Generation and Chemical Fate of 2,2,2-Trifluoro-1-phenylsulfonylethyl Carbanion

Kenji Uneyama* and Makoto Momota
Department of Applied Chemistry, Faculty of Engineering, Okayama University, Okayama 700

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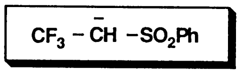
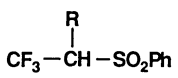
Synopsis. 2,2,2-Trifluoro-1-phenylsulfonylethyl carbanion generated by the action of LDA in THF-HMPA can be methylated and iodinated, where the tetraethylammonium cation plays an essential role for the stabilization of the carbanion.

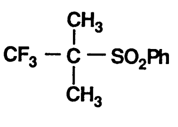
The development of reactions at the carbon atom bearing trifluoromethyl group is a subject of interest regarding the preparation of biologically active trifluoromethylated organic compounds.1) Carbanions bearing the trifluoromethyl group are too reactive to be alkylated and mostly undergo defluorination. Thus, both trifluoroethyl phenyl ether2) and sulfide2,3) undergo facile defluorination by the action of LDA. Ishikawa demonstrated an alkylation of dimethyl trifluoromethylmalonate in the presence of a large excess of cesium fluoride where the nucleophilic addition of fluoride anion to the difluoromethylenemalonate occurs, consequently, to maintain a moderate concentration of the carbanion.4) Recently, Fuchigami and Nakagawa showed an efficient alkylation of dimethyl trifluoromethylmalonate by the aid of electrogenerated base.5) The alkylation of 2,2,2-trifluoroethyl phenyl sulfide and the subsequent desulfurization of the alkylated products would provide us with a promising process for the preparation of the trifluoromethylated compounds. The phenylsulfonyl group stabilizes any carbanion more effectively than the phenylthio group; there would thus still be a chance to trap 2,2,2-trifluoro-1-phenylsulfonylethyl carbanion **1** by an electrophile. The present note describes a method regarding the alkylation conditions in which the tetraethylammonium cation in THF-HMPA plays an essential role.


$CF_3-\overset{-}{C}H-SO_2Ph$

1


$CF_3-\overset{R}{\overset{|}{C}}H-SO_2Ph$

2 ; R = H
3 ; R = CH_3
5 ; R = $CH_2CH=CH_2$
6 ; R = I


$CF_3-\underset{CH_3}{\overset{CH_3}{C}}-SO_2Ph$

4

Results and Discussion

Both the phenylsulfonyl and trifluoromethyl groups activate the methylene proton of **2** so that even weak bases such as triethylamine, sodium hydroxide, and sodium methoxide can abstract a proton from **2**. However, the carbanion **1** is so unstable that it instantaneously undergoes defluorination rather than nucleophilic substitution. At −70 °C, stronger bases are required for this purpose. At first, LDA was employed in a mixed solvent of THF and HMPA. The carbanion can be trapped with methyl iodide, which must be employed in large excess (tenfold). Under these conditions a mixture of mono- and dimethylated sulfones **3** and **4** was obtained. An increase in methyl iodide resulted in the formation of the dimethylated sulfone **4**, even by the use of one equivalent of LDA (Run 1). This result suggests the existence of the dianion of **2** as an intermediate in an LDA-THF-HMPA system.6) HMPA is a useful cosolvent for the present methylation. Otherwise, no methylation proceeds and defluorination exclusively occurs in THF where the lithium cation tightly associates with the electron lobe of the carbanion **1** and induces an intramolecular defluorination, as suggested.7) The reaction temperature is also critical. At a higher temperature the total yields of **3** and **4** become lower (Run 3), suggesting that defluorination is faster than methylation under the reaction conditions.

Then, the effect of a base and the counter cation of diisopropylamide was examined so as to realize an exclusive monomethylation. Hard bases, such as butyllithium and ethylmagnesium bromide, failed in methylation (Runs 5 and 6). Lithium hexamethyldisilazide, potassium *t*-butoxide, and sodium methoxide gave a mixture of **3** and **4**. In contrast, replacing the lithium of LDA with tetraethylammonium leads to exclusive monomethylation (Run 10). Fuchigami and Nonaka demonstrated that a pyrrolidone anion with tetraethylammonium promoted the alkylation of

Table 1. Methylation of 2,2,2-Trifluoroethyl Phenyl Sulfone 2a)

Run	Base (equiv)	Additive (equiv)	Temp °C	Yield/% 3	Yield/% 4	Recovery/% 2
1	LDA (1)	—	−70	38	10	40
2	LDA (3)	—	−70	0	69	0
3	LDA (3)	—	−30	11	1	0
4	LiN $(SiMe_3)_2$	—	−70	36	27	0
5	*n*-BuLi	—	−70	0	0	0
6	EtMgBr	—	−70	0	0	0
7	*t*-BuOK	—	−30	29	17	0
8	LDA (1)	TEAC(1)b)	−70	35	0	52
9	LDA (2)	TEAC(2)b)	−70	61	0	23
10	LDA (3)	TEAC(3)b)	−70	80	0	0

a) THF : HMPA=1 : 0.9 (v/v), CH_3I (10eq). b) Tetraethylammonium chloride.

Table 2. Reaction of **1** with Some Electrophiles[a]

Electrophile	Yield/%
CH_3I	80
CH_3CH_2I	0
$CH_2{=}CH{-}CH_2I$	12
$PhCH_2Br$	0
I_2	82

a) THF : HMPA=1 : 0.9 (v/v), LDA (3 equiv), TEAC (3 equiv), −70 °C.

dimethyl trifluoromethylmalonate.[5] It is well-known that tetraalkylammonium salts affect the electroreductive carbon-carbon bond formation in an aprotic solvent, although the effect has not yet been clearly explained.[8] The dianion of **2** would abstract a proton from tetraethylammonium leading to the monoanion **1**.

The monomethylation conditions were applied to the other electrophiles (Table 2). Allyl iodide gave the allylated sulfone in a poor yield (12%). Neither ethyl iodide nor benzyl bromide can trap the carbanion **1** under the present reaction conditions. Interestingly, the reaction of **1** with iodine provides the desired iodinated sulfone **6** as crystals in 82% yield, rather than the oxidative dimer of **1**.[9]

Experimental

Materials and Measurements: All of the solvents were distilled and stored under nitrogen. The ^{1}H NMR spectra were recorded at 500 MHz by using a Varian VXR-500 spectrometer with tetramethylsilane as the internal standard in $CDCl_3$. The IR spectra were recorded on a Hitachi 270-30 spectrometer.

1,1-Dimethyl-2,2,2-trifluoroethyl Phenyl Sulfone (4): To a solution of **2** (112 mg, 0.5 mmol) and methyl iodide (0.4 ml, 5 mmol) in THF (1 ml) and HMPA (0.9 ml) was added dropwise the LDA solution (1.5 mmol), and the mixture was stirred at −70 °C. After 10 min, the reaction mixture was neutralized with saturated NH_4Cl aq and 10% HCl aq, then extracted with ether/hexane (1 : 1). The extract was washed with water, dried over Na_2SO_4, and then evaporated in vacuo. The crude product was chromatographed on silica gel with hexane/AcOEt (10 : 1) as an eluent to yield 87 mg (69%) of **4** as a viscous oil; bp 125—130 °C/399 Pa; IR (neat) 1343, 1145 (SO_2) cm^{-1}; ^{1}H NMR δ=1.54 (s, 6H, CH_3), 7.55—8.00 (m, 5H, Ph). Found: C, 47.46; H, 4.47%. Calcd for $C_{10}H_{11}F_3O_2S$: C, 47.62; H, 4.40%.

1-Methyl-2,2,2-trifluoroethyl Phenyl Sulfone (3): To a suspension of tetraethylammonium chloride (260 mg, 1.6 mmol) in THF (1 ml) was added the LDA solution (1.6 mmol) at −70 °C; the mixture was then stirred at room temperature for 20 min. A supernatant liquid of the suspension was dropped into a solution of **2** (112 mg, 0.5 mmol) and methyl iodide (0.4 ml, 5 mmol) in THF (1 ml)-HMPA (0.9 ml) at −70 °C. After 10 min, the mixture was neutralized with saturated NH_4Cl aq and 10% HCl aq, and then extracted with ether/hexane (1 : 1). The extract was washed with water, dried over Na_2SO_4, and then evaporated in vacuo. The crude product was chromatographed on silica gel with hexane/AcOEt (10 : 1) as an eluent to yield 96 mg (80%) of **3** as a viscous oil; bp 125—130 °C/399 Pa; IR (neat) 1328, 1150 (SO_2) cm^{-1}; ^{1}H NMR δ=1.61 (d, J=7.4 Hz, 3H, CH_3), 3.75 (qq, J_{H-H}=7.4, J_{H-F}=8.5 Hz, 1H, CH), 7.55—8.00 (m, 5H, Ph). Found: C, 45.41; H, 3.69%. Calcd for $C_9H_9F_3O_2S$; C, 45.38; H, 3.81%.

1-Iodo-2,2,2-trifluoroethyl Phenyl Sulfone (6): Yield (82%) as colorless crystals; mp 72—74 °C; IR (Nujol) 1338, 1156 (SO_2) cm^{-1}; ^{1}H NMR δ=5.51 (q, J=7.2 Hz, 1H, CH), 7.45—8.05 (m, 5H, Ph). Found: C, 27.62; H, 1.75%. Calcd for $C_8H_6F_3IO_2S$: C, 27.45; H, 1.73%.

1-Trifluoromethyl-3-butenyl Phenyl Sulfone (5): Yield (12%) as a viscous oil, bp 95—100 °C/133 Pa; IR (neat) 1650 (C=C), 1330, 1150 (SO_2) cm^{-1}; ^{1}H NMR δ=2.62—3.10 (m, 2H, CH_2), 3.63—3.81 (m, 1H, CH). 5.13—5.26 (m, 2H, =CH_2), 5.75—6.00 (m, 1H, =CH), 7.56—8.00 (m, 5H, Ph). Found: C, 49.80; H, 4.11%. Calcd for $C_{11}H_{11}F_3O_2S$; C, 50.00; H, 4.20%.

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