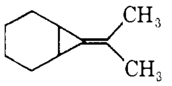
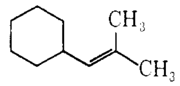
0.5% solution in cyclohexene, is irradiated[3] for 8 hr at −40°, 7-isopropylidenebicyclo[4.1.0]heptane (**3**) is obtained in *ca.* 3% yield (isolated). The alkene **3**, purified by preparative glpc, is identical[12] with an authentic sample prepared by an alternate route.[2b] Furthermore, irradiation[3] of a 0.5% solution of **1c** in cyclohexane at 30–40° for 9 hr affords the anticipated carbon–hydrogen insertion product, 1-cyclohexyl-2-methylpropene (**4**),[13] albeit in less than 1% yield. Thus, both of the characteristic reactions that might be anticipated for isopropylidenecarbene, *viz.*, addition to carbon–carbon double bonds and insertion into carbon–hydrogen bonds, are exhibited by the species resulting from photolysis of **1c**.[14]



3



4

It is noteworthy that observation of the insertion reaction with alkanes differentiates our photochemically generated species from that studied by Newman, *et al.*[2] Generation of isopropylidenecarbene in cyclohexane by their procedure gives no insertion product.[15] Consequently, the possibility arises that the chemistry previously[2] ascribed to isopropylidenecarbene, and the provocative mechanisms associated therewith, should actually be attributed to some other intermediate, *e.g.*, a carbenoid.

Additional aspects of the chemistry of the intermediate formed by irradiation of arylmethylenecyclopropanes, such as the sensitivity of the addition reaction to steric and electronic effects in substrate alkenes and the possibility that intramolecular processes may account for the inefficiency of the intermolecular insertion reaction, are the subjects of current investigations.

(*Tetrahedron Lett.*, 845 (1970)) for a discussion of thermal isomerizations of this type.

(12) Identity was established by comparison of ir and nmr spectra and by equivalence of retention times on three different glpc columns.

(13) An authentic sample of 4 was obtained as the major isomer from the dehydration of 1-cyclohexyl-2-methyl-2-propanol: nmr (CCl_4) δ 4.9 (doublet of multiplets, $J = 9.0$ and $J \sim 1.3$ Hz, 1 H), 1.64 (d, $J \sim 1.2$ Hz, CH_3), 1.57 (d, $J \sim 1.3$ Hz, CH_3), 2.5–0.7 (broad m, total area of 17); ir 1670, 830 cm^{-1}; *m/e* 138.1410 (calcd for $C_{10}H_{18}$, 138.1408). The adduct 4 isolated from the photolysis had a retention time identical with that of the authentic material on three different glpc columns [4 m 30% TCEP on 60–80 Chromosorb P(AW); 2 m 30% SE-30 on 60–80 Chromosorb P; 5 m FFAP on 60–80 Chromosorb P(AW)] and gave an ir spectrum (CCl_4) which, although very weak owing to the low yield of the insertion reaction, had all of the major peaks of authentic 4, and no spurious absorptions.

(14) Initial observations are that photolysis of 1c in either *cis-* or *trans*-4-methyl-2-pentene affords a mixture of both the cis and the trans adducts. Control experiments have shown, however, that the methylenecyclopropanes undergo a facile photochemical geometrical isomerization which accounts for at least part, if not all, of the nonstereospecificity.

(15) We estimate that had 4 been formed, a yield of as little as 0.1% could have been detected by our glpc method of analysis.

(16) The support of this research by the Robert A. Welch Foundation is gratefully acknowledged. The mass spectrometer was purchased with funds provided by the National Science Foundation (Grant No. GP-8509).

(17) NDEA Title IV Fellow, 1967–1970.

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Photofluorination with Fluoroxytrifluoromethane, a General Method for the Synthesis of Organic Fluorine Compounds. Direct Fluorination of Bioactive Molecules

Sir:

We wish to report the discovery of the first general method for substitutive fluorination of organic compounds.

The known methods for substitutive fluorination (RH → RF) are either nonselective and degradative (*e.g.*, the methods involving elementary fluorine or high-valency oxidative metallic fluorides, as CoF_3, etc.) or are applicable (*e.g.*, perchloryl fluoride) only with especially activated substrates. A further deterrent is the extremely dangerous nature of most of the above reagents.[1]

We found that light-induced—thus presumably radical type—liquid-phase interaction of fluoroxytrifluoromethane, CF_3OF,[2] with organic compounds represents an exceedingly useful new approach for the substitution of hydrogen atoms by fluorine in a variety of organic compounds. Irradiation with very high luminous flux density is of key importance for the success of this method.[3]

$$RH + CF_3OF \xrightarrow[\text{liquid phase}]{h\nu} RF$$

A solution of benzene (25 mmol) in 80 ml of trichlorofluoromethane was irradiated[3] at −78° (acetone–Dry Ice bath) under stirring while CF_3OF gas[4] (20 mmol) was passed in within 1 hr.[5] After 30 min of further irradiation the solvent was distilled off and the residue analyzed by quantitative gas–liquid chromatography,[6] indicating 65% yield of fluorobenzene, with 10% trifluoromethoxybenzene ($C_6H_5OCF_3$) as by-product.[7] A similar experiment, without irradiation, gave a complex mixture of products with only 17% yield of fluorobenzene; addition of CF_3OF in the dark followed by uv irradiation also gave a low yield. These results may be explained as follows: the rate of the nonradical (electrophilic) interaction of benzene and CF_3OF—giving an untractable mixture of products—is unaltered by the uv irradiation, whereas the radical reaction—leading to fluorobenzene—is accelerated. The decisive influence of the conditions is reflected by the result recorded in the pioneering work of Allison and Cady,[8] according to which the *gas-phase* reaction between CF_3OF and benzene gave—even under uv

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(1) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969, pp 52–70 and 132–149.

(2) K. B. Kellogg and G. H. Cady, *J. Amer. Chem. Soc.*, **70**, 3986 (1948); G. H. Cady, *Inorg. Syn.*, **8**, 165 (1966). CF_3OF is commercially available from PCR Inc., Gainesville, Fla. 32601.

(3) A 1000-W Hanovia mercury–xenon lamp (Catalog No. 9778-1) fitted into a quartz projector (Type LH 151-N of Schoeffel Instrument Co., Westwood, N. J.) was employed throughout this work. The luminous flux density provided by this source—parallel beam of ~5 cm diameter—is ~100–200 times higher than what is generally employed in photochemical experiments.

(4) From PCR Inc., ref 2.

(5) A special KEL-F reactor designed and built with the cooperation of Mr. R. Geiger, equipped with transparent KEL-F window [J. Kollonitsch, G. A. Doldouras, and V. F. Verdi, *J. Chem. Soc. B*, 1093 (1967)], was employed.

(6) 20% QF-1 on 80–100 Gas-Chrom Z.

(7) The identity of products was ascertained by glc–mass spectrometry (LKB 9000). Mass spectra were compared in every case with those of the authentic fluorine compounds.

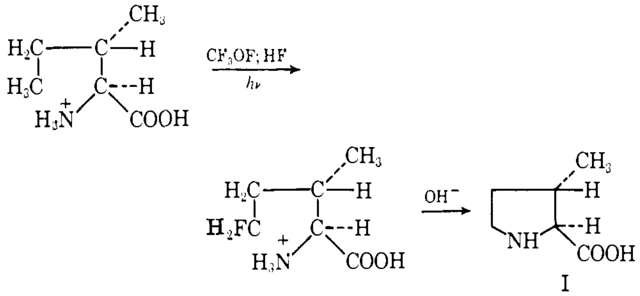
(8) J. A. C. Allison and G. H. Cady, *J. Amer. Chem. Soc.*, **81**, 1089 (1959).

irradiation—only 5% fluorobenzene, accompanied by a similar amount of $C_6H_5OCF_3$.

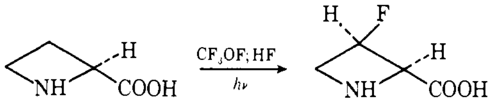
Toluene was also photofluorinated, to give 34% *o*-fluorotoluene and 25% benzyl fluoride,[7] whereas anisole led to a mixture[9] of *o*-fluoroanisole (38%), *m*- and *p*-fluoroanisole (4%), and anisole (52%).[7,10]

Cyclohexane was also smoothly photofluorinated ($CFCl_3$ solvent, −78°) to give fluorocyclohexane in 44% yield.[7] (Without uv irradiation there was no reaction observed.) Under similar conditions, isobutyric acid gave a mixture of 2-fluoro- and 3-fluoroisobutyric acid[7] (yields 31 and 39%, respectively).

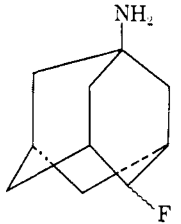
Direct *fluorination of bioactive molecules* is an important application of this method. Substitution of fluorine—a "superhalogen" with a van der Waals' radius close to the one of the hydrogen atom[11]—for hydrogen in organic compounds is a unique way to change the electron-distribution pattern without substantially changing the shape or size of the molecule. Thus, C-fluorinated bioactive molecules are of great interest to the biological sciences.[12] Surprisingly selective fluorinations have been observed by reacting amino acids with CF_3OF in liquid hydrogen fluoride as solvent. L-Isoleucine (10 mmol) dissolved in 50 ml of HF was photofluorinated (at −78°, 1 hr), the solvent evaporated, and the residue dissolved in water and basified. Amino acid analysis (Spinco-Beckman) indicated the presence of 3.9 mmol of *trans*-3-methyl-L-proline (I)[13] besides small amounts of other amino acids. The high extent of δ fluorination (minimum 39%) is unexpected. *Photochlorination* of L-isoleucine gave not more than 33% δ chlorination;[13] moreover, the selectivity of fluorinations involving F· is substantially lower than that of chlorinations with Cl.[14] L-Azetidine-2-carboxylic acid (40 mmol) was also smoothly photofluorinated (in 70 ml of HF) under similar conditions.[15] 1-Aminoadamantane (antiviral drug Symmetrel) gave a mixture of IV and V.[16] As a model for peptides and proteins, polycaprolactam (Nylon 6) was also photofluorinated in liquid HF to furnish a snow-white C-fluorinated polyamide with 1.25 g-atoms of F/unit mol.



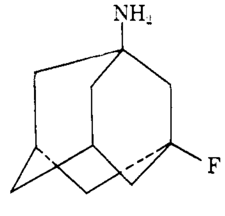
I



II III



IV



V

Fluoroxytrifluoromethane displays continuous absorption of light below 370 nm, the primary photolytic process[17] being

$$\mathrm{CF_3OF} \xrightarrow{h\nu} \mathrm{F}\cdot + \mathrm{CF_3O}\cdot$$

Thus, in first approximation, photofluorination by CF_3OF may be considered as a radical chain reaction, with either F· or CF_3O· as chain carriers. The selectivities observed in liquid HF solvent are probably explainable by the participation of the protonated (cationic) substrate, in analogy to the demonstration of a similar effect of protonation on radical chlorination.[5,13]

Further extension and application of this method are being explored.

Acknowledgment. We thank Dr. B. Arison and Dr. A. W. Douglas for recording and interpretating several pmr spectra, Dr. J. L. Beck and Mr. J. L. Smith for the glc–mass spectroscopy, Mr. W. E. Tait for some of the glc data, Mr. C. F. Homnick for the amino acid analyses, and Mr. R. N. Boos and associates for the microanalyses.

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[9] Glc as in ref 6.

[10] Electrophilic (additive and substitutive) reactions of *olefins* and *activated aromatics* with CF_3OF have already been studied: R. S. Porter and G. H. Cady, *J. Amer. Chem. Soc.*, **79**, 5625, 5628 (1957); P. D. Schuman, E. C. Stump, and G. Westmoreland, 152nd National Meeting of the American Chemical Society, Sept 1966, New York, N. Y., Abstract K25. The studies of D. H. R. Barton and coworkers are especially important [D. H. R. Barton, L. S. Godinho, R. H. Hesse, and M. M. Pechet, *Chem. Commun.*, 804 (1968); D. H. R. Barton, A. K. Ganguly, R. H. Hesse, S. N. Loo, and M. M. Pechet, *ibid.*, 806 (1968); D. H. R. Barton, L. J. Danks, A. K. Ganguly, R. H. Hesse, G. Tarzia, and M. M. Pechet, *ibid.*, 227 (1969)]. Barton and coworkers established the *nonradical, electrophilic* character of their reactions.

[11] L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 82.

[12] P. Goldman, *Science*, **164**, 1123 (1969).

[13] J. Kollonitsch, A. N. Scott, and G. A. Doldouras, *J. Amer. Chem. Soc.*, **88**, 3624 (1966).

[14] P. S. Fredricks and J. M. Tedder, *J. Chem. Soc.*, 144 (1960); P. C. Anson, P. S. Fredricks, and J. M. Tedder, *ibid.*, 918 (1959).

[15] *cis*-3-Fluoro-L-azetidine-2-carboxylic acid (III) (new compound) was isolated in 53% yield by chromatography of the residue obtained on evaporation of the HF solution on Dowex 50-X8 (analytical grade) resin column, eluent 2 *M* HCl; III (columns) was characterized by C, H, N, and F analysis and pmr spectroscopy; $[\alpha]_D$ −90° (*c* 2, 1 *M* HCl).

[16] IV and V, new compounds, were characterized by C, H, N, and F analysis and pmr spectra; yields 27 and 25%, respectively.

[17] P. J. Aymonino, *Photochem. Photobiol.*, **7**, 761 (1968).

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Thermolysis and Photolysis of Tricyclo[2.1.0.0^{2,5}]pentan-3-one Derivatives

Sir:

Disubstituted tricyclo[2.1.0.0^{2,5}]pentan-3-ones (I) were synthesized[1] and the proposed structures were subsequently established by an X-ray crystal analysis.[2]

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[1] S. Masamune, *J. Amer. Chem. Soc.*, **86**, 735 (1964); W. E. von Doering and M. Pomerantz, *Tetrahedron Lett.*, 961 (1964).

[2] J. Trotter, C. S. Gibbons, N. Nakatsuka, and S. Masamune, *J.*