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Studies on Organic Fluorine Compounds. XLIII.[1] The Ene Reaction of Hexafluoroacetone

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The reaction of hexafluoroacetone with phenyl-substituted allyl compounds was found to give the ene products. Thus, allylbenzene gave 1,1,1-trifluoro-5-phenyl-2-(trifluoromethyl)pent-4-en-2-ol. Allyl phenyl ether and thioether gave the corresponding ene products. The product from the latter cyclized to 5-phenylthio-2,2-bis(trifluoromethyl)tetrahydrofuran. *N*-Allyl-*N*-methylaniline reacted with the ketone to give the 4-(1,1,1,3,3,3-hexafluoro-2-hydroxy-2-propyl) derivative *via* the Friedel–Crafts reaction, and this compound further reacted in the ene reaction to give unusual products.

Keywords——ene reaction; hexafluoroacetone; allylbenzene; allyl; aniline; trifluoromethyl; tetrahydrofuran; thioether; bis(trifluoromethyl)carbinol; ether

The reaction of hexafluoroacetone (**1**) with methylvinyl compounds was reported by Urry *et al.*,[2] who obtained 2 : 1 products by means of a stepwise reaction, now called the "ene reaction." They reported high reactivity of **1**, but did not mention its reaction with allylbenzenes. In the present work, we examined the reaction with allylbenzene and related compounds in order to develop a method for the synthesis of a new class of fluorine compounds, and found that the reaction is useful for the synthesis of allylbis(trifluoromethyl)carbinols.

A solution of allylbenzene and **1** in benzene was shaken in a stainless steel tube at 120°C to give 1,1,1-trifluoro-5-phenyl-2-(trifluoromethyl)pent-4-en-2-ol (**2**) in a yield of 80.7%. The similar reaction of 2-phenylpropene gave the 4-phenylisomer (**3**) of **2** and 1,1,1,7,7,7-hexafluoro-4-phenyl-2,6-bis(trifluoromethyl)hept-3-en-2,6-diol (**4**), the 1 : 2-product. The reaction of 1-phenylpropene did not proceed at all even at 170°C. These results show that **1** reacts as a good enophile with an ene component having a terminal vinyl group, while a non-terminal olefin is much less reactive.

The reaction of 4-allylanisole at 100 °C gave a 4′-methoxy derivative (**5**) of **2** in 82.5% yield. This product isomerized on heating at 150 °C to 5-(4-methoxyphenyl)-2,2-bis(trifluoromethyl)tetrahydrofuran (**6**). The latter compound is presumably formed by the intramolecular cyclization of **5**.

Next, the reaction of an allyl group connected to a benzene ring by a hetero atom was investigated, since this reaction was expected to be useful for the synthesis of an aldehyde-equivalent having a novel fluorine-containing substituent. However, the reaction of allyl-phenyl ether at 130°C resulted in complete recovery of the starting material, and even at 150 °C only 16.2% of the ene product (**7**) was obtained, with recovery of the starting material. This result shows that the introduction of an oxygen atom into the methylene moiety reduces the reactivity probably due to the high electronegativity of the oxygen atom. Therefore, the reaction of *N*-allyl-*N*-methylaniline was examined, since nitrogen is less electronegative than

oxygen. Heating of a solution of this amine and **1** in benzene at 150°C resulted in the formation of 4-(1,1,1,3,3,3-hexafluoro-2-hydroxy-2-propyl)-*N*-allyl-*N*-methylaniline (**8**) and the deallylated analogue (**9**) of **8** in yields of 39.5 and 14.4%, respectively. These results suggested that the Friedel–Crafts reaction occurred first to give **8** and that **8** reacted with **1** to give the ene product, which was hydrolyzed to **9** during the work-up. To confirm these points, the reaction was carried out at 80 °C with an equimolar amount of **1**. In this case, only **8** was obtained in a yield of 75.4%. By the reaction of **8** with **1** at 140 °C, **9** and 4-(1,1,1,3,3,3-hexafluoro-2-hydroxy-2-propyl)-*N*-[2,2-bis(trifluoromethyl)-5-(1,1,1,3,3,3-hexafluoro-2-

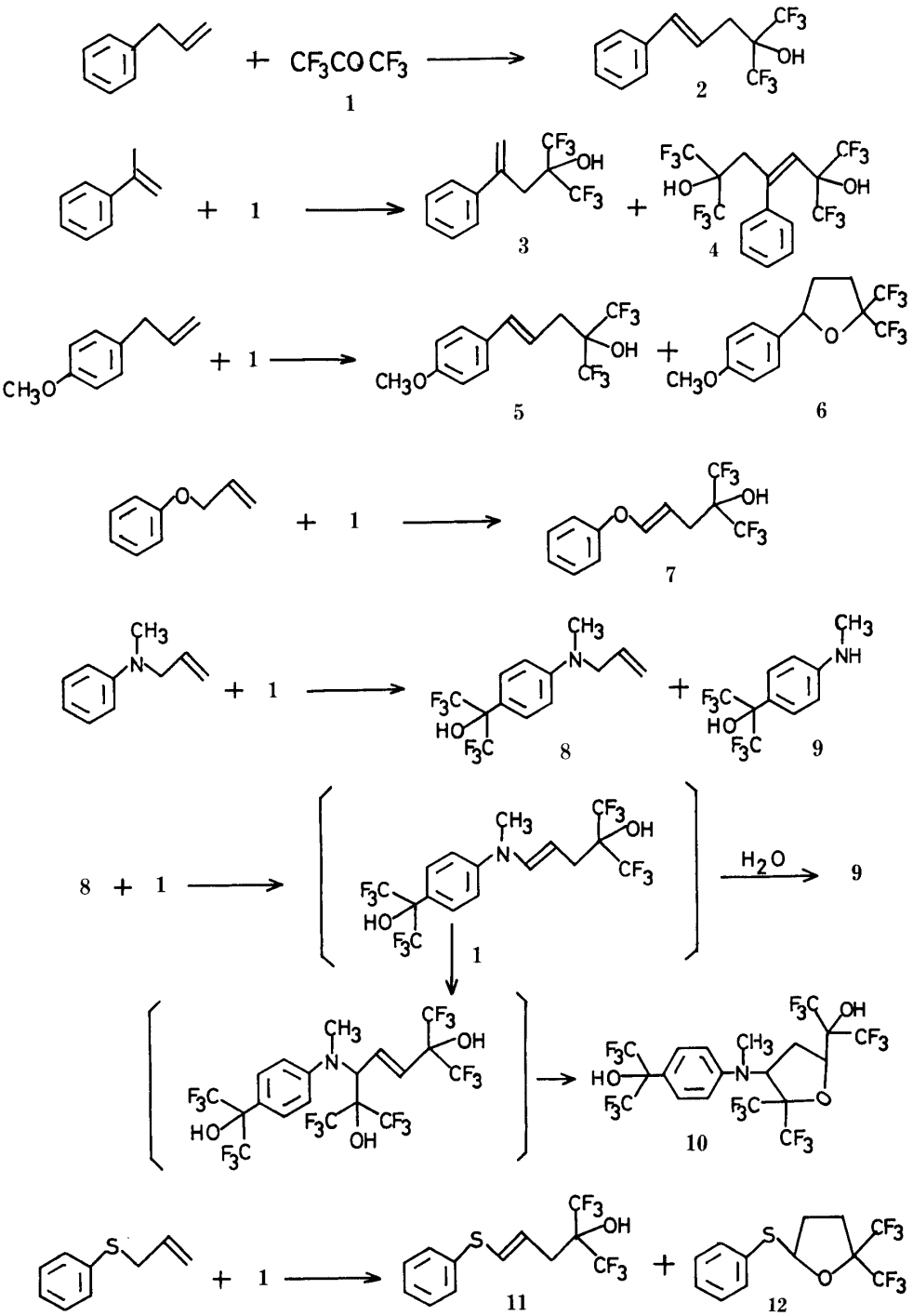

Chart 1

hydroxy-2-propyl)-3-tetrahydrofuryl]-*N*-methylaniline (**10**) were obtained in yields of 22.2 and 53.8%, respectively. Thus, the electronegativity of nitrogen is not so strong as to prevent the reaction. Further, the primary ene product has the enamine structure; it reacts with another molecule of **1** and the product cyclizes easily to give **10**. This is the first example of the reaction of **1** with a non-terminal olefin.

Finally, the reaction of allyl phenyl thioether with **1** was examined at 150 °C, where 1,1,1-trifluoro-5-phenylthio-2-(trifluorometyl)pent-4-en-2-ol **11** and its cyclized product **12** were obtained in yields of 67.7 and 17.8%, respectively. The treatment of **11** at a higher temperature gave **12**. The results of these reactions are summarized in Chart 1.

The mechanism of formation of the cyclization products is assumed to be as shown in Chart 2. Thus, the proton of the hydroxy group is highly acidic due to the electronic effect of the trifluoromethyl groups. If the olefinic part is activated for electrophilic attack by an electron-donating group, it is protonated intramolecularly and the zwitterionic intermediate cyclizes to a tetrahydrofuran compound.

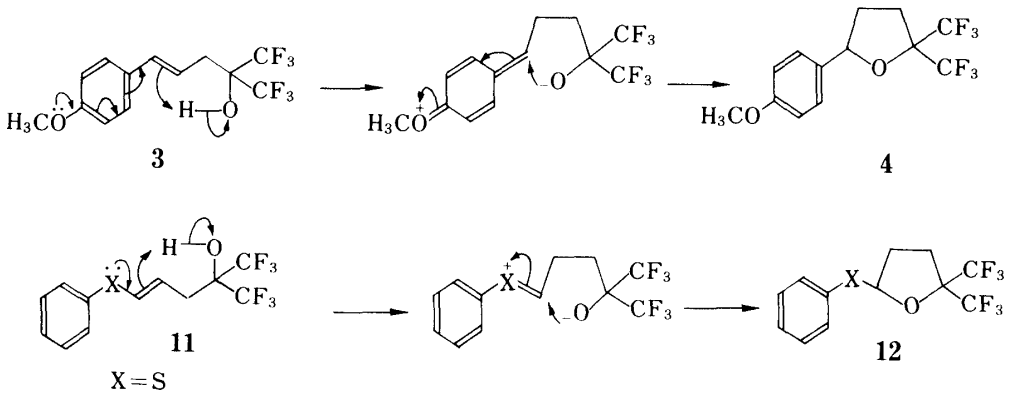

Chart 2

In summary, the ene reaction of hexafluoroacetone with allylbenzene was found to give the ene adduct, which did not react further. This is in contrast to the fact that propene and other aliphatic olefins were reported to give 1 : 2 products.[2] In the case of an allyl compound having a hetero substituent, the electronegativity of the hetero atom determines the reactivity. The ene product cyclizes intramolecularly to a bis(trifluoromethyl)tetrahydrofuran.

Experimental

Melting points were determined on a Yanaco MP apparatus and are uncorrected. ^{1}H-Nuclear magnetic resonance (NMR) spectra were obtained on Varian EM-360L and EM-390 NMR spectrometers. ^{19}F-NMR spectra were determined with the EM-360L spectrometer using benzotrifluoride as an internal standard (upper field taken as plus). ^{13}C-NMR spectra were determined on a JEOL FX-100 spectrometer. Spectral patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Mass spectra (MS) were determined with a Hitachi Double Focusing Mass Spectrometer M-80. Analytical and preparative gas chromatography (GC) were performed on Hitachi 163 Gas Chromatograph.

Reaction of Allylbenzene——A solution of allylbenzene (2 g) in benzene (10 ml) was placed in a stainless-steel tube and hexafluoroacetone (**1**, 3 ml at −78 °C) was added through a vacuum line. The sealed tube was shaken at 120 °C for 5 h, and the mixture was extracted with CH_2Cl_2. After evaporation of the solvent, the residue was distilled under a vacuum to give 1,1,1-trifluoro-5-phenyl-2-(triflurometyl)pent-4-en-2-ol (**2**); a colorless oil; bp 77—78 °C/6 mmHg. MS *m/e*: 284 (M^+); high-resolution MS calcd for $C_{12}H_{10}F_6O$: 284.063. Found: 284.063.^{1}H-NMR ($CDCl_3$) δ: 2.86 (2H, d, J=7.5 Hz), 3.26 (1H, s), 6.13 (1H, dt, J=16.2, 7.5 Hz), 6.59 (1H, d, J=16.2 Hz), 7.16—7.42 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: 13.80 (s). This compound was found to consist of *trans* and *cis* isomers (93 : 7) from

GC.

Reaction of 2-Phenylpropene——The title compound (2 g) was treated as described above at 130 °C. The products were separated by SiO_2–CH_2Cl_2 column chromatography to give 1,1,1-trifluoro-4-phenyl-2-(trifluoromethyl) pent-4-en-2-ol (**3**, 1.87 g, 38.8%) and 1,1,1,7,7,7-hexafluoro-4-phenyl-2,6-bis(trifluoromethyl)hept-3-en-2,6-diol (**4**, 4.41 g, 57.9%). **3**: Colorless oil; bp 78—79 °C/13 mmHg. MS *m/e*: 284 (M^+); high-resolution MS calcd for $C_{12}H_{10}F_6O$: 284.063. Found: 284.065. ^{1}H-NMR ($CDCl_3$)δ: 2.71 (1H, s), 3.18 (2H, s), 5.28 (1H, s), 5.49 (1H, s), 7.20—7.30 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: 13.78 (s). **4**: Colorless crystals; mp 126—127 °C. MS *m/e*: 450 (M^+); high-resolution MS calcd for $C_{15}H_{10}F_{12}O_2$: 450.049. Found: 450.049. ^{1}H-NMR ($CDCl_3$) δ: 3.68 (2H, s), 5.90 (1H, s), 7.23—7.53 (5H, m), 7.67 (2H, br s). ^{19}F-NMR ($CDCl_3$) δ: 13.35 (6F, s), 14.71 (6F, s).

Reaction of 4-Allylanisole——(a): A solution of 4-allylanisole (2 g) in benzene (10 ml) treated with **1** (3 ml) at 100 °C for 3 h. The mixture was extracted with CH_2Cl_2. After evaporation of the solvent, the residue was passed through an SiO_2 column in CH_2Cl_2–hexane (1 : 3) to give 0.47 g of the starting material and 5-(4-methoxyphenyl)-1,1,1-trifluoro-2-(trifluoromethyl)pent-4-en-2-ol (**5**, 2.68 g). **5**: Colorless crystals; mp 52.5—53.5 °C. MS *m/e*: 314 (M^+); high-resolution MS calcd for $C_{13}H_{12}F_6O_2$: 314.074. Found 314.073: ^{1}H-NMR ($CDCl_3$) δ: 2.82 (2H, d, J= 7.8 Hz), 3.58 (1H, s), 3.73 (3H, s), 5.88 (1H, dt, J=16.2, 7.8 Hz), 6.50 (1H, d, J=16.2 Hz), 6.86 (2H, d, J=8.7 Hz), 7.27 (2H, d, J=8.7 Hz). ^{19}F-NMR ($CDCl_3$) δ: 13.81 (s).

(b): When the same reaction mixture as in (**a**) was heated at 150 °C for distillation, 5-(4-methoxyphenyl)-2,2-bis(trifluoromethyl)tetrahydrofuran (**6**, 3.0 g, 79%) was obtained, together with recovered starting material (0.2 g) and **5** (0.75 g, 20%). **6**: Colorless oil. MS *m/e*: 314 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.60—2.82 (4H, m), 4.01 (3H, s), 4.83—5.33 (1H, m), 6.83 (2H, d, J=8.7 Hz), 7.21 (2H, d, J=8.7 Hz). ^{19}F-NMR δ: 14.14 (q, J=7.8 Hz), 14.54 (q, J=7.8 Hz).

Reaction of Allyl Phenyl Ether——When the title ether (2 g) was treated as described above at 130 °C, the starting material was recovered nearly quantitatively. After the reaction had been carried out at 150 °C, the mixture was extracted with CH_2Cl_2. The extract was passed through an SiO_2 column in CH_2Cl_2–hexane (3 : 7) to give 1,1,1-trifluoro-5-(phenoxy)-2-(trifluoromethyl)pent-4-en-2-ol (**7** 0.725 g, 16.2%, *trans*/*cis*=5/1 as estimated from the ^{19}F-NMR spectrum). Both isomers were separated by repeating the column chromatography. *trans*-**7**: Colorless oil. MS *m/e*: 300 (M^+); high resolution MS calcd for $C_{12}H_{10}F_6O_2$: 300.059. Found: 300.059.^{1}H-NMR ($CDCl_3$) δ: 2.67 (2H, d, J=7.8 Hz), 3.35 (1H, br s), 5.26 (1H, dt, J=12.0, 7.8 Hz), 6.60 (1H, d, J=12.0 Hz), 6.83—7.46 (5H, m), ^{19}F-NMR ($CDCl_3$) δ: 12.67 (s). *cis*-**7**: Colorless oil; MS data are the same as for the *trans*. ^{1}H-NMR ($CDCl_3$) δ: 2.93 (2H, d, J= 7.8 Hz), 3.62 (1H, s), 4.88 (1H, dt, J=6.0, 7.8 Hz), 6.68 (1H, d, J=6.0 Hz), 6.90—7.47 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: 13.00 (s).

Reaction of *N*-methylaniline——(a): The title aniline (1.99 g), **1** (3 ml) and benzene (10 ml) were shaken at 150 °C for 20 h in a stainless-steel tube. The reaction mixture was extracted with CH_2Cl_2. After evaporation of the solvent, the residue was distilled under a vacuum and separated on an SiO_2 column in CH_2Cl_2–hexane (1 : 4) to give **8** and **9**. **8**: Colorless oil; bp 120—130 °C/25 mmHg. MS *m/e*: 313 (M^+); high-resolution MS calcd for $C_{13}H_{13}F_6NO$: 313.090. Found: 313.090. ^{1}H-NMR ($CDCl_3$) δ: 2.98 (3H, s), 3.30 (1H, s), 3.83—4.10 (2H, m), 4.93—5.43 (3H, m), 5.53—6.20 (1H, m), 6.76 (2H, d, J=9.8 Hz), 7.53 (2H, d, J=9.8 Hz). ^{19}F-NMR δ: 13.06 (s). **9**: Colorless crystals; mp 88.5—89.5 °C. MS *m/e*: 273 (M^+); high-resolution MS calcd for $C_{10}H_9F_6NO$: 273.059. Found: 273.058. ^{1}H-NMR ($CDCl_3$) δ: 2.85 (3H, s), 3.60 (2H, br s), 6.67 (2H, d, J=9.0 Hz), 7.55 (2H, d, J=9.0 Hz). ^{19}F-NMR ($CDCl_3$) δ: 13.15 (s).

(b): *N*-Allyl-*N*-methylaniline (1.0 g), **1** (1 ml) and benzene (10 ml) were shaken in a stainless-steel tube at 80 °C for 20 h. The mixture was treated as above. Distillation of the product gave **8** (1.6 g, 75.4%).

(c): Compound **8** (595.0 mg), **1** (1 ml) and benzene (20 ml) were shaken in a stainless-steel tube at 140 °C for 25 h. The products were separated by flash column chromatography [SiO_2, CH_2Cl_2–hexane (1 : 1)] to give **9** (115.3 mg, 22.2%) and 4-(1,1,1,3,3,3-hexafluoro-2-hydroxy-2-propyl)-*N*-[2,2-bis(trifluoromethyl)-5-(1,1,1,3,3,3-hexafluoro-2-hydroxy-2-propyl)-3-tetrahydrofuryl]-*N*-methylaniline (**10**) (659.9 mg, 53.8%). **10**: Colorless crystals: mp 98—99 °C. MS *m/e*: 645 (M^+); high-resolution MS calcd for $C_{19}H_{13}F_{18}NO_3$: 645.061. Found: 645.061. ^{1}H-NMR ($CDCl_3$) δ: 2.57 (1H, dd, J=14.1, 8.8 Hz), 2.65 (1H, dd, J=14.1 14.1 Hz), 2.97 (3H, s), 3.07 (1H, ddd, J=14.1, 10.3, 8.8 Hz), 3.21 (1H, s), 5.55 (1H, s), 5.76 (1H, d, J=10.3 Hz), 7.22 (2H, d, J=9.6 Hz), 7.70 (2H, d, J=9.6 Hz). ^{19}F-NMR ($CDCl_3$) δ: 9.58 (3F, q, J=10.1 Hz), 12.97 (6F, s), 14.83 (3F, q, J=10.1 Hz), 14.85 (3F, q, J=7.1 Hz), 15.14 (3F, q, J=7.1 Hz).

Reaction of Allyl Phenyl Thioether——The title thioether (2 g) was treated as described for **1** at 150 °C for 15 h and the products were separated by flash column chromatography [SiO_2, CH_2Cl_2–hexane (1 : 9)] to give 5-phenylthio-2,2-bis(trifluoromethyl)tetrahydrofuran (**12**, 0.68 g, 17.8%) and 1,1,1-trifluoro-5-phenylthio-2-(trifluoromethyl)pent-4-en-2-ol (**11**, 2.58 g, 67.7%). Distillation of **11** caused its isomerization to 5-phenylthio-2,2-bis(trifluoromethyl)tetrahydrofuran (**12**). **11**: Colorless oil. MS *m/e* 316 (M^+). *Anal.* Calcd for $C_{12}H_{10}F_6OS$: C, 45.57; H, 3.19; S, 10.14; F, 36.05. Found: C, 45.63; H, 3.20; S, 10.00; F, 36.03. This was found to be a *cis*/*trans* mixture by GC (*cis*/*trans*=1/2). (*trans*)^{1}H-NMR ($CDCl_3$) δ: 2.80 (2H, d, J=7.5 Hz), 3.00 (1H, s), 5.72 (1H, dt, J=15, 7.5 Hz), 6.50 (1H, d, J=15 Hz), 7.08—7.54 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: 13.81. (*cis*) ^{1}H-NMR ($CDCl_3$) δ: 2.97 (2H, d, J= 7.5 Hz), 3.11 (1H, s), 5.82 (1H, dt, J=9, 7.5 Hz), 6.60 (1H, d, J=9 Hz), 7.22—7.52 (5H, m), ^{19}F-NMR ($CDCl_3$) δ: 14.13. **12**: Colorless oil, MS *m/e*: 316 (M^+). ^{1}H-NMR ($CDCl_3$)δ: 1.83—2.77 (4H, m), 5.45—5.85 (1H, m), 7.06—7.80 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: 13.90 (q, J=8.5 Hz), 14.42 (q, J=8.5 Hz).

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