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EFFICIENT PREPARATION OF PEPTIDYL PENTAFLUOROETHYL KETONES

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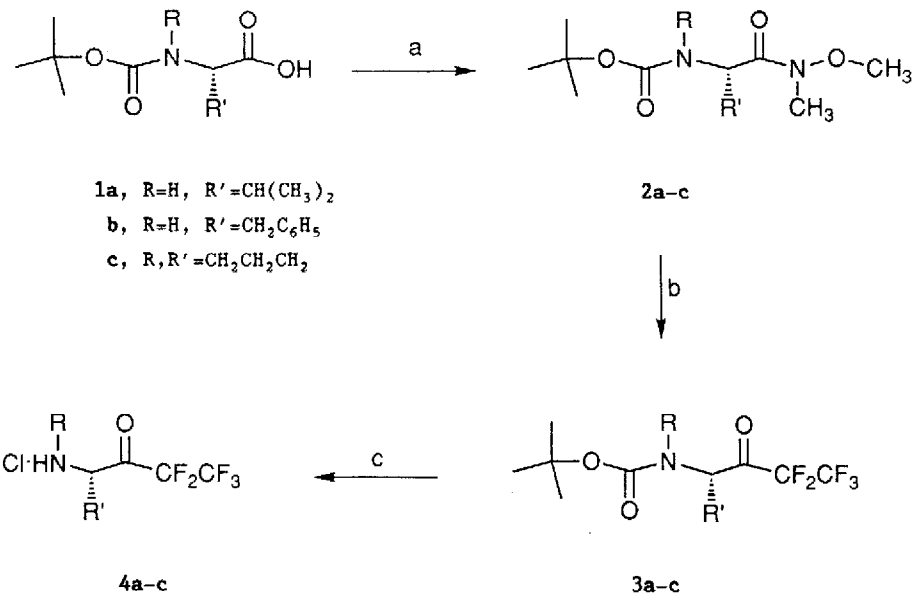
Summary: A concise method for the preparation of α-amino pentafluoroethyl ketone salts from amino acids is described. These intermediates are useful for the preparation of peptidyl pentafluoroethyl ketones.

We have recently described synthetic routes to proteinase inhibitors in which the scissile amide linkage of a peptide is replaced with trifluoromethylketone, α-diketone and α-keto ester electrophilic functionalities.[1] In this report, we describe the synthesis of α-amino pentafluoroethyl ketone salts which are useful for the preparation of peptidyl pentafluoroethyl ketones.

Scheme I



1a, R=H, R′=$CH(CH_3)_2$
b, R=H, R′=$CH_2C_6H_5$
c, R,R′=$CH_2CH_2CH_2$

2a-c

4a-c

3a-c

Reagents: a) Isobutyl chloroformate, N-methylmorpholine, N,O-dimethylhydroxylamine hydrochloride, CH_2Cl_2 for **2a**, **2b** and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, N-methylmorpholine, 4-dimethylaminopyridine, N,O-dimethylhydroxylamine hydrochloride, CH_2Cl_2 for **2c**; b) CF_3CF_2I, $CH_3Li \cdot LiBr$, ether; c) EtOAc, HCl.

The α-amino pentafluoroethyl ketones were prepared as shown in Scheme I. N-(*tert*-Butoxycarbonyl)-L-amino acids 1a-c were coupled to N,O-dimethylhydroxylamine to give the Weinreb amides[2] 2a-c. We have found that pentafluoroethyllithium, when generated *in situ* from pentafluoroethyl iodide and methyllithium·lithium bromide complex, cleanly adds to hydroxamates[3] 2a-c to give pentafluoroethyl ketones 3a-c in good yield (71-80%), as shown in Table I. Also displayed in Table I are ^{19}F NMR and HRMS data for 3a-c. The CF_3 signal appeared as a singlet (or two singlets for 3c) at ca. -82 ppm, whereas the diastereotopic CF_2 fluorine atoms appeared as a pair of doublets (or two pairs of doublets for 3c) at ca. -120 ppm.[4]

Table I. Spectral Data and % Yield for Pentafluoroethyl Ketones 3a-c

	^{19}F NMR[a]			HRMS		
Compound	CF_3[b]	CF_2[b]	J(Hz)	Calcd (MH^+)	Found (MH^+)	% Yield[c]
3a	-82.3	-121.7	296	320.1285	320.1285	73
		-123.0	296	($C_{12}H_{19}NO_3F_5$)		
3b	-82.2	-121.0	296	368.1285	368.1259	71
		-122.8	296	($C_{16}H_{19}NO_3F_5$)		
3c	-82.41[d]	-121.8[d]	299	318.1129	318.1135	80
		-122.1[d]	299	($C_{12}H_{17}F_5NO_3$)		
	-82.43[e]	-122.5[e]	296			
		-122.7[e]	296			

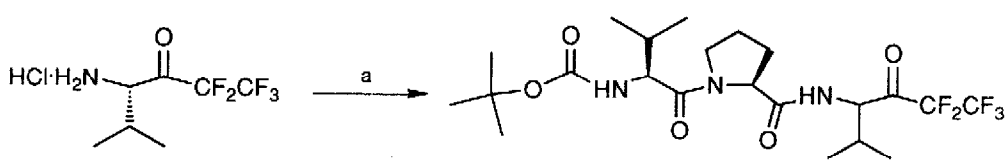
[a]Spectra were recorded in $CDCl_3$. [b]Chemical shifts are recorded in ppm from $CFCl_3$. [c]Isolated yield. [d]Chemical shifts for rotamer one (two rotamers were observed due to hindered rotation about the proline carbamate bond). [e]Second rotamer (see footnote d).

Pentafluoroethyl ketones have previously been prepared[5] by treating phosphonium ylides with perfluoropropionic anhydride;[6] the addition of phenyllithium to ethyl pentafluoroacetate;[7] addition of pentafluoroethyl lithium to an aldehyde followed by Dess-Martin oxidation of the pentafluoroethyl alcohol;[8] acylation of an N-acylated amino acid with pentafluoropropionic anhydride, followed by oxalic acid hydrolysis of the resulting oxazolone;[9] and by treating unactivated esters with excess pentafluoroethyl lithium (a procedure which also produces tertiary alcohols).[10] We feel that the process shown in Scheme I will prove to be the most versatile preparation of this important compound class.

The preparation of pentafluoroethyl ketone **3c** is performed as follows. To a stirred solution of amide **2c** (1.03 g, 4.00 mmol) in ether (35 mL) under argon at -78°C was added condensed CF_3CF_2I (1.1 mL, 9.6 mmol) followed by $CH_3Li \cdot LiBr$ (5.9 mL of a 1.5M solution in Et_2O, 8.8 mmol). After 30 min at -78°C, the solution was warmed to 0°C in an ice bath, and after 20 minutes, the resulting mixture was quenched by adding a solution of $KHSO_4$ (1.07 g, 7.8 mmol) in water (8 mL).[11] After several minutes of stirring, the two clear layers which formed were separated and the organic layer was washed with $NaHCO_3$ solution (35 mL) and brine (25 mL) and dried ($MgSO_4$). The solution was concentrated to a pale yellow oil which was purified by flash chromatography on silica gel, eluting with 15:85::EtOAc:hexane to provide 1.02 g (3.22 mmol) of **3c** (80% yield) as a colorless oil.

Pentafluoroethyl ketones **3a-c** were quite stable and could be stored prior to use. Compounds **4a-c** were generated immediately before use with EtOAc/HCl. The utility of these α-amino pentafluoroethyl ketones is demonstrated by the preparation of peptidyl pentafluoroethyl ketone **5**. Carbamate **3a** (1.20 g, 3.76 mmol) in EtOAc (75 mL) was cooled to 0°C, treated with HCl gas (10 min) and stirred (2 h). Solvent was removed and the hydrochloride salt **4a** was used without purification. In a separate flask, a solution of Boc-L-Val-L-Pro-OH (1.10 g, 3.50 mmol) was dissolved in CH_2Cl_2 (20 mL) and N-methylmorpholine (0.40 mL, 3.68 mmol) and cooled to -17°C. To this solution was added isobutyl chloroformate (0.45 mL, 3.50 mmol). After stirring for 20 min, additional N-methylmorpholine (0.40 mL, 3.68 mmol) was added followed by a light suspension of **4a** (0.88 g, 3.50 mmol) in CH_2Cl_2 (10 mL) and CH_3CN (10 mL). After 1 hr at -17°C, the mixture was warmed to room temperature, diluted with CH_2Cl_2 (100 mL) and the organic layer was washed with 10% HCl (3x75 mL), saturated $NaHCO_3$ (2x75 mL), brine (50 mL) and dried (Na_2SO_4). Concentration gave **5** (1.59 g, 88%) as a white foam.[12]

Scheme II



4a **5**

Reagents: a) Isobutyl chloroformate, N-methylmorpholine, Boc-L-Val-L-Pro-OH, CH_2Cl_2, CH_3CN.

Peptidyl pentafluoroethyl ketone 5 is a potent inhibitor of human neutrophil elastase. The biological properties of 5 and related compounds will be reported elsewhere.

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11. For **3a**, optimum yields were obtained by stirring the reaction mixture at -78°C for 3 hr and quenching directly.
12. The ^1H NMR, ^{19}F NMR and ^{13}C NMR spectra for pentafluoroethyl ketone 5 were consistent with structure and indicated a mixture of diastereomers (93:7) which we believe is due to partial epimerization of the center adjacent to the pentafluoroethyl ketone by N-methylmorpholine. We have not ruled out the possibility that slight epimerization occurred during preceding steps. Compound 5 also gave a satisfactory elemental analysis (C,H,N).

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