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An Improved Synthesis of Perfluoroaldehydes[1]

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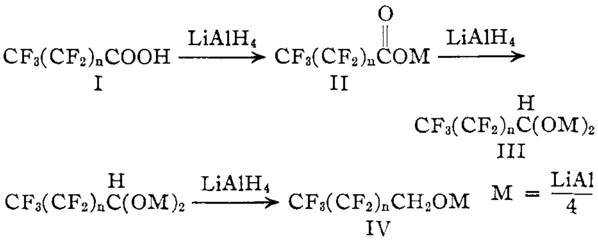
Published methods for the preparation of perfluoroaldehydes by reduction of the corresponding acid chloride,[2] or nitrile[3] and the oxidative nitration of 1,1,1-trifluoropropane[4] are inconvenient and give low yields of the desired aldehydes. The reduction of the corresponding perfluoro acid with lithium aluminum hydride,[2b] while more direct and convenient since it does not require the preparation of intermediates or catalysts, does not give a good yield of the perfluoroaldehyde. A substantial amount of the corresponding 1,1-dihydroperfluoro alcohol is also obtained by this reduction.

Greatly improved yields of perfluoroaldehydes have been obtained in this laboratory by the reduction of the appropriate perfluoro acids with lithium aluminum hydride by employing an inverse addition of the hydride to the acids.[5] The reductions were carried out at low temperature (−5 to 0°) using a 1:2 *M* ratio of hydride to acid and relatively concentrated ethereal solutions of the reactants. Only small quantities of the corresponding 1,1-dihydroperfluoro alcohols are obtained by this method. The liberation of the free aldehyde from its hydrate, the product of the reduction reaction, was most advantageously accomplished by adding it to a preheated mixture of phosphoric anhydride and concentrated sulfuric acid rather than either reagent alone. The dehydration medium did not thicken and the aldehyde was isolated without prolonged refluxing which leads to polymerization. Trifluoroacetic, pentafluoropropionic and heptafluorobutyric acids have been reduced by this method to give the corresponding perfluoroaldehydes in 77.5, 60 and 64% yield, respectively.

If the lithium aluminum–acid complex II is less easily reduced than the acid I, it will undergo little further attack in the absence of excess reducing agent (present in the normal order of addition) while any unreacted acid is present. When the transformation of the acid to complex II has been completed, the addition of more reducing agent will yield the aldehyde precursor III. The presence of an excess of hydride would favor further attack on III to give the alcohol precursor IV at the expense of the aldehyde. Thus the inverse order of addition favors the formation of the aldehyde.



$$\underset{I}{CF_3(CF_2)_nCOOH} \xrightarrow{LiAlH_4} \underset{II}{CF_3(CF_2)_n\overset{\overset{O}{\|}}{C}OM} \xrightarrow{LiAlH_4} \underset{III}{CF_3(CF_2)_n\overset{H}{C}(OM)_2}$$

$$CF_3(CF_2)_n\overset{H}{C}(OM)_2 \xrightarrow{LiAlH_4} \underset{IV}{CF_3(CF_2)_nCH_2OM} \qquad M = \frac{LiAl}{4}$$

A similar explanation has been reported[6] for the reduction of lactones to hydroxyaldehydes by lithium aluminum hydride using the inverse addition procedure.

Experimental

A solution of one mole of the perfluoro acid in 1 l. of anhydrous ether was cooled to −5° (brine-bath) in a 3-l. flask fitted with addition funnel, stirrer and condenser. The system was flushed with nitrogen while cooling. A slurry of 21.5 g. of lithium aluminum hydride in 750 ml. of anhydrous ether was added slowly with continuous stirring at −5° to 0° during 1.5 hours. Stirring was continued at −5° for one hour.

The reaction mixture was hydrolyzed with 40 ml. of water followed by 80 ml. of concentrated sulfuric acid in 200 ml. of water. The ether was decanted, and the solids remaining in the flask were dissolved in 300 ml. of water. The aqueous solution was extracted with ether, and the extracts were combined with the main ether portion and fractionally distilled to remove the solvent and alcohol leaving as a residue the crude aldehyde hydrate.

The crude aldehyde hydrate was dropped slowly into a vigorously stirred mixture of phosphorus pentoxide and concentrated sulfuric acid heated to 85–90°. The free aldehyde was collected in a suitably cooled receiver.

One mole of trifluoroacetic acid, after being subjected to the described reduction procedure, gave 21 g. of trifluoroethanol, crude, b.p. 68–85° and 110 g. of the crude aldehydrol. A 50-g. portion of the crude aldehydrol was dehydrated in a mixture of 21.6 g. of phosphorus pentoxide and 83 ml. of 96.7% sulfuric acid. There was obtained 34.5 g. of trifluoroacetaldehyde, representing a 77.5% overall yield. The aldehyde gave a 2,4-dinitrophenylhydrazone, m.p. 149°, and a hydrate, m.p. 69–70°.[2b]

Similarly treated, perfluoropropionic acid gave a 60% yield of perfluoropropionaldehyde, b.p. 1–2°, and perfluorobutyric acid gave a 64% yield of perfluorobutyraldehyde, b.p. 29°.

The physical constants observed for the aldehydes or their derivatives are in agreement with previous literature values.[2b]

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Synthesis of 8-C^{14} and of S^{35}-6-Mercaptopurine

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The marked biological activities of 6-mercaptopurine[1–5] made the study of its metabolism in various species of considerable interest. For this reason

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