Direct Fluorination of 2,2,4,4-Tetramethylpentane. Sterically Protected Residual Protons?

L. A. Shimp and R. J. Lagow*

Department of Chemistry, University of Texas at Austin, Austin, Texas 78712

Received September 20, 1976

The low-temperature direct-fluorination technique is used to control the reaction of fluorine gas under precisely regulated conditions with an organic or inorganic compound. This technique has been shown to be useful for making a wide variety of fluorine-containing compounds ranging from perfluoro carbons[1] to perfluoro ethers[2] and to unusual compounds such as partially fluorinated carboranes,[3] perfluoroganmetallic compounds,[4] and perfluoro sulfur–nitrogen ring compounds.[5]

In reactions where fluorine is used to replace hydrogen atoms, it has been found that, as the reaction proceeds, the remaining hydrogen atoms become progressively harder to replace. The reasons for this behavior are not definitely known, though the increasing acidity of the remaining protons as well as the increasing steric protection of their sites, due to the larger fluorine atoms becoming bonded to adjacent sites (convalent radius of F = 0.71 Å, of H = 0.37 Å),[6] would seem to be the most likely causes. The present work was initiated to determine if steric effects were strong enough to allow a molecule containing hydrogen atoms on hindered sites to become otherwise completely fluorinated, except for the hindered protons. The compound chosen for this study was 2,2,4,4-tetramethylpentane, because the two hydrogens on the center carbon atom were surrounded by two *tert*-butyl groups.

The expected products from this reaction are interesting in themselves and because they also have potential for use as fluorocarbon blood substitutes. Their highly branched structures are desirable, since branched molecules tend to form more stable water emulsions than unbranched molecules.[7] Furthermore, their molecular weights are such that their expected oxygen-dissolving capabilities and their expected volatilities are within the range necessary for a blood substiutute.[8]

Results and Discussion

The first series of reactions resulted in the formation of the perfluoro, monohydro and dihydro compounds in ratios of about 0.20 to 0.66 to 0.14 (Figure 1) with a total yield of about 70%. The second series of reactions, run under the same conditions except that the time interval with pure fluorine was increased from 36 to 85 h, gave the same ratios of the perfluoro, monohydro, and dihydro products, but the total yield was increased to about 95%. The third series of reactions, which were identical to the second except that half the amount of starting material was used, gave the same results as the second series.

The first set of fluorination conditions were nearly identical to those used in the fluorination of hexamethylethane. The latter reaction resulted in a 9.8% yield of perfluorohexamethylethane,[1] while the 2,2,4,4-tetramethylpentane reaction resulted in a combined yield of the monohydro, dihydro, and perfluoro compounds of about 70%. Hexamethylethane and 2,2,4,4-tetramethylpentane have quite similar structures and volatilities, so that the large differences in the yields of the fluorinated products are unexpected.

The observations that the length of time of the tetramethylpentane reaction and the amount of fluorine used did not affect the product distribution, as well as the fact that the dihydro product was unchanged after being exposed to pure fluorine for 72 h, show that (at −78 °C) the fluorine reaction with the protons located on the central carbon atom of the molecule apparently stopped after the methyl groups became fully fluorinated. This is assumed to be primarily a steric effect from the bulky CF_3 groups shielding the hydrogens on the center carbon atom from further fluorine attack. It is not primarily an electronic effect (from the increasing acidity of the remaining hydrogen atoms). If this were the case, it would be expected that compounds with one or two hydrogens remaining on the methyl groups, and with the center carbon atom completely fluorinated, would be found.

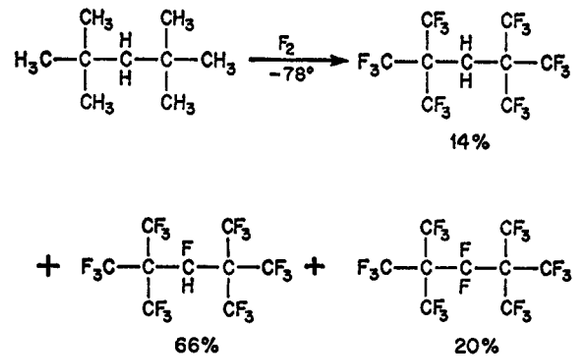


Figure 1. Reaction scheme.

Experimental Section

Mass spectra were measured on a Hitachi RMU 6D mass spectrometer at 70 eV. NMR spectra were taken on a Perkin-Elmer R20-B spectrometer at 60 MHz for protons and 56.4 MHz for fluorine. Gas chromatography was done on a Bendix gas chromatograph equipped with a cryogenic controller and a thermal-conductivity detector. A 25-ft × $^3/_8$-in. column packed with 10% SE 30 on Chromosorb P and a 10-ft × 0.25-in. column packed with 15% dinonyl phthalate on Chromosorb P were used. Analyses were done by Schwarzkopf Microanalytical Laboratory. Infrared data were collected on a Beckman IR 20A instrument. All experiments were carried out in a four-zone cryogenic reactor system, described previously.[1]

Fluorination of 2,2,4,4-Tetramethylpentane. The fluorination system was flushed with helium for 12 h, and then the first two zones of the reactor were cooled to −78 °C and the 2,2,4,4-tetramethylpentane was injected. Three sets of fluorination conditions were used. For the first set of reactions, the helium flow was set to 20 cm^3/min and the fluorine flow was set to 1.5 cm^3/min. After 18 h, zones two and three were cooled and the helium flow was reduced to 8 cm^3/min. After an additional 24 h, zones three and four were cooled and the helium flow was terminated. The reaction was then allowed to continue for an additional 36 h. In the second series of reactions, the conditions were the same as above for the initial 42 h, but the final conditions, when zones three and four were cooled, were held for 85 h, not 36. The last series of reactions was run with conditions identical with those of the second series, except that only 0.8 g of starting material was used. The reaction was ended by flushing the system for 12 h with helium, then warming the reactor and transferring the volatile products to a liquid-nitrogen-cooled trap.

The products from the trap were initially separated on the SE-30 column at 30 °C. 3,3-Dihydrooctadecafluoro-2,2,4,4-tetramethylpentane had a retention time of 15 min, while the monohydro and perfluoro compounds both had a retention time of 24 min. The latter two materials were then separated on the dinonyl phthalate column held at 10 °C. Perfluoro-2,2,4,4-tetramethylpentane had a retention time of 10 min and 3-hydrononadecafluoro-2,2,4,4-tetramethylpentane had a retention time of 12 min.

3,3-Dihydrooctadecafluoro-2,2,4,4-tetramethylpentane. Anal. Calcd: C, 23.89; H, 0.44; F, 75.66. Found: C, 23.69; H, 0.39; F, 75.64. The ^{19}F NMR consisted of a singlet at −11.7 ppm from an external trifluoroacetic acid reference. The ^1H NMR consisted of a singlet at τ 7.18. The gas-phase infrared spectrum contained bands at (cm^{-1}) 3025 (w), 1460 (w), 1315 (s), 1295 (vs), 1260 (s), 1215 (w), 1185 (m), 1095 (m), 1045 (s), 990 (m), 740 (m), 695 (m). The mass spectrum at 70 eV contained a peak at *m/e* of 433 assigned to the parent minus fluorine. The melting point was between −38 and −39 °C.

3-Hydrononadecafluoro-2,2,4,4-tetramethylpentane. Anal. Calcd: C, 22.98; H, 0.21; F, 76.81. Found: C, 22.93; H, 0.18; F, 76.72.

The ^{19}F NMR consisted of a doublet (from the CF_3 groups) centered at −13.8 ppm from an external trifluoroacetic acid reference. The coupling constant, J_{FF}, was 15.9 Hz. The signal from the fluorine on the center carbon atom would be expected to be a doublet of two 19 line multiplets, split by the hydrogen and the CF_3 groups, respectively, but was of too low an intensity to be observed. The ^1H NMR spectrum consisted of a doublet centered at τ 4.34. The coupling constant, J_{FH}, was 36.6 Hz. The gas-phase infrared spectrum contained bands at (cm^{-1}) 1440 (w), 1365 (m), 1300 (vs), 1290 (vs), 1265 (s), 1225 (w), 1195 (m), 1165 (w), 1080 (w), 1045 (s), 995 (s), 975 (w), 795 (w), 775 (m), 745 (m), 715 (m). The mass spectrum at 70 eV contained no peaks above m/e 381($C_8F_{15}^+$). The melting point was between −33 and −34 °C.

Perfluoro-2,2,4,4-tetramethylpentane. Anal. Calcd: C, 22.13; F, 77.87. Found: C, 22.58; F, 77.63. The ^{19}F NMR spectrum consisted of triplet (from the CF_3 groups) centered at −17.1 ppm from an external trifluoroacetic acid reference. The coupling constant, J_{FF}, was 14.9 Hz. The signal from the two fluorines on the center carbon atom would be expected to be a 19-line multiplet, but was of too low intensity to be observed. The gas-phase infrared spectrum contained bands at (cm^{-1}) 1300 (vs), 1285 (vs), 1270 (s), 1235 (w), 1195 (s), 1175 (w), 1150 (w), 1095 (w), 1025 (w), 990 (s), 815 (m), 750 (m), 740 (s), 715 (m). The mass spectrum at 70 eV contained a peak at m/e 469, assigned to the parent minus fluorine. The melting point was between −24 and −25 °C.

Fluorination of 3,3-Dihydrooctadecafluoro-2,2,4,4-tetramethylpentane. The fluorination system was flushed with helium for 12 h, and then the first two zones of the reactor were cooled to −78 °C and 0.5 g of 3,3-dihydrooctadecafluoro-2,2,4,4-tetramethylpentane was injected. The helium flow was terminated and the fluorine flow was set to 1.5 cm^3/min. After 24 h, reactor zones 3 and 4 were cooled to −78 °C and the first two zones were warmed to room temperature. After an additional 48 h, the reaction was terminated and the product was collected. The product was found to consist entirely of the starting material.

Registry No.—2,2,4,4-Tetramethylpentane, 1070-87-7; 3,3-dihydrooctadecafluoro-2,2,4,4-tetramethylpentane, 41296-82-6; 3-hydrononadecafluoro-2,2,4,4-tetramethylpentane, 62375-53-5; perfluoro-2,2,4,4-pentamethylpentane, 62375-54-6.

References and Notes

(1) N. J. Maraschin, B. D. Catsikis, L. H. Davis, G. Jarvinen, and R. J. Lagow, *J. Am. Chem. Soc.*, **97**, 513 (1975).
(2) J. L. Adcock and R. J. Lagow, *J. Org. Chem.*, **38**, 3617 (1973); *J. Am. Chem. Soc.*, **96**, 7588 (1974); J. L. Adcock, R. A. Beh, and R. J. Lagow, *J. Org. Chem.*, **40**, 3271 (1975).
(3) J. L. Margrave and R. J. Lagow, *J. Inorg. Nucl. Chem.*, **35**, 2084 (1973); N. J. Maraschin and R. J. Lagow, *Inorg. Chem.*, **14**, 1855 (1975).
(4) E. Liu and R. J. Lagow, *J. Am. Chem. Soc.*, **98**, 8270 (1976).
(5) N. J. Maraschin and R. J. Lagow, *J. Am. Chem. Soc.*, **94**, 8601 (1972).
(6) J. E. Huheey, in "Inorganic Chemistry", Harper and Row, New York, N.Y. 1972, p 84.
(7) J. W. Sargent and R. J. Seffl, *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **29**, 1699 (1970); M. Hill, *Chem. Ind. (London)*, 118 (1975).
(8) L. C. Clark, Jr., F. Becattini, and S. Kaplan, *Ala. J. Med. Sci.*, **9**, 16 (1971).

Conversion of Virescenol A into Virescenol B

Paolo Ceccherelli* and Massimo Curini

Instituto di Chimica Organica della Facoltà di Farmacia, Università degli Studi, Perugia, Italy

Roberto Pellicciari

Instituto di Chimica Farmaceutica e Tossicologica, Università degli Studi, Perugia, Italy

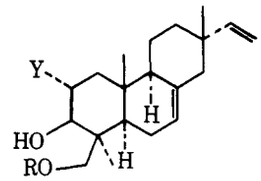
M. S. Raju and Ernest Wenkert

Department of Chemistry, Rice University, Houston, Texas 77001

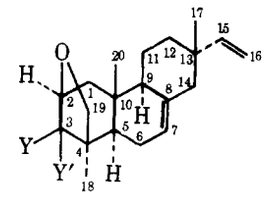
Received April 12, 1977

In connection with a study of the chemistry of virescenol A (**1a**), the aglycone of several of the fungal, virescenoside metabolites,[1] the tetrahydrofuran **2a** has been encountered frequently and now has been utilized for the conversion of virescenol A into B (**1b**).[2]

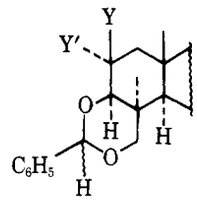
Treatment of virescenol A (**1a**) with benzaldehyde and zinc chloride yielded the benzylidene derivative **3a**,[3] whose reduction with lithium aluminum hydride in the presence of aluminum chloride led to ether **1e**. Attempted tosylation of the latter in pyridine solution gave the hydroxy ether **2a**, presumably by sequential formation of **1f** and the oxonium salt **4**, followed by pyridine debenzylation of the latter.



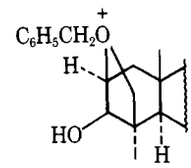
1a, R = H; Y = OH
b, R = Y = H
c, R = Ts; Y = OH
d, R = Ts; Y = OTs
e, R = $CH_2C_6H_5$; Y = OH
f, R = $CH_2C_6H_5$; Y = OTs
g, R = H; Y = OTs



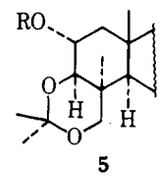
2a, Y = OH; Y′ = H
b, Y + Y′ = O
c, Y = H; Y′ = OH



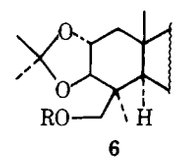
3a, Y = H; Y′ = OH
b, Y + Y′ = O
c, Y = OH; Y′ = H



4



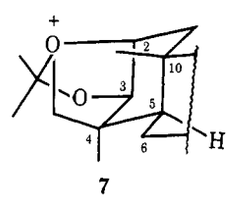
5



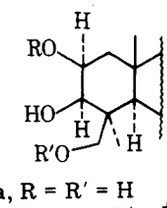
6

a, R = H
b, R = Ts

Treatment of virescenol A (**1a**) with acetone and cupric sulfate produced the isopropylidene derivatives **5a**[4] and **6a**, whose tosylation afforded sulfonic esters **5b** and **6b**, respectively. Even though the latter was stable, tosylate **5b** was converted into the ether **2a** on standing or on exposure to silica gel in benzene. This transformation may be the consequence of displacement of the tosylate by a ketal oxygen (cf. **7**), followed by hydrolysis, or prior hydrolytic formation of dihydroxytosylate **1g** and subsequent internal displacement.



7



8a, R = R′ = H
b, R = (−); R′ = $^+SMe_2$

Collins oxidation of the hydroxy acetal **3a** and sodium borohydride reduction of the resultant ketone **3b** gave the isomeric hydroxy acetal **3c**, whose acid hydrolysis yielded 2-