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# SELECTIVE REDUCTION OF β-FLUOROAZIDES TO β-FLUOROAMINES

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## SUMMARY

Three methods were tested to reduce chemoselectively β-fluoroazides into β-fluoroamines : catalytic hydrogenation, catalytic transfer hydrogenation, and reduction with triphenyl phosphine. The last was the best.

## INTRODUCTION

Primary β-fluoroalkylamines exhibit biological activity on the central nervous system [ 1] . The most general synthetic routes to these compounds described in the literature are : aziridine ring opening by HF : pyridine [ 2,3] and fluorodehydroxylation of amino-alcohols using $SF_4$ in liquid HF [ 4] .

In fact, with the above cited methods it was not possible to obtain some regio or stereoisomerically pure fluoro amines. We looked for a stereospecific synthesis of β-phenyl β-fluoro primary amines which could work for amines with an optically active carbon, β carbon and/or α carbon (including the case of a deuterium introduced stereospecifically on an α primary carbon). Stereo or regioisomerically pure fluoroazides, obtained with good yields [ 5] were used as key intermediates. The last step to obtain the fluoro amines was by reduction of the azido group without hydrogenolysis of the C-F bond. Although hydrogenolysis of C-F bond is more difficult than that of C-other halides bonds [ 6] , it occurs rather easily in allylic or benzylic fluorides and even in vinylic and aromatic fluorides [ 7] .

In the literature the reduction step of functionalized azides to the corresponding primary amines has been reported by several reagents such as [ 8]

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hydrogen with a catalyst, metallic hydrides, thiols, diborane, derivate of transition elements, sodium hydrogenotellurate, triphenyl phosphine with a slight excess of water. The aim of this paper is to use three methods known to work easily and chemoselectively with other functions, and to test them on fluorinated amines : catalytic hydrogenation, catalytic transfer hydrogenation, reduction with triphenyl phosphine.

## RESULTS AND DISCUSSION

Reduction of azido group to amines was carried out on 2-phenyl-1 azido-2 fluoro ethanes 1a-1g (table 1) substituted on C α and C β :

$$Z\ Ph\ \underset{\beta}{C}FR_1\underset{\alpha}{C}(N_3)R_2R_3\ (1a\text{-}g) \longrightarrow Z\ Ph\underset{\beta}{C}FR_1\underset{\alpha}{C}(NH_2)R_2R_3\ (2a\text{-}g)$$

Catalytic hydrogenation, used for reduction of β-hydroxy azides [9] leads to low and non reproductible yields of fluoroamines, with hydrodefluorinated amines as by-products, as already known for alkyl-fluoroazides [10] and in the steroïd series [11].

"Catalytic transfer hydrogenation" [12] with ammonium formate as hydrogen donor, was recently used for reduction of 1-azido-polyoxyethylene alcohols [13]. It gives good selectivity in the reduction of β-fluoroazides. For too long reaction times or too high amounts of ammonium formate, hydrogenolysis can take place (exept for 1a). But in all cases reduction of the azide group is achieved before hydrogenolysis of the C-F bond and the fluoroamine can be obtained by examining the progress of the reaction through the IR band ($2130cm^{-1}$) of the reactant azide.

Reduction with triphenyl phosphine with a slight excess of water, a method described for functionalised azides [8h], produces only fluoroamines even with excess $Ph_3P$ and even longer reactions times. This is the most interesting method especially because it can be applied to a mixture of fluoroazides and diethyl amide of chlorofluoro-acetic acid (mixture obtained from reaction of azido alcohol and 2 chloro-1,1,2 trifluoro triethylamine (or Fluoroamine reagent, FAR). In this case the extraction procedure must be modified (see experimental part).

Table 1 gives yields obtained by use of the two last reduction methods.

For the studied compounds, the last method is the easiest to work. The methods can be extended to compounds with a β substituted phenyl ring.

TABLE I

Reduction of β-fluoroazides 1a - 1g to the corresponding primary β-fluoroamines 2a - 2g (Yield (%) for the two methods : catalytic transfer hydrogenation (CTH) and with phosphine)

| Azide | Z | $R_1$ | $R_2$ | $R_3$ | Config | CTH % | $Ph_3P$ % |
|---|---|---|---|---|---|---|---|
| 1a | H | H | H | H | - | 90 | 80 |
| 1b (e) | H | H | H | D | $R^*S^*$ | 90 | 80 |
| 1c (e) | H | H | H | Me | $R^*S^*$ | 85 | 70 |
| 1c (t) | H | H | H | Me | $R^*R^*$ | 85 | 70 |
| 1d (p) | F | H | H | H | - | 90 | 80 |
| 1e | H | H | Me | Me | - | 85 | 75 |
| 1f (e) | H | H | H | Ph | $R^*S^*$ | 85 | 70 |
| 1f (t) | H | H | H | Ph | $R^*R^*$ | 85 | 70 |
| 1g | H | Me | H | H | - | 80 | 65 |

EXPERIMENTAL

Fluoroazides were prepared by a method described previously [5]

Representative procedure for reduction of azide by catalytic transfer hydrogenation

0.5 g of ammonium formate (four times excess) and 0,1 g of 5 % palladium - carbon was added to a solution of $2.10^{-3}$ mole of fluoroazides in methanol (25 ml). The mixture was stirred for 24 h at room temperature. Progress of the reaction was examined through the IR band at $2130cm^{-1}$($N_3$group). The solvent was evaporated and the residue was dissolved in a saturated sodium hydrogen carbonate solution and extracted with methylene chloride. After drying of the extract and removal of the solvent, fluoro amines were obtained and their chlorhydrates were crystallised.

Representative procedure for reduction of azide by triphenyl phosphine

2.62 g of triphenyl phosphine were added to a solution of $10^{-2}$ mole of fluoroazide and 15 mmole of water in 10 ml of THF. The mixture was stirred for 24 h at room temperature and THF was evaporated.

Fluoroamines can be extracted using two procedures :

- a mixture of petroleum ether - diethy ether 1 : 1 was added to the residue and the triphenyl phosphine oxide precipitated and the solvent evaporated [8h].

- 20 ml of 5 % HCl were added to the residue and undesired organic products were extracted with methylene chloride. $NH_4OH$ was added to the aqueous layer until basic pH was attained and extraction was performed with methylene chloride. The organic layer was dried, the solvent evaporated and chlorhydrate of fluoro amines were crystallised. The last procedure was used in the case of the mixture of fluoroazide and diethyl amide of chloro-fluoro-acetic acid.

Physical characteristics of products

Melting points of fluoroamine chlorhydrates and NMR parameters of the fluoro amines in $CDCl_3$ were in agreement with those described in the literature [2,3]. NMR parameters of the chlorhydrates were measured in $CD_3OD$ : for $^1H$ NMR on a AM BRUKER apparatus (300 MHz) for compounds 2a, 2b(e) 2g and on a WP 100 BRUKER apparatus (100 MHz) for the other compounds : for $^{19}F$ on a WP 100 BRUKER apparatus (94,18 MHz), using $C_6F_6$ as a secondary reference (- 163 ppm versus $CFCl_3$). The $^{19}F$ chemical shifts are those obtained at infinite dilution. We can see from the following data that the parameters which are very similar for the diastereoisomeric free amines 2c(e) and (t) 2f (e) and (t) are clearly distinct for the corresponding chlorhydrates and were used for configuration attribution [14].

2a $^1H$ NMR $\delta$ 7,45 (s, 5H, arom.), $\delta$ 5,82 (K part from ABKX, 1H, $^2J(FH)$ = 48, -CHF-), $\delta$ 3,50 and 3,43 (AB part from ABKX, 2H, $^3J(HH)$ = 9,6 and 2,4, $^3J(FH)$ = 14,4 and 32,4 $-CH_3$-); $^{19}F$ NMR $\delta_F$-19,0(ddd, $^3J(FH)$= 14,4 and 32,4, $^2J(FH)$ = 48).

2b(e) $^1H$ NMR $\delta$ 7,50 (s, 5H, arom.), $\delta$ 5,97 (d large, 1H, $^2J(FH)$ = 48, -CHF-), $\delta$ 3,40 (d large, 1H, $^3J(FH)$ = 32,9,-CHD-) ; $^{19}F$ NMR $\delta_F$ - 19,2 (ddt, $^3J(FH)$ = 32,2 $^2J(FH)$ = 48 $^3J(FD)$ = 2,5), (large means signal with unresolved J(DH) coupling).

2c(e) $^1$H NMR δ 7,45 (s, 5H, arom.) δ 6,04 (dd, 1H, $^3$J(HH) = 2,6 $^2$J(FH) = 47,5, -CHF-), δ 3,75 (qdd, 1H, - CH $CH_3$, δ 1,25 (d, 3H, $^3$J(HH) = 6,2 $-CH_3$) ; $^{19}$F NMR $\delta_F$ - 38,4 (dd, $^3$J(FH) = 26,2, $^2$J(FH) = 47,5).

2c(t) $^1$H NMR δ 7,50 (s, 5H, arom.) δ 5,58 (dd, 1H, $^3$J(HH) = 9,2, $^2$J(FH) = 47,5, -CHF), δ 3,75 (qdd, 1H, -CH $CH_3$) δ 1,16 (d, 3H, $^3$J(HH) = 6,0, $-CH_3$) ; $^{19}$F NMR $\delta_F$ - 10,5 (dd, $^3$J(FH) = 9,4, $^2$(FH) = 48,0).

2d $^1$H NMR δ 7,5 and 7,2 (ma., 4H, arom.) δ 5,8 (K part from ABKX, 1H $^2$J(FH) = 48, -CHF) δ 3,45 (ma., AB part from ABKX, 2H, $-CH_2$-) ; $^{19}$F NMR $\delta_F$ - 17,33 (ddd, 1F, $^2$J(FH) = 48,5, -CHF) $\delta_F$ (ma., 1F, (p)F)

2e $^1$H NMR δ 7,45 (s, 5H, arom.) δ 5,64 (d, 1H, $^2$J(FH) = 45,6, -CHF-), δ 1,32 (s, 3H, $-CH_3$), δ 1,19 (s, 3H, $-CH_3$) $^{19}$F NMR $\delta_F$ - 23,9 (d, $^2$J(FH) = 45,6).

2f(e) $^1$H NMR δ 7,25 (ma. 10H, arom.), δ 6,0 (dd, 1H, $^3$J(HH) = 3,0, $^2$J(FH) = 46,0, -CHF-) δ 4,43 (dd, 1H, $^3$J(HH) = 3,0, $^3$J(FH) = 27, -CH $NH_2$-) ; $^{19}$F NMR $\delta_F$ - 32,1 (dd, $^3$J(FH) = 26,5, $^2$J(FH) = 46)

2f(t) $^1$H NMR δ 7,2 (s, 10H, arom.), δ 5,64 (dd, 1H, $^3$J(HH) = 8,0 $^2$J(FH) = 47,7, -CHF-), δ 4,43 (dd, 1H, $^3$J(HH) = 8,0 $^3$J(FH) = 8,7, -CH $NH_2$-) ; $^{19}$F NMR $\delta_F$ - 8,9 (dd, $^2$J(FH) = 47,5, $^3$J(FH) = 8,7).

2g $^1$H NMR δ 7,45 (s, 5H, arom.) δ 3,45 and 3,52 (AB part from ABX, 2H, $-CH_2$-) δ 1,79 (d, 3H, $^3$J(FH) = 22,6, $-CH_3$) ; $^{19}$F NMR $\delta_F$ + 9,24 (sext, $^3$J(FH) = 22,5, $^3$J(FH) = 22,5).

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