

Reduction of Organofluorine Compounds with Lithium Triethylborohydride

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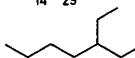
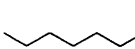
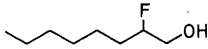
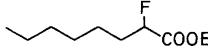


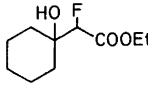
The reductive cleavage of the C–F bond with lithium triethylborohydride is strongly retarded by steric hindrance but is accelerated by adjacent hydroxyl groups in the organofluorine compound (Table 1). The effect of the hydroxyl group is strongest when it is tertiary, and compounds having such hydroxyl groups are evidently reduced exclusively *via* epoxides.

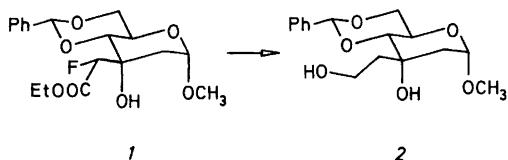
Lithium triethylborohydride is an efficient reducing agent which for many purposes is superior to lithium aluminium hydride.^{1,2} Several functional groups have been reduced with lithium triethylborohydride,^{1,2} but there seems to be only one example in the literature of a reductive cleavage of a carbon–fluorine bond.³ We found that the reduction *1*→*2* occurred with remarkable ease and *2* was isolated in a 56 % yield, whereas treatment of *1* with lithium aluminium hydride gave only traces of *2*.³ These results prompted us to undertake a more extensive study of the reduction of organofluorine compounds with lithium triethylborohydride, including both an investigation of structure–reactivity relationships and a mechanistic study.

Eight organofluorine compounds (*3*–*10*) were synthesized and their reduction with lithium triethylborohydride in THF (22 or 65 °C) fol-

lowed by GLC. The relative rates of reduction of the alkylfluorides *3*–*5* (Table 1) demonstrate a pronounced sensitivity to steric effects. Thus, while the primary alkylfluoride *3* was completely (>99.5 %) reduced in one hour at 65 °C, the

Table 1. Approximate relative rate constants for the reductive cleavage of the C–F bond in compounds *3*–*10* with lithium triethylborohydride. The reductions were performed at two different temperatures (see Experimental). Compounds *8* and *9* are mixtures of diastereomers and each compound therefore gives two relative rate constants.

Compound	k_{rel}
<i>3</i> $n\text{-C}_{14}\text{H}_{29}\text{F}$	1
<i>4</i> 	0.08
<i>5</i> 	0.0009
<i>6</i> 	0.005
<i>7</i> 	0.005
<i>8</i> 	0.0003 0.0006
<i>9</i> 	0.04 0.13
<i>10</i> 	14



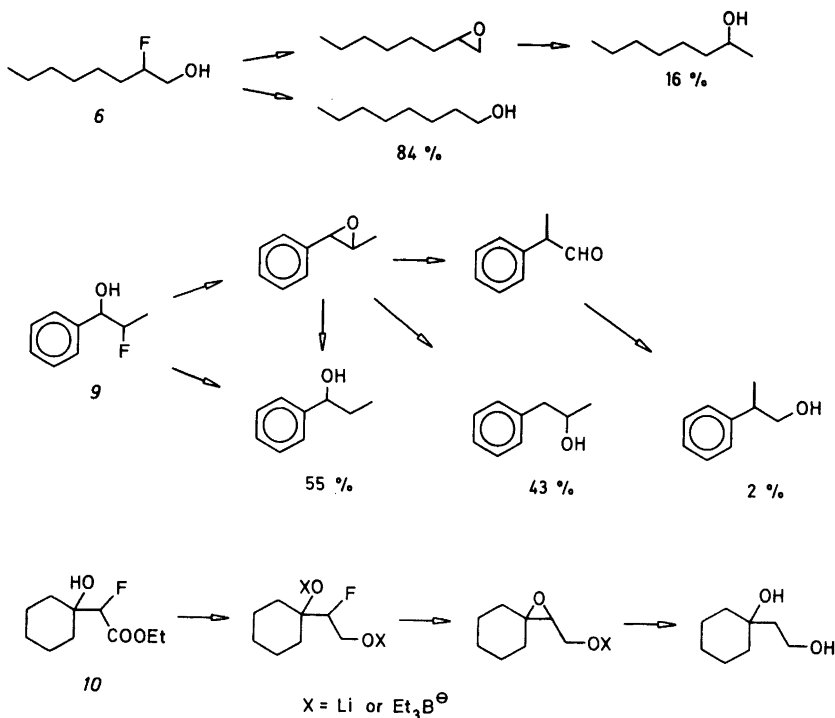


Fig. 1. The structures of the products obtained on reduction of 6, 9 and 10 with lithium triethylborohydride and the relative rates of reduction (Table 1) strongly indicate the intermediacy of the epoxides shown.

secondary fluoride 5 was only reduced to about 3 % under these conditions. After 24 h (65 °C), 42 % of 5 had been reduced and, since competing reactions such as eliminations were negligible, it should also be possible to obtain high yields in the reduction of secondary alkyl fluorides.

Further inspection of Table 1 shows that an adjacent hydroxyl group, or a functional group which is reduced to a hydroxyl group during the initial stage of the reaction, accelerates the reductive cleavage of the carbon-fluorine bond. This increase in reaction rate seems at least in part to be due to the formation of epoxide intermediates. The fact that mixtures of isomeric products are obtained in the reductions of 6 and 9 is strong evidence in favour of such intermediates (Fig. 1). Since 1,2-epoxybutane¹ and 1,2-epoxyoctane⁸ are reduced to 2-alkanols exclusively, one may conclude that 16 % of 6 is reduced *via* an epoxide. An adjacent methoxy group has an effect on the reduction rate which is opposite to that of the hydroxyl group (*cf.* Table 1, com-

pound 8), probably due to the increased steric hindrance.

Compound 9 is a 53:47 mixture of diastereomers, 9_{major} and 9_{minor}. On reduction with lithium triethylborohydride, it yields a mixture of three compounds (Fig. 1). Since the yield of 1-phenyl-2-propanol is 43 %, one may conclude that at least 43 % of 9 must be reduced *via* an epoxide. By studying the composition of the reduction mixture as a function of reaction time, we found that 9_{major} was reduced about three times faster than 9_{minor} and that 1-phenyl-1-propanol was formed faster than 1-phenyl-2-propanol. Reduction of *trans*-1-phenyl-1,2-epoxypropane with lithium triethylborodeuteride yields⁴ deuteriated analogues of 1-phenyl-1-propanol and 1-phenyl-2-propanol in the approximate ratio 1:9; reduction of the corresponding *cis* epoxide with the protium reagent gives⁸ the approximate ratio 11:1. These results indicate that the main precursor to 1-phenyl-2-propanol is the *trans* epoxide which in turn should be formed from (1*RS*,2*SR*)-

9. For the minor product 2-phenyl-1-propanol ($\approx 2\%$) a reduction pathway involving an epoxide to aldehyde rearrangement may be envisaged. An analogous epoxide to ketone rearrangement followed by reduction is a formally possible route to 1-phenyl-2-propanol. It cannot, however, be the major route since reduction with lithium triethylborodeuteride leads to a monodeuteriated 1-phenyl-2-propanol which has its deuterium at C-1 rather than at C-2 ($^1\text{H NMR}$).

Of the organofluorine compounds in Table 1, compound *10*, which is structurally similar to *1*, has the most reactive C-F bond. The only product detected on reduction of *10*, 1-(2-hydroxyethyl)-cyclohexanol, was isolated in a 78% yield. Thus, the reactivity increases in going from *6* to *9* to *10*. These three compounds all have a secondary fluorine and an adjacent hydroxyl group which is primary, secondary or tertiary, respectively. We interpret the increased reactivity as being due to an increasing ease of formation of an epoxide intermediate (*cf.* Ref. 5). The high reactivity of *10* indicates that it is the tertiary rather than the primary hydroxyl group which is involved in the epoxide formation. Both mono- and trisubstituted epoxides are reduced exclusively by attack at the least substituted carbon.¹ Therefore, the structure of the single product from *10* is a further indication of the intermediacy of the trisubstituted epoxide (Fig. 1).

Besides the direct displacement of fluorine by hydride and the reduction *via* epoxide, a third, minor mechanism may also be operating. After reduction and oxidative work-up using alkaline hydrogen peroxide, significant amounts of 2-butanol were detected (GLC) in the crude reaction products obtained from *6*, *7*, *9* and *10*, but not in those from *3*, *4*, *5*, and *8* ($< 1\%$). On reduction of *6* with lithium triethylborodeuteride, deuteriated analogues of 1-octanol and 2-octanol were obtained in 77 and 23% yields, respectively; the molar ratio 2-butanol:1-octanol was 0.19:1. The deuterium contents of 1-octanol and 2-octanol, as found by mass spectra of *o*-(methylamino)-benzoates,⁶ were approximately 90 and 95%, respectively. In view of the four times excess of reagent and a deuterium isotope effect of presumably normal magnitude, it seems not unreasonable to obtain as much as 5% of nondeuteriated 2-octanol. On the other hand, the percentage of nondeuteriated 1-octanol was unexpectedly high. A reduction mechanism con-

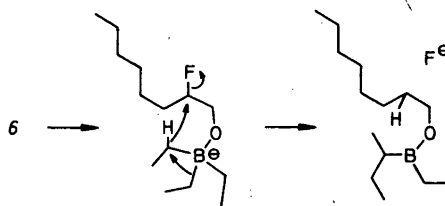


Fig. 2. Hypothetical minor reaction pathway which accounts for the formation of both 2-butanol and nondeuteriated 1-octanol in the reduction of *6* with lithium triethylborodeuteride.

tent with the formation of both 2-butanol and nondeuteriated 1-octanol is shown in Fig. 2. However, if this kind of reaction occurs, it seems to be responsible for only about 25% (*i.e.* $5/19$) of the total formation of 2-butanol. An intermolecular hydride-transfer accompanied by a rearrangement of the same kind as that in Fig. 2 occurs *e.g.* in reductions with lithium 9,9-dibutyl-9-borabicyclo[3.3.1]nonanate.⁷

A fourth mechanistic possibility is the elimination of fluoride ion by a hydride shift from the adjacent hydroxyl-bearing carbon. Such a shift occurs *e.g.* in the reduction of methyl 4,6-*O*-benzylidene-2-*O*-(4-methylbenzenesulfonyl)- α -*D*-mannopyranoside to methyl 4,6-*O*-benzylidene-[3- $^2\text{H}_1$]- α -*D*-ribo-hexopyranoside with lithium triethylborodeuteride,⁸ and in the reactions between fluorohydrins and Grignard reagents.⁹ However, reduction of *9* with lithium triethylborodeuteride leads to a monodeuteriated 1-phenyl-1-propanol in which H-1 integrated for 1.0 H and one may therefore conclude that the hydride shift mechanism plays no significant role in this reduction.

Even though no reaction intermediates or isomeric products were found in the reduction of *1*, the product distribution and the reactivity in the series *6*, *9* and *10* indicates that the reduction of *1* with lithium triethylborohydride occurs *via* a trisubstituted epoxide analogous to the reaction pathway shown for *10* in Fig. 1.

EXPERIMENTAL

THF was distilled over LiAlH_4 before use. Lithium triethylborohydride and lithium triethylborodeuteride were obtained (Aldrich) as 1 M solutions in THF. Reductions were carried out under an atmosphere of nitrogen. Analytical

GLC was performed on a Hewlett-Packard 5830 A gas chromatograph (electronic integration) equipped with an SP 2100 or an FFAP fused silica capillary column (25 m \times 0.2 mm). The latter column was used for the determination of 2-butanol. GLC-MS was performed on a Varian MAT 311 instrument; ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on a JEOL JNM-FX 100 instrument.

1-Fluorotetradecane (3) was obtained as a commercial product.

2-Ethyl-1-fluorohexane (4) was prepared from 2-ethylhexyl tosylate largely as described for 1-fluorooctane¹⁰ (20 h, 60–65 °C). After work-up, the crude reaction product was treated with bromine to a persistent colour in order to convert the alkene(s) into dibromide(s). Subsequent distillation (70–71 °C, \approx 12 kPa) gave 4 in a 16 % yield and in a purity of 99 % (GLC). ^1H NMR: δ 4.35 (2 H, d of d, J_{HF} 47.0 Hz, J_{HH} 6.0 Hz), 1.5–0.7 (15 H, m). ^{13}C NMR: 85.9 (d, J_{CF} 168.5 Hz), 40.7 (d, J_{CF} 18.3 Hz), 30.0 (d, J_{CF} 6.1 Hz), 29.3, 23.4 (d, J_{CF} 6.1 Hz), 23.2, 14.0 and 11.1 ppm.

2-Fluorooctane (5) was prepared from 2-octanol using the method of Olah and Watkins.¹¹ As in the synthesis of 4, the crude product was treated with bromine. The b.p. and ^1H NMR spectrum of 5 were as previously described;¹² GLC purity: 99.7 %.

2-Fluoro-1-octanol (6). 1,2-Epoxyoctane (19.2 g), prepared from 1-octene and *m*-chloroperbenzoic acid, was dissolved in methylene chloride and allowed to react with 42 % hydrogen fluoride in pyridine¹³ (22 °C, 43 h). Work-up, including washing with aqueous sodium carbonate, afforded a crude mixture (8.0 g) containing 49 % (GLC) of 6. Separation of the component on silica gel (light petroleum–ethyl acetate; 5:1) followed by distillation (67.5–69 °C, 0.3 kPa) gave 6 in a purity of 99.2 % (GLC). Lit.¹⁴ b.p. 98–100 °C/12 Torr. ^1H NMR: $\delta \approx$ 4.5 (1 H, d of m, $J_{\text{HF}} \approx$ 47 Hz), 3.7 (2 H, broad d, $J_{\text{HF}} \approx$ 27 Hz), 2.1 (1 H, broad s), 2–0.7 (m, 13 H). ^{13}C NMR: 94.8 (d, J_{CF} 168.5 Hz), 64.9 (d, J_{CF} 22.0 Hz), 31.7, 31.0 (d, J_{CF} 20.8 Hz), 29.1, 24.9 (d, J_{CF} 4.9 Hz), 22.6 and 14.0 ppm.

Ethyl 2-fluorooctanoate (7) was prepared from the corresponding α -bromo ester and potassium fluoride in acetamide.¹⁵ After work-up and treatment of the crude reaction product with bromine, 7 was distilled at 60–61.5 °C, 80 Pa (31 %, GLC purity 88 %); ^1H NMR: 4.3–4.0 (m, 3 H), 2.1–0.7 (m, 19 H), ^{13}C NMR: 170.0 (d, J_{CF} 23.8 Hz), 89.0 (d, J_{CF} 183.7 Hz), 61.2, 32.4 (d, J_{CF} 20.8 Hz), 31.5, 28.7, 24.3 (d, J_{CF} 3.1 Hz), 22.5, 14.1, and 13.9 ppm.

2-Fluoro-1-methoxy-1-phenylpropane (8) was

prepared from 9, silver(I) oxide and methyl iodide;¹⁶ B.p. 30 °C, 0.1 kPa; 90 % yield. GLC purity 97 %; diastereomeric ratio 53:47. ^{13}C NMR: 138.1, 137.9, 128.5–127.7 (six signals), 92.0 (d, J_{CF} 173.3 Hz), 91.6 (d, J_{CF} 175.2 Hz), 86.7, 86.1, 85.8, 85.2 (four signals from C–1), 56.9, 56.8, 17.4, 16.5, 16.3 and 15.4 ppm, the latter four signals from C–3.

2-Fluoro-1-phenyl-1-propanol (9) was prepared by reduction of the corresponding ketone¹⁷ with excess sodium borohydride in methanol (0–23 °C, 1 h); b.p. 76–77 °C, 27 Pa; diastereomeric ratio 53:47; GLC purity 96.3 %. The ^1H NMR spectrum was in accord with the structure.

Ethyl 2-fluoro-2-(1-hydroxycyclohexyl)ethanoate (10) was prepared using a modification³ of a published procedure.¹⁸ After distillation it showed a GLC purity of 99 %; ^{13}C NMR: 168.4 (d, J_{CF} 24.4 Hz), 93.4 (d, J_{CF} 190.4 Hz), 72.4 (d, J_{CF} 19.5 Hz), 61.7, 32.8 (d, J_{CF} 2.4 Hz), 32.7 (d, J_{CF} 3.7 Hz), 25.4, 21.2, 21.1, 14.2 ppm.

Determination of reduction rates for 3–10. The organofluorine compound (1 mmol) was allowed to react with lithium triethylborohydride in THF (22 or 65 °C). Nonane or tetradecane (for the reduction of 10) was used as internal standard. The amounts of reagent and THF were chosen so that a 0.8 M solution (4 mmol) of the reagent was left for reduction of the C–F bond after reaction with hydroxyl and ester groups. In the reductions of 7 and 10 the concentrations were, however, 0.7 and 0.6 M, respectively. Three to six aliquots (0.2 ml each) were withdrawn with a syringe at reaction times between 0.5 and 28 h and quenched and oxidized with aqueous NaOH (1 M, 0.5 ml) + aqueous H_2O_2 (35 %, 0.5 ml). After 30 min at 65 °C, the mixture was cooled, the organic components extracted with methylene chloride (3 \times 1 ml) and the combined extracts dried (MgSO_4) and analyzed by GLC.

Compounds 3 and 10 were reduced at 22 °C, compounds 5–8 at 65 °C, and compounds 4 and 9 at both temperatures. The reductions were treated as pseudo first order reactions and the rate constant was divided by the concentration of the reducing agent left after its reaction with the hydroxyl and ester groups. Points corresponding to high or low conversions of the starting material were deleted and a mean rate constant was calculated from the remaining points. Second order rate constants were also calculated but the differences between these k_{rel} values and the values in Table 1 were insignificant. The largest difference was found for 9 which showed nearly doubled values of k_{rel} .

The structures of the reduction products were confirmed by comparison with authentic samples

(capillary column GLC and MS). One of the products isolated and characterized by NMR was 1-(2-hydroxyethyl)-cyclohexanol. Compound 10 (1 mmol) was allowed to react with lithium triethylborohydride (7 mmol) in THF (65 °C, 10 min). After work-up as described above, the crude reaction product was purified on a silica gel column (ethyl acetate) and the diol was obtained as a colourless oil in a 78 % yield; GLC purity 98 %; ¹³C NMR: 71.4, 57.9, 40.7, 36.7, 24.9 and 21.3 ppm.

Reduction of 6 with lithium triethylborodeuteride. A mixture of 6 (2 mmol) and lithium triethylborodeuteride (10 mmol) in THF (10 ml) was heated under reflux (43 h). Work-up as described above gave a mixture of 1-octanol (42.2 %), 2-octanol (12.3 %) and 6 (45.4 %). For the conversion into *o*-(methylamino)-benzoates, a sample of the above mixture (20 mg) and *N*-methyl-isatoic anhydride (50 mg) was heated (115 °C, 20 h) in pyridine (1 ml) and triethylamine (5 drops) in a sealed tube. After evaporation of the solvents, the products were analyzed by GLC-MS using an OV-225 packed column. The deuterium contents were calculated from the intensities in the molecular ion groups and are only approximate because of the isotope separation on GLC.

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