Synthesis of 1,1-Difluoro Olefins. II. Reactions of Ketones with Tributylphosphine and Sodium Chlorodifluoroacetate

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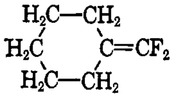
1,1-Difluoro olefins were prepared from several ketones by heating a solution of a ketone, tributylphosphine, and sodium chlorodifluoroacetate in a polar solvent.

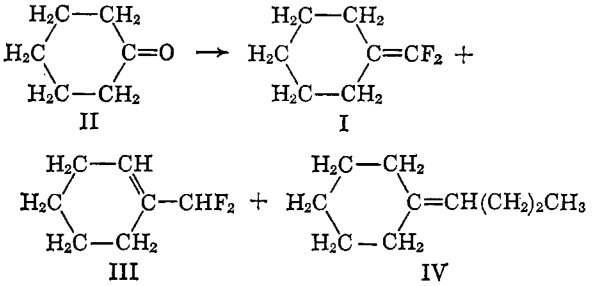
Reaction of aldehydes with triphenylphosphine and sodium chlorodifluoroacetate was reported to be a facile, general, one-step synthesis of 1,1-difluoro olefins.[2] Attempts to apply the same conditions to prepare 1,1-difluoro olefins from ketones were not successful. Thus, a gas chromatography (g.l.c.) examination of the reaction mixture of cyclohexanone, triphenylphosphine, and sodium chlorodifluoroacetate in 2,2′-dimethoxydiethyl ether (diglyme) showed none of the desired product. Replacement of triphenylphosphine with tributylphosphine or replacement of diglyme with N-methylpyrrolidone resulted in a 1–2% yield (g.l.c.) of difluoromethylenecyclohexane (I).



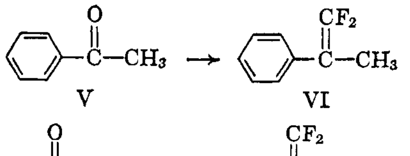
I

However, use of both tributylphosphine and N-methylpyrrolidone gave a 46% yield of I. Other satisfactory polar solvents, used with tributylphosphine, were tetramethylurea, dimethylformamide, dimethylacetamide, and dimethyl sulfoxide. A 41% yield of I (based on sodium chlorodifluoroacetate) was obtained using excess cyclohexanone as solvent.[3]

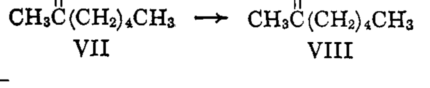
In general, poorer yields of 1,1-difluoro olefins were obtained from ketones, compared with aldehydes; in several cases, none of the desired product was found, and side reactions occurred. Isolation and identification of several of the side products provided justification for the proposed reaction path through a Wittig-type ylid intermediate.[2]



II I III IV (1)



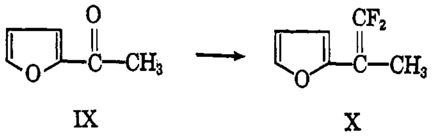
V VI (2)



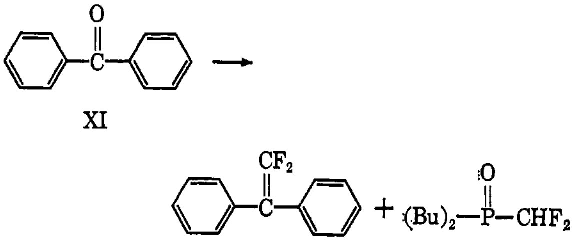
$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}(CH_2)_4CH_3 \longrightarrow CH_3\overset{CF_2}{\overset{\|}{C}}(CH_2)_4CH_3}\qquad (3)$$

VII VIII

Results are summarized in the series of equations given (1–6). None of the desired 1,1-difluoro olefins could be detected among the reaction products of the following ketones with tributylphosphine and sodium chlorodifluoroacetate: phenyl-2-pyridyl ketone, trifluoroacetophenone, benzoquinone, hexachloroacetone, and camphor.



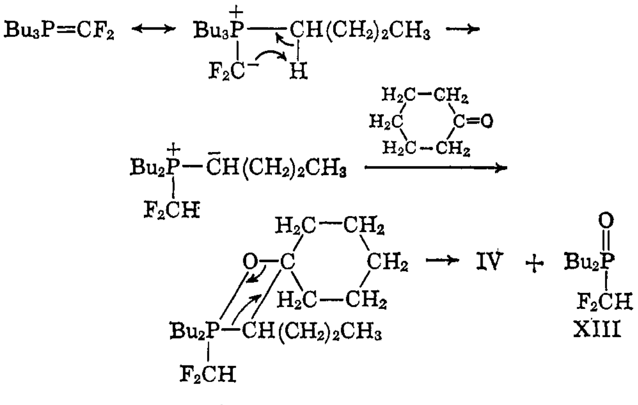
IX X (4)



XI XII XIII (5)

XIV XV (6)

The presence of 1-(difluoromethyl)-1-cyclohexene (III) among the products isolated from the cyclohexanone reaction (eq. 1) probably merely reflects isomerization of the primary reaction product, difluoromethylenecyclohexane (I), although a mechanism for addition of the ylid to the enol of cyclohexanone can be written. The following mechanism is offered to explain the presence of butylidenecyclohexane (IV) and the other butylidene compounds (XVII and XXI) isolated from several reactions. The other predictable product, dibutyldifluoromethylphosphine oxide (XIII), was isolated from the reaction mixture of the benzophenone reaction (5).



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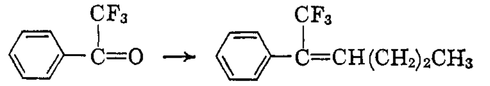
[1] Deceased.

[2] S. A. Fuqua, W. G. Duncan, and R. M. Silverstein, *J. Org. Chem.*, **30**, 1027 (1965).

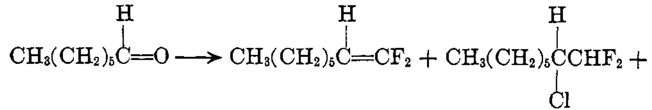
[3] Preliminary communication, *Tetrahedron Letters*, **No. 9**, 521 (1965).

The only product isolated from the reaction of trifluoroacetophenone[3a] (XVI) with tributylphosphine and sodium chlorodifluoroacetate was the rearrangement product, 1,1,1-trifluoro-2-phenyl-2-hexene (XVII). An



XVI XVII

attempt to improve the yield of 1,1-difluoro-1-octene (XIX) from heptanal,[2] by using tributylphosphine instead of triphenylphosphine, was not successful; the result was a decreased yield and contamination by side products XX and XXI.



$$CH_3(CH_2)_5\overset{H}{\overset{|}{C}}{=}O \longrightarrow CH_3(CH_2)_5\overset{H}{\overset{|}{C}}{=}CF_2 + CH_3(CH_2)_5\underset{\underset{Cl}{|}}{\overset{H}{\overset{|}{C}}}CHF_2 +$$

XVIII XIX XX

$$CH_3(CH_2)_5CH{=}CH(CH_2)_2CH_3 \quad (7)$$

XXI

The presence of 2-chloro-1,1-difluorooctane (XX) in the products of the reaction with heptanal (XVIII) (eq. 7) is probably a result of chloride ion (sodium chloride from decomposition of sodium chlorodifluoroacetate) attack on the olefin, 1,1-difluorooctene (XIX). *trans*-4-Undecene (XXI) is a rearrangement product from the ylid intermediate.

Identification of the reaction products on the basis of mass, infrared, and n.m.r. spectra is unequivocal except possibly in the case of butylidenecyclohexane (IV). In this case, preference for the *exo* rather than the *endo* isomer rests on the presence of a prominent peak in the mass spectrum at m/e 109. This peak must result from allylic cleavage of the chain, and would not be expected to be a major peak had the compound been the *endo* isomer. In the case of 2-chloro-1,1-difluorooctane (XX), the proton and fluorine n.m.r. spectra can be acommodated only by the structure written. It may be noted that each of the fluorine atoms occurs at a different shift position—*i.e.*, they are not equivalent because of the asymmetry of the adjacent carbon atom. However, both fluorines are equally coupled with the geminal proton, and almost equally coupled to the vicinal proton. Assignment of a *trans* configuration to 4-undecene (XXI) is justified by the strong infrared band at 10.30 μ.

Experimental

Infrared spectra were obtained on Beckman IR5 and Perkin-Elmer 221 spectrometers, and mass spectra on a CEC21-103C spectrometer. Proton n.m.r. spectra were run at 60 Mc., and F^{19} spectra at 56.4 Mc. on a Varian HR-60 (carbon tetrachloride solutions, tetramethylsilane reference for protons, fluorotrichloromethane reference for F^{19}). Gas chromatography was carried out on an Aerograph A90P. Column A was 25% LAC on Chromosorb W, 6 ft. × 0.25 in. Column B was 15% DC550 on Chromosorb W, 5.5 ft. × 0.25 in. Column C was 15% DC550 on Chromosorb W, 10 ft. × 0.25 in. A spinning-band column (18 in. × 6 mm. i.d.) was used for fractional distillation.

A description of the apparatus, preparation of sodium chlorodifluoroacetate, and a discussion of the *precautions used to prevent buildup and violent exothermic decomposition of sodium chlorodifluoroacetate* are given in the previous paper.[2] Reagents and solvents were obtained and treated as follows: cyclohexanone, Eastman, dried over sodium sulfate; acetophenone, Eastman, dried over sodium sulfate; 2-heptanone, Eastman, as received; benzophenone, Eastman, as received; heptanal, Eastman, distilled *in vacuo;* methyl furyl ketone, Chemical Procurement Laboratories, distilled *in vacuo;* methyl 2-thienyl ketone, Aldrich, distilled *in vacuo;* trifluoroacetophenone, Peninsular Chemical Research Inc., as received; N-methylpyrrolidone, Matheson, dried over sodium sulfate; and tributylphosphine, M and T Chemicals, as received.

The general synthesis procedure is exemplified by the first experiment. The proportions of reactants and solvents were the same in all the procedures.

Difluoromethylenecyclohexane (I).—To a stirred hot (180° bath) solution of 5.88 g. (0.06 mole) of cyclohexanone (II), 13.35 g. (0.066 mole) of tributylphosphine, and 10 ml. of N-methylpyrrolidone, was added dropwise from an equilibrating dropping funnel, over a period of about 1 hr., a warm (60°) solution of 18.3 g. (0.12 mole) of sodium chlorodifluoroacetate in 50 ml. of N-methylpyrrolidone. The flask contents were flash distilled at 1 mm. and a bath temperature of 150° into a receiver cooled with Dry Ice. Fractional distillation gave 2.85 g. of product, b.p. 104–106, that was 98% pure by g.l.c. A total yield of 3.70 g. (46.7%) of product was obtained. Analytical samples were prepared by g.l.c. as follows: column A, 80°, helium flow 35 cc./min., retention time 4.5 min.; column B, 90°, helium flow 29 cc./min., retention time 11.2 min.; column C, 130°, helium flow, 47.2 cc./min., retention time 3.6 min. Infrared absorptions were λ^{film} 3.42, 5.70 ($C{=}CF_2$), 6.90, 7.90, 8.16, 8.26, 8.85, 9.10, 9.30, 10.50, 11.10, 11.75, 12.10, and 13.95 μ; n.m.r. τ 7.95 [4 protons $(CH_2)_2$, unresolved] and 8.50 [6 protons, $(CH_2)_3$ unresolved]. Mass spectrum calcd.[4] for $C_7H_{10}F_2$: parent mass, 132; parent + 1, 7.72% of parent; parent + 2, 0.26% of parent. Found: parent mass, 132; parent + 1, 7.7% of parent; parent + 2, 0.29% of parent.

Anal. Calcd. for $C_7H_{10}F_2$: C, 63.62; H, 7.63; F, 28.75. Found C, 63.90; H, 7.41; F, 28.88.

1-(Difluoromethyl)-1-cyclohexene (III).—Continued fractional distillation of the products from the reaction of cyclohexanone (see previous experiment) gave 1.4 g. of distillate, b.p. 106–149°. A fraction was trapped on g.l.c. under the following conditions: column C, 130°, helium flow 47.2 cc./min., retention time 6.0 min.; yield 0.11 g. (1.4%). Infrared absorptions were λ^{film} 3.4, 5.95 ($C{=}C$), 7.28, 7.65, 8.38, 9.10, 9.38, 9.85, 10.8, 11.8, 12.45, 12.85, and 14.2 μ; n.m.r. τ 4.04 (1 proton, $=CH$, unresolved), 4.17 (1 proton, CHF_2, triplet, $J_{HF} = 56.1$ c.p.s.), 7.89 [4 protons, $(CH_2)_2$, unresolved], and 8.33 [4 protons $(CH_2)_2$ multiplet]; F^{19} n.m.r. ϕ +115.34 (pair of doublets, $J_{HF} =$ 56.3 c.p.s, $J_{HF} = 1.0$ c.p.s.). Mass spectrum calcd. for $C_7H_{10}F_2$: parent mass, 132; parent + 1, 7.72% of parent; parent + 2, 0.26% of parent. Found: parent mass, 132; parent + 1, 7.92% of parent; parent + 2, 0.36% of parent.

Butylidenecyclohexane (IV).—This material was also isolated by g.l.c. fractionation of the distillate (b.p. 106–149°) described in the previous experiment, by trapping under the following conditions: column A, 80°, helium flow 35 cc./min., retention time 21.5 min.; column B, 95°, helium flow 44 cc./min., retention time 26 min. The yield was 0.23 g. (2.9%): λ^{film} 3.40 and 6.90 μ; n.m.r. τ 5.07 (1 proton, $=CH$, triplet), 8.0 [6 protons, $(CH_2)_3$, multiplet], 8.5 [8 protons, $(CH_2)_4$, multiplet], and 9.1 (3 protons, CH_3, triplet). Mass spectrum calcd. for $C_{10}H_{18}$: parent mass, 138; parent + 1, 11.09% of parent; parent + 2, 0.56% of parent. Found: parent mass, 138; parent + 1, 11.1% of parent; parent + 2, 0.56% of parent; major fragmentation peak at mass 109.

β,β-Difluoro-α-methylstyrene (VI).—The starting material was 9.61 g. (0.08 mole) of acetophenone (V); the solvent was N-methylpyrrolidone. The flash distillate was fractionally distilled; 4.26 g. (34.6%) was collected at 155–157°. This fraction gave a single peak on g.l.c. under the following conditions: column A, 140°, helium flow 17 cc./min., retention time 10.7 min. Infrared absorptions were λ^{film} 3.30, 5.80 ($C{=}CF_2$), 6.66, 6.92, 7.10, 7.18, 8.10, 8.83, 9.33, 9.70, 11.15, 13.15, 14.18,

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[3a] NOTE ADDED IN PROOF.—D. J. Burton and F. B. Herkes [*Tetrahedron Letters*, in press] obtained good yields of 1,1-difluoro olefins from trifluoroacetophenone and ring-substituted trifluoroacetophenones by using the "aldehyde" conditions given in our first report: S. A. Fuqua, W. G. Duncan, and R. M. Silverstein, *ibid.*, **No. 23**, 1461 (1964).

[4] R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1963, p. 9.

and 14.45 μ; n.m.r. τ 2.75 (5 protons, aromatic, unresolved) and 8.05 (3 protons, CH_3, triplet, J_{HF} = 3.0 c.p.s.).

Anal. Calcd. for $C_9H_8F_2$: C, 70.15; H, 5.23; F, 24.66. Found: C, 69.95; H, 5.14; F, 25.08.

1,1-Difluoro-2-methyl-1-heptene (VIII).—The starting material was 5.71 g. (0.05 mole) of 2-heptanone (VII). The solvent was N,N-dimethylformamide. The bath temperature was 150–155°. The flash distillate was fractionally distilled; 2.10 g. (28.4%) was collected at 59–60° (95 mm.). An analytical sample was collected on g.l.c. under the following conditions: column B, helium flow 24.6 cc./min., 91°, retention time 7.1 min. Infrared absorptions were λ^{film} 3.4, 5.68 ($C{=}CF_2$), 6.80, 7.88, 8.20, 8.63, and 9.40 μ.

Anal. Calcd. for $C_8H_{14}F_2$: C, 64.83; H, 9.52; F, 25.64. Found: C, 64.61; H, 9.41; F, 25.62.

1,1-Difluoro-2-(2-furyl)-2-methylethylene (X).—The starting material was 5.50 g. (0.05 mole) of methyl furyl ketone (IX); the solvent was N-methylpyrrolidone. The flash distillate decomposed on attempted fractional distillation *in vacuo;* however, a boiling point of 62° (28 mm.) for the desired product was obtained. A pure product (estimated yield *ca.* 35%) was obtained from g.l.c. by trapping at Dry Ice temperature under the following conditions: column B, helium flow 47.6 cc./min., 85°, retention time 7.0 min. The product, sealed under nitrogen, showed evidence of decomposition after about 15 min. at room temperature (no meaningful combustion analysis was obtained): infrared λ^{film} 5.77 ($C{=}CF_2$), 8.00, 8.15, 8.60, 8.80, 9.24, 9.30, 9.82, 10.63, 11.62, 12.45, and 13.65 μ. Mass spectrum calcd. for $C_7H_6F_2O$: parent mass, 144; parent + 1, 7.78% of parent; parent + 2, 0.55% of parent. Found: parent mass, 144; parent + 1, 7.70% of parent; parent + 2, 0.46% of parent.

1,1-Difluoro-2,2-diphenylethylene (XII)[5] and Dibutyldifluoromethylphosphine Oxide (XIII).—The starting material was 9.11 g. (0.05 mole) of benzophenone (XI), the solvent was N,N-dimethylformamide, and the bath temperature was 160°. The flash distillate was fractionally distilled, a broad cut (80–140° at 20 mm.) was taken, and the components were isolated by g.l.c. under the following conditions: column A, helium flow 31.2 cc./min., 188°, retention time for XII 18.5 min., retention time for XIII, 28.6 min. Yields were determined by calibration of g.l.c. peaks with pure compounds: yield of compound XII, 1.4 g. (13%); yield of compound XIII, 0.67 g. (6.3%).

A film of compound XII absorbed in the infrared at 5.85 ($C{=}CF_2$), 6.68, 6.90, 8.00, 8.22, 10.10, 13.10, and 14.35 μ.

Anal. Calcd. for $C_{14}H_{10}F_2$: C, 77.75; H, 4.67; F, 17.57. Found: C, 76.89; H, 4.66; F, 17.91.

Compound XIII showed the following spectral properties: infrared λ^{film} 3.40, 6.80, 8.40, 9.15, 9.60, 11.10, and 12.30 μ; n.m.r. τ 3.93 (1 proton, CHF_2, triplet of pairs, J_{HF} = 49.4 c.p.s., J_{HP} = 19.4 c.p.s.), 8.3 [12 protons, $(CH_2)_6$, multiplet], and 9.03 [6 protons, $(CH_3)_2$, triplet]. Mass spectrum calcd. for $C_9H_{19}F_2OP$: parent mass, 212; parent + 1, 10.07% of parent; parent + 2, 0.65% of parent. Found: parent mass, 212; parent + 1, 11.0% of parent; parent + 2, 1.2% of parent; major peak at mass 161 (parent − CHF_2).

Anal. Calcd. for $C_9H_{19}F_2OP$: C, 50.95; H, 9.03. Found: C, 50.36; H, 8.95.

1,1-Difluoro-2-(2-thienyl)-2-methylethylene (XV).—The starting material was 6.30 g. (0.05 mole) of methyl 2-thienyl ketone (XIV). The solvent was N-methylpyrrolidone. The flash distillate was fractionally distilled; a 1.00-g. (12.5%) cut was taken at 49–50° (13 mm.). An analytical sample was trapped by g.l.c. under the following conditions: column A, 128°, helium flow 34.0 cc./min., retention time 10.3 min. Infrared absorptions were λ^{film} 5.82 ($C{=}CF_2$), 7.68, 8.05, 8.90, 11.46, 11.90, 12.15, and 14.14 μ.

Anal. Calcd. for $C_7H_6F_2S$: C, 52.50; H, 3.78. Found: C, 52.16; H, 3.82.

1,1,1-Trifluoro-2-phenyl-2-hexene (XVII).—The starting material was 8.72 g. (0.05 mole) of trifluoroacetophenone (XVI). The solvent was N-methylpyrrolidone. The mixture darkened severely after about 10 min. The flash distillate was washed with water to remove the solvents. The residual material (2.0 g.) was examined by g.l.c. but none of the desired product was found. The major product (*ca.* 15% yield) was compound XVII which was isolated under the following conditions: column A, helium flow 51 cc./min., 158°, retention time 3 min. The infrared spectrum had λ^{film} 3.40, 5.99 ($C{=}C$), 6.68, 6.85, 7.20, 7.65, 8.50, 8.90, 10.55, 10.90, 12.95, and 14.22 μ. Mass spectrum calcd. for $C_{12}H_{13}F_3$: parent mass, 214; parent + 1, 13.14% of parent; parent + 2, 0.90% of parent. Found: parent mass, 214; parent + 1, 13.18% of parent; parent + 2, 0.80% of parent; prominent peak at mass 185 (allylic cleavage).

2-Chloro-1,1-difluorooctane (XX) and *trans*-4-Undecene (XXI).[6]—Synthesis of the desired product, 1,1-difluoro-1-octene, was carried out in 7.0% yield from 5.26 g. (0.0461 mole) of heptanal in the usual manner[2] except that tributylphosphine and N-methylpyrrolidone were substituted for triphenylphosphine and diglyme. The flash distillate showed two additional peaks on g.l.c. examination under the following conditions: column B, helium flow 45.4 cc./min., 139°. Compound XX (0.2 g., 2.0% yield estimated) had a retention time of 5.7 min.; compound XXI (2.5 g., 35% yield estimated), 7.3 min.

Compound XX showed these properties: infrared absorptions were λ^{film} 3.4, 3.5, 8.62, 8.95, 9.35, 13.90; n.m.r. τ 4.30 (1 proton, CHF_2, triplet of doublets, J_{HF} 56.2 c.p.s., J_{HH} 4.5 c.p.s.), 6.30 (1 proton, CHCl, multiplet), 8.7 (10 protons $(CH_2)_5$, multiplet), 9.10 (3 protons, CH_3, deformed triplet); n.m.r. F^{19} ϕ +119 (Fa^{19}, 2 pairs of doublets, $J_{F_aF_b\,gem}$ = 279 c.p.s., $J_{F_aH\,gem}$ = 56.2 c.p.s., $J_{F_aH\,vic}$ = 9.5 c.p.s.), +125 (2 pairs of doublets, $J_{F_bF_a\,gem}$ = 279 c.p.s., $J_{F_bH\,gem}$ = 56.2 c.p.s., J_{F_bH} = 11.9 c.p.s.). In the mass spectrum, the parent peak at mass 184 was present but too weak to permit measurement of isotope contributions; however, the characteristic Cl^{35}/Cl^{37} ratio was present at 169, 171; 155, 157; and 141, 143.

Compound XXI had infrared λ^{film} 3.40, 3.50, 6.81, 7.23, 10.30 (*trans*-CH=CH), and 13.85 μ. Mass spectrum calcd. for $C_{11}H_{22}$: parent mass, 154; parent + 1, 12.24% of parent; parent + 2, 0.68% of parent. Found: parent mass, 154; parent + 1, 12.0% of parent; parent + 2, 0.66% of parent. The fragmentation pattern was in accord with the structure written.

Anal. Calcd. for $C_{11}H_{22}$: C, 85.61; H, 14.37. Found: C, 85.55; H, 14.43.

Acknowledgment.—This work was supported by Stanford Research Institute Research and Development Funds. The mass spectra were obtained by Mr. B. Mass, and the n.m.r. spectra by Mr. W. A. Anderson, Jr.

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(5) A. L. Dittman and J. M. Wrightson, U. S. Patent 2,705,706 (1955); *Chem. Abstr.*, **49**, 13695*f* (1955).

(6) N. A. Dobson, *et al.*, *Tetrahedron*, **16**, 16 (1961).