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ALKYLATION OF MALONATES OR SCHIFF BASE ANIONS WITH DICHLOROFLUOROMETHANE AS A ROUTE TO α-CHLOROFLUOROMETHYL OR α-FLUOROMETHYL α-AMINO ACIDS

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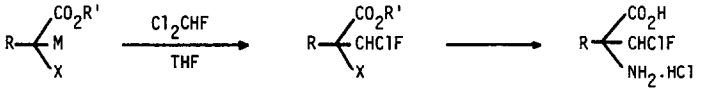
Abstract: α-Chlorofluoromethyl-alanine, -phenylalanine, -m-tyrosine, -ornithine and -glutamic acid are prepared through alkylation of appropriate α-amino acids precursors with dichlorofluoromethane. Intermediates in the sequence can be efficiently reduced with tri-n-butyltin hydride to give access to the corresponding α-fluoromethyl α-amino acids.

α-Halogenomethyl-α-amino acids have been convincingly demonstrated to be enzyme-activated irreversible inhibitors of the parent pyridoxal phosphate dependent α-amino-acid decarboxylases[1]. We described two general approaches to the synthesis of α-chloromethyl, α-fluoromethyl and α-difluoromethyl α-aminoacids which relied on a direct introduction of the halomethyl group via an halomethylation reaction of the anions derived from malonate esters 1[2] or Schiff base esters of α-amino acids 2[3]. We now have successfully extended these approaches to the synthesis of α-chlorofluoromethyl α-amino acids 6[12].

Upon alkylation with an excess of dichlorofluoromethane (Freon 21)[4] 1 and 2[5] afforded the corresponding α-chlorofluoromethyl derivatives 3[6,12] and 5[12] in fair to good yields, as summarized in tables 1 and 2 (scheme 1).

Scheme 1



1 X= $CO_2tC_4H_9$
2 X= $N{=}CHC_6H_5$

3 X= $CO_2tC_4H_9$
4 X= $N{=}CHC_6H_5$
5 X= NH_2
9 X= $NHCO_2R''$

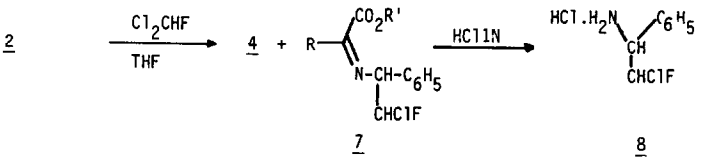
6

R'= CH_3 or C_2H_5; R"= CH_3 or tC_4H_9; M= Na or K

The halomethylation of 2 with dichlorofluoromethane proved less regiospecific than with chlorodifluoromethane (Freon 22). In all cases 4 was contaminated with 2 to 10% of the

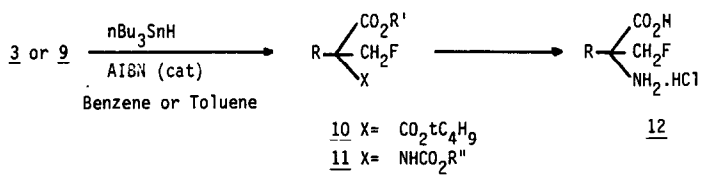
chlorofluoromethylimine 7 which upon hydrolysis yielded β-chloro-β-fluoro-α-phenethylamine 8 (scheme 2). Due to the asymmetry of the newly introduced chlorofluoromethyl group, 3 and 4 were obtained as mixtures of pair of diastereoisomers which could be conveniently separated by chromatography, after transformation to the corresponding carbamates 9[7,11].

Scheme 2



Interestingly 3 and 9[12] have also been found to be efficiently reduced to the corresponding monofluoromethyl derivatives 10 and 11 by tri-n-butyltin hydride in presence of a catalytic amount of AIBN in refluxing benzene or toluene[8] (scheme 3) (Tables 1 and 2). This reaction offers an attractive alternative to the presently available synthesis of α-monofluoromethyl α-amino acids which utilize either toxic (CH_2FCN[9], SF_4/HF[10]) or not easily available (CH_2ClF)[3,9] reagents.

Scheme 3



As expected, most of these α-substituted α-amino acids are enzyme-activated irreversible inhibitors of their corresponding decarboxylating enzymes[11]. The kinetic constants of 6d for the irreversible inhibition of ornithine decarboxylase are similar to those of α-difluoromethyl ornithine[15].

Procedure for the chlorofluoromethylation of anion 1 and 2

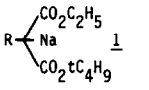
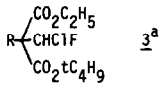
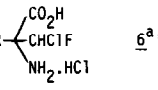
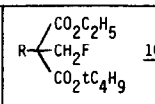
Freon 21 (20mL)[4] is added through a refrigerated funnel to a solution of the anion 1 or 2 (70mmol) in anhydrous THF (140mL) at room temperature. The mixture is then stirred for 16h. Usual work up with diethyl ether affords the expected chlorofluoromethyl derivatives 3[13a] or 4. The imines 4 are directly hydrolysed in 1N HCl, at room temperature to the amino esters hydrochloride. The aqueous layer is washed with diethyl ether (3x, to remove benzaldehyde) and its pH adjusted to 9-10. Extraction with diethyl ether affords the free aminoesters 5[13b].

Procedure for the reduction of 3 and 9 to α-fluoromethyl derivatives 10 and 11

The chlorofluoromethyl derivative (5mmol) is dissolved in dry benzene or toluene (30mL). Tri-n-butyltin hydride (6 mmol, 1.2g) is added along with few cristals of azobisisobutyronitrile (AIBN) and the mixture is refluxed under nitrogen for 2 h. The excess of

tri-n-butyltin hydride is destroyed with carbon tetrachloride. The solvent is evaporated under reduced pressure. The monofluoromethyl derivative is purified either by distillation under reduced pressure or by flash chromatography on silica gel using a mixture of hexane and ethyl acetate as eluant.

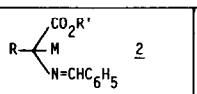
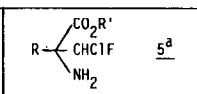
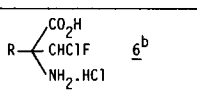
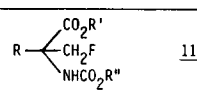
Table 1

			
1a R=$CH_3O_2CCH_2$-	3a 47%	-	10a 90%
1b R= 	3b 48%	6b 38%	-
1c R= 	3c 68%	-	10c 83%
1d R=PhtN$(CH_2)_3$-	3d[13a] 30%	6d 50%	-
1e R= 	3e 36%	-	10e 80%

a) analytically pure compound

b) obtained from 3 as described in ref. 6

Table 2

	M	T°C			
2a R=CH_3 R'=C_2H_5	Na	40°	5a 32%	6a 60%	11a R"=tC_4H_9 78%
2b R=$(CH_2)_2$ $CH=CH_2$ R'=CH_3	Na	20° or 40°	5b 20%	6d[14a] R= $(CH_2)_3NH_2$ 30% 6f[14b] R=$(CH_2)_2CO_2H$ 27%[c]	- -
2c R=$CH_2C_6H_5$ R'=CH_3	K	20°	5c[13b] 25%	6c 90%	11c R"=tC_4H_9 57%
2d R=$(CH_2)_3$ $N=CHC_6H_5$ R'=C_2H_5	Na	40°	5d low yield	-	-

a) isolated compound

b) analytically pure compound

c) overall yields from 5b

References and notes:

1.a) J. KOLLONITSCH, A.A. PATCHETT, S. MARBURG, A.L. MAYCOCK, L.M. PERKINS, G.A. DOULDOURAS, D.E. DUGGAN, A.S. ASTER, Nature (London), 274, 906, (1978).

b) P. BEY, "Enzyme Activated Irreversible Inhibitors", N. SEILER, M.J. JUNG, and J. KOCH-WESER, Eds, Elsevier, Amsterdam, 1978, p. 27.

2) P. BEY, D. SCHIRLIN, Tetrahedron Lett., 1978, 5225.

3) P. BEY, J.P. VEVERT, V. VAN DORSSELAER, M. KOLB, J. Org. Chem. 44, 2732 (1979).

4) Available from Fluorochem. Ltd. Peakdale Road, Glossop, Derlyshire SK 13 9XE, England. Freon 21 was condensed at -20°C in a graduated cylinder. A large excess of alkylating agent was used.

5) Contrarily to Freon 22[3], no alkylation of anion 2 occured with Freon 21 when LDA was used as metallating agent.

6) Compounds 3 were converted to 6 as described in ref. 2. 1) TFA, 0°C; 2) $SOCl_2$; 3) NaN_3, H_2O/acetone; 4) Δ, CH_3OH; 5) HCl or HBr, conc or 6N .

7) Medium pressure liquid chromatography (silica gel; 25°C; ethyl acetate/cyclohexane mixtures). This technique has been successfully used to separate pair of diastereoisomers of compounds 6b, 6d and 6e.

8) This reagent has been used to dechlorinate gem-chlorofluorocyclopropanes, without loss of fluorine. T. ANDO, T. ISHIHARA, E. OHTANI and H. SAWADA. J. Org. Chem. 46, 4446 (1981).

9) P. BEY, F. GERHART, V. VAN DORSSELAER, C. DANZIN. J. Med. Chem. 26, 1551 (1983).

10) J. KOLLONITSCH, S. MARBURG, LEROY M. PERKINS. J. Org. Chem. 44, 771 (1979).

11) The kinetic parameters of inhibition of each pair of diastereoisomers of 6b, 6d and 6e are markedly different for the inactivation of AADC, ODC and GAD respectively. M.J. JUNG, C. DANZIN, J.M. HORNSPERGER, unpublished results.

12) All new compounds (with the exception of compounds of type 5) gave satisfactory combustion analyses. All spectral data were consistent with the proposed structures.

13) a) ^1H and ^{19}F chemical shifts and coupling constants of nuclei of the CHClF substituent in 3d as representative of compounds 3: ^1H NMR ($COCl_3$, TMS): 6.60 ppm (d, J_{HF}= 48 Hz, C<u>H</u>ClF); ^{19}F NMR ($CDCl_3$, int.ref. C_6F_6): +21.5 and + 21.8 ppm (2d, J_{HF}= 48Hz, CHCl<u>F</u>).

b) in 5c as representative of compound 5 : ^1H NMR ($CDCl_3$, TMS) : δ6,38 ppm (d, J_{HF}= 48 Hz, C<u>H</u>ClF); ^{19}F NMR ($CDCl_3$, int. ref. C_6F_6): δ+22,6 ppm (d, J_{HF}= 48 Hz, CHCl<u>F</u>).

14.a) α-Chlorofluoromethyl ornithine 6d was prepared from α-chlorofluoromethyl amino ester 5b through the following sequence:
1) o-phthaloyl chloride, CH_2Cl_2, NEt_3, 72h.; 2) OsO_4, NMMO, tBuOH; 3) $NaIO_4$, THF: H_2O 2/1; 4) $NaBH_3CN$, MeOH, pH 4.5) DEAD, $P\phi_3$, phthalimide, THF; 6) AcOH, HCl 12N, Δ.

b) Compound 5b was converted to the carbamate 9 (R"=tC_4H_9) [$(BOC)_2O$, THF, Δ, 60h. before final conversion to α-chlorofluoromethyl glutamic acid 6f 1) $KMnO_4$, AcOH; 2) LiOH, DME:H_2O 4/1; 3) HCl g., Et_2O].

15) B.W. METCALF, P. BEY, C. DANZIN, M.J. JUNG, P. CASARA and J.P. VEVERT. J. Am. Chem. Soc. 100, 2551 (1978).

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