BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 48(4), 1335—1336 (1975)

# Syntheses of Fluorine-Containing Chromans: A Radical Cycloaddition of Phenyl Alkyl Ethers with Hexafluoropropene

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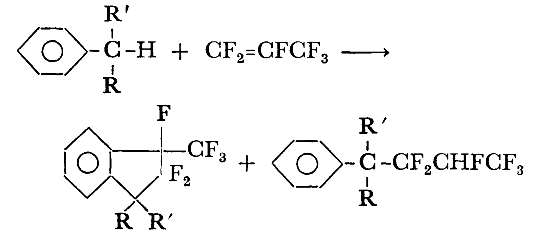
(Received October 22, 1974)

**Synopsis.** Four 2-substituted 4-trifluoromethyl-3,3,4-trifluorochromans were synthesized in one step by the radical cycloaddition of phenyl alkyl ethers and hexafluoropropene in the presence of di-*t*-butyl peroxide.

Although the syntheses of compounds containing a five or six membered ring fused to an aromatic ring are established in the ionic process, such as the Friedel-Crafts ring closure and various condensation reactions, only a few investigations have been reported on the radical process, such as the radical cycloaddition reaction of aromatic compounds with olefins.

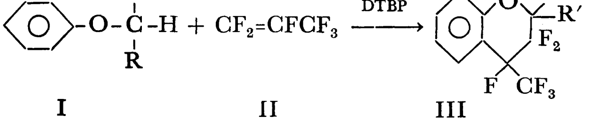
In a previous communication[1] we reported on the syntheses of 1-trifluoromethyl-1,2,2-trifluoroindanes by the radical cycloaddition reaction of alkylbenzenes with hexafluoropropene.



(R, R′ : H, $CH_3$)

The present work was undertaken with the aim of extending this type of cycloaddition to phenyl alkyl ethers(I), and preparing the fluorine-containing chromans(III).

Four 4-trifluoromethyl-3,3,4-trifluorochromans(III) were synthesized in one step from I and hexafluoropropene(II) in the presence of di-*t*-butyl peroxide.



I II III

(Ia, IIIa: R=R′=H; Ib, IIIb[2]: R=H, R′=$CH_3$; Ic, IIIc: R=R′=$CH_3$)

To investigate the effect of dilution with a solvent, two kinds of experimental procedure were employed: method A in which no solvent was used, and method B in which inert solvent was used. The reaction conditions and product yields are given in Table 1.

Table 1. The radical cycloaddition reaction of phenyl alkyl ethers and hexafluoropropene

| | Phenyl alkyl ether (mol) | HFP (mol) | DTBP (mol) | Method[a] | Conversion (%) | Yield[b] (%) | Higher boiling products (g) |
|---|---|---|---|---|---|---|---|
| Ia | 0.400 | 0.660 | 0.410 | A | 39.9 | 44.1 | 59 |
| Ia | 0.400 | 0.579 | 0.410 | B | 33.0 | 66.7 | 44 |
| Ib | 0.400 | 0.641 | 0.410 | A | 38.7 | 36.0 | 83 |
| Ib | 0.400 | 0.561 | 0.410 | B | 31.9 | 85.9 | 41 |
| Ic | 0.400 | 0.683 | 0.410 | A | 37.6 | 56.1 | 49 |
| Ic | 0.400 | 0.608 | 0.410 | B | 17.5 | 74.3 | 49 |

a) Method A: no solvent; Method B: $CCl_2FCClF_2$ (1.00 mol) as a solvent.
b) Yields are calculated from the amounts of the consumed phenyl alkyl ether.

As compared with the case of cycloaddition reactions of alkylbenzenes,[1] less reactive phenyl alkyl ethers afford the cycloadducts in a lower conversion, no 1 : 1 adduct, $C_6H_5OCRR'CF_2CHFCF_3$ being formed. Lack of 1 : 1 adduct formation might be due to the incapability of the intermediate radical ($C_6H_5OCRR'CF_2$-$\dot{C}FCF_3$) to abstract a hydrogen from less reactive phenyl alkyl ethers.

Of the two methods A and B, the former is slightly better in total conversion, although a larger quantity of higher boiling products is produced. Higher yields of III were eventually obtained by method B. The yield of III was almost the same with each of the three kinds of phenyl alkyl ethers. Two stereoisomers, IIIb-1 and IIIb-2, were obtained from Ib in the ratio 1 : 3.

In order to prepare the corresponding chromen, dehydrofluorination of IIIa was attempted by treating it with an alcoholic potassium hydroxide solution, but no reaction occurred even in a reflux condition.

The structures of III were elucidated by IR, NMR and mass spectra.

In the mass spectrum, the large molecular ion peak was observed in each chroman(III). Another large ion peak of IIIa, IIIb-1 and IIIb-2 was generated by the loss of $CF_3$ group from the molecule, IIIc being cleaved to two fragments, *m/e* : 92 $C_6H_4O$ and *m/e* : 192 $(CH_3)_2CCF_2CFCF_3$. Two stereoisomers, IIIb-1 and IIIb-2, gave an identical pattern of fragmentation.

The effect of temperature on the proton NMR spectra was studied in the region from −80 °C to 35 °C. No variation of the spectra was observed. Since no temperature variation was observed in $^1H$ NMR spectrum, it seems that most of the molecules have a fixed conformation at room temperature.[3] The predominant conformation of the dihydropyrane ring of III may be that of the half-chair form in the same manner as for cyclohexene.[4] Since the $CF_3$ group is bulky, the molecules are fixed in a position having the $CF_3$ group in the *quasi*-equatorial position. Non-equivalent *quasi*-axial and equatorial fluorines of each $CF_2$ group of all the chromans and protons of the $CH_2$ group of IIIa produced separate AB patterns, methyl groups of IIIc being also non-equivalent. Two isomers, IIIb-1 and IIIb-2, could be observed between the methyl group having a *quasi*-axial position and that having a *quasi*-equatorial one. These configurations were estimated by means of the vicinal H–F coupling constants. By irradiation on methyl protons, quartet splitting was removed from complex multiplet of their tertiary proton spectrum, leaving doublets of doublets ($J$=7.2 Hz, 18.4 Hz for lower boiling isomer, IIIb-1 and $J$=5.2 Hz, 23.7 Hz for higher boiling isomer, IIIb-2). The largest doublet splitting (23.7 Hz) might be due to the vicinal coupling of *quasi*-axial hydrogen with *quasi*-axial fluorine.[5] Thus higher boiling isomer (IIIb-2), which was predominant, seems to have its methyl group in the *quasi*-equatorial position.

Characterization of the NMR spectra was made on the basis of the following rules;

(1) chemical shifts of fluorine
$\delta\mathrm{CF} > \delta\mathrm{CF_2} > \delta\mathrm{CF_3}$

(2) coupling type in the fragment H-C-C-F[5]
$J_{\mathrm{H^{ax}-F^{ax}}} > J_{\mathrm{H^{eq}-F^{eq}}} > J_{\mathrm{H^{ax}-F^{eq}}},\ J_{\mathrm{H^{eq}-F^{ax}}}$

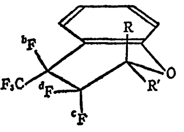
(3) coupling type in the fragment F-C-C-F[6]
$J_{\mathrm{F^{ax}-F^{eq}}} > J_{\mathrm{F^{ax}-F^{ax}}}$

(4) coupling type in the fragment F-C-C-$\mathrm{CF_3}$[7]
$J_{\mathrm{F^{ax}-CF_3{}^{eq}}} > J_{\mathrm{F^{eq}-CF_3{}^{eq}}}$

Since signals of $\mathrm{CH_2}$ and $\mathrm{CF_2}$ appeared in a complex ABXY pattern in the spectrum of IIIa, it is not certain to which fluorine nuclei the $\mathrm{CH_2}$ proton couples by first-order analysis. Many sets of heteronuclear and fluorine-fluorine decoupling experiments were needed in order to characterize the spectrum completely. Very weak long-range proton-fluorine couplings were indicated by the signal width.

TABLE 2. MASS AND NMR SPECTRAL DATA OF CHROMANS

Compounds



| R | H | $\mathrm{CH_3}$ | H | $\mathrm{CH_3}$ |
|---|---|---|---|---|
| R′ | H | H | $\mathrm{CH_3}$ | $\mathrm{CH_3}$ |
| | IIIa | IIIb-1 | IIIb-2 | IIIc |
| Chemical shift[a] (ppm) | | | | |
| $\tau\mathrm{CH_2}$ | 5.8 AB m | — | — | — |
| $\tau\mathrm{CH}$ | — | 5.38 d-d-q | 5.80 d-d-q | — |
| $\tau\mathrm{CH_3{}^{ax}}$ | — | 8.55 d | — | 8.48 s |
| $\tau\mathrm{CH_3{}^{eq}}$ | — | — | 8.56 d-d | 8.67 d |
| $\delta\mathrm{CF_3}$ | −4.7 d-d-d | −3.0 d-d-d | −7.0 d-d-d | −6.5 d-d-d |
| $\delta\mathrm{CF_2{}^{ax}}$ | 46.3 AB m | 49.6 AB m | 57.4 AB m | 46.1 AB m |
| $\delta\mathrm{CF_2{}^{eq}}$ | 42.6 m | 50.0 m | 50.2 m | 50.2 m |
| $\delta\mathrm{CF}$ | 85.6 m | 100.7 m | 67.8 m | 73.5 m |
| Coupling constant[b] (Hz) | | | | |
| $J\,{}^{a}\mathrm{F}-{}^{b}\mathrm{F}$ | 9.3 | 9.1 | 9.3 | 8.5 |
| $J\,{}^{a}\mathrm{F}-{}^{c}\mathrm{F}$ | 13.0 | 13.1 | 13.4 | 15.2 |
| $J\,{}^{a}\mathrm{F}-{}^{d}\mathrm{F}$ | 9.0 | 8.5 | 11.8 | 11.0 |
| $J\,{}^{b}\mathrm{F}-{}^{c}\mathrm{F}$ | | | 5.1 | 6.2 |
| $J\,{}^{b}\mathrm{F}-{}^{d}\mathrm{F}$ | | 8.5 | 8.5 | 7.3 |
| $J\,{}^{c}\mathrm{F}-{}^{d}\mathrm{F}$ | 272 | 270 | 272 | 269 |
| $J\,{}^{c}\mathrm{F}-\mathrm{H}$ | | 7.2 | 23.7 | — |
| $J\,{}^{d}\mathrm{F}-\mathrm{H}$ | | 18.4 | 5.2 | — |
| $J\,\mathrm{H}-\mathrm{H}$ | — | 6.5 | 6.4 | — |
| Mass spectra $m/e$ (relative abundance) | | | | |
| | 256 ( 58.2) | 270 ( 93.9) | 280 ( 67.1) | 284 ( 44.2) |
| | 187 (100 ) | 201 (100 ) | 201 (100 ) | 192 (100 ) |
| | 139 ( 26.3) | 139 ( 29.0) | 139 ( 26.0) | 145 ( 19.5) |
| | 109 ( 51.9) | 65 ( 31.8) | 65 ( 31.5) | 92 ( 27.4) |

a) Neat liquid, using TMS as an internal standard for $^1$H and $\mathrm{CF_3COOH}$ as an external standard for $^{19}$F; the signals being denoted by s(singlet), d(doublet), q(quartet), m(multiplet) and AB(AB pattern). b) Values are of first-order.

TABLE 3. PHYSICAL PROPERTIES AND ANALYTICAL DATA OF CHROMANS

| Compound | Bp (°C) | $n_D^{20}$ | $d_4^{20}$ | Formula | Elemental analysis (%) C Found (Calcd) | H Found (Calcd) |
|---|---|---|---|---|---|---|
| **IIIa** | 187 | 1.4458 | 1.446 | $\mathrm{C_{10}H_6OF_6}$ | 47.06<br>(46.89) | 2.38<br>(2.36) |
| **IIIb-1** | 203 | 1.4358 | 1.386 | $\mathrm{C_{11}H_8OF_6}$ | 49.08<br>(48.90) | 3.22<br>(2.98) |
| **IIIb-2** | 205 | 1.4385 | 1.421 | $\mathrm{C_{11}H_8OF_6}$ | 48.66<br>(48.90) | 3.12<br>(2.98) |
| **IIIc** | 210 | 1.4453 | 1.361 | $\mathrm{C_{12}H_{10}OF_6}$ | 51.07<br>(50.71) | 3.66<br>(3.55) |

Mass and NMR spectral data are shown in Table 2 and physical properties and analytical data in Table 3.

## Experimental

Phenyl isopropyl ether (Ic) was prepared (yield 69%) from phenol and isopropyl bromide in the presence of sodium hydroxide, according to the method of Marvel and Tanenbaum.[8]

*General Procedures Used in the Cycloaddition Reactions of Phenyl Alkyl Ethers(I) with Hexafluoropropene(II).* *Method A*: A mixture of I (0.40 mol), II (0.64—0.68 mol) and DTBP (60 g, 0.41 mol) was heated in a 300 ml stainless steel autoclave at temperature gradually rising from 130 °C to 160 °C for about 6 hr. The products were separated by vacuum distillation.

*Method B*: A solution of I (0.40 mol), II (0.56—0.61 mol) and DTBP (60 g, 0.41 mol) in 1,1,2-trichloro-1,2,2-trifluoroethane (187 g, 1.00 mol) was heated in a 500 ml stainless steel autoclave, under the same conditions as used for method A. After removal of the solvent, the residue was distilled *in vacuo*.

The stereoisomers IIIb-1 and IIIb-2 were separated on preparative glc (with an aluminum column, length 6 m, dia. 10 mm, packed with 20% Silicone DC550-Celite 545).

## References

1) H. Kimoto, H. Muramatsu, and K. Inukai, *Chem. Lett.*, **1974**, 791.

2) IIIb consists of two stereoisomers.

3) Some comparable compounds, perfluoromethylcyclohexane and perfluoro(*N*-fluoro-methylpiperidines), were reported to have a conformationally rigid structure at room temperature. J. Feeney and L. H. Sutcliffe, *Trans. Faraday Soc.*, **56**, 1559 (1960); J. Lee and K. G. Orrell, *ibid.*, **63**, 16 (1967).

4) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **77**, 2505 (1955); R. Bucourt, *Bull. Chim. Soc. Fr.*, **1963**, 1262.

5) It was proposed that the dihedral angle ($\theta$) dependence of vicinal proton-fluorine coupling constants ($J^{\mathrm{vic}}_{\mathrm{H-F}}$) is similar to vicinal $J_{\mathrm{H-H}}$— a maximum at 0°, a minimum at 90° and a maximum at 180°—and can be expressed as follows.

$$J^{\mathrm{vic}}_{\mathrm{H-F}} = A\cos^2\theta$$

K. L. Williamson, Y. F. Hsu, F. H. Hall, and S. Swager, *J. Amer. Chem. Soc.*, **90**, 6717 (1968); A. M. Ihrig and S. L. Smith, *ibid.*, **92**, 759 (1970).
The calculated dihedral angles between substituent of 4 and 5 carbon of the cyclohexene by using the Bucourt model[4] are axial-axial : 169°; axial-equatorial : 58°; and equatorial-equatorial : 53°

6) The vicinal axial fluorine-equatorial fluorine coupling constant has the largest value for 1,2,4-trichloroheptafluorocyclohexene.

J. Feeney, L. H. Sutcliffe and S. M. Walker, *Trans. Faraday Soc.*, **62**, 2650 (1966).

7) From a consideration of the through space contribution of fluorine-fluorine coupling, the nearest fluorine-fluorine distance of $\mathrm{F^{ax}}$—$\mathrm{CF_3{}^{eq}}$ is shorter than that of $\mathrm{F^{eq}}$—$\mathrm{CF_3{}^{eq}}$.

8) C. S. Marvel and A. L. Tanenbaum, "Organic Syntheses", Coll. Vol. I, p. 435 (1956).