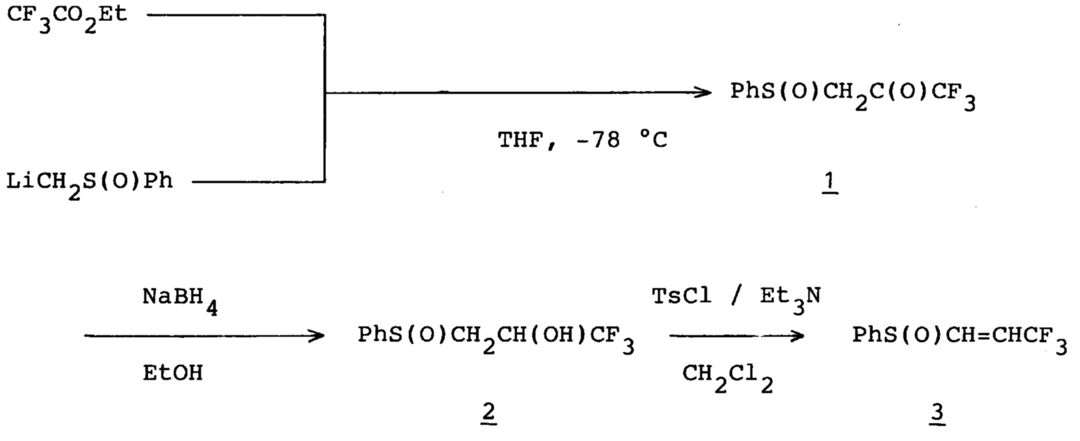
CHEMISTRY LETTERS, pp. 889-892, 1985.

(*E*)-3,3,3-TRIFLUORO-1-PROPENYL PHENYL SULFOXIDE. A USEFUL BUILDING BLOCK FOR TRIFLUOROMETHYLATED ORGANIC MOLECULES[1)]

Takashi YAMAZAKI and Nobuo ISHIKAWA*
Department of Chemical Technology, Tokyo Institute of Technology,
Meguro-ku, Tokyo 152

(*E*)-3,3,3-trifluoro-1-propenyl phenyl sulfoxide as the building block for the introduction of trifluoromethyl group was prepared from ethyl trifluoroacetate in three steps (72% yield) and high diastereoselectivity was observed for the Michael reaction of this compound with various enolate anions.

In recent years, organic molecules bearing a trifluoromethyl group have been drawing attention because of their possible biological activities.[2)] A number of synthetic methods for trifluoromethylated compounds, which involve direct trifluoromethylation[3)] and use of building blocks[4)] have been developed so far. On the other hand, sulfinyl groups are known to be powerful synthetic tools, for example, a) RR'CHS(O)R'' is the synthetic equivalent to the carbonyl compounds RR'C=O,[5)] b) sulfinyl groups are easily removable,[6)] c) using chiral sulfinyl groups, asymmetric induction can be achieved,[7)] and so on. In spite of these utility of the sulfinyl groups, very few examples were reported on the reaction of vinylic sulfoxides with enolate anions derived from ketones.[8)] From these point of view and considering that vinylic sulfoxides can be used as a Michael acceptor, we tried to prepare 3,3,3-trifluoro-1-propenyl phenyl sulfoxide (3), which gave good results for the reaction with various nucleophiles. In our continuous work for the preparation of the building blocks containing trifluoromethyl group like this type 3,[9)] we wish here to report the synthesis of 3 and the results of the reaction of 3 with nucleophiles.



$$CF_3CO_2Et + LiCH_2S(O)Ph \xrightarrow[\text{THF, -78 °C}]{} \underset{1}{PhS(O)CH_2C(O)CF_3}$$

$$\xrightarrow[\text{EtOH}]{NaBH_4} \underset{2}{PhS(O)CH_2CH(OH)CF_3} \xrightarrow[CH_2Cl_2]{TsCl\ /\ Et_3N} \underset{3}{PhS(O)CH=CHCF_3}$$

The sulfoxide 3 was prepared as follows. To a THF solution of ethyl trifluoroacetate, which is one of the cheapest materials containing trifluoromethyl group, was added lithiated phenyl methyl sulfoxide at -78 °C. After stirring for 2 h, usual work-up gave 3-phenylsulfinyl-1,1,1-trifluoropropan-2-one (1), which was successively treated with sodium borohydride in ethanol and tosyl chloride / Et_3N in CH_2Cl_2 to afford 3 as an E/Z mixture (E/Z = 85/15) in 72% yield for the three steps, whereas 3 could be easily separated by silica gel chromatography (eluent : AcOEt / hexane = 2/3).[11,12]

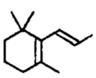
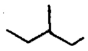
Michael reaction of 3 with various ketone enolates was carried out at the next stage. In our case,[10] it was found that the reaction smoothly proceeded at -78 °C (LDA was used for the generation of enolates) or 0 °C (sodium hydride was used) for 2 h, and furnished the products (4) in fair to excellent yield (see Table 1).

The following procedure is representative : To a solution of LDA (prepared from 0.34 ml (2.4 mmol) of diisopropylamine and 1.52 ml of n-BuLi (2.4 mmol)) in 5 ml of THF at -78 °C was added 0.26 ml (2.4 mmol) of acetophenone and stirred at that temperature. After 0.5 h, resulting enolate was treated with 0.44 g (2.0 mmol) of (E)-3,3,3-trifluoro-1-propenyl phenyl sulfoxide 3 with 3 ml of THF and the whole was stirred for 1.5 h at -78 °C and 0.5 h at 0 °C. Quenching the reaction mixture with HCl (1 mol dm^{-3}), it was extracted with CH_2Cl_2, which after evaporation was chromatographed on silica gel to give 0.67 g of (2-trifluoromethyl-3-phenylsulfinyl)propyl phenyl ketone as a white solid (97% yield, mp 93-94 °C).

From the analyses of ^{19}F NMR and HPLC, resulting Michael adducts were found to show the very high degree of diastereoselectivity. For instance, the reaction of (E)-3 with acetophenone gave a single peak (-7.28 ppm by ^{19}F NMR ; 55.4 min by HPLC),[13] whereas employing (Z)-3 instead of (E) isomer, two peaks were detected (-7.67 and -7.28 ppm ; 49.1 and 55.4 min), the ratio being 85:15, respectively. Treatment of these compounds with MCPBA led to identical sulfone, alternatively, these two peaks obtained in Entry 2 were apparently due to their diastereomers. On the other hand, when diethyl ketone was used, four peaks were observed by ^{19}F NMR and HPLC (-12.63, -11.88, -10.43, and -10.13 ppm ; 22.8, 34.7, 26.1,and 35.4 min). In this case, their relationship was determined likewise, two peaks appearing at lower field and those at higher field being attributable to the diastereomers of $-CH(CF_3)-CH(CH_3)-$ and two peaks in each sets being due to the ones between PhS(O)- and $-CH(CF_3)-$.[14] Although the reaction of (E)- or (Z)-3 with diethyl ketone exhibited only moderate diastereoselectivity for newly created chiral centers, the selections between PhS(O)- and $-CH(CF_3)-$ was very high (from 70 to >94% diastereomeric excess) as well as was remarkably reversed of their relative configurations by the geometry of 3 (Entry 4 and 5). Unfortunately, the configurations of these compounds are not known, but from these results depicted above, our vinylic sulfoxide 3 seems to be promising for the preparation of trifluoro-

$$\underset{(\underline{E})\text{-}\underline{3}}{PhS(O)CH\text{-}CHCF_3} + RC(O)CH_2R' \xrightarrow[THF]{LDA} \underset{\underline{4}}{PhS(O)CH_2CH(CF_3)CH(R')C(O)R}$$

Table 1. Reactions of 3 with various enolate anions[11]

Entry	R	R'	Isolated yield / %	Diastereomeric ratio[a,b]
1	Ph	H	97	(<3 : >97)
2[e]	Ph	H	95	(85 : 15)
3	$\text{-}(CH_2)_5\text{-}$		97	71[c](<3:>97) : 29[c](<3:>97)
4	Et	Me	99	25[c](<3:>97) : 75[c](88:12)
5[e]	Et	Me	88	71[c](96: 4) : 29[c](19:81)
6[d]	Et	Me	74	59[c](<3:>97) : 41[c](85:15)
7		H	91	(<3 : >97)
8	t-Bu	H	92	(<3 : >97)
9		Me	99	44[c](<3:>97) : 56[c](90:10)
10[f]	CH_2CO_2Et	H	68	(<3 : >97)
11[g]	OEt	CO_2Et	95	(<3 : >97)

a) Diastereomeric ratios were determined by ^{19}F NMR and/or HPLC.

b) These values in parentheses, which were arranged in the order of the peaks with lower chemical shifts observed by ^{19}F NMR, refer to that of PhS(O)- and $-CH(CF_3)-$.

c) These values arranged in the same order as above represent that of $-CHR'-CH(CF_3)-$.

d) 1.1 equiv. of HMPA was used for the generation of enolate anions.

e) ($\underline{Z}$)-$\underline{3}$ was used instead of ($\underline{E}$) isomer.

f) The reaction of $\underline{3}$ with dianion of ethyl acetacetate.

g) NaH was used instead of LDA.

methyl-containing compounds which possess good to excellent optical purity in excellent yields if introducing the chiral sulfinyl moiety to $\underline{3}$.

Desulfurization of $\underline{4}$, its conversion to aldehydes (Pummerer rearrangement) and related work are in progress.

References

1) This report should be the Part II of a series of " Building Blocks for Trifluoromethylated Organic Molecules. " For the Part I, see ref. 4.

2) " Biomedicinal Aspects of Fluorine Chemistry, " ed by R. Filler and Y. Kobayashi, Kodansha & Elsevier Biomedical (1983).

3) T. Kitazume and N. Ishikawa, *Chem. Lett.*, 1981, 1679 and references cited therein.

4) T. Yamazaki and N. Ishikawa, *Chem. Lett.*, 1984, 521 and references cited therein.

5) T. Numata and S. Oae, *Yuki Gosei Kagaku Kyoukai Shi*, 35, 726 (1977); T. Numata, *ibid.*, 36, 845 (1978).

6) By Raney Ni, see G. R. Pettit and E. E. van Tamelen, *Org. React.*, 12, 356 (1962): By Na/Hg, see B. M. Trost, H. C. Arndt, P. E. Strege, and T. R. Verhoeven, *Tetrahedron Lett.*, 1976, 3477; G. H. Posner and D. J. Brunelle, *J. Org. Chem.*, 38, 2747 (1973): By Zn, see G. A. Russell and G. J. Mikol, *J. Am. Chem. Soc.*, 88, 5498 (1966).

7) G. Solladie, *Synthesis*, 1981, 185; " Asymmetric Synthesis vol. 2," ed by J. D. Morrison, Academic Press (1983).

8) P. J. Brown, D. N. Jones, M. A. Khan, N. A. Meanwell, and P. J. Richards, *J. Chem. Soc., Perkin Trans.* 1, 1984, 2049.

9) Very recently, the preparation and the asymmetric reaction of 3,3,3-trifluoro-1-propenyl phenyl sulfone was reported. see, Y. Kobayashi, *et al.*, *Tetrahedron Lett.*, in press.

10) G. Tsuchihashi, S. Mitamura, S. Inoue, and K. Ogura, *Tetrahedron Lett.*, 1973, 323.

11) All new compounds gave satisfactory spectroscopic and elemental analyses.

12) (E)-(3) : ^{1}H NMR (δ ppm) 6.62 (d,q,1H), 7.12 (d,q,1H), 7.53 (m,5H)
J_{H-H} = 14.85 Hz ^{19}F NMR (δ ppm) -14.7 (d,d)
IR (cm^{-1}) 1640, 965 (C=C, trans), 1050 (SO)
(Z)-(3) : ^{1}H NMR (δ ppm) 6.05 (d,q,1H), 6.62 (d,1H), 7.60 (m,5H)
J_{H-H} = 10.95 Hz ^{19}F NMR (δ ppm) -20.5 (d)
IR (cm^{-1}) 1635, 740 (C=C, cis), 1050 (SO)

13) Chemical shifts of ^{19}F NMR were calculated by using CF_3CO_2H as an external standard and expressed by δ value. For HPLC, 1,4-dioxane / hexane = 1 / 10 was employed as an eluent.

14) The discrimination of two kinds of diastereomers was made from the fact that the oxidation of resulting adducts by MCPBA led to diastereomeric sulfones due to $-CH(CF_3)-CH(CH_3)-$, whose chemical shifts in ^{19}F NMR were -11.67 and -9.78 ppm.

(Received March 16, 1985)