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SYNTHESIS OF NEW F-ALKYL β -AMINO ALCOHOLS

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Abstract : F-alkyl oxiranes 1 and p-methylbenzenesulfonate ester intermediates 3 derived from 2-F-alkyl ethane -1,2-diols 2 are converted into F-alkyl β -amino alcohols 5 respectively by a two-step process.

The insertion of an amino group into organic molecules via azides derivatives is an important process to produce nucleotides, aminosugars, α -amin(acids or β -aminoalcohols^{1,2}.

There is a great deal of classical and recent methods to obtain vicinal alkylated azidohydrins 3^{-4} and to achieve their reduction into β -amino alcohols 5^{-7} . But a survey of literature revealed very few examples of F-alkyl azides 8^{-12} and we did'nt find examples of α -hydroxyl azides with long F-alkylated chain.

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In this paper, we describe the preparation of Falkyl β -amino alcohols from F-alkyl oxiranes $R_F^{-CH-CH}CH_2^{-13}$ 1¹³and 2-F-alkyl ethane 1,2-diols $R_F^{-CH-CH}CH_2^{-14}$ with $R_F^{-1} = C_4 F_9$, C_6F_{13} , C_8F_{17} . The transformation of the epoxides 1 into the corresponding azidohydrins 4 with

the NaN₃ $/H_2$ O/dioxan reagent was attempted but the yields don't exceed 30-45%; but we found that the NaN₃ $/NH_4$ Cl/H₂ O reagent in MeOH is a convenient reagent system to give the 2-F-alkyl 2-hydroxy azides 4 in good yields (TABLE) and good regioselectivity according to the pathway A.

 $R_{F} = CH = CH_{2} \xrightarrow{\text{NaN}_{3}/\text{NH}_{4}\text{Cl}} R_{F} = CH = CH_{2} = N_{3}$ $I = H_{2}O/MeOH = H_{2}O/MeOH = H_{2}OH = H_{2}OH$ $I = H_{2}O/MeOH = H_{2}OH = H_{2}OH$ $I = H_{2}O/MeOH = H_{2}OH$ $I = H_{2}O/MeOH$ $I = H_{2}O/MeOH$ I =

Pathway A

We obtained also the azidohydrins 4 according to the pathway B. At first, the diols 2 were transformed into the corresponding monotosylates 3 with p-toluenesulfonyl chloride and in the presence of pyridine ¹⁵. Then the tosyl group is substituted by the azide group with sodium azide dissolved in water and in

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TABLE	P
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Compounds Yields (%) b.p.or m.p.(°C) $150/5.10^{-3}$ mm Hg 83 3 a 3 b 82 68 3 C 84 75 -/56²) 4a $75^{1})/51^{2})$ 4b 50/55 mm Hg 821)/522) 60 4 C 5a 5b 68 66 5 c 7295

hway A

hway B

nce of a phase transfer reagent such as aliquat 336*16

 $R_{F} \xrightarrow{\text{CH-CH}_{2}\text{OH}} OH \xrightarrow{\text{p-ClTs}} R_{F} \xrightarrow{\text{CH-CH}_{2}\text{OTs}} OH \xrightarrow{\text{NaN}_{3}/\text{H}_{2}\text{O}} R_{F} \xrightarrow{\text{CH-CH}_{2}\text{N}_{3}} R_{F} \xrightarrow{\text{CH-CH}_{2}\text{N}_{3}} PCT \xrightarrow{\text{OH}} PCT \xrightarrow{\text{OH}} OH$ $3a(R_F = C_4F_9)$ 2 $3b(R_{F} = C_{6}F_{13})$ $3c(R_{F} = C_{8}F_{17})$ Pathway B

*Aliquat 336 = Methyl Tricapryl Ammonium Chloride (PCT)

Pathway B is longer than pathway A as the reaction proceeds through one more derivative, the monotosylate 3. In addition, pathway B gives the azidohydrins 4 with diminished yields in comparison with those obtained with the pathway A. After isolation of azidohydrins 4 we could reduce them easily into the corresponding β -aminoalcohols 5 by means of tin chloride in methanol. The reaction is effected at room temperature during 20 hours and the yields are satisfactory (TABLE).

$$R_{F} \stackrel{\text{CH-CH}}{\stackrel{\text{OH}}{\text{OH}}} R_{F} \stackrel{\text{CH-CH}}{\stackrel{\text{CH-CH}}{\stackrel{\text{OH}}{\text{OH}}} R_{F} \stackrel{\text{CH-CH}}{\stackrel{\text{CH-CH}}{\stackrel{\text{OH}}{\text{OH}}} 2NH_{2}$$

$$4 \qquad 5a (R_{F} = C_{4}F_{9})$$

$$5b (R_{F} = C_{6}F_{13})$$

$$5c (R_{F} = C_{8}F_{17})$$

EXPERIMENTAL PART

 ^{1}H NMR spectra were recorded in CDCl₃on a Brücker W-80 spectrometer operating at 80 Mz using $(CH_3)_4$ Si ¹⁹F NMR spectra were as internal standard. (TMS) recorded in CDCl₃ on a Brücker W-90 spectrometer at 84,67 Mz using CFCl₃ as internal operating standard. Infrared spectra were performed on a Brücker 45 spectrometer and mass spectra were run on a IFS Nermag R 10-10 C Mass spectrometer coupled with a gas chromatograph. Microanalyses were determined by the CNRS laboratories in Lyon (France).

Typical procedure for 2-F-hexyl-2-hydroxyethyl tosylate 3b :

To a solution of 10 mmoles of p-toluenesulfonyl chloride in anhydrous diethyl ether cooled in an ice bath (0°C), are added in small portions with constant stirring 5 mmoles of diol 2 and 10 mmoles of pyridine in anhydrous diethyl ether. The mixture, which is stirred for 2 hours at 0°C then for 3 days at 40°C, is hydrolysed by a solution of 2N hydrochloric acid. The aqueous layer is washed with water, aqueous 5% sodium bicarbonate, then dried over sodium sulphate the ether removed. The residue is purified and by column chromatography on silica gel eluting with hexane /ethyl acetate 3:1 to afford the monotosylate 3b.

C ${}_{15}F_{13}$ H ${}_{11}$ O₄ S(534). Elem.Anal. : Calc(%) C 33,72, F 46,22 , H 2,07 , S 6,00 , Found (%) C 33,80 , F 46,53 , H 2,00 , S 5,68 ; MS : M⁺534, Ts⁺ 155, (M-R_F)⁺ 215, (CH₂=O-Ts)⁺185 , CF₃⁺ 69 , C₂F₅⁺ 119 , C₃F₅⁺ 131, C₃ F₇⁺ 169 ; I.R. (cm⁻¹) : v_{C-F}=1350-1100 , v_{SO2}=1370, v_{C=C}(Ts) 1590 , v_{O-H}=3500 ; ¹H NMR (CDCl₃) δ (ppm) : CH₃=

2,4 (s,3H) ,
$$CH_3 = 7,5(d,2H)$$
 , CH_3

=7,9(d,2H) , $R_{F} - CH(OH)CH_{2} = 4,5(m,3)$, (OH) = 2,9(s,1H) ;¹⁹F NMR (CDCl₃) δ (ppm) : CF₃ -81,1 , CF₂ ω ^{-126,5} CF₂ $\gamma^{+CF_{2}}\omega^{-122,9}$, CF₂ $\alpha^{-119,6}$ and -126,2 (J=290 Hz). Typical procedure for 2-F-hexyl-2-hydroxyethyl azide 4b :

Pathway A : A mixture of 10 mmoles of monotosylate 20 mmoles of sodium azide in 3,8 mi of water and 3b. 0,5 mmole of Aliquat 336 is heated for 20 hours at 100 °C , then is decanted under heat . The lower organic layer is dissolved in diethylether. The ethereal is dried over sodium sulphate, filtered and the layer ether is removed to afford the azide derivative 4b purified by distillation under reduced which i s pressure.

Pathway B : to a solution of 40 mmoles of sodium azide and 8,4 mmoles of ammonium chloride in 4 ml of water, are added 4 mmoles of epoxide 1 dissolved in 32 ml of methanol. The mixture is stirred for 7 hours at reflux, then methanol is removed under atmospheric pressure. Then 20 ml of water and diethyl ether are added to the residue. The ethereal layer is dried over sodium sulphate, filtered and the ether is removed to afford the azide derivative 4b as a yellow oil which is distilled under reduced pressure.

C8 F₁₃ H4 N₃ O (405). Elem.Anal. : Calc.(%) C 23,66 , F 60,81 , H 1,24 , N 10,35 , Found (%) C 23,64, F 60,84 , H 1,23, N 10,32 ; MS : M⁺505 , CF₂=CF-CH= $\stackrel{+}{O}$ H 111 , CH₂ N₃⁺ 56 , C₆F₁₃-CH= $\stackrel{+}{O}$ H 349 , N₃⁺ 42 , CF₃⁺ 69,C₂F₅⁺ 131; I.R.(cm⁻¹): $v_{C-F}^{1350-1100}$, $v_{C-N_3}^{2114}$, v_{C-OH}^{200} 3425; ¹H NMR (CDCl₃) δ (ppm): C-<u>H</u> 4,3(m,1H), CH₂ 3,7 (d,2H), O<u>H</u> 3,2(s,1H).

Typical procedure for 2-F-alkyl-2-hydroxyethyl amine 5b

To a solution of 4,5 mmoles of tin chloride in 4 ml of methanol are added 3,25 mmoles of azidohydrins 4 in 2 ml of methanol. The mixture is stirred for 20 hours at room temperature. The methanol is removed. To the residue are added 10 ml of caustic soda 2N and diethyl ether.

The ethereal layer is dried over sodium sulphate, filtered and evaporated to give the amine derivative 5b which is purified by recrystallization from petroleum ether.

 $C_8F_{13}H_6NO$ (379) Elem.Anal. Calc.(%) C 25,33, F 65,17, H 1,58, N 3,69. Found(%) C 25,30, F 65,20, H 1,59, N 3,67; MS: M⁺479, NH -CH -CH=ÖH 60, CF₃⁺ 69,C₂F₅⁺ 131. I.R. (cm⁻¹) v_{C-F} 1350-1100, v_{NH_2} and v_{OH} 3400-3300; ¹H NMR (CDCl₃) δ (ppm) C-H 4,5(m,1H), CH₂ 3,6(d,2H), OH 2,8(s,1H), NH₂ 1,3(s,2H).

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