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GENERAL APPROACH TO THE SYNTHESIS OF α-DIFLUOROMETHYL AMINES AS POTENTIAL ENZYME-ACTIVATED IRREVERSIBLE INHIBITORS

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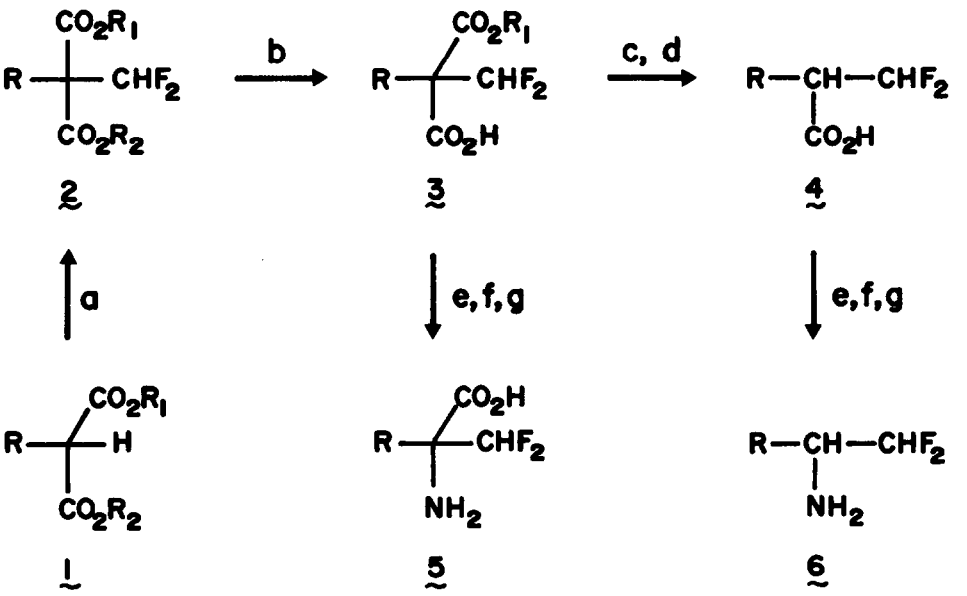
We recently demonstrated that 1-carboxy-lyases can be irreversibly inhibited by the α-difluoromethyl derivatives of their parent α-amino acid substrates or by the α-acetylenic analogues of their parent amine products [1,2]. The mechanistic rationalization of the inactivation by the α-acetylenic amines [1] suggested that the α-fluorinated methyl derivatives of the amine products could also be potential enzyme-activated irreversible inhibitors of the corresponding 1-carboxy-lyases. We report now an efficient and general synthesis of the novel class of α-difluoromethyl amines via a sequence which also allows the preparation of the corresponding α-difluoromethyl-α-amino acids.

Our approach is depicted in Scheme I and relies, as the key step, on the alkylation of the sodio derivative (sodium hydride, 1 equiv) of the readily available monosubstituted diesters 1[3] (R_1=R_2=tBu, or R_1=Et, R_2=tBu) (0.5 M in anhydrous tetrahydrofuran) with an excess of chlorodifluoromethane [4] at room temperature. Under these conditions, the difluoromethyl adducts 2 were obtained in good to excellent yield (see table 1). Reaction of the di-tert-butyl esters 2 (R_1=R_2=tBu) with trifluoroacetic acid at room temperature for 1 hr afforded quantitatively the corresponding malonic acids 3 (R_1=H) which could be decarboxylated in good yield to the α-difluoromethyl carboxylic acid 4 under carefully controlled conditions (glacial acetic acid, 100 to 125°C for 12 to 24 hr) so as to minimize the oxidative decarboxylation which entails the loss of fluoride ion. Similar treatment applied to the tert-butyl ethyl esters 2 (R_1=Et, R_2=tBu) gave intermediarily the malonic acid hemiester 3 (R_1=Et) in excellent yield and then the ethyl ester derivatives of 4 which could be hydrolysed to the carboxylic acids 4 either under drastic acidic conditions (40% sulfuric acid, reflux, 12 to 24 hr) or alternatively under neutral conditions when deemed necessary, as for the ethyl ester of 4f, by using

trimethylsilyliodide [5] (neat, reflux, 4 hr). It is noteworthy that the diethyl esters of the fluorinated adducts 2 (R_1=R_2=Et) proved to be extremely resistant to acid hydrolysis. Thus,



SCHEME I

a) NaH, 1 equiv, THF; $ClCHF_2$ excess, r.t.; b) CF_3CO_2H, r.t., 1 hr; c) glacial AcOH, 100-125°C, 12 hr; d) 40% SO_4H_2:DME, 100°C, 12 to 36 hr; e) $SOCl_2$, reflux; f) NaN_3, 1 equiv, H_2O-Acetone, 0°C; g) reflux in benzene, 12 to 24 hr; H_3O^+ reflux, 12 hr.

2a (R_1=R_2=Et) was recovered essentially unchanged after treatment in 48% hydrobromic acid at 120°C for 12 hr or in a mixture of acetic acid-6M hydrochloric acid (1:2) at 120°C for 16 hr. Attempts to hydrolyse the diethyl ester 2a under basic conditions (sodium hydroxide, 1M, 3 equiv) in a mixture of water-ethanol (1:1) (reflux, 24 hr) resulted in the loss of the difluoromethyl functionality as clearly evidenced by the absence in the ^1H NMR spectrum of the crude reaction product of the triplet (centered around δ=6ppm, J≈52-55 Hz) characteristic of the signal of the hydrogen in a CHF_2 group.

Transformation of the carboxylic acid function of 3 (R_1=Et) and 4 to a primary amine could be achieved under the standard Curtius rearrangement sequence [6] to afford the desired α-difluoromethyl-α-amino acids 5 [7] and α-difluoromethyl amines 6 in fair to good yield (see table 1). This result was gratifying in view of the low yield reported for the rearrangement of 3,3,3-trifluoropropionyl azide to the corresponding isocyanate [8]. Interestingly, the

modified Curtius reaction using the non-explosive diphenylphosphoryl azide reagent [9] failed to give any detectable amount of α-difluoromethyl-α-amino acids or α-difluoromethyl amines [10].

TABLE 1

	R		YIELD * 1 → 2	4 → 6	2 → 5
a	$C_6H_5CH_2$	A	89%	60%	76%
b	$3\text{-}(CF_3)C_6H_4CH_2$	A	85%	20%	-
c	$3,4\text{-}(Cl)_2C_6H_3CH_2$	A	70%	41%	-
d	$3\text{-}(CH_3O)C_6H_4CH_2$	A	70%	30%	-
e	$3,4\text{-}(CH_3O)_2C_6H_3CH_2$	A	58%**	30%	-
		B	90%**		-
f	$PhtN(CH_2)_3$	A	54%	70%***	85%***
		B	33%		

Starting synthon: Method A: $tBuO_2CCH_2CO_2Et$; Method B: $CH_2(CO_2tBu)_2$;
All new compounds gave acceptable elemental analyses. ^1H NMR and ^{19}F NMR spectra were consistent with the proposed structure.

* Yields of distilled, crystallized or chromatographied products.

** Decomposition of tert-butyl ester occurs during distillation. Method B affords a crystalline derivative, thus explaining the large difference in yields.

*** The phthalimido group (Pht) falls off during the acidic treatment. The products were isolated as dihydrochlorides.

As anticipated, α-difluoromethyl dopamine [11], obtained from 6e by cleavage of the ether functions (48% hydrobromic acid, reflux, 4 hr) and α-difluoromethyl putrescine 6f were shown to inhibit irreversibly L-aromatic-α-amino acid decarboxylase (E.C. 4.1.1.26) and ornithine decarboxylase (E.C. 4.1.1.17) respectively [12].

Acknowledgements

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References and Notes

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(12) We are indebted to Dr. G. Ribereau-Gayon and Dr. C. Danzin for measuring the inhibitory properties of these α-difluoromethyl amines.

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