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SYNTHESIS OF β-FLUOROAZIDES : A ROUTE TO PRIMARY β-FLUORO AMINES

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SUMMARY

Two ways for the synthesis of β-fluoroazides are presented. The first one uses 1,2,2-trifluoro-2-chloro triethylamine (FAR) as a fluorinating reagent on the corresponding azidoalcohols. It is a smooth reaction at room temperature, but is not stereospecific ; it works well for phenyl substituted or primary α-carbon β-fluoroazides. The second route is the substitution of the azide group for bromine on an appropriate fluorobromide in phase transfer conditions. It is stereospecific (except for one case). It works well to give pure diastereoisomers of β-fluoroazides with pseudo primary (with deuterium) or secondary α-carbon atoms.

INTRODUCTION

Several series of β-fluoroamines, which can have interesting biological activities [1], have already been prepared using several approaches :
(i) opening of aziridines with pure liquid HF or with mixtures of HF and tertiary amines (trialkylamines or pyridine) [2].
(ii) dehydroxyfluorination of aminoalcohols with SF_4, a relatively toxic reagent [3], or with Olah's reagent on reactive alcohols [4].
(iii) dehydroxyfluorination of hydroxy tertiary amines with the fluoroamine reagent FAR i.e. 1,2,2-trifluoro-2-chloro triethylamine [5]. This reaction works only with tertiary amines, since FAR reacts with primary and secondary amines through a reaction of another type which prevents the dehydroxyfluorination [6]. Hexafluoropropene diethylamine [7] can also be used instead of FAR.

These methods are restricted to a limited number of substrate structures or are unable to give regio- or stereo-specific reaction products.

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We were researching a way of access to pure diastereoisomers or phenyl substituted derivates of primary β-phenyl-β-fluoroamines $ZPhC_\beta R_3FC_\alpha R_1R_2NH_2$. The key product is the corresponding azide : $ZPhC_\beta R_3FC_\alpha R_1R_2N_3$. The method to reduce specifically the azide to the primary amine gives rise to some problems and will be published elsewhere [8]. The aim of this paper is to report routes to pure diastereoisomers of phenyl substituted derivatives of β-phenyl-β-fluoroazides from easily accessible starting materials (ketones or alkenes). Two methods will be described, covering two aspects, ease of reaction and retention of stereochemistry :

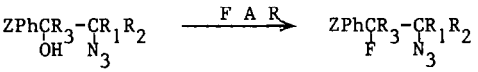
(i) dehydroxyfluorination using FAR on hydroxyazides ; going through azides avoids the use of FAR with primary amines.

(ii) substitution of bromine by an azide in a fluorobromide.

RESULTS

Dehydroxyfluorination of azidoalcohols using FAR

The dehydroxyfluorination of azidoalcohols using a fluoroamine reagent (FAR ; 2-chloro-1,2,2-trifluorotriethylamine) was undertaken on several azidoalcohols numbered from 1a to 1i (1e is not used to prevent confusion with notation e and t for erythro and threo diastereoisomers) according to the following scheme;



1a - 1i 3a - 3i

The azidoalcohols were synthesized using several known reactions according to the nature of the α carbon ; primary [1a, 1b (pseudo-primary), 1c and 1d], secondary (1f, 1g, 1h), or tertiary 1i ; and to the stereochemistry on C_α and C_β carbons (1f, 1g, 1h, erythro and threo isomers) :

(i) stereospecific substitution of bromine in bromohydrins by the azide group [9] (1a, 1b, 1d, 1f, 1g)

(ii) reduction with sodium borohydride of ketoazides (1a, 1c, 1i, 1f, 1h). 1f and 1h obtained by $NaBH_4$ reduction of the corresponding azides were mixtures of the two diastereoisomers (70 % t and 30 % e)

(iii) opening of an appropriate epoxide by sodium azide [10] (1h). The assignment of configuration of the azidoalcohols 1f, 1g, 1h was made from

that of the primary hydroxylamine hydrochlorides obtained by stereoselective catalytic hydrogenation of the azides [11].

FAR, which does not react with the azido group (in contrast to the NH_2 group) was a convenient reagent and effected the substitution of hydroxyl groups at room temperature in about 15 hours with methylene chloride as solvent. The overall yields were about 90 %.

The main NMR parameters (δH_α, δH_β, δF, $^3J(HH)$ and $^3J(FH)$ of the fluoroazides are given in Table 1. The assignment of the configuration of the two fluoroazides 3b was made from the assignment of the two methylenic protons pro-R and pro-S of azide 3a using an already described procedure with the four coupling constants $^3J(HH)$ and $^3J(FH)$. We were unable to make the assignment of the configuration of the fluoroazides 3f, 3g, and 3h directly from their NMR parameters, as they are quite close from an isomer to the other, but the assignment was undertaken from that of the corresponding primary amine hydrochlorides obtained by stereoselective reduction of the azides [11,8].

The results of the stereochemistry of the dehydroxyfluorination are given in Table 2. The reaction is clearly non stereospecific. From 1be, the mixture of two almost equimolecular diastereoisomers with a slight preference for inversion of configuration was obtained. From 1fe and 1ft the same mixture of fluoroazides (65 % e and 45 % t) was obtained whatever was the configuration of the starting compound. From 1he and 1ht the reaction was stereoselective with some retention of configuration.

Substitution in fluorobromides of bromine by an azide group

The substitution of bromine by an azide group was undertaken on fluorobromides numbered 2a to 2h according the following scheme :

$$ZPhCFR_3CR_1R_2Br \xrightarrow[(nBu)_4N^+Br]{NaN_3/H_2O} ZPhCFR_3CR_1R_2N_3$$

2a - 2h 3a - 3h

sodium azide was the reagent used in phase transfer conditions with tetrabutylammonium bromide (TBAB) at 50°C. The reaction was also performed on the tertiary non-benzylic fluoride $PhCHBrCMe_2F$ (2i') to give the benzylic azide $PhCHN_3CMe_2F$ (3i').

TABLE 1

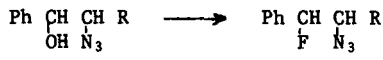
^1H Chemical shifts δ_H (in ppm from T M S), ^{19}F chemical shifts δ_F (in ppm from C_6F_6) and three-bond coupling constants in Hz for fluoroazides 3 $ZPhC_\beta CFR_3C_\alpha R_1R_2N_3$

Z	R_1	R_2	R_3	n°	conf	δH_α	δH_β	δ_F	^3J HH	^3J HF
H	H	H	H	a	--	H_1=3.67 [a]	5.58	-19.67	$^3J H_1H_\beta$=8.0	J H_1F=18.5
						H_2=3.44			$^3J H_2H_\beta$=3.0	J H_2F=28.5
H	D	H	H	b	e	3.5	5.58	-20.05	$^3J H_2H_\beta$=3.0	^3J H F=28.5
									$^3J D_1H_\beta$= [b]	^3J DF = 2.5 [c]
					t	3.68	5.62	-20.10	$^3J H_1H_\beta$=7.5	$^3J H_1F$=18
									$^3J DH_\beta$ = [b]	^3J DF = 4.25 [c]
pF	H	H	H	c	-	3.6	5.59	-17.9	3.4	18
						3.4			7.6	27.5
H	H	H	CH_3	d	-	3.47	--	+10.3	-	18.5and 21.5
H	CH_3	H	H	f	e	3.70	5.37	-25.3	4.8	17
					t	3.78	5.25	-17.75	6.5	15
pF	CH_3	H	H	g	t	3.8	5.38	-25.2	6.0	15.4
H	Ph	H	H	h	e	4.85	5.5	-17.85	5.85	13.3
					t	4.76	5.5	-16.2	7.4	14
H	CH_3	CH_3	H	i	-	--	5.24	-22.5	--	--
Ph	$\overset{\alpha}{C}H$	$\overset{\beta}{C}$	$(CH_3)_2$							
	N_3	F		3'i	-	4.6	--	+18.0	--	14.5

[a] $H_1 \equiv$ pro-S ; $H_2 \equiv$ pro-R [b] large signal with unresolved ^3J(DH) coupling [c] J(DF) = J(HF)/6,514

TABLE 2

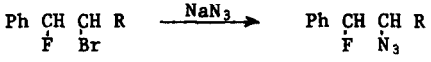
Stereochemistry of the dehydroxyfluorination of azidoalcohols 1b e, 1f e, 1f t, 1h e, 1h t, by FAR



R		Configuration of azidoalcohols 1	Configuration of fluoroazide 3 %e	%t
D	b	e	45	55
CH_3	f	e	65	45
CH_3	f	t	65	45
Ph	h	e	83	17
Ph	h	t	30	70

TABLE 3

Stereochemistry of the substitution of bromide by an azide group in fluorobromides



R		Configuration of fluorobromide 2	Configuration of fluoroazide 3
D	b	t	e
CH_3	f	e	t
CH_3	f	t	80 % e 20 % t
Ph	h	e	t
Ph	h	t	e

The fluorobromide were synthesized using stereospecific reactions : (i) electrophilic addition of "FBr" to appropriate alkenes, using N-bromosuccinimide in the HF : pyridine mixture with the appropriate molar ratio [12]. (ii) dehydroxyfluorination on bromohydrins using FAR or the HF : pyridine mixture as fluorinating reagent [12].

The substitution of bromine by an azide group in fluorobromides is rather difficult. The reaction times are strongly dependent on the structure : with the following conditions (50°C, with 0.6 molar equivalent of TBAB) these times are : 24 h for 2a - 2b - 2c, 66 h for 2h, 168 h for 2f - 2g ; only 50 % of 2d had reacted after 168 h and only 10 % of $PhCF_2CH_2Br$ after 100 h. The reaction on $PhCHBrCMe_2F$ (2i') gives the benzylic and not the tertiary azide.

The assigment of the stereochemistry of the reaction products has already been described (Table 1). Some results on conversions of fluorobromides to fluoroazides using this reaction have been reported but without any stereochemical information [13]. The results of the stereochemistry of this substitution are given in Table 3. The reaction is stereospecific with inversion of configuration with 2bt, 2fe, 2he, and 2ht and only stereoselective with 2ft with preponderance of inversion of configuration.

DISCUSSION

Dehydroxyfluorination of azido alcohols using FAR

This reactions occurs smoothly at room temperature.

The reaction products have rather complicated stereoselectivity as in most dehydroxyfluorinations of benzylic alcohols [14]. The results of Table 2 can be interpreted through the evolution of a benzylic carbonium ion.

(i) the most stable form of the carbonium ion from 1b and 1f is evolved through free rotation about the $C_\alpha C_\beta$ bond in relation with the steric hindrance of the substitutents.

(ii) the carbonium ion from 1h evolves with participation of the neighbouring β-phenyl group occurring before the formation of the CF bond.

Substitution in fluorobromides of bromine by an azide group

This reaction is rather difficult, contrary to the case of the corresponding bromohydrins where the reaction occurs completely at room temperature after 24 h. A fluorine group (and even more a fluorine

and an alkyl group (2d)) on the carbon adjacent to the reaction center is strongly deactivating. No elimination is observed, contrary to the case of $PhCHFBrCO_2Et$ where only the elimination product is obtained.

The substitution reaction in most cases is stereospecific with inversion of configuration except in the case of the threo diastereoisomer of 2f where the reaction is only stereoselective with only a preponderance of the 3fe isomer. In the cases of the bromohydrin analogues, the reaction of substitution is stereospecific in all cases with inversion of configuration.

Conclusions

The two ways studied to obtain β-fluoroazides are complementary.
(i) the way using FAR as a fluorinating reagent is not stereospecific but is easy to carry out ; it is preferable for fluoro-azides having no diastereoisomers [α primary carbon (3a, 3c, 3d) or α-tertiary carbon with two identical R_1R_2 (3i)] or with substituted phenyl groups [easy access of the starting material, via the corresponding ketone (3c, 3g)] .
(ii) the way using the bromoazide exchange on fluorobromides is stereospecific (except for 3fe) and allows the preparation of pure diastereoisomers of 3be, 3bt, 3ft, 3he and 3ht. It is also regiospecific to obtain 3'i without 3i from 2'i. Pure enantiomeric fluoroazides (and then fluoroamines after a selective reduction [8]) could be obtained this way.

EXPERIMENTAL

^1H NMR spectra were obtained on a AM 300 Bruker apparatus (300 MHz) for compounds 1a, 1b, 3a, 3b, on a WP 100 Bruker for others. ^{19}F NMR spectra were obtained on a WP 100 Bruker apparatus (94,18 MHz) using C_6F_6 as a secondary reference (- 163 ppm versus $CFCl_3$). $CDCl_3$ is used as solvent.

Preparation of azidoalcohols 1

I - Substitution of bromine by azide on bromohydrins (1a,1b,1d,1f, 1g) [9]

0.01 mole of bromohydrin (obtained by hydrohalogenation of alkenes [15] or reduction of bromoketones by $NaBH_4$), 0.015 mole of sodium azide,

0.6 mole of tetrabutylammonium bromide in 4 ml of water were stirred 24 hours at 40°C. Extraction with methylene chloride afforded azidoalcohols. The reaction of $PhC(CH_3)(OH)CH_2Br$ with NaN_3 in phase transfer condition led only to the regioisomer of 1f ; $PhC(CH_3)(N_3)CH_2OH$. When reaction of 0,01 mole of bromohydrin with 0.015 mole of NaN_3 was performed in 50 ml of dimethylformamide and 4 ml of water (24 hours at 90°C) only 1f was obtained.

II - Reduction of ketoazides with $NaBH_4$ (1a, 1c, 1f, 1h, 1i)

0.015 mole of $NaBH_4$ was added by little portions to 0.01 mole of ketoazide in 50 ml of methanol at 0°C. After one hour, the mixture was poured into saturated solution of potassium phosphate and extracted with methylene chloride. 1f and 1h were obtained as a mixture of two diastereoisomers (70 % t and 30 % e).

III - Epoxide ring opening by sodium azide (1h)

Azidoalcohols 1h e and t were obtained by epoxide ring opening with sodium azide by a described method [10]. The two diastereoisomers which have similar ^1H NMR parameters can be distinguished through their trifluoroacetate esters $PhCH(OCOCF_3)CHN_3Ph$.

1a ^1H NMR δ 7.2 (m, 5H, arom.) δ 4,86 (K part from ABK, 1H -CHOH) δ 3.37 and 3.46 (AB part from ABK, 2H, $^3J(HH)$ = 7.0 and 4.5, $^2J(HH)$ = -10.5, $-CH_2-$)

1b e ^1H NMR δ 7.25 (m, 5H, arom.) δ 4.80 (d, 1H, $^3J(HH)$ = 4.5, -CHOH) δ 3.35 (d, 1H, $^3J(HH)$ = 4.5, -CHD-)

1c ^1H NMR δ 7.3 and 7.1 (m, 4H, arom.) δ 4.84 (K part from ABK, 1H, -CHOH) δ 3.41 (AB part from ABK)

^{19}F NMR δ_F + 58.87 (ma, (p) F)

1d ^1H NMR δ 7.35 (m, 5H, arom.) δ 3.45 (AB part, 2H, $-CH_2N_3$) δ 1.55 (s, 3H, CH_3)

1f e ^1H NMR δ 7.35 (s, 5H, arom.) δ 4.72 (d, 1H, $^3J(HH)$ = 3.2, -CHOH) δ 3.75 (qd, 1H, $^3J(HH)$ = 3.2 and 6.7, $-CHCH_3$) δ 1.15 (d, 3H, $^3J(HH)$ = 6.7, $-CH_3$)

1f t ^1H NMR δ = 7.30 (s, 5H, arom.) δ 4.46 (d, 1H, $^3J(HH)$ = 7.2, -CHOH) δ 3.48 (qd, 1H, $^3J(HH)$ = 7.2 and 6.6, - $CHCH_3$) δ 1.05 (d, 3H, $^3J(HH)$ = 6.6, $-CH_3$)

1h e ^{1}H NMR δ 7.28 (ma, 10H, arom.) δ 4.72 (AB, 2H) PhCH(OCOCF$_3$)CHN$_3$Ph e δ 7.35 (ma, 10H, arom.) δ 5.99 (d, 1H, ^{3}J(HH) = 6.9, - CH (OCOCF$_3$)) δ 4.90 (d, 1H, ^{3}J(HH) = 6.9, -CHN$_3$)

1h t ^{1}H NMR δ 7.20 (ma, 10H, arom.) δ 4.88 (AB, 2H) PhCH(OCOCF$_3$) CHN$_3$Ph t δ 7.30 (ma, 10H, arom.) δ 5.96 (d, 1H, ^{3}J(HH) = 8.5, CH (OCOCF$_3$)) δ 4.88 (d, 1H ^{3}J(HH) = 8.5, -CHN$_3$)

1i ^{1}H NMR δ 7.3 (s, 5H, arom.) δ 4.45 (s, 1H, -CHOH) δ 1.23 (s, 3H, CH$_3$) δ 1.16 (s, 3H, CH$_3$)

Preparation of fluorobromides 2

The fluorobromides were prepared stereospecifically using a described method [12] : by electrophilic addition of "FBr" on alkenes using N-bromo-succinimide in HF - pyridine or by dehydrofluorination of bromohydrins using FAR or HF - pyridine.

Preparation of fluoroazides 3

I - Dehydrofluorination of azidoalcohols using FAR

0.015 mol of FAR (3 ml) was added slowly to 0.01 mole of azido-alcohol in 5 ml of methylene chloride at 0°C. After 15 hours at room temperature the mixture was poured in ice and a saturated bicarbonate solution was added until basic pH was attained. Extraction was performed with methylene chloride. The organic layer was dried, the solvent evaporated and fluoro-azide was separated from the diethylamide of chlorofluoroacetic acid by chromatography on silica gel (petroleum ether/chloroform ; 9:1)

II - Substitution of bromine by the azide group on fluorobromides

Substitution of bromine by the azide group on fluorobromides was performed as for bromohydrins. The reaction times at 50°C are given in the text.

3a ^{1}H NMR δ 7.35 (s, 5H, arom.) δ = 5.63 (K part from ABKX, 1H, -CHF) δ 3.67 and 3.44 (AB part from ABKX, 2H, ^{3}J(HH) = 3.0 and 8.0, ^{3}J(FH) = 18.5 and 28.5, ^{2}J(HH) = - 13.5, -CH$_2$-) ^{19}F NMR δ_F - 19.67 (X part from ABKX)

3b e ^{1}H NMR δ 7.40 (s, 5H, arom.) δ=5.58 (d large, 1H, ^{2}J(FH) = 47.5, -CHF) δ 3.5 (d. mult. 1H, ^{3}J(FH) = 28.5, -CHD) ^{19}F NMR δ_F - 20.05 (tdd, ^{3}J(FH) = 28.5, ^{2}J(FH) = 47.5, ^{2}J(DF) = 2.5)

3b t ^{1}H NMR δ 7.40 (s, 5H, arom.) δ 5.68 (dd, 1H, ^{3}J(FH) = 48. ^{3}J(HH) = 7.5, -CHF) δ 3.68 (tdd, 1H, ^{3}J(HH) = 7.5, ^{3}J(FH) = 18, ^{2}J(DH) = 2.0, -CHD) ^{19}F NMR δ_F - 20.10 (tdd, ^{3}J(FH) = 18, ^{2}J(FH) = 48. ^{3}J(FD) = 4.25)

3c ^{1}H NMR δ 7.3 and 7.1 (m, 4H, arom.) δ 5.59 (K part from ABKX, 1H, -CHF) AB part from ABKX centered at δ 3.5 ^{19}F NMR δ - 17.9 (ddd, 1F, ^{3}J(HF) = 18 and 27.5, ^{2}J(FH) = 48, -CHF) δ + 49.5 (ma, 1F, (p)F)

3d ^{1}H NMR δ 7.33 (s, 5H, arom.) δ 3.47 (AB part from ABKX, 2H, ^{3}J(FH) = 18.5 and 21.5, $-CH_2N_3$) δ 1.68 (d, 3H, ^{3}J(FH) = 22.0, $-CH_3$) ^{19}F NMR δ_F + 10.3 (q.d., ^{3}J(FH) = 18.5 and 22.0)

3f e ^{1}H NMR δ 7.34 (s, 5H, arom.), δ 5.37 (dd, 1H, ^{3}J(HH) = 4.8, ^{2}J(FH) = 47.0, -CHF) δ 3.70 (m, 1H, -CH CH_3) δ 1.24 (dd, 3H, ^{3}J(HH) = 7.5, ^{4}J(FH) = 1.2, $-CH_3$) ^{19}F NMR δ_F - 25.3 (dd, ^{3}J(FH) = 17, ^{2}J(FH) = 47.0)

3f t ^{1}H NMR δ 7.34, (s, 5H, arom.), δ 5.25 (dd, 1H, ^{2}J(HH) = 6.5, J(FH) = 47.1, - CHF) δ 3.78 (m, 1H, -CH CH_3) δ 1.1 (d, 3H, ^{3}J(HH) = 7.0, $-CH_3$) ^{19}F NMR δ_F - 17.75 (dd, ^{3}J(FH) = 15, ^{2}J(FH) = 47.1)

3g t ^{1}H NMR δ 7.35 and 7.1 (m, 4H, arom.) δ 5.28 (dd, 1H, ^{3}J(HH) = 6.5 ^{2}J(FH) = 46.5, - CHF) δ 3.8 (m, 1H, $-CHN_3$) δ 1.1 (d, 3H, ^{3}J(HH) = 6.5, - CH_3) ^{19}F NMR - 16.95 (dd, ^{3}J(FH) = 15.5 ^{2}J(FH) = 47.0) δ + 49.7 (m, (p)F)

3h e ^{1}H NMR δ 7.3 (m, 10H, arom.) δ 5.5 (dd, 1H, ^{3}J(HH) = 5.8, ^{2}J(FH) = 45.3, - CHF) δ 4.85 (dd, 1H, ^{3}J(HH) = 5.8, ^{3}J(FH) = 13.3, $-CHN_3$) ^{19}F NMR δ_F - 17.85 (dd, ^{2}J(FH) = 45.3, ^{3}J(FH) = 13.3)

3h t ^{1}H NMR δ 7.18 (m, 10H, arom.) δ 5.5 (dd, 1H, ^{3}J(HH) = 7.4 ^{2}J(FH) = 46.5, - CHF) δ 4.76 (dd, 1H ^{3}J(HH) = 7.4, ^{3}J(FH) = 14 -CH N_3) ^{19}F NMR δ_F - 16.2 (dd, ^{3}J(FH) = 14, ^{2}J(FH) = 46.5)

3i ^{1}H NMR δ 7.36 (s, 5H, arom.) δ 5.24 (d, 1H, ^{2}J(FH) = 49.9, - CHF) δ 1.28 (s, 6H, $-CH_3$) ^{19}F NMR δ_F -22.5 (d, ^{2}J(FH) = 45.0)

3i' ^{1}H NMR δ 7.33 (s, 5H,arom.) δ 4.6 (d, 1H, ^{3}J(FH) = 14.5), δ 1.32 and 1.34 (d, 6H, ^{3}J(FH) = 21.0) ^{19}F NMR δ_F + 18.0 (hept d, ^{3}J(FH) = 14.5 and 21.0)

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