STUDIES ON ORGANIC FLUORINE COMPOUNDS. LIII. PREPARATION OF FUNCTIONALIZED TRIFLUOROMETHYLATED COMPOUNDS USING 1-PHENYLSULFONYL-3,3,3-TRIFLUOROPROPENE[a,b]

Takeo TAGUCHI, Ginjiro TOMIZAWA, Akihiro KAWARA, Masaharu NAKAJIMA, and Yoshiro KOBAYASHI*

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03 (Japan)

SUMMARY

Reaction of 1-phenylsulfonyl-3,3,3-trifluoropropene(1) with carbonyl-stabilized enolate anions smoothly proceeded to give the addition products(7) in good yield while with an alkyllithium or Grignard reagent the formation of the vinyl anion(8) was one of the reaction pathways. Reaction of 1 with the chiral nucleophiles(11, 16) was carried out to give the functionalized trifluoromethylated compounds(13, 7b) in 7-43% ee.

INTRODUCTION

Trifluoromethylated compounds have been attracting attention due to their characteristic properties, particularly related to biologically active compounds [?]. Trifluoromethylation [3], fluorination[4], and the halogen exchange reaction [5] are possible methods for introducing the trifluoromethyl group into a molecule. However, such methods are sometimes

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[a] Dedicated to Emeritus Professor W.K.R. Musgrave on the occasion of his 70th birthday.

[b] Part LII. see ref. [1].

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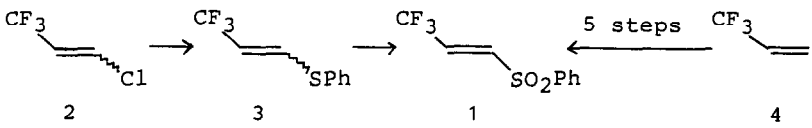
accompanied by low reactivity and low selectivity. Another promising approach is to use a proper trifluoromethylated building block which is readily available and has suitable functional group(s) in it. Recently, we reported the Michael addition reaction and the Diels-Alder reaction of 3,3,3-trifluoro-1-phenylsulfonylpropene(1) as a useful building block for the preparation of trifluoromethylated compounds [6] related to the vitamin D_2 analog [7] and naphthoquinones [8]. The importance of chirality in biologically active compounds is well documented and this is also the case in trifluoromethylated compound as shown in our peptidyl renin-inhibitor having 5,5,5-trifluoroleucinol [9]. Therefore, exploration of versatile fluorinated chiral building blocks is considered a crucial process for the preparation of fluorinated biologically active compounds. Although a number of approaches for the preparation of fluorinated chiral molecules have been reported[10], there are few reports dealing with asymmetrically bifunctionalized molecules in which the trifluoromethyl group is substituted on a chiral tertiary carbon atom [9a,10,11]. In this paper we report the nature of 1 as a Michael acceptor and the reaction with chiral nucleophiles.

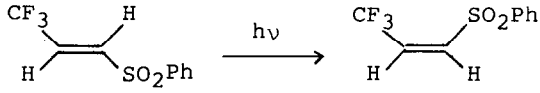
RESULTS AND DISCUSSION

Preparation of 1

1 was prepared from 3,3,3-trifluoropropene(4) or 1-chloro-3,3,3-trifluoropropene(2) as shown in Scheme 1. The E-stereochemistry of 1 prepared by either procedure was confirmed by comparing the coupling constant of olefinic protons with that of the photoisomerized compound(5).



Scheme 1



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Reaction of 1 with enolate anion

Due to the strong electron-withdrawing nature of both phenylsulfonyl and trifluoromethyl groups, 1 showed a high reactivity as a Michael acceptor towards a variety of enolates (TABLE 1). For example, reaction of 1 with lithium enolate of tert-butyl acetate at -78°C for 10 min afforded the adduct(7a) in 90% yield.

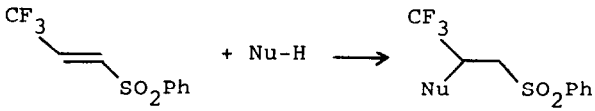

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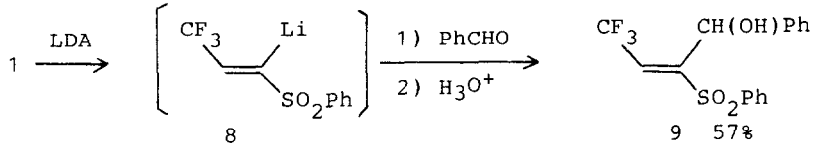
TABLE 1.

Reaction of 1 with nucleophile(6)

Run	Nucleophile(6)	Base	Solvent	7	Yield(%)
1	CH_3COO^tBu	LDA*	THF	7a	90
2	CH_3COPh	NaH(10 mol %)	THF-^{t}BuOH	7b	60
3	CH_3CH_2COPh	NaH(10 mol %)	THF	7c	95
4	$(CH_3)_2CHCOPh$	KH	Et_2O	7d	68
5	$CH_2(COOEt)_2$	NaH(10 mol %)	THF	7e	quant.

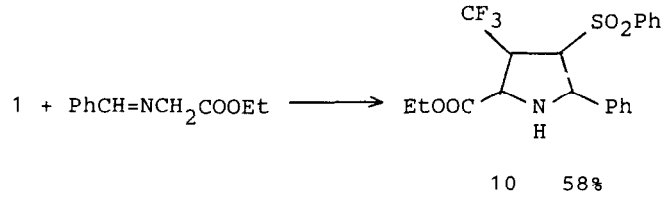
Although carbonyl-stabilized anions reacted with a to give the adducts(7), reaction of 1 with a Grignard reagent or alkyllithium in the absence or presence of cuprous iodide did not give the addition product. In these cases, formation of the thermally unstable vinyl anion(8) was one of the reaction pathways. Trapping the vinyl anion was clearly demonstrated by the reaction of 1 with LDA followed by the addition of benzaldehyde to give the alcohol(9) in 57% yield.

* Lithium diisopropylamide



Scheme 2

4,4,4-Trifluorovaline was effectively prepared through the reaction of 1 with diethyl acetamidomalonate [6]. When the lithium enolate of N-benzylideneglycinate was reacted with 1, the corresponding pyrrolidine derivative(10) was obtained in 58% yield via stepwise addition reactions or 1,3-dipolar reaction.



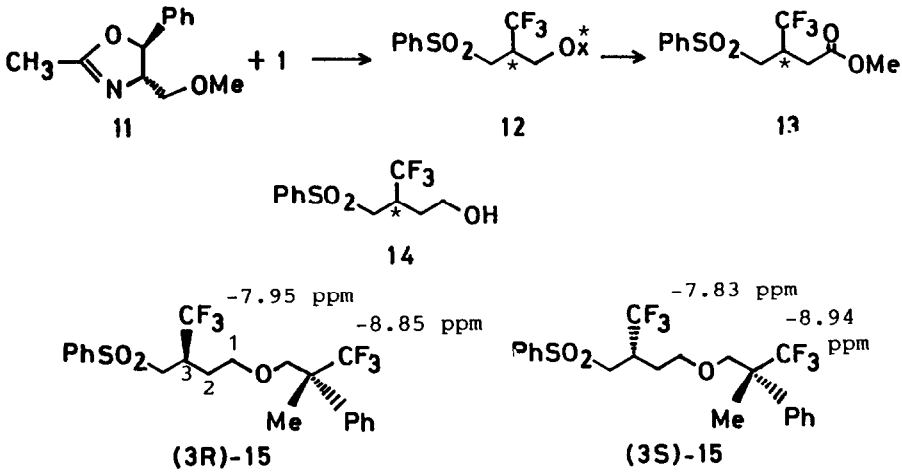
Scheme 3

Reaction of 1 with chiral nucleophiles

Considering the functionality and the synthetic utility of the adduct derived from the Michael-type reaction of 1 with enolate anion, we investigated the reaction of 1 with chiral nucleophiles. We choose Meyers' oxazoline(11) and the Schiff bases(16) derived from acetophenone and optically pure amines, because the adducts would be converted to 4-phenylsulfonyl-3-trifluoromethylbutanoic acid, whose functionality makes it possible to form carbon-carbon bond at C-1, 2 and 4, and to convert tne sulfonyl and ester groups into other functional groups [6-8].

After treating the oxazoline [13] with LDA in THF at -78°C, 1 was reacted with the anion for 20 min at the same temperature to give a diastereomeric mixture of the adduct(12). From the ^{19}F-nmr spectrum and liquid-chromatographic analysis of 12, the diastereomeric ratio was about 3:2. The adduct(12) was convert-

ed into the methyl ester(13) in 65% yield from 1, which was reduced to the alcohol(14) by treating with $LiAlH_4$. The ^{19}F-nmr spectrum of the MTPA* ester of 14, recorded on a JEOL FX-200 (188 MHz), was compared with that of the ester of optically pure (S)-(+)-14 obtained via optical resolution of 3-trifluoromethyl-γ-butyrolactone [9]. The enantiomeric excess of 13 obtained by the above reaction was 20% in (S)-isomer predominant.

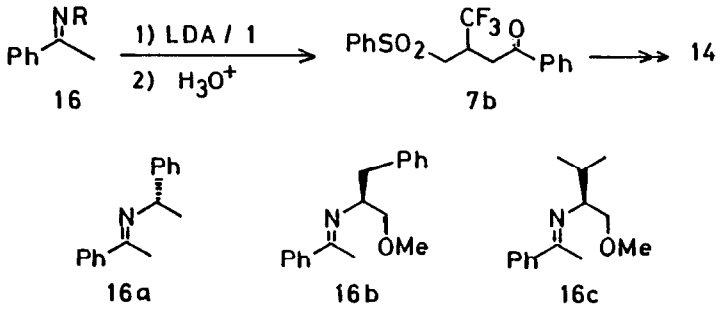


Scheme 4

Results of reaction of 1 with chiral imines(16) [14] are shown in TABLE 2. Similarly to above, the determination of absolute configuration and optical purity was carried out by converting the adduct(7b) into the alcohol(14). Thus, the Baeyer-Villiger oxidation of the phenyl ketone(7b) with trifluoroperacetic acid gave the phenyl ester, which is reduced to the alcohol(14). From these results, solvent effect on the degree of the chiral induction was observed in the case of 16a(run 1, 2), whereas any appreciable solvent effect was not realized with 16b(run 3, 4). This may be explained by the conformational rigidity of the azaallyllithium intermediate through the intramolecular chelation between lithium and methoxyl group in the latter case [14a, 15]. More data are required to discuss about the

* α-Methoxy-α-trifluoromethylphenylacetic acid.

transition states in the present reactions. We are currently carrying out this and developing more efficient reactions using 1.



Scheme 5

TABLE 2

Reaction of 1 with chiral imine(16)

Run	16	Solvent	7b (Yield %)	$[\alpha]_D$ (CH_2Cl_2)	ee(%)	Configuration
1	16a	THF	37	-17.47°	24	R
2	16a	Et_2O	44	-5.04°	7	R
3	16b	THF	53	+29.42°	40	S
4	16b	Et_2O	51	+31.03°	43	S
5	16c	THF	40	+22.67°	31	S

EXPERIMENTAL

Melting points were determined with a hot-stage microscope and are uncorrected. Proton nuclear magnetic resonance (^{1}H-nmr) spectra were recorded on a Varian EM 390 spectrometer. Chemical shifts are reported in parts per million(ppm) on scale relative to tetramethylsilane as internal standard. ^{19}F-nmr spectra were recorded on a Varian EM 360L (56.4 MHz) or JEOL FX-200 spectrometer with benzotrifluoride as an external standard. Infrared(ir) spectra were recorded on a JASCO IRA-1 spectro-

photometer. Mass spectra(MS) were recorded on a Hitachi RMU-7L instrument. (S)-MTPA-OH, (L)-phenyalaninol, (L)-valinol and butyllithium were purchased from Aldrich Co. Inc.

1-Phenylsulfonyl-3,3,3-trifluoropropene(1)

A mixture of benzenethiol(25.2 g), potassium hydroxide (15.3 g) and ethanol(40 ml) in a stainless-steel autoclave(400 ml) was cooled with dry ice-acetone bath and evacuated by vacuum pump. To this was introduced 1-chloro-3,3,3-trifluoropropene(44 ml at -78°C) and the reaction mixture was heated at 100°C for 3 days. The autoclave was cooled with dry ice-acetone bath, then opened. The reaction mixture was poured onto ice-water and extracted with ether. The extract was successively washed with 1N NaOH, brine and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was distilled under reduced pressure to give the stereoisomeric mixture of 1-phenylthio-3,3,3,3-trifluoropropene(38.7 g, 83%), bp 78-80°C(9 mmHg). ^{1}H-nmr($CDCl_3$)δ: 4.15(0.4H, dq, J=12 and 6.8 Hz, 2-H of Z-isomer), 5.45(0.6H, dq, J=16 and 6.8 Hz, 2-H of E-isomer), 7.20(1H, m, 1-H), 7.45(5H, m, aromatic); ^{19}F-nmr ($CDCl_3$)δ: 2.0(dd, J=6.8 and 2.8 Hz, E-isomer), -10.0(d, J=6.8 Hz, Z-isomer); m/z: 204, 123. To a solution of the sulfide(38 g) in acetic acid(75 ml) was added 30% H_2O_2 dropwise and the reaction mixture was stirred for 1 day at room temperature, then for 1 day at 60°C. After the addition of dimethylsulfide (5 ml), the reaction mixture was concentrated in vacuo. The residue was diluted with 1N NaOH and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, then concentrated in vacuo to leave solid mass, which was recrystallized from hexane to give 1(30.2 g, 80%) as colorless needles. 1: mp 66-66.5°C; ir ν_{max}^{KBr} cm^{-1}: 1325, 1140, 960; ^{1}H-nmr($CDCl_3$)δ: 6.87(1H, dq, J=15 and 4.7 Hz, 2-H), 7.15(1H, d, J=15 Hz, 1-H), 7.52-8.50(5H, m, aromatic); ^{19}F-nmr($CDCl_3$)δ: -0.7(d, J=4.7 Hz). Analysis: Found: C, 45.99; H, 3.04; F, 24.01; S, 13.42 %. $C_8H_7F_3O_2S$ requires C,45.76; H, 2.99; F, 24.13; S, 13.57.

Z-isomer of 1(5)

After a solution of 1(200 mg) in acetone(0.4 ml) in pyrex glass tube was irradiated with high pressure mercury lamp for

2 h, the reaction mixture was chromatographed on a silica gel column eluted with hexane-ethyl acetate(6:1 v/v) to give Z-isomer of 1(51.4 mg, 27%) and recovered 1(140 mg, 70%). 5: colorless oil, ^{1}H-nmr($CDCl_3$)δ: 6.25(1H, dq, J=12 and 9 Hz, 2-H), 6.83(1H, d, J=12 Hz, 1-H), 7.53-8.20(5H, m, aromatic); ^{19}F-nmr($CDCl_3$)δ: 7.5(d, J=9 Hz). High-resolution MS: Found: 236.0118. $C_9H_7F_3O_2S$ requires 236.0091.

3,3-Dimethyl-4-phenyl-1-phenylsulfonyl-2-trifluoromethylbutan-4-one(7d)

Under argon atmosphere a mixture of isobutyrophenone(470 mg, 3.2 mmol) and potassium hydride(1.2 mmol) in ether(4 ml) was stirred for 40 min at 0°C. The reaction mixture was cooled down with dry ice-acetone bath and treated with 1(266 mg, 1.13 mmol) for 1 h. After quenching the reaction by the addition of 10% HCl, the whole was extracted with ether. The extract was washed with brine, dried over $MgSO_4$, then concentrated in vacuo. The residue was chromatographed on a silica gel column eluted with hexane-ethyl acetate(6:1 v/v) to give 7d(295 mg, 68%) after recrystallized from cyclohexane. 7d: mp 99-100°C. ir ν_{max}^{KBr} cm^{-1}: 1680; ^{1}H-nmr($CDCl_3$)δ: 1.33(3H, s, CH_3), 1.47(3H, s, CH_3), 3.45(2H, d, J=3.8 Hz, 1-H), 4.00(1H, tq, J=3.8 and 7.5 Hz), 7.40-8.10(10H, m, aromatic); ^{19}F-nmr($CDCl_3$) δ: -0.3(d, J=7.5 Hz); m/z: 384(M^+), 243, 143, 105. Analysis: Found: C, 59.66; H, 5.00; F, 14.65; S, 8.08 %. $C_{19}H_{19}F_3O_3S$ requires C, 59.37; H, 4.98; F, 14.83; S, 8.34.

1-Phenyl-2-phenylsulfonyl-4,4,4-trifluorobut-2-en-1-ol(9)

Under argon atmosphere to an etheral solution of LDA(0.9 mmol) was added 1(152 mg, 0.65 mmol) at -78°C. After being stirred for 10 min, benzaldehyde(1 mmol) was reacted at the same temperature for 10 min. The reaction mixture was quenched by addition of 1N HCl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, then concentrated. The residue was chromatographed on a silica gel column eluted with hexane-ethyl acetate(4:1 v/v) to give 9(125 mg, 57%) as colorless needles after recrystallized from hexane. 9: mp

127-8°C; ^{1}H-nmr($CDCl_3$)δ: 3.92(1H, d, J=10.5 Hz, OH), 6.13(1H, d, J=10.5 Hz, H-1), 7.20(5H, s), 7.07-7.67(6H, m); ^{19}F-nmr ($CDCl_3$)δ: +7.3(d, J=7.5 Hz); m/z: 324(M^+-H_2O), 200, 143, 105. Analysis: Found: C, 56.18; H, 3.82; F, 16.89; S, 9.60 %. $C_{16}H_{13}F_3O_3S$ requires C, 56.14; H, 3.83; F, 16.65; S, 9.37.

Pyrrolidine derivative(10)

After a THF solution of LDA(1.8 mmol) and ethyl N-benzylideneglycinate(350 mg, 1.8 mmol) was stirred for 10 min at -78 °C, to this was added 1(400 mg, 1.7 mmol) and then the reaction mixture was stirred for 10 min at the same temperature. Extractive work-up(ethyl acetate for extraction) followed by the chromatographic purification by a silica gel column(hexane-ethyl acetate, 10:1 v/v) gave 10(425 mg, 58%) as a stereoisomeric mixture. ^{19}F-nmr($CDCl_3$)δ: -2.2(d, J=8.5 Hz) and -5.2(d, J=8.5 Hz); ir $\nu_{max}^{CCl_4}cm^{-1}$: 3320, 3080, 1760; m/z: 427(M^+), 354, 285. High-resolution MS: Found: 427.1063. $C_{20}H_{20}F_3NO_4S$ requires 427.1067.

Methyl 3-trifluoromethyl-4-phenylsulfonylbutanoate(13)

Under argon atmosphere to a THF solution(4 ml) of LDA prepared from N,N-diisopropylamine(160 µl) and butyllithium(1.1 mmol) was added (4S,5S)-2-methyl-4-methoxymethyl-5-phenyl-2-oxazoline(218 mg) at -78°C. After being stirred for 20 min at -78°C, to this solution was added a THF solution of 1(238 mg) and the reaction mixture was stirred for 20 min at the same temperature, then poured onto cold water and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and then concentrated in vacuo. After the residue was refluxed in 10% HCl for 2 h, the reaction mixture was extracted with dichloromethane. The extract was washed with water, dried over $MgSO_4$, then concentrated in vacuo to leave the residue, which was treated with diazomethane in Et_2O at 0°C. After removal of the solvent in vacuo, the residue was chromatographed on a silica gel column eluted with hexane-ethyl acetate(6:1 v/v) to give 13(218 mg, 66%). Recrystallization from ethanol afforded colorless needles, mp 66-67°C. ir ν_{max}^{KBr} cm^{-1}: 1740, 1150; ^{1}H-nmr($CDCl_3$)δ: 2.90(2H, m, 2-H), 3.40(3H, m, 3- and 4-H), 3.75

(3H, s, COOMe), 7.60-8.20(5H, m, aromatic); ^{19}F-nmr($CDCl_3$)δ: -7.8(d, J=7.7 Hz); m/z: 310, 279, 169. Analysis: Found: C, 46.41; H, 4.19; F, 18.20; S, 10.06 %. $C_{12}H_{13}F_3O_4S$ requires C, 46.45; H, 4.22; F, 18.37; S, 10.33.

4-Phenylsulfonyl-3-trifluoromethylbutan-1-ol(14) from 13

After treatment of 13 with $LiAlH_4$ in Et_2O at 0°C for 1 h, the reaction mixture was quenched by addition of ethyl acetate, then 1N HCl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on a silica gel column eluted with hexane-ethyl acetate(1:1 v/v) to give the alcohol(14) as colorless oil. ^{1}H-nmr($CDCl_3$)δ: 2.00(1H, tq, J=6 and 1 Hz, 2-H), 2.58(1H, br, OH), 3.02(1H, m, 3-H), 3.35(2H, m, 4-H), 3.80(2H, t, J=6 Hz, 1-H), 7.50-8.10(5H, m, aromatic); ^{19}F-nmr($CDCl_3$)δ: -7.0(d, J=9.4 Hz); m/z: 282, 252, 168, 142. High resolution MS: Found: 252.0431. $C_{10}H_{11}F_3O_2S(M^+-CH_2O)$ requires 252.0465.

4-Phenylsulfonyl-3-trifluoromethyl-1-phenylbutan-1-one(7b): Reaction of 1 with chiral imine(16)

Under argon atmosphere to a solution of LDA prepared from N,N-diisopropylamine(1.1 mmol) and butyllithium(1.1 mmol) was added the imine(1.05 mmol) at -78°C. After being stirred for 20 min at -78°C, 1(1 mmol) was reacted at the same temperature. The reaction mixture was treated with 10% HCl for 1 h at room temperature, and then extracted with ether. The extract was washed with brine, dried over $MgSO_4$, then concentrated in vacuo. The residue was chromatographed on a silica gel column eluted with hexane-ethyl acetate(8:1 v/v) to give 7b as solid mass. Recrystallization from ethanol afforded colorless needles, mp 130°C. ir ν_{max}^{KBr} cm^{-1}: 1680; ^{1}H-nmr($CDCl_3$)δ: 3.65 (5H, m), 7.40-8.20(5H, m); ^{19}F-nmr($CDCl_3$)δ: -7.2(d, J=7.7 Hz); m/z: 356, 309, 251, 215, 105. Analysis: Found: C, 57.30; H, 4.18; F, 16.10; S, 8.92 %. $C_{17}H_{15}F_3O_3S$ requires C, 57.30; H, 4.24; F, 15.99; S, 9.00.

Conversion of 7b into the alcohol(14)

After a mixture of 7b(130 mg), trifluoroacetic anhydride (350 mg) and 90% H_2O_2(0.05 ml) in dichloromethane(5 ml) was

stirred for 7 days at room temperature, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with 5% $NaHCO_3$, water, dried over $MgSO_4$, and then concentrated in vacuo to give the phenyl ester; m/z: 372(M^+), 279(M^+-PhO), 251(M^+-COOPh), 137; ^{19}F-nmr($CDCl_3$)δ: -9.0(d, J=7.5 Hz). The phenyl ester was treated with $LiAlH_4$ (21 mg) in Et_2O for 10 min at 0°C. Extractive work-up and the subsequent chromatographic purification afforded the alcohol(14) in 77% yield.

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