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REGIOSPECIFIC α-HEXAFLUOROISOPROPYLIDENATION OF KETONES USING HEXAFLUOROACETONE

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SUMMARY

Hexafluoroacetone (HFA) reacted regiospecifically with various enol silyl ethers at -30 to -35°C in the presence of a Lewis acid to give HFA aldols, or α-bis(trifluoromethyl)hydroxymethyl carbonyl compounds, in good yields. The reaction of HFA with dienol silyl ethers, on the other hand, cleanly proceeded even in the absence of a Lewis acid to provide [4+2]cycloadducts, or bistrifluoromethylated tetrahydropyran-4-one derivatives, quantitatively. The former HFA aldols were converted in excellent yields into α-hexafluoroisopropylidene ketones by the action of methyl chlorosulfite and pyridine.

INTRODUCTION

Hexafluoroacetone (HFA) is known to undergo Lewis acid-catalyzed or thermal Friedel-Crafts type reactions with aromatic [1,3] or vinylic compounds [2,3], giving 1:1 adducts of HFA, or bis(trifluoromethyl)hydroxymethyl derivatives, in fair to good yields. The product obtained in these reactions is, however, usually an isomeric mixture and frequently contaminated with di- and tri-adducts. Although the reactions of HFA with metal enolates derived from a variety of carbonyl compounds have been examined [3] and found to be usable for preparing aldols or re-

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lated derivatives of HFA, their regiospecificity is generally low and, moreover, they are often accompanied by side reactions such as self-condensation or polyaldol condensation.

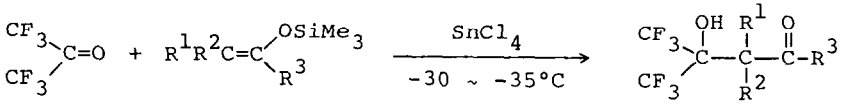
In addition to these disadvantages, there is another factor that has limited the synthetic application of the reactions of HFA; the bis(trifluoromethyl)hydroxymethyl compounds obtained in the above reactions are so resistant to dehydration that it is extremely difficult to convert them into more useful, versatile derivatives. In fact, no methods for converting an HFA aldol into an α,β-unsaturated carbonyl compound have appeared in the literature, except for a limited number of specific systems [4].

In studies to extend the use of HFA and other fluorinated compounds as a starting material for regio- or stereospecifically introducing a perfluoroalkyl or related groups into organic molecules, we have now found that HFA reacts regiospecifically with enol silyl ethers in the presence of a Lewis acid, and the products can be dehydrated with methyl chlorosulfite and pyridine under very mild conditions. This reaction sequence gives good yields of α-hexafluoroisopropylidene ketones, which otherwise are often very troublesome to prepare. It has also been found that bistrifluoromethylated tetrahydropyran-4-ones can be prepared in excellent yields by the regiospecific 1,4-addition of HFA to dienol silyl ethers.

RESULTS AND DISCUSSION

Reaction of HFA with enol silyl ethers (1)

Under the influence of a Lewis acid, HFA readily reacted with a variety of enol silyl ethers (1) at -30 to -35°C to give crossed aldols (2) between HFA and the corresponding carbonyl compound [5]. Among the Lewis acids used in the present study, stannic chloride and titanium tetrachloride were the most effective in catalyzing this reaction. Other Lewis acids such as aluminum trichloride, boron trifluoride diethyl etherate, or zinc chloride caused either considerable decrease in yields of aldol products or self-condensation of the carbonyl compound corresponding to the starting enol silyl ether. Thus, the



1

2

a: R^1 = Et, R^2 = R^3 = H

b: R^1 = R^2 = Me, R^3 = H

c: R^1 = R^2 = H, R^3 = i-Pr

d: R^1 = R^2 = R^3 = Me

e: R^1 = Me, R^2 = H, R^3 = Et

f: R^1 = R^2 = H, R^3 = Ph

g: R^1 = Me, R^2 = H, R^3 = Ph

h: R^1 = R^3 = $-(CH_2)_4-$, R^2 = H

i: R^1 = R^3 = $-(CH_2)_3-$, R^2 = H

j: R^1 = R^3 = $-CH_2CH_2CH(t\text{-Bu})CH_2-$, R^2 = H

treatment of HFA with 1-trimethylsiloxycyclohexene (1h) in the presence of aluminum trichloride gave a 30% yield of 2-cyclohexylidenecyclohexanone, in addition to a small amount of 2-[bis(trifluoromethyl)hydroxymethyl]cyclohexanone (2h). The use of boron trifluoride diethyl etherate depressed the formation of the former but the yield of the latter increased only slightly. On examination of the reaction conditions, the optimum molar ratio of stannic chloride:HFA:enol silyl ether (1), reaction temperature, and reaction time have been found to be 35:30:40, -30 to -35°C, and 2-3 h, respectively. The results of the reactions effected under these conditions are summarized in Table 1, together with some physical properties of the products. Since the use of a solvent generally resulted in a substantial decrease of the yield, all reactions were conducted without a solvent, except for 1-trimethylsiloxystyrene (1f) which underwent polymerization under the reaction conditions. In this particular case, a better yield (56%) was obtained when THF was used as a solvent.

As can be seen from Table 1, this reaction has several characteristic features. Firstly, the reactions proceed smoothly at

TABLE 1

Reaction of HFA with enol silyl ethers (1)

Enol silyl ether	HFA aldol	Yield %	Bp °C/mmHg	n_D (°C)
1a	2a	71	90-93/80	1.3621 (27.5)
1b	2b	72	96-97/76	76.5-77.0[a]
1c	2c	66	83-87/37	1.3571 (24.5)
1d	2d	58	90-95/47	1.3707 (23.5)
1e	2e	74	72-73/29	1.3718 (18.5)
1f	2f	12 (56)[b]	87-90/7	1.4537 (18.5)
1g	2g	67	78-82/2	1.4552 (19.0)
1h	2h	72	102-105/25	1.3931 (24.0)
1i	2i	83	86-90/27	1.3810 (20.0)
1j	2j	70	93-94/3	1.4111 (26.5)

a) Melting point.

b) THF was used as solvent.

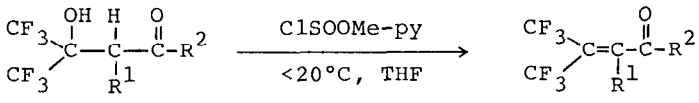
low temperature to provide crossed aldols of HFA in good yields and neither polyaldol condensation products nor self-condensation products are formed at all. Phenyl-substituted enol silyl ethers (1f and 1g) react selectively on their enol double bond, not on the phenyl ring. Secondly, this Lewis acid-catalyzed reaction takes place in a regiospecific manner at the olefinic position of enol silyl ethers, as evidenced by the difference in the stereochemical outcome of the reactions of two structural isomers of enol silyl ethers prepared from 3-methyl-2-butanone, i.e., 3-methyl-2-trimethylsiloxy-1-butene (1c) and 2-methyl-3-trimethylsiloxy-2-butene (1d), with HFA. Enol silyl ether 1c reacted with HFA to give 1-[bis(trifluoromethyl)hydroxymethyl]-3-methyl-2-butanone (2c) in 66% yield, whereas enol silyl ether 1d and HFA afforded 3-[bis(trifluoromethyl)hydroxymethyl]-3-methyl-2-butanone (2d) in 58% yield exclusively.

In the reaction of HFA with 4-tert-butyl-1-trimethylsiloxycyclohexene (1j) were formed both of the two possible stereoisomers of the aldol product, i.e., cis- and trans-2-[bis(trifluoromethyl)hydroxymethyl]-4-tert-butylcyclohexanone (2j), in the ratio of 95:5. The ^{19}F NMR spectrum of the reaction mixture showed two quartets (J = 10.0 Hz) at 2.14 and 6.53 ppm due to the former and additional two quartets (J = 10.0 Hz) at 2.84 and 5.70 ppm due to the latter. The ^{1}H NMR spectrum of the cis-isomer [6] revealed that the 2-hydrogen is coupled with the adjacent two ring hydrogens with coupling constants of 10.5 and 4.2 Hz. The stereochemical result observed in this reaction cannot necessarily reflect the original stereochemical course of the reaction, because the trans-isomer can be isomerized to the thermodynamically more stable cis-isomer during the reaction.

Reaction of HFA aldols (2) with methyl chlorosulfite

α-Bis(trifluoromethyl)hydroxymethyl carbonyl compounds thus obtained are known to have much resistance to dehydration and, in fact, it was extremely difficult to convert them into the corresponding α,β-unsaturated carbonyl compounds by conventional methods [7]. Out of a variety of dehydration agents examined in the present study, methyl chlorosulfite was found to be the most

effective; the treatment of the HFA aldols with methyl chlorosulfite and pyridine below room temperature gave α-hexafluoroisopropylidene carbonyl compounds in good to excellent yields, as shown in Table 2.



2 3

e: R^1 = Me, R^2 = Et

f: R^1 = H, R^2 = Ph

g: R^1 = Me, R^2 = Ph

h: R^1 = R^2 = $-(CH_2)_4-$

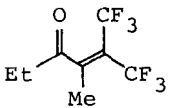
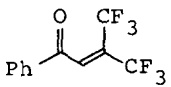
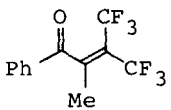
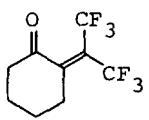
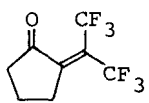
i: R^1 = R^2 = $-(CH_2)_3-$

Probably this reaction involves the formation of methyl sulfites from HFA aldols and methyl chlorosulfite, followed by stepwise or synchronous decomposition of the sulfites to the products. When a base such as pyridine was absent, the reaction did not occur, resulting in the recovery of the starting aldol. It seems that the hydrogen to be eliminated in the reaction must be activated in the molecule. α,α-Bis(trifluoromethyl) alcohols such as 1,1-bis(trifluoromethyl)-2-phenylethanol, in which the hydrogen to be eliminated is not activated, could not be dehydrated under the above-described conditions. Unfortunately, the HFA aldols derived from aldehydes did not undergo dehydration, in spite of a hydrogen activated by a carbonyl function being present in the molecule. The combined sequence described herein, i.e., aldolization of HFA using enol silyl ethers and successive dehydration of the aldols, provides a useful method for the regiospecific preparation of α-hexafluoroisopropylidene ketones.

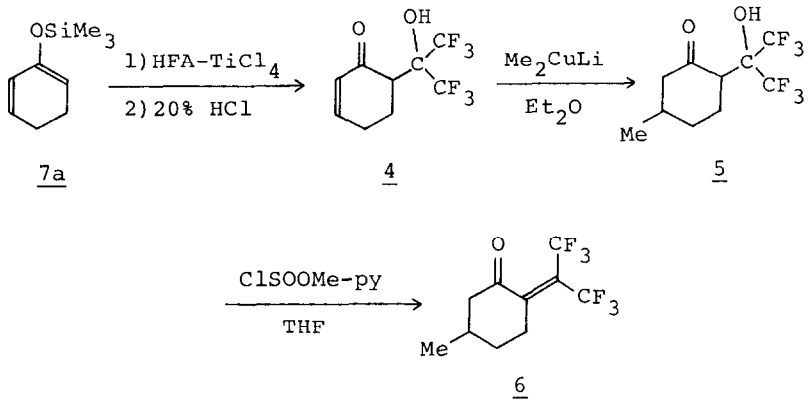
Hexafluorinated pulegone (6) was synthesized as an application of this combined sequence. Thus, HFA was treated with 2-trimethylsiloxy-1,3-cyclohexadiene (7a) in the presence of titanium tetrachloride, followed by hydrolysis with 20% HCl, to give 6-[bis(trifluoromethyl)hydroxymethyl]-2-cyclohexenone (4)

TABLE 2

α-Hexafluoroisopropylidene ketones (3) from HFA aldols (2)

HFA aldol	Product		Yield of 3 %	Bp °C/mmHg	n_D (°C)
2e		(3e)	62	79-81/96	1.3619 (19.7)
2f		(3f)	85	87-90/15	1.4461 (19.7)
2g		(3g)	79	63-65/2	1.4483 (20.0)
2h		(3h)	77	83-85/27	36.5-37.5[a)]
2i		(3i)	84	80-83/16	1.3906 (24.0)

a) Melting point.



7a 4 5

6

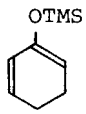
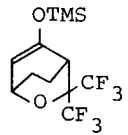
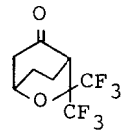
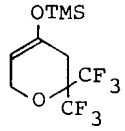
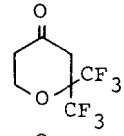
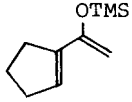
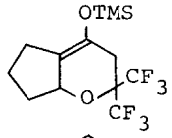
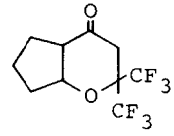
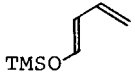
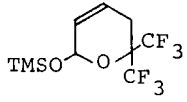
in 70% isolated yield. This HFA aldol was allowed to react with 2 equiv of lithium dimethylcuprate in diethyl ether to convert it into 2-[bis(trifluoromethyl)hydroxymethyl]-5-methylcyclohexanone (5), whose isolated yield was 90%. The treatment of the methylated aldol 5 with methyl chlorosulfite and pyridine produced the fluorinated pulegone, 2-hexafluoroisopropylidene-5-methylcyclohexanone (6), in 76% isolated yield.

Reaction of HFA with dienol silyl ethers (7)

During the course of the studies on the preparation of fluorinated pulegone described above, it was noticed that in the reaction of HFA with dienol silyl ether 7a, 1,4-cycloadduct (8a) could be obtained in 35% yield, in addition to the corresponding aldol (4), from the reaction mixture before acidic treatment. The adduct 8a could be converted into the aldol 4 by the treatment with 20% HCl at 95°C. This finding prompted us to examine the reaction of HFA with a variety of dienol silyl ethers (7). The reactions were found to proceed even in the absence of a Lewis acid at -40 to -45°C, giving the corresponding 1,4-cycloadducts (8) as the sole product. The results are summarized in Table 3. In view of the extremely low reactivity of HFA toward ordinary dienes [8], it seems to be noted that HFA is highly reactive toward the dienol silyl ethers. It is also to be noted that all addition reactions occurred with regiospecificity; the

TABLE 3

Cycloaddition of HFA with dienol silyl ethers (7) [a]

Dienol silyl ether	Cycloadduct (8)	Yield of 8 [b] %	Hydrolyzed product (9)	Yield of 9 [b] %
 (7a)	 (8a)	84	 (9a)	90
 (7b)	 (8b)	64	 (9b)	91
 (7c)	 (8c)	90	 (9c)	87
 (7d)	 (8d)	91	—	—

a) TMS stands for the trimethylsilyl group.

b) Isolated yields. Each of the products showed only one peak on gas chromatography.

addition occurs in such a mode that is expected from directions of polarization of the carbonyl group in HFA and of the double bond in the dienol silyl ether. The cycloadducts (8) thus obtained were easily hydrolyzed with 10% HCl at room temperature to give bistrifluoromethylated tetrahydropyran-4-one derivatives (9), which otherwise are difficult to prepare.

EXPERIMENTAL

All boiling and melting points are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-400 infrared spectrometer. A Varian EM-390 spectrometer was used to measure ^{1}H and ^{19}F NMR spectra for solutions in CCl_4. Proton and fluorine chemical shifts are expressed in parts per million downfield from internal tetramethylsilane and from external trifluoroacetic acid, respectively. Mass (MS) spectra were taken on a Hitachi RMS-4 mass spectrometer at an ionization potential of 70 eV. Gas chromatographic analyses were performed with a Shimadzu GC-6A or a Jeolco JGC-20KT gas chromatograph.

All chemicals are of reagent grade and, if necessary, were distilled prior to use. Enol silyl ethers (1) and dienol silyl ethers (7) were prepared according to the reported methods [9].

General procedure for the reaction of HFA with enol silyl ethers (1)

Stannic chloride (35 mmol) was placed in a four-necked flask equipped with a mechanical stirrer, a condenser, a thermometer, and an inlet tube for HFA. The flask was cooled to -30°C, and to it was introduced HFA (30 mmol). After the introduction was complete, the inlet tube was replaced with a dropping funnel, through which an enol silyl ether (1) (40 mmol) was dropwise added to the mixture at such a rate that the temperature did not rise above -30°C. The reaction mixture was stirred at -30 to -35°C for several hours until the refluxing of HFA ceased. The mixture was warmed up to room temperature and the reaction was quenched with water. The resultant solution was

extracted with pentane. The extracts were washed with a saturated NaCl solution, dried over anhydrous sodium sulfate, and concentrated by use of a rotary evaporator. The residual oil was distilled under reduced pressure to give aldol (2). All boiling points listed in Table 1 are oven temperature on a Kugelrohr distillation apparatus.

2-[Bis(trifluoromethyl)hydroxymethyl]butanal (2a)

71% yield; IR (film) 3335, 2970, 2880, 1720, 1466, 1390, 1233, 1140, 1092, 1019, 959, 849, 780, 717 cm^{-1}; ^{1}H NMR δ 1.03 (t, J = 7.4 Hz, 3H), 1.93 (dq, J = 7.4 and 7.4 Hz, 2H), 2.74 (br t, J = 7.4 Hz, 1H), 4.88 (s, 1H), and 9.72 (br s, 1H); ^{19}F NMR δ 3.56 (q, J = 9.7 Hz, 3F) and 5.62 (q, J = 9.7 Hz, 3F); MS m/e (relative intensity) no parent to 238, 210 (67), 172 (57), 150 (14), 145 (26), 141 (100), 123 (46), 121 (24), 103 (70), 97 (30), 91 (21), 77 (28), 73 (39), 71 (50), 69 (82).

2-[Bis(trifluoromethyl)hydroxymethyl]-2-methylpropanal (2b)

72% yield; IR (KBr) 3280, 1710, 1273, 1210, 1122, 1033, 1010, 970, 944, 900, 820, 750, 717, 690 cm^{-1}; ^{1}H NMR δ 1.39 (s, 6H), 5.38 (br s, 1H), and 9.68 (s, 1H); ^{19}F NMR δ 7.9-8.1 (br s, 6F).

1-[Bis(trifluoromethyl)hydroxymethyl]-3-methyl-2-butanone (2c)

66% yield; IR (film) 3310, 2975, 1702, 1470, 1320, 1200, 1090, 1047, 1023, 965, 710, 700 cm^{-1}; ^{1}H NMR δ 1.16 (d, J = 7.0 Hz, 6H), 2.67 (sept, J = 7.0 Hz, 1H), 2.92 (s, 2H), and 6.70 (br s, 1H); ^{19}F NMR δ 2.27 (s, 6F); MS m/e (relative intensity) no parent to 252, 209 (83), 191 (9), 181 (21), 161 (19), 147 (5), 111 (6), 97 (12), 73 (7), 71 (100), 69 (25).

3-[Bis(trifluoromethyl)hydroxymethyl]-3-methyl-2-butanone (2d)

58% yield; IR (film) 3200, 2990, 1690, 1482, 1420, 1365, 1200, 1018, 965, 945, 892, 845, 765, 735, 717 cm^{-1}; ^{1}H NMR δ 1.47 (s, 6H), 2.31 (s, 3H), and 7.20 (s, 1H); ^{19}F NMR δ 8.72

(s, 6F); MS m/e (relative intensity) 252 (M^+, 1), 221 (15), 209 (48), 145 (20), 139 (23), 111 (13), 97 (35), 86 (17), 85 (22), 77 (13), 71 (73), 69 (100), 65 (12), 61 (27).

2-[Bis(trifluoromethyl)hydroxymethyl]-3-pentanone (2e)

74% yield; IR (film) 3300, 2975, 1700, 1460, 1240, 1170, 1100, 1072, 1021, 998, 958, 928, 712 cm^{-1}; ^1H NMR δ 1.10 (t, J = 7.0 Hz, 3H), 1.34 (dq, J = 7.0 and 1.4 Hz, 3H), 2.60 (q, J = 7.0 Hz, 2H), 3.15 (q, J = 7.0 Hz, 1H), and 6.34 (s, 1H); ^{19}F NMR δ 3.10 (q, J = 11.2 Hz, 3F) and 5.73 (dq, J = 11.2 and 1.4 Hz, 3F); MS m/e (relative intensity) no parent to 252, 223 (7), 175 (7), 147 (4), 125 (12), 97 (3), 69 (7), 57 (100).

α-[Bis(trifluoromethyl)hydroxymethyl]acetophenone (2f)

56% yield; IR (film) 3285, 3055, 2925, 1668, 1600, 1580, 1452, 1355, 1320, 1220, 1032, 1010, 965, 847, 752, 712, 680 cm^{-1}; ^1H NMR δ 3.45 (s, 2H), 6.8-7.1 (br s, 1H), and 7.3-8.2 (m, 5H); ^{19}F NMR δ 0.72 (s, 6F); MS m/e (relative intensity) 286 (M^+, 7), 268 (2), 147 (5), 120 (5), 105 (100), 77 (34), 69 (5).

α-[Bis(trifluoromethyl)hydroxymethyl]propiophenone (2g)

67% yield; IR (film) 3275, 3060, 2980, 1667, 1600, 1581, 1451, 1390, 1353, 1233, 1162, 1076, 1000, 980, 932, 761, 720, 700, 681 cm^{-1}; ^1H NMR δ 1.44 (dq, J = 7.0 and 2.0 Hz, 3H), 4.06 (q, J = 7.0 Hz, 1H), 6.76 (s, 1H), and 7.3-8.2 (m, 5H); ^{19}F NMR δ 3.38 (q, J = 11.0 Hz, 3F) and 5.51 (br q, J = 11.0 Hz, 3F); MS m/e (relative intensity) no parent to 300, 286 (2), 134 (3), 133 (2), 105 (100), 77 (32), 69 (3).

2-[Bis(trifluoromethyl)hydroxymethyl]cyclohexanone (2h)

72% yield; IR (film) 3280, 2950, 1700, 1450, 1232, 1148, 1084, 1044, 1020, 724, 715, 660 cm^{-1}; ^1H NMR δ 1.2-3.3 (m, 9H) and 6.91 (s, 1H); ^{19}F NMR δ 2.20 (q, J = 10.3 Hz, 3F) and 6.41 (q, J = 10.3 Hz, 3F); MS m/e (relative intensity) 264 (M^+, 19), 246 (3), 236 (7), 235 (9), 221 (4), 195 (11), 177 (4), 151 (4), 125 (8), 97 (28), 83 (10), 79 (9), 70 (8), 69 (26), 55 (100).

2-[Bis(trifluoromethyl)hydroxymethyl]cyclopentanone (2i)

83% yield; IR (film) 3400, 2967, 2880, 1725, 1450, 1407, 1320, 1235, 1140, 1072, 1040, 950, 890, 742, 720 cm^{-1}; ^{1}H NMR δ 1.3-3.0 (m, 7H) and 6.67 (s, 1H); ^{19}F NMR δ 0.87 (q, J = 9.4 Hz, 3F) and 6.67 (q, J = 9.4 Hz, 3F); MS m/e (relative intensity) 250 (M^{+}, 16), 190 (2), 181 (4), 153 (6), 135 (5), 125 (9), 115 (9), 83 (5), 69 (13), 60 (8), 57 (5), 55 (100).

2-[Bis(trifluoromethyl)hydroxymethyl]-4-tert-butylcyclohexanone (2j)

70% yield; IR (film) 3300, 2980, 1705, 1455, 1372, 1230, 1145, 1090, 1066, 1030, 995, 959, 939, 720 cm^{-1}; ^{1}H NMR δ 1.1-2.8 (m, 7H), 3.15 (dd, J = 10.5 and 4.2 Hz, 1H), and 6.92 (s, 1H) for cis-isomer; ^{19}F NMR δ 2.14 (q, J = 10.0 Hz, 3F) and 6.53 (q, J = 10.0 Hz, 3F) for cis-isomer, 2.84 (q, J = 10.0 Hz, 3F) and 5.70 (q, J = 10.0 Hz, 3F) for trans-isomer.

General procedure for the dehydration of HFA aldols (2) using methyl chlorosulfite

To a solution of an HFA aldol (10 mmol) and pyridine (40 mmol) in anhydrous THF, cooled to -5 to -10°C by immersing in an ice-salt bath, was added dropwise methyl chlorosulfite (80 mmol). This mixture was stirred below room temperature for 12 h and, thereafter, additional pyridine (40 mmol) and methyl chlorosulfite (80 mmol) were introduced to the reaction mixture at -5 to -10°C. This addition was repeated twice every twelve hours. The reaction mixture was then poured into water and the resultant solution was extracted with pentane. The extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was distilled by use of a Kugelrohr apparatus to afford α-hexafluoroisopropylidene ketone (3).

2-Hexafluoroisopropylidene-3-pentanone (3e)

62% yield; IR (film) 2980, 1720, 1660, 1450, 1416, 1340, 1260, 1220, 1155, 1080, 1010, 952, 800, 743, 708 cm^{-1}; ^{1}H NMR δ 1.15 (t, J = 7.4 Hz, 3H), 2.1-2.4 (m, 3H), and 2.57 (q, J = 7.4 Hz, 2H); ^{19}F NMR δ 18.4-18.9 (m, 3F) and 19.1-19.6 (m, 3F); MS m/e (relative intensity) 234 (M^+, 18), 215 (100), 177 (69), 157 (43), 137 (15), 113 (15), 89 (9), 77 (8), 75 (8), 69 (28).

α-Hexafluoroisopropylideneacetophenone (3f)

85% yield; IR (film) 3070, 3025, 1680, 1600, 1580, 1452, 1382, 1320, 1220, 1042, 1022, 980, 932, 901, 784, 756, 722, 687, 674 cm^{-1}; ^{1}H NMR δ 7.3-7.9 (m, 6H); ^{19}F NMR δ 14.1 (q, J = 6.7 Hz, 3F) and 18.6 (q, J = 6.7 Hz, 3F); MS m/e (relative intensity) 268 (M^+, 42), 249 (6), 201 (5), 151 (5), 105 (100), 79 (7), 77 (38), 75 (7), 69 (8), 57 (11).

α-Hexafluoroisopropylidenepropiophenone (3g)

79% yield; IR (film) 3065, 2935, 1683, 1599, 1581, 1452, 1346, 1326, 1254, 1217, 1157, 1126, 1096, 1034, 950, 738, 718, 699, 682 cm^{-1}; ^{1}H NMR δ 2.2-2.3 (m, 3H) and 7.3-8.0 (m, 5H); ^{19}F NMR δ 19.7-20.2 (m, 3F) and 20.5-21.0 (m, 3F); MS m/e (relative intensity) 282 (M^+, 8), 263 (2), 215 (2), 105 (100), 77 (36), 69 (3), 57 (3).

2-Hexafluoroisopropylidenecyclohexanone (3h)

77% yield; IR (Nujol) 1710, 1670, 1412, 1277, 1250, 1210, 1136, 1110, 1080, 972, 912, 833, 738, 714, 690 cm^{-1}; ^{1}H NMR δ 1.8-2.2 (m, 4H) and 2.5-3.0 (m, 4H); ^{19}F NMR δ 20.3 (q, J = 8.6 Hz, 3F) and 21.3 (q, J = 8.6 Hz, 3F).

2-Hexafluoroisopropylidenecyclopentanone (3i)

84% yield; IR (film) 2950, 2900, 1745, 1653, 1408, 1335, 1247, 1218, 1160, 1070, 1016, 953, 919, 879, 817, 792, 742, 702 cm^{-1}; ^{1}H NMR δ 1.9-2.3 (m, 2H), 2.3-2.6 (m, 2H), and 2.9-3.2 (m, 2H); ^{19}F NMR δ 19.4 (q, J = 9.5 Hz, 3F) and 20.8 (dq, J = 9.5 and 1.4 Hz, 3F); MS m/e (relative intensity) 232 (M^+, 29), 204 (15), 176 (42), 171 (16), 163 (15), 79 (10), 69 (17), 55 (100).

Preparation of hexafluorinated pulegone (6)

To a solution of titanium tetrachloride (35 mmol) and HFA (30 mmol) in THF (20 ml) was added slowly 1-trimethylsiloxy-1,3-cyclohexadiene (25 mmol) at -45°C. This mixture was stirred at -40 to -45°C for several hours and then water was added to it. The resulting solution was extracted with ether and the extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The residual oil was dissolved in a solution of 20% HCl (20 ml) and dioxane (20 ml). After being stirred at 95°C for 24 h, the mixture was poured into water, followed by extraction with ether. The ethereal extracts were dried, filtered, and concentrated in vacuum. The residual oil was distilled to give 6-[bis(trifluoromethyl)hydroxymethyl]-2-cyclohexenone (4) in 70% yield: bp 76-78°C (4 mmHg); mp 55.0-56.0°C; IR (KBr) 3150, 2950, 1648, 1460, 1415, 1397, 1314, 1133, 1082, 991, 940, 921, 719 cm^{-1}; ^{1}H NMR δ 1.9-3.2 (m, 5H), 6.07 (d, J = 10.2 Hz, 1H), 7.0-7.3 (m, 1H), and 8.85 (s, 1H); ^{19}F NMR δ 2.74 (q, J = 9.6 Hz, 3F) and 7.02 (q, J = 9.6 Hz, 3F). To a solution of lithium dimethylcuprate (35 mmol) in anhydrous ether (15 ml) was added a solution of aldol 4 (10 mmol) in ether (5 ml) at -50°C. This mixture was stirred at the same temperature for 20 min and then warmed up to room temperature. After being stirred at room temperature for 40 min, the reaction mixture was acidified with a saturated solution of ammonium chloride, followed by treatment with sodium sulfite. This solution was extracted with ether and the extracts were dried, filtered, and concentrated. Distillation of the residual oil gave 2-[bis(trifluoromethyl)hydroxymethyl]-5-methylcyclohexanone (5) in 90% yield: bp 83-86°C (4 mmHg); IR (film) 3290, 2960, 1700, 1457, 1392, 1321, 1261, 1210, 1147, 1103, 1082, 1045, 1017, 1005, 938, 873, 742, 735 cm^{-1}; ^{1}H NMR δ 0.7-3.0 (m, 8H), 1.08 (d, J = 5.4 Hz, 3H), and 6.96 (s, 1H); ^{19}F NMR δ 2.32 (q, J = 10.3 Hz, 3F) and 6.52 (q, J = 10.3 Hz, 3F). By the treatment of this aldol (5) with methyl chlorosulfite as described above, hexafluorinated pulegone, i.e., 2-hexafluoroisopropylidene-5-methylcyclohexanone (6) was obtained in 76% yield: bp 86-89°C (16 mmHg); IR (film) 2960, 1720, 1655, 1452, 1347, 1321, 1270, 1206, 1082, 1056, 1024, 957, 902, 887, 733, 709 cm^{-1}; ^{1}H NMR δ 0.7-3.3 (m, 7H) and 1.34 (d, J = 6.0 Hz, 3H); ^{19}F NMR δ 20.2 (q, J = 8.5 Hz, 3F) and 21.3 (q, J = 8.5 Hz,

3F); MS m/e (relative intensity) 260 (M^+, 11), 245 (3), 232 (18), 217 (9), 176 (9), 163 (13), 121 (5), 109 (8), 95 (8), 81 (7), 73 (6), 71 (9), 69 (100), 65 (6).

General procedure for the reaction of HFA with dienol silyl ethers (7)

Into a dienol silyl ether (20 mmol), cooled to -40 to -45°C, was introduced HFA (30 mmol) under a nitrogen atmosphere. The mixture was kept at this temperature with stirring for 2 h and was distilled under reduced pressure to give cycloadduct (8) in quantitative yield. The treatment of this adduct with 10% HCl at room temperature afforded 2,2-bis(trifluoromethyl)tetrahydropyran-4-one derivative (9).

3,3-Bis(trifluoromethyl)-2-oxabicyclo[2.2.2]octan-5-one (9a)

76% yield; bp 67-70°C (4 mmHg); IR (film) 2950, 1748, 1452, 1400, 1290, 1222, 1144, 1120, 1103, 1052, 1014, 980, 958, 912, 876, 827, 718 cm^{-1}; ^1H NMR δ 1.6-2.6 (m, 5H), 2.7-3.0 (m, 2H), and 4.5-4.7 (m, 1H); ^{19}F NMR δ 3.43 (q, J = 11.4 Hz, 3F) and 6.47 (q, J = 11.4 Hz, 3F); MS m/e (relative intensity) 262 (M^+, 32), 234 (8), 220 (16), 203 (5), 187 (6), 172 (7), 171 (9), 151 (11), 147 (21), 131 (15), 103 (17), 97 (13), 73 (14), 69 (29), 68 (40), 57 (11), 55 (100).

2,2-Bis(trifluoromethyl)tetrahydropyran-4-one (9b)

59% yield; bp 86-89°C (46 mmHg); IR (film) 2930, 1748, 1425, 1400, 1337, 1278, 1210, 1149, 1129, 1086, 1067, 1003, 962, 953, 872, 848, 714 cm^{-1}; ^1H NMR δ 2.57 (t, J = 6.0 Hz, 2H), 2.83 (s, 2H), and 4.33 (t, J = 6.0 Hz, 2H); ^{19}F NMR δ -0.71 (s, 6F).

3,3-Bis(trifluoromethyl)-2-oxabicyclo[4.3.0]nonan-5-one (9c)

79% yield; bp 93-97°C (14 mmHg); IR (film) 2970, 2880, 1725, 1432, 1323, 1205, 1093, 1058, 1037, 1012, 992, 944, 929, 719, 701 cm^{-1}; ^1H NMR δ 1.5-2.9 (m, 7H), 2.77 (s, 2H), and 4.7-5.0 (m, 1H); ^{19}F NMR δ 0.27 (q, J = 9.4 Hz, 3F) and 3.18 (q, J = 9.4

TABLE 4

Molecular formulae and elemental analysis data of products

Compd[a]	Molecular formula	Calcd (%)			Found (%)		
		C	H	F	C	H	F
2a	$C_7H_8F_6O_2$	35.31	3.39	47.87	35.61	3.68	47.26
2b	$C_7H_8F_6O_2$	35.31	3.39	47.87	35.75	3.54	47.53
2c	$C_8H_{10}F_6O_2$	38.11	4.00	45.20	38.34	4.08	45.31
2d	$C_8H_{10}F_6O_2$	38.11	4.00	45.20	38.51	4.27	44.45
2e	$C_8H_{10}F_6O_2$	38.11	4.00	45.20	38.02	3.89	45.02
2f	$C_{11}H_8F_6O_2$	46.17	2.82	39.83	46.41	3.03	39.44
2g	$C_{12}H_{10}F_6O_2$	48.01	3.36	37.97	48.35	3.58	37.96
2h	$C_9H_{10}F_6O_2$	40.92	3.82	43.15	41.40	3.73	42.84
2i	$C_8H_8F_6O_2$	38.41	3.22	45.57	38.63	3.48	45.15
3e	$C_8H_8F_6O$	41.04	3.44	48.69	40.79	3.28	48.21
3f	$C_{11}H_6F_6O$	49.27	2.25	42.51	49.01	2.33	42.74
3g	$C_{12}H_8F_6O$	51.08	2.86	40.39	51.44	2.99	40.46
3h[b]	$C_9H_8F_6O$	43.91	3.28	46.31	44.28	3.02	45.87
3i	$C_8H_6F_6O$	41.39	2.61	49.11	41.56	2.81	48.63
6	$C_{10}H_{10}F_6O$	46.16	3.87	43.81	46.48	4.09	43.27
9a	$C_9H_8F_6O_2$	41.23	3.08	43.38	41.01	3.02	42.93
9b	$C_7H_6F_6O_2$	35.61	2.56	48.26	35.99	2.87	47.45
9c	$C_{10}H_{10}F_6O_2$	43.49	3.65	41.27	43.31	3.68	41.38

a) All new compounds, except for 3h.

b) See, J. Fluorine Chem., 12, 101 (1978).

Hz, 3F); MS m/e (relative intensity) 276 (M^+, 6), 248 (7), 235 (30), 139 (4), 95 (13), 84 (10), 83 (10), 69 (19), 68 (100), 67 (66), 57 (13).

5,5-Bis(trifluoromethyl)-3-trimethylsiloxy-4-oxacyclohexene (8d)

91% yield; bp 105-107°C (66 mmHg); IR (film) 2970, 2900, 1644, 1446, 1407, 1354, 1302, 1256, 1214, 1140, 1056, 1014, 958, 886, 869, 848, 757, 704 cm^{-1}; ^1H NMR δ 0.20 (s, 9H), 2.4-2.6 (m, 2H), 5.54 (br s, 1H), and 5.84 (br s, 2H); ^{19}F NMR δ 1.62 (s, 6F); MS m/e (relative intensity) 308 (M^+, 16), 293 (31), 197 (5), 169 (14), 151 (7), 129 (6), 121 (12), 101 (5), 97 (6), 77 (38), 75 (17), 73 (100), 69 (15).

Analytical

The elemental analyses of 2a-i, 3e-i, 6, and 9a-c gave satisfactory results, which are listed in Table 4.

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REFERENCES

1 B.S. Farah, E.E. Gilbert, and J.P. Sibilia, J. Org. Chem., 30 (1965) 998; B.S. Farah, E.E. Gilbert, M. Litt, J.A. Otto, and J.P. Sibilia, ibid., 30 (1965) 1003; W.A. Sheppard, J. Am. Chem. Soc., 87 (1965) 2410; W.A. Sheppard, J. Org. Chem., 33 (1968) 3297; J.J. Murray, ibid., 33 (1968) 3306.

2 V.A. Pattison, J. Org. Chem., 34 (1969) 3650; V.A. Pattison, ibid., 35 (1970) 2096.

3 C.G. Krespan and W.J. Middleton, Fluorine Chem. Rev., 1 (1967) 145; M. Hudlicky, Chemistry of Organic Fluorine Compounds,

2nd ed., John Wiley, New York, N.Y., 1976; R.E. Banks and M.G. Barlow, Fluorocarbon and Related Chemistry, Vol. I, The Chemical Society, London, 1971; Vol. II, The Chemical Society, London, 1974; R.D. Chambers, Fluorine in Organic Chemistry, John Wiley, New York, N.Y., 1973.

4 C.M. Langkammerer, Chem. Abstr., 76 (1972) 98556c.

5 The Lewis acid-catalyzed reactions of enol silyl ethers with fluorine-free aldehydes and ketones have appeared in the literature; T. Mukaiyama, K. Banno, and K. Narasaka, J. Am. Chem. Soc., 96 (1974) 7503.

6 The ^{1}H NMR analysis of the trans-isomer was not done because all attempts to isolate this isomer in a pure form failed.

7 The attempts made for dehydrating HFA aldols include the treatment of HFA aldols with strong acids, the reaction of their tosylates with bases, the treatment of HFA aldols with thionyl chloride and pyridine, and the thermal decomposition of their xanthates. They were all unsuccessful, resulting in recovery of the starting aldol or in polymerization.

8 W.J. Linn, J. Org. Chem., 29 (1964) 3111.

9 H.O. House, L.J. Czuba, M. Gall, and H.D. Olmstead, J. Org. Chem., 34 (1969) 2324; G.M. Rubottom and J.M. Gruber, ibid., 42 (1977) 1051, and references cited therein.