclic compounds. Similarly, perfluoroacylacetate type keto esters were widely used to prepare trifluoromethyl or, more generally, perfluoroalkyl substituted heterocycles. In particular, trifluoromethylpyrazolinones derivatives are interesting compounds.[1] On the other hand, there are very few examples of the preparation of heterocyclic compounds from α-hydroperfluoro-β-keto esters **2**. To our knowledge, only pyrimidine[2] and benzodiazepine[3] series were approached. This scarcity could be explained by the fact that, until recently, the sole method for preparing **2** was the Claisen condensation from alkyl fluoroacetates, a class of highly toxic compounds.

We[4] and others[5] proposed recently different methods to prepare keto esters **2**. Our very simple and convenient methodology used alkyl α-hydroperfluoroalkanoates **1** as starting material. We wish to report in this paper the use of compounds **1** and **2** to synthesize the hitherto unknown polyfluorinated heterocycles in the pyrazole series.

β-Enamino esters are intermediates in the synthesis of pyrazoles from β-keto esters and hydrazines.[6] Such enamino esters are efficiently obtained by the reaction of amines with α-hydroperfluoroalkanoates **1**,[7] which prompted us to try a direct synthesis of **3** by reacting **1** with hydrazines. No reaction took place, even in the presence of a strong base such as triethylamine used in order to generate in situ the α,β-unsaturated analog of **1**. This failure of reactivity of hydrazines towards **1** and its unsaturated analog is due both to its low basic and nucleophilic properties.

It was therefore necessary to prepare the intermediate ketoester **2**. The previously reported procedure starting from **1**[4] was applied and yielded a crude keto ester **2** which was, without purification, reacted with hydrazine. At room temperature, in tetrahydrofuran as solvent, and in the presence of sodium sulfate as drying agent, a very mild and clean reaction took place yielding 5-hydroxy-5-perfluoroalkyl-4-fluoropyrazolidin-3-ones **3**. The results are summarized in Table 1, together with the mass spectral data. IR and NMR data are reported in Table 2. All products present very similar spectral characteristics, consistent with the proposed structure **3**.

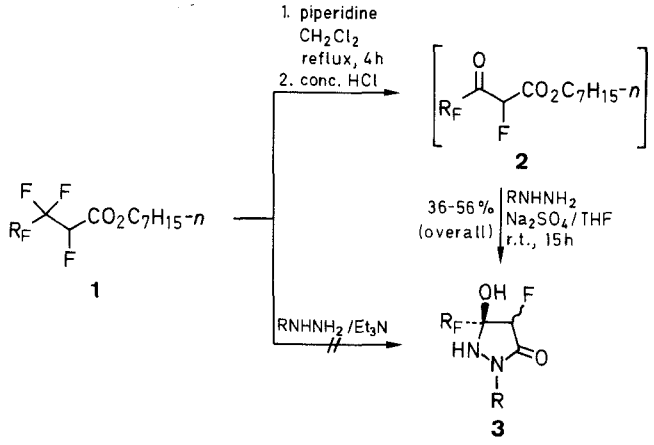

Table 1. Fluorinated Hydroxypyrazolidinones **3** Prepared

Product	R	R_F	Yield (%)[a]	Molecular Formula[b]	MS (70 eV) *m/z* (%)
3a	Ph	*n*-C_4F_9	56	$C_{13}H_8F_{10}N_2O_2$ (414.2)	414 (M^+, 65), 396 (19), 135 (33), 77 (100)
3b	Ph	*n*-C_5F_{11}	53	$C_{14}H_8F_{12}N_2O_2$ (464.2)	464 (M^+, 50), 446 (19), 135 (32), 77 (100)
3c	Ph	*n*-C_6F_{13}	54	$C_{15}H_8F_{14}N_2O_2$ (514.2)	514 (M^+, 84), 496 (10), 135 (65), 77 (100)
3d	H	*n*-C_4F_9	40	$C_7H_4F_{10}N_2O_2$ (338.1)	339 ($M^+ + 1$,77), 338 (M^+, 30), 321 (3), 119 (54), 91 (100)
3e	Me	*n*-C_6F_{13}	36	$C_{10}H_6F_{14}N_2O_2$ (452.1)	452 (M^+, 41), 434 (12), 165 (31), 133 (100)

[a] Purified isolated product. Overall yield from **1**.
[b] Satisfactory microanalyses (C ±0.3, H ±0.1, N ±0.2) or HRMS (*m/z* ±0.003 amu) obtained.

These results deserve several comments:

(i) Yields reported in Table 1 are overall yields from **1**, they are not optimized. This procedure is then both convenient and efficient, especially for phenylhydrazine derived products.

(ii) Instead of obtaining the expected pyrazolinone, the reaction led to a hydroxypyrazolidinone, which can be considered as a hydrate of the former. These hydroxypyrazolidinones were in fact very stable. The sole indication about the lability of water was a weak M^+-18 peak in the mass spectrum of **3** (Table 1). Moreover, no tautomerism was observed.

(iii) Whatever the starting substituted hydrazine used, only the 2-substituted pyrazolidin-3-one was obtained. In non-fluorinated series, a mixture of the 1- and 2-substituted regioisomers were generally formed, apart from phenylhydrazine, by reacting hydrazines with α,β-unsaturated esters.[8] This high regioselectivity indicates that in the first step, hydrazine adds to the carbonyl of **2**,[6] and the intramolecular condensation involves the adduct instead of the corresponding hydrazone.

(iv) Independent of the starting hydrazine used, the reaction yielded a mixture of two diastereoisomers, in a ratio of about 90:10. These isomers were observed by NMR (Table 2) and could not be separated.

Table 2. IR and NMR Spectral Data of Compounds **3** Prepared

Product	IR (KBr) (cm^{-1})		^{1}H-NMR (acetone-d_6/TMS)			^{13}C-NMR (acetone-d_6/TMS)			Others[d]
	$\nu_{OH,NH}$ (br)	$\nu_{C=O}$	H-4[a]	OH[b,c]	NH-1[b]	C-3[c]	C-4[c]	C-5	
3a	3280	1700	5.44, 5.86 (2d, J = 51)	6.9, 7.0 (2s)	7.34 (br s)	163.1, 164.0 (2d, J = 23.5)	87.7, 93.3 (2d, J = 207, 201)	88.7 (m)	–[e]
3b	3270	1700	5.44, 5.86 (2d, J = 51)	6.9, 7.0 (2s)	7.40 (br s)	162.2, 162.8 (2d, J = 23.5)	86.9, 92.5 (d, J = 207, 199)	87.9 (m)	–[e]
3c	3270	1700	5.44, 5.86 (2d, J = 51)	6.9, 7.0 (2s)	7.30 (br s)	162.5, 163.2 (2d, J = 23.6)	87.3, 92.8 (2d, J = 216, 201)	88.3 (m)	–[e]
3d	3265	1700	5.04, 5.59 (2d, J = 51)	6.1, 6.2 (2s)	7.04 (br s)	166.2, 167.5 (2d, J = 22, 19)	85.9, 91[f] (d, J = 204)	89.9 (m)	9.1 (NH)
3e	3270	1700	5.10, 5.56 (2d, J = 51)	6.4, 6.6 (2s)	7.13 (br s)	161.9, 162.3 (2d, J = 23)	86.4, 91.9 (2d, J = 203, 199)	88.2 (m)	3.06 (CH_3) 31.26 ($\underline{C}H_3$)

[a] The higher δ corresponds to the major diastereomer.
[b] Exchangeable with D_2O.
[c] The lower δ corresponds to the major diastereomer.
[d] All products exhibit a strong ν_{CF} absorption at 1100–1270 cm^{-1} and similar ^{19}F-NMR Spectra (acetone-d_6/$CFCl_3$): δ = –80.8 (CF_3), ~121.2 ($CF_2\alpha$, β...), –125.7 ($CF_2\omega$), –207.4 (CF-4).
[e] Characteristic IR and NMR absorptions of the Ph group; e.g. **3a**: IR, ν = 1590, 1500; ^{13}C-NMR, δ = 139.4, 129.4, 125.8, 119.1.
[f] Partly overlaped by the C-5 multiplet.

In summary, we have presented a convenient method to synthesize new polyfluorinated hydroxypyrazolidinones. Owing to the simplicity of the two steps and the use of the crude intermediate keto ester **2**, one can consider that it is a "quasi direct" procedure from the α-hydroperfluoroalkanoates **1**, illustrative of the interest of these compounds, and justifying further research for their synthesis.

^{1}H- and ^{13}C-NMR spectra, and ^{19}F spectra were recorded on Brucker AC 300 and WP 60 spectrometers respectively, using acetone-d_6 as solvent, and TMS and $CFCl_3$ as internal standards, respectively. IR spectra were recorded on a Philips SP 3-300 spectrophotometer. Mass Spectra were recorded on a Jeol D 300 spectrometer (EI, 70 eV). Solvents and common reagents were purified by standard procedures. Kieselgel 60 PF 254 + 366 (Merck) was used for chromatographic purifications. Starting alkyl α-hydroperfluoroesters were prepared from the corresponding perfluoroesters, according to our previously described photoreduction procedure.[9]

4-Fluoro-5-hydroxy-5-perfluoroalkylpyrazolidin-3-ones 3; General Procedure:

Piperidine (3 mmol) was added to a solution of heptyl 2-hydroperfluoroester **1** (1 mmol) in CH_2Cl_2 (4 mL). After refluxing for 4 h, conc. HCl (1 mL) was added, and stirring was continued for 1 h at r.t. The organic layer was decanted, washed with water and dried ($MgSO_4$). The solvent was removed and the crude keto ester **2** was dissolved in THF (4 mL). Hydrazine or substituted hydrazine (1.8 mmol) and freshly dried Na_2SO_4 (~0.2 g) were then added and the suspension was stirred overnight at r.t. The reaction mixture was filtered, the solvent evaporated, and the product purified on silica gel plates (petroleum ether (bp 40–60 °C)/EtOAc, 70:30) to give **3** as a solid, mixture of diastereomers (Tables 1 and 2).

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