Journal of Fluorine Chemistry, *22* (1983) 493–497

Received: October 28, 1982; accepted: November 16, 1982

PRELIMINARY NOTE

Some New Chemical Properties of Fluorohydrins

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SUMMARY

Methyl 2-fluorolactates and 3-fluorocyanohydrins were found to give respectively 3-fluoro 1,2-diols and 3-fluoroethanolamine derivatives by direct reduction of carboxylic groups and cyano groups using lithium aluminium hydride in ether solution. Treatment of 3-fluoro-2-tosyloxynitriles with tetra n-butylammonium bromide gives 3-fluoro-2-bromonitriles.

We have recently reported a facile synthesis, with good yields, of some 3-fluoro-2-hydroxy esters and 3-fluoro-2-hydroxynitriles [1]. Some chemical reactions of the latter products have shown already that they are versatile intermediates for the synthesis of some 3-fluoro-2-amino acid [2] and 3-fluoroketo acid derivatives [3]. We now wish to describe other chemical properties of 3-fluorocyanohydrins and 3-fluoro 2-hydroxy esters which allowed us to synthesize new monofluorinated compounds.

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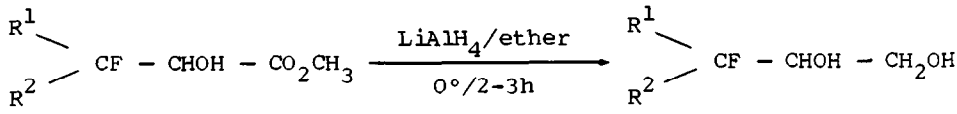
3-Fluorolactate derivatives were converted to 3-fluoro-1,2-diols by direct reduction of the carboxylic group. When methyl 3-fluoro lactates were treated by $LiAlH_4$ at 0° in ether solution the corresponding 3-fluoro 1,2-diols were obtained (scheme I). The products were purified by column chromatography. Yield 40-45 %.



$$R^1 = CH_3,\ C_6H_5, \quad R^2 = CH_3,\ H,$$

Scheme I

$(CH_3)_2\ CF - CH(OH)\ CH_2OH$

^1H NMR ($CDCl_3$, int.TMS) δ 1,4(d, 6H, $(CH_3)_2C$ J_{FH} = 22Hz) ; 3,6(m, $CH - CH_2$) ; 4,5(s, 2OH).

^{19}F NMR ($CDCl_3$, int. CCl_3F) ϕ 150,2 (heptuplet).

I.R ($CHCl_3$, cm^{-1}) 3635 (OH).

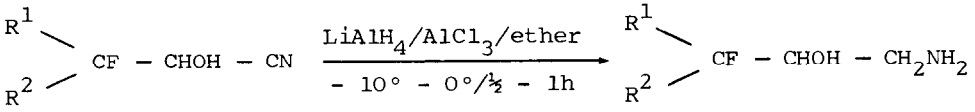
$C_6H_5 - \overset{\beta}{C}HF - \overset{\alpha}{C}HOH - CH_2OH$

^1H NMR ($CDCl_3$, int.TMS) δ 3,5(m) 4,1 (s, 2OH), 5,3(dd, J_{FH_β} = 47Hz) 7,1 - 7,2 (m, 5H, C_6H_5)

^{19}F NMR ($CDCl_3$, int. CCl_3F) ϕ 188,1 (dd, J_{FH_α} = 21Hz, J_{FH_β} = 46,8 Hz) 185,2 (dd, J'_{FH_α} = 15 Hz, J'_{FH_β} = 46,5 Hz) threo and erythro.

I.R ($CHCl_3$, cm^{-1}) 3630 (OH).

Following that, the reduction was applied to the cyano group of 3-fluorocyanohydrins using, in the same manner, $LiAlH_4$ and $AlCl_3$ as a catalyst [4] which gave 3-fluoroethanolamine derivatives (scheme II). The products were purified by column chromatography. Yield 35-40 %.



$R^1 = CH_3, C_6H_5, \quad R^2 = CH_3, H,$

Scheme II

$(CH_3)_2CF - CH(OH)CH_2NH_2$

^1H NMR ($CDCl_3$, int.TMS) δ 1,5(d, 6H, $(CH_3)_2C$ J_{FH} = 20 Hz) 3,2 - 4,2(m, broad).

^{19}F NMR ($CDCl_3$, int. CCl_3F) ø 152 (heptuplet).

I.R ($CHCl_3$, cm^{-1}) 3630 (OH), 3300 (NH_2).

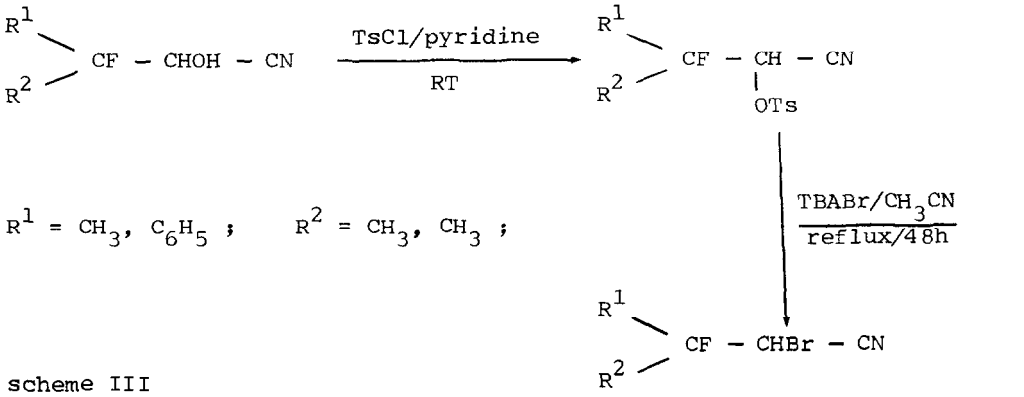
$C_6H_5\overset{\beta}{C}HF - \overset{\alpha}{C}H(OH)CH_2NH_2$

^1H NMR ($CDCl_3$, int.TMS) δ 3,3 - 4,4(m), 5,6 (dd, J_{FH_β} = 46Hz), 7,2 - 7,3(m, C_6H_5)

^{19}F NMR ($CDCl_3$, int. CCl_3F) ø 189 (dd J_{FH_α} = 21Hz, J_{FH_β} = 47Hz), 185(dd J'_{FH_α} = 15,2Hz, J'_{FH_β} = 45,7Hz) threo and erythro

I.R ($CHCl_3$, cm^{-1}) 3620 (OH) 3340 (NH_2).

The fluorocyanohydrins may be used for the synthesis of 3-fluoro-2-bromo nitriles in a two-step process involving preparation of the tosylate and displacement of tosylate by bromide. Indeed, nucleophilic displacement of a tosylate anion has been utilized in the preparation of secondary bromo compounds [5]. We tried the displacement of the tosylate by NaBr in DMF or DMSO as solvent but this approach failed. When 3-fluoro-2-tosyloxynitriles were treated with tetra n-butylammonium bromide in acetonitrile and the mixture heated under reflux for 48 hr, 3-fluoro-2-bromonitriles were obtained in about 45-50 % yield (scheme III).



$R^1 = CH_3, C_6H_5$; $R^2 = CH_3, CH_3$;

scheme III

In summary, these results clearly indicate that fluorohydrins are useful intermediates in the synthesis of new monofluorinated products such as 3-fluoroketoacids, 3-fluoro 1,2-diols, 3-fluoroethanolamine derivatives, etc. We are continuing to explore the reactivity of these fluorohydrins and their derivatives.

$(CH_3)_2CF - CHBr - CN$.

^1H NMR ($CDCl_3$, int.TMS) δ 1,6 (d, 6H, $(CH_3)_2C$ J_{FH} = 21Hz), 4,3 (d, 1H, C<u>H</u>Br, J_{FH} = 12Hz)

^{19}F NMR ($CDCl_3$, int. CCl_3F) $\emptyset$ 150 (heptuplet).

I.R ($CHCl_3$, cm^{-1}) 2230 (CN).

$C_6H_5CF(CH_3)CHBr - CN$.

^1H NMR ($CDCl_3$, int.TMS) δ 1,75(d, 3H, CH_3F, J_{FCCH_3} = 22 Hz), 1,78 (d, 3H, CH_3F, J_{FCCH_3} = 22Hz), 4,7 (d, 1H, C<u>H</u>Br, J_{FCCH} = 16Hz), 4,9 (d, 1H, C<u>H</u>Br, J_{FCCH} = 14Hz), 7,4 (m, 5H, C_6H_5) erythro and threo.

^{19}F NMR ($CDCl_3$, int. CCl_3F) $\emptyset$ 155(dq, J_{FCCH_3} = 23 Hz), 157(dq, J'_{FCCH_3} = 21 Hz) erythro and threo.

I.R ($CHCl_3$, cm^{-1}) 2235 (CN).

ACKNOWLEDGEMENT

We thank Dr. A.I. Ayi for his helpful discussions in this work.

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