1*H*,1*H*-Perfluoroalkylation of Enol Silyl Ethers with (1*H*,1*H*-Perfluoroalkyl)phenyliodonium Triflates. A New Method for the Preparation of *β*- and *δ*-Trifluoromethyl Carbonyl Compounds and Their Higher Perfluoroalkyl Homologues[1)]

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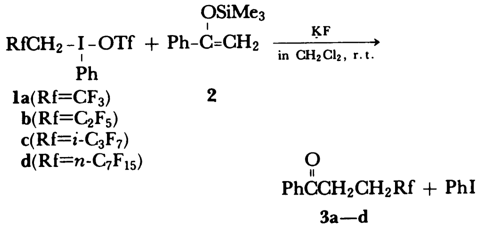
Synopsis. The reaction of enol trimethylsilyl ethers of carbonyl compounds with (1*H*,1*H*-perfluoroalkyl)phenyliodonium triflates was promoted successfully by potassium fluoride in dichloromethane at room temperature, giving *β*-perfluoroalkyl (Rf; CF_3, C_2F_5, *i*-C_3F_7, *n*-C_7F_{15}) carbonyl compounds in good yields. An enol silyl ether of an *α*,*β*-unsaturated carbonyl compound gave a *δ*-Rf-*α*,*β*-unsaturated carbonyl compound selectively.

Much attention is being denoted to polyfluoroalkyl groups from the viewpoint of the development of new chemicals or materials having characteristic properties, because they have high electronegativity, stability, lipophilicity, strong surface intension- and refractive index-decreasing effects, and so on.[2)] Among them, trifluoromethyl (CF_3) or 2,2,2-trifluoroethyl (CF_3CH_2) group in particular has been of increasing importance in the development of new medicines or agricultural chemicals owing to its unique effects on the bioactivity.[2,3)] However, the introduction of the fluoroalkyl groups into the desired sites of the organic molecules was troublesome.[4)]

Recently we have developed (1*H*,1*H*-perfluoroalkyl)phenyliodonium triflates **1** (FMITS) as the most reactive reagents for the source of $RfCH_2$ cations.[5,6)] In this paper, we described potassium fluoride-promoted 1*H*,1*H*-perfluoroalkylation of enol silyl ethers with FMITS under mild conditions, giving *β*- or *δ*-CF_3 carbonyl compounds or their higher perfluoroalkyl (Rf) homologues in good yields.[7)]

Results and Discussion

We examined the reaction of **1** with *α*-(trimethylsiloxy)styrene (**2**), and the results are shown in Table 1. It was found that **1a** smoothly reacted with an equimolar amount of **2** in dichloromethane at room temperature in the presence of a large excess of potassium fluoride (KF) as an additive to give phenyl 3,3,3-trifluoropropyl ketone (**3a**) in a high yield along with an almost quantitative yield of iodobenzene (Run 1).



$$RfCH_2-\underset{\substack{|\\ Ph}}{I}-OTf + Ph-\overset{\substack{OSiMe_3\\ |}}{C}=CH_2 \xrightarrow[\text{in } CH_2Cl_2,\ r.t.]{KF} Ph\overset{\substack{O\\ \|}}{C}CH_2CH_2Rf + PhI$$

1a($Rf=CF_3$)
b($Rf=C_2F_5$)
c($Rf=i\text{-}C_3F_7$)
d($Rf=n\text{-}C_7F_{15}$)
2
3a—d

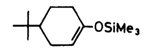
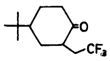
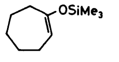
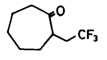
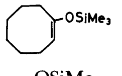
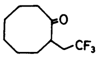
The product **3a** was also contaminated with the starting acetophenone, the amount of which increased as the yield of **3a** decreased. **3a** was easily purified by chromatography on silica gel. When **1a** was treated with **2** without an additive, the yield of **3a** was low (Run 10). When using 2,4,6-collidine, *N*-(2,2,2-trifluoroethyl)pyridinium triflate was obtained in a 60% yield along with **3a** (30%) (Run 9). Sodium bicarbonate as a solid base afforded a trace of **3a** (Run 7). Since the treatment of an enol trimethylsilyl ether with methyllithium in tetrahydrofuran (THF) has been known as the effective method for the generation of an enolate anion,[8,9)] the results of Run 8 indicated that the direct reaction of **1a** with an enolate anion of acetophenone in THF resulted in the low yield of **3a**. One of the causes may be that the enolate anion competitively abstracted a proton from the acidic CH_2 protons of **1a**, since triflates **1** were found to be easily deprotonated with such a base as sodium hydride.[5b)] KF is insoluble in dichloromethane and the reaction of **1a** with **2** proceeded slightly without an additive. Moreover, it is reasonable that electron-deficient iodine atom-containing **1** forms a complex with electron-rich double bond-containing **2**. From the above facts and discussion, it may be suggested that solid KF successfully promoted

Table 1. 2,2,2-Trifluoroethylation of **2** with **1a**

Run	Additive(equiv)[a)]	Solv.	Temp	Time/h	Yield/%[b)]/3a
1	KF(5.2)	CH_2Cl_2	R.t.	1.5	87
2	KF(2)	CH_2Cl_2	R.t.	3	40
3	KF(5.5)	$CHCl_3$	R.t.	4	45
4	KF(5.5)	Et_2O	R.t.	4	39
5	KF(5.5)	THF	R.t.	5	38
6	CsF(3)	CH_2Cl_2	R.t.	11[e)]	23
7	$NaHCO_3$(1.2)	CH_2Cl_2	R.t.	5	<7
8[c)]	MeLi (1)	THF	0 °C→R.t.	1	27
9	2,4,6-Collidine(1)	CH_2Cl_2	R.t.	1	30[d)]
10	None	CH_2Cl_2	R.t.	5	16

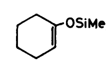
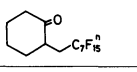
a) KF used was spray-dried KF.[10)] The values in parentheses mean the molar equivalency of the additive to **1a**. An equimolar amount of **2** to **1a** was used in all the runs . b) Isolated Yields except for Run 6 (GC Yield). c) **1a** was added after **2** was allowed to react with MeLi at 0°C in THF for 15 min. d) *N*-(2,2,2-Trifluoroethyl)pyridinium triflate as another product was obtained in a 60% yield. e) Overnight.

Table 2. 2,2,2-Trifluoroethylation of Enol Silyl Ethers with **1a**

Run[a]	Silyl ether	Product		Yield/%[b]
1	$Ph\overset{OSiMe_3}{C}{=}CHCH_3$	$Ph\overset{O}{\overset{\|}{C}}\underset{CH_2CF_3}{CH}CH_3$	(**4**)	55
2	$PhCH{=}CH\overset{OSiMe_3}{C}{=}CH_2$	$PhCH{=}CH\overset{O}{\overset{\|}{C}}CH_2CH_2CF_3$	(**5**)[c]	75
3	$Ph\overset{OSiMe_3}{C}{=}CHCH{=}CH_2$	$Ph\overset{O}{\overset{\|}{C}}CH{=}CHCH_2CH_2CF_3$	(**6**)[d]	42
		$Ph\overset{O}{\overset{\|}{C}}\underset{CH_2CF_3}{CH}CH{=}CH_2$	(**7**)	0.8
4			(**8**)	53
5			(**9**)	49
6			(**10**)	71
7	$n\text{-}C_6H_{13}\overset{OSiMe_3}{C}{=}CH_2$	$n\text{-}C_6H_{13}\overset{O}{\overset{\|}{C}}CH_2CH_2CF_3$	(**11**)	80
8	$n\text{-}C_6H_{13}CH{=}\overset{OSiMe_3}{C}OCH_3$	$n\text{-}C_6H_{13}\overset{CH_2CF_3}{CH}COOCH_3$	(**12**)	76
9	$PhCH{=}\overset{OSiMe_3}{C}OCH_2CH_3$	$Ph\overset{CH_2CF_3}{CH}COOCH_2CH_3$	(**13**)	92

a) The reaction conditions were the same as for Run 1 in Table 1. b) Isolated Yields except for Run 8 (GC yield). c) Trans-isomer. d) The configuration around the double bond was not determined.

Table 3. 1*H*,1*H*-Perfluoroalkylation of Enol Silyl Ethers with **1b**—**d**

Run[a]	Ether	**1**	Temp	Time/h	Product	Yield/%[b]
1	**2**	**1b**	R.t.	4	**3b**	67
2	**2**	**1b**	Reflux	3	**3b**	87
3	**2**	**1c**	R.t.	8	**3c**	18
4	**2**	**1c**	Reflux	7	**3c**	32
5	**2**	**1d**	R.t.	12	**3d**	50
6	**2**	**1d**	Reflux	10	**3d**	54
7	$n\text{-}C_6H_{13}\overset{OSiMe_3}{C}{=}CH_2$	**1b**	R.t.	4	$n\text{-}C_6H_{13}\overset{O}{\overset{\|}{C}}CH_2CH_2C_2F_5$ (**14**)	63
8	$n\text{-}C_6H_{13}\overset{OSiMe_3}{C}{=}CH_2$	**1d**	R.t.	8	$n\text{-}C_6H_{13}\overset{O}{\overset{\|}{C}}CH_2CH_2C_7F_{15}{}^{n}$ (**15**)	45
9		**1d**	R.t.	7	 (**16**)	21

a) In all the runs, 5—5.5 equimolar amounts of spray-dried KF and dichloromethane as a solvent were used. b) Isolated yields.

the reaction of the complex of **1** with **2** giving **3**, by attacking the silyl site of the enol silyl ether moiety of the complex under the conditions of Run 1. The use of cesium fluoride (CsF) which is expected to have better solubility than KF resulted in the low yield of **3a** (Run 6). This may be explained by the high reactivity of CsF, compared to KF, which can disturb the triple-molecular reaction.

This method was successfully applied to the 2,2,2-trifluoroethylation of a variety of carbonyl compounds (Table 2). An enol trimethylsilyl ether of an α,β-unsaturated ketone underwent selective γ-trifluoroethylation (Run 3). Only a trace of the α-trifluoroethylated product was obtained. Similarly, keten trimethylsilyl acetals derived from esters gave α-CF_3CH_2 esters in good yields.

We also examined the reaction of **1** having a long chain of Rf group with the enol silyl ethers in the presence of KF (Table 3). Since the reactivity decreased as the carbon number of Rf group increased, the high reaction temperature or long reaction time was needed.

Since a variety of the enol silyl ethers can easily be prepared by the advanced synthetic methods,[9] our technique with FMITS reagents is expected to be widely utilized for the preparation of the β- and δ-Rf carbonyl compounds.

Experimental

General. Melting points were uncorrected. ^1H NMR spectra were recorded with a Varian XL-100 NMR spectrometer, a Varian EM 390 NMR spectrometer, or a Bruker AM-400 NMR spectrometer with chloroform-*d* as a solvent and tetramethylsilane as an internal standard. ^{19}F NMR spectra were measured with a Varian XL-100 NMR spectrometer or a Hitachi R-20 B NMR spectrometer, and chloroform-*d* as a solvent. ^{19}F NMR chemical shifts were reported in ppm upfield from trichlorofluoromethane as an internal standard. IR spectra were measured on a Jasco A-202 diffraction grating infrared spectrometer. Mass spectra were recorded on a Hitachi RMU-6MG spectrometer at 70 eV and 100 °C.

Materials. FMITS reagents were prepared according to the method reported previously.[5] The enol silyl ethers were prepared by the usual methods.[9] Spray-dried KF[10] commercially available from Morita Kagaku Company, Japan, was dried under vacuum at 140 °C for 11 h before use.

***1H*,*1H*-Perfluoroalkylation of Enol Silyl Ethers with 1. General Procedure;** **1** (1 mmol) was added into a mixture of an enol silyl ether (1 mmol) and spray-dried KF (5—5.5 mmol) in 3 ml of dry dichloromethane under argon atmosphere and the mixture was stirred for 1.5 h at room temperature. After the filtration through the short column of silica gel, the resulting residue was purified by thin-layer chromatography on silica gel to give the Rf carbonyl compounds. **3a**: Mp 59—60 °C; ^{1}H NMR δ=2.20—2.80 (2H, m, CH_2), 3.10—3.35 (2H, m, CH_2), 7.30—7.70 (3H, m, *m*,*p*-PhH), 7.83—8.10 (2H, m, *o*-PhH); ^{19}F NMR 65.3 (t, *J*=11 Hz, CF_3); IR (KBr, cm^{-1}) 1690 (CO); MS 202 (M$^+$). Found: C, 59.46; H, 4.46%. Calcd for $C_{10}H_9F_3O$: C, 59.41; H, 4.49%. **3b**: Mp 67—68 °C; ^{1}H NMR δ=2.20—2.90 (2H, m, CH_2), 3.13—3.43 (2H, m, CH_2), 7.30—7.76 (3H, m, *m*,*p*-PhH), 7.83—8.13 (2H, m, *o*-PhH); ^{19}F NMR 85.9 (3F, s, CF_3), 117.0 (2F, t, *J*=16.9 Hz, CF_2); IR (KBr, cm^{-1}) 1690 (CO); MS 252 (M$^+$). Found: C, 52.12; H, 3.63%. Calcd for $C_{11}H_9F_5O$: C, 52.39; H, 3.60%. **3c**: Mp 28—29 °C; ^{1}H NMR δ=2.33—2.87 (2H, m, CH_2), 3.13—3.43 (2H, m, CH_2), 7.31—7.71 (3H, m, *m*,*p*-PhH), 7.80—8.10 (2H, m, *o*-PhH); ^{19}F NMR 76.5 (6F, d, *J*=7 Hz, CF_3), 184.1 (1F, m, CF); IR (KBr, cm^{-1}) 1690 (CO); MS 302 (M$^+$). Found: C, 47.59; H, 3.02%. Calcd for $C_{12}H_9F_7O$: C, 47.69; H, 3.00%. **3d**: Mp 80—81 °C; ^{1}H NMR δ=2.20—2.90 (2H, m, CH_2), 3.10—3.43 (2H, m, CH_2), 7.30—7.68 (3H, m, *m*,*p*-PhH), 7.80—8.13 (2H, m, *o*-PhH); ^{19}F NMR 81.5 (3F, t, *J*=10 Hz, CF_3), 114.6 (2F, m, CF_2), 122.4 (4F, m, CF_2), 123.3 (2F, m, CF_2), 123.8 (2F, m, CF_2), 126.7 (2F, m, CF_2); IR (KBr, cm^{-1}) 1690 (CO); MS 502 (M$^+$). Found: C, 38.03; H, 1.84%. Calcd for $C_{16}H_9F_{15}O$: C, 38.26; H, 1.81%. **4**: Oil; ^{1}H NMR δ=1.30 (3H, d, *J*=6 Hz, CH_3), 1.90—3.20 (2H, m, CH_2), 3.60—4.00 (1H, m, CH), 7.30—7.70 (3H, m, *m*,*p*-PhH), 7.85—8.10 (2H, m, *o*-PhH); ^{19}F NMR 64.5 (t, *J*=11 Hz, CF_3); IR (neat, cm^{-1}) 1690 (CO); MS 216 (M$^+$). Found: C, 61.27; H, 5.17%. Calcd for $C_{11}H_{11}F_3O$: C, 61.11; H, 5.13%. **5**: Bp 140 °C (bath temperature)/400 Pa, mp 48—49 °C; ^{1}H NMR δ=2.20—2.78 (2H, m, CH_2), 2.80—3.10 (2H, m, CH_2), 6.73 (1H, d, *J*=16.5 Hz, olefin proton), 7.30—7.73 (6H, m, PhH and olefin proton); ^{19}F NMR 66.8 (t, *J*=10 Hz, CF_3); IR (KBr, cm^{-1}) 1700 (CO); MS 228 (M$^+$). Found: C,62.86; H, 4.80%. Calcd for $C_{12}H_{11}F_3O$: C, 63.15; H, 4.86%. **6**: Mp 37 °C; ^{1}H NMR δ=2.20—2.80 (4H, m, CH_2), 6.80—7.03 (2H, m, olefin protons), 7.25—7.65 (3H, m, *m*,*p*-PhH), 7.80—8.05 (2H, m, *o*-PhH); ^{19}F NMR 66.0 (t, *J*=10 Hz, CF_3); IR (neat, cm^{-1}) 1675 (CO); MS 228 (M$^+$). Found: C, 62.91; H, 4.47%. Calcd for $C_{12}H_{11}F_3O$: C, 63.15; H, 4.86%. **7**: Oil; ^{1}H NMR δ=2.20—3.10 (2H, m, CH_2), 4.20—4.55 (1H, m, CH), 5.10—5.40 (2H, m, =CH_2), 5.60—6.10 (1H, m, olefin proton), 7.35—7.70 (3H, m, *m*,*p*-PhH), 7.83—8.06 (2H, m, *o*-PhH); ^{19}F NMR 64.0 (t, *J*=11 Hz, CF_3); MS 228 (M$^+$). **8**: Oil; ^{1}H NMR δ=0.90 (9H, s, *t*-Bu), 1.20—3.00 (9H, m); ^{19}F NMR 64.1 (t-d, *J*=10, 1.4 Hz, CF_3); IR (neat, cm^{-1}) 1720 (CO); MS 236 (M$^+$). Found: C, 60.74; H, 7.82%. Calcd for $C_{12}H_{19}F_3O$: C, 61.00; H, 8.11%. **9**: Oil; ^{1}H NMR δ=1.00—2.35 (10H, m), 2.35—3.16 (3H, m); ^{19}F NMR 64.1 (t, *J*=10 Hz, CF_3); IR (neat, cm^{-1}) 1710 (CO); MS 194 (M$^+$). Found: C, 55.46; H, 6.74%. Calcd for $C_9H_{13}F_3O$: C, 55.66; H, 6.75%. **10**: Oil; ^{1}H NMR δ=1.30—3.20 (m); ^{19}F NMR 64.9 (t, *J*=10 Hz, CF3); IR (neat, cm^{-1}) 1715 (CO); MS 208 (M$^+$). Found: C, 57.89; H, 7.03%. Calcd for $C_{10}H_{15}F_3O$: C, 57.68; H, 7.26%. **11**: Oil; ^{1}H NMR δ=0.78—1.06 (3H, m, CH_3), 1.13—1.83 (8H, m, CH_2), 2.23—2.80 (6H, m, CH_2); ^{19}F NMR 66.8 (t, *J*=9.9 Hz, CF_3); IR (neat, cm^{-1}) 1725 (CO); MS 210 (M$^+$). Found: C, 57.11; H, 8.14%. Calcd for $C_{10}H_{17}F_3O$: C, 57.13; H, 8.15%. **12**: Oil; ^{1}H NMR δ=0.75—1.00 (3H, m, CH_3), 1.10—1.80 (10H, m, CH_2), 1.95—2.80 (3H, m, CH_2CH), 3.70 (3H, s, OCH_3); ^{19}F NMR 65.3 (t, *J*=10 Hz, CF_3); IR (neat, cm^{-1}) 1740 (CO); MS 240 (M$^+$). Found: C, 55.24; H, 7.83%. Calcd for $C_{11}H_{19}F_3O_2$: C, 54.99; H, 7.94%. **13**: Bp 78 °C/400 Pa; ^{1}H NMR δ=1.20 (3H, t, *J*=6.6 Hz, CH_3), 2.10—3.50 (2H, m, CH_2), 3.80—4.00 (1H, m, CH), 4.16 (2H, q-d, *J*=6.6, 2.4 Hz, OCH_2), 7.33 (5H, s, Ph); ^{19}F NMR 65.3 (t, *J*=11 Hz, CF_3); IR (neat, cm^{-1}) 1740 (CO); MS 246 (M$^+$). Found: C, 58.23; H, 5.28%. Calcd for $C_{12}H_{13}F_3O_2$: C, 58.53; H, 5.02%. **14**: Oil; ^{1}H NMR δ=0.78—1.03 (3H, m, CH_3), 1.13—1.80 (8H, m, CH_2), 2.00—2.83 (6H, m, CH_2); ^{19}F NMR 85.9 (3F, s, CF_3), 117.8 (2F, t, *J*=17 Hz, CF_2); IR (neat, cm^{-1}) 1720 (CO); MS 260 (M$^+$). Found: C, 50.76; 6.64%. Calcd for $C_{11}H_{17}F_3O$: C, 50.77; H, 6.58%. **15**: Mp 43—44 °C; ^{1}H NMR δ=0.80—1.00 (3H, m, CH_3), 1.13—1.81 (8H, m, CH_2), 2.20—2.88 (6H, m, CH_2); ^{19}F NMR 81.0 (3F, t, *J*=10 Hz, CF_3), 113.6 (2F, m, CF_2), 121.5 (6F, m, CF_2), 123.0 (2F, m, CF_2), 125.6 (2F, m, CF_2); IR (KBr, cm^{-1}) 1720 (CO); MS 510 (M$^+$). Found: C, 37.60; H, 3.40%. Calcd for $C_{16}H_{17}F_{15}O$: C, 37.66; H, 3.36%. **16**: Oil; ^{1}H NMR δ=1.30—3.30 (m); ^{19}F NMR 81.2 (3F, m, CF_3), 111.5 (1F, A part of AB system, *J*=283 Hz, CF_2), 114.8 (1F, B part of AB system, *J*=283 Hz, CF_2), 122.4 (4F, m, CF_2), 123.2 (2F, m, CF_2), 124.0 (2F, m, CF_2), 126.6 (2F, m, CF_2); IR (neat, cm^{-1}) 1720 (CO); MS 480 (M$^+$). Found: C, 35.07; H, 2.37%. Calcd for $C_{14}H_{11}F_{15}O$: C, 35.01; H, 2.31%.

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