SYNTHESIS OF 1-(3,3,3-TRIFLUORO-1-PROPENYLSULFONYL)PYRROLIDINE AND ITS MICHAEL ADDITION WITH SOME SELECTED NUCLEOPHILES

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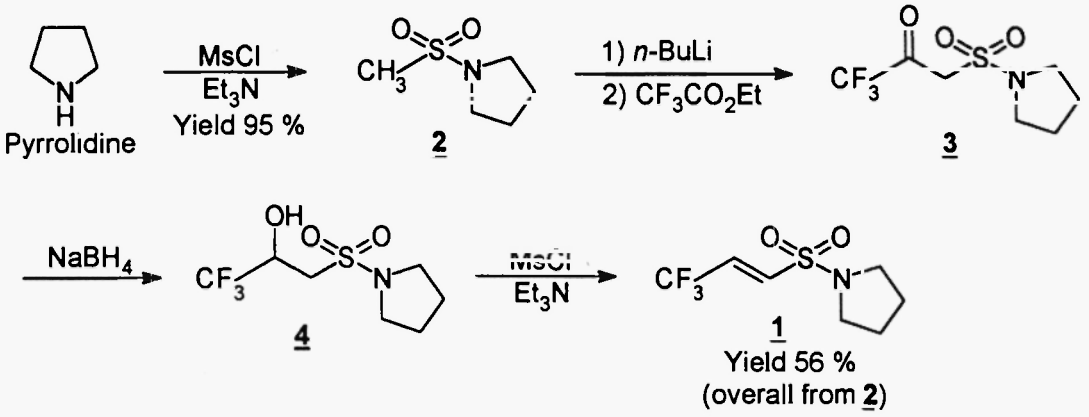
Abstract: 1-(3,3,3-Trifluoro-1-propenylsulfonyl)pyrrolidine 1 was synthesized from *N*-mesylpyrrolidine and ethyl trifluoroacetate. Michael addition of 1 with some selected nucleophiles including enolate anions and an amine gave the adducts regioselectively in high yields (58-100 %), although no adducts with organometallics were obtained.

Much attention has been addressed to trifluoromethylated compounds because they often exhibit unique biological activities (1). For introduction of the trifluoromethyl group into a carbon skeleton, the use of a proper building block, which already has the trifluoromethyl group in it, is one of the most efficient approaches (2). From this point of view, we are interested in the use of trifluoropropenylsulfonyl compounds for the synthesis of trifluoromethylated compounds (3). Some organic compounds containing the trifluoropropenyl group also exhibit remarkable pharmaceutical activities (4). In this paper, we wish to report the synthesis of 1-(3,3,3-trifluoro-1-propenylsulfonyl)pyrrolidine 1 as a new class of trifluoromethylated building blocks and the Michael addition of 1 with some selected nucleophiles.

Michael additions have been employed as powerful carbon - carbon bond or carbon - heteroatom bond formation methodologies for organic synthesis (5). A number of examples of Michael additions using the olefin with an electron-withdrawing group were reported (5), however, there seems to be no report of the use of α,β-unsaturated sulfonamide as a Michael acceptor.

As the starting amine, we chose the five-membered pyrrolidine because this Michael addition could be extended into the asymmetric reaction by use of optically active pyrrolidine derivatives. The sulfonamide 1 was synthesized as outlined in Scheme 1. Mesylation of pyrrolidine with methanesulfonyl chloride and triethylamine at 0 °C gave the amide 2 (95 % yield). Treatment of 2 with *n*-BuLi at -78 °C – 0 °C followed by addition of ethyl trifluoroacetate afforded the ketone 3. $NaBH_4$ reduction of 3 to the alcohol 4 and the following dehydration with

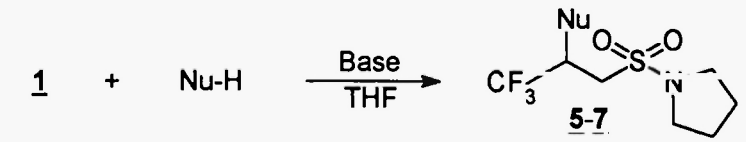
Scheme 1



methanesulfonyl chloride in the presence of an excess amount of triethylamine to give the sulfonamide 1 in good yield (56 % yield from 2).

Michael addition of 1 with some selected nucleophiles was examined as summarized in Table 1. Michael addition of 1 with dimethyl malonate deprotonated with NaH at room temperature gave the adduct 5 quantitatively. When lithium enolate of acetophenone was used as a nucleophile, the Michael addition took place at -78 °C to afford the adduct 6 in 66 % yield. Since the Michael addition of sodium benzylamide was very slow at room temperature, the reaction was carried out at 80 °C for 3 h to obtain the adduct 7 in 58 % yield. Several attempts of the reaction of 1 with organometalic reagents (alkyl lithiums, Grignard reagents, and organo copper reagents) failed probably because of the relatively high acidity of the hydrogen adjacent to the sulfonyl group in 1.

Table 1. Michael addition of 1 with some selected nucleophiles



Nu-H	Base	Reaction conditions	Product	Yield (%)
$CH_2(CO_2CH_3)_2$	NaH	rt, 1 h	5	100
CH_3COPh	LDA	-78 °C, 2 h	6	66
$BnNH_2$	NaH	80 °C, 3 h	7	58
RM[a]				complex mixture

[a] RM (BuLi, PhLi, PhMgBr, PhMgBr/CuI, Bu_2CuI, Bu_2CuCN) were used.

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR 5300 spectrometer. ^1H and ^{13}C NMR spectra were obtained with a Varian GEMINI-200 spectrometer at 200 and 50 MHz, respectively, for samples in $CDCl_3$ solution with Me_4Si as an internal standard. ^{19}F NMR spectra were obtained with a Hitachi FT-NMR R-90F spectrometer at 85 MHz for samples in $CDCl_3$ solutions with $CFCl_3$ as an internal standard. CI mass spectra were recorded on a JEOL JMS-AX 505 HA mass spectrometer at 70 eV with isobutane as the reagent gas. Flash chromatography was performed with a silica gel column (Fuji-Davison BW-300). Analytical thin-layer chromatography (TLC) was performed on Merck Kieselgel $60F_{254}$. Microanalyses were performed with a Perkin-Elmer 2400S CHN elemental analyzer.

(*E*)-1-(3,3,3-Trifluoro-1-propenylsulfonyl)pyrrolidine 1. To a solution of pyrrolidine (8.4 mL, 100 mmol) and triethylamine (10 mL, 120 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C was added methanesulfonyl chloride (9.3 mL, 120 mmol) under nitrogen atmosphere. After being stirred for 1 h at 0 °C, the solution was poured into 1 M aqueous K_3PO_4 solution (200 mL) and extracted with $CHCl_3$ (3 × 100 mL). The combined extracts were washed with 1 M aqueous HCl (3 × 100 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallized from hexane-AcOEt to give 2 as a colorless solid (14 g, 95 % yield), mp 66-69 °C (lit. (6) 70-71 °C). To a solution of 2 (14 g) in dry THF (90 mL) at -78 °C, *n*-BuLi (1.6 M hexane solution, 88 mL, 143 mmol) was added under nitrogen atmosphere in 15 min. The solution was stirred for 15 min at -78 °C and then for additional 1 h at 0 °C. To the resulting solution was added ethyl trifluoroacetate (28 mL, 238 mmol) in 15 min at -78 °C. After being stirred overnight at room temperature, the solution was poured into saturated aqueous NaCl solution (150 mL) and extracted with AcOEt (3 × 80 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the ketone 3 (25 g; R_f 0.33 (AcOEt); IR = 3567, 1593 cm^{-1}). Without purification, $NaBH_4$ (5.4 g, 143 mmol) was added to a solution of 3 (25 g) in MeOH (20 mL). After being stirred overnight at room temperature, the solution was poured into saturated aqueous NaCl solution (50 mL) and extracted with AcOEt (3 × 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the alcohol 4 (16 g; R_f 0.17 (CH_2Cl_2); IR = 3430 cm^{-1}). Without purification, methanesulfonyl chloride (7.6 mL, 98 mmol) was added to a solution of 4 (16 g) and triethylamine (27 mL, 197 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C under nitrogen atmosphere. After being stirred for 1 h at 0 °C, the solution was poured into 1 M aqueous K_3PO_4 solution (100 mL) and extracted with $CHCl_3$ (50 mL × 3). The combined extracts were washed with 1 M aqueous HCl (3 × 50 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallized from hexane-$CHCl_3$ to give 1 as a colorless solid (12 g, 56 % yield from 2): mp 45-48 °C; IR (KBr) 1134, 1354, 1462 cm^{-1}; ^1H NMR δ 1.92-1.99 (4 H, m), 3.31-3.38 (4 H, m), 6.69 (1 H, dq, J = 15.2, 5.9 Hz), 6.88 (1 H, dq, J = 15.2, 1.5 Hz); ^{13}C NMR δ 25.9, 48.1, 121.8 (q, J = 271 Hz), 129.3 (q, J = 36 Hz), 133.6 (q, J = 6 Hz); ^{19}F NMR δ -65.2 (d, J = 6 Hz); MS (CI) *m/z* 230 ($M + H^+$). Anal. Calcd for $C_7H_{10}F_3NO_2S$: C, 36.68; H, 4.40; N, 6.11. Found: C, 36.62; H, 4.52 ; N, 5.89.

1-[3,3-Bis(carbomethoxy)-2-(trifluoromethyl)propylsulfonyl]pyrrolidine 5. To a solution of dimethyl malonate (159 mg, 1.2 mmol) in dry THF (3 mL) at 0 °C was added NaH (60 % oil dispersion, 48 mg, 1.2 mmol) portionwise under nitrogen atmosphere. The solution was stirred for 10 min at room temperature and then a solution of 1 (230 mg, 1.0 mmol) in dry THF (2 mL) was added. After being stirred for 1 h at room

temperature, the solution was poured into saturated aqueous NaCl solution (15 mL) and extracted with $CHCl_3$ (3 × 5 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (3 : 1 hexane : AcOEt) to give 5 as a yellow solid (360 mg, 100 % yield): mp 42-44 °C; IR (KBr) 1746, 1339, 1154 cm^{-1}; ^1H NMR δ 1.92-1.99 (4 H, m), 3.35-3.42 (4 H, m), 3.62-3.76 (3 H, m), 3.79 (3 H, s), 3.81 (3 H, s), 4.02 (1 H, d, J = 3.8 Hz); ^{13}C NMR δ 25.9, 39.8 (q, J = 29 Hz), 44.8 (q, J = 2 Hz), 48.0, 48.7, 53.2, 53.5, 125.9 (q, J = 280 Hz), 167.2, 167.5; ^{19}F NMR δ -69.4 (d, J = 7 Hz); MS (CI) *m/z* 362 ($M + H^+$). Anal. Calcd for $C_{12}H_{18}F_3NO_6S$: C, 39.89; H, 5.02; N, 3.88. Found: C, 39.94; H,5.00 ; N, 3.83.

1-[4-Oxo-4-phenyl-2-(trifluoromethyl)propylsulfonyl]pyrrolidine 6. To a solution of LDA, prepared from *n*-BuLi (1.6 M hexane solution, 1.4 mL, 2.2 mmol) and diisopropylamine (202 mg, 2.0 mmol) in dry THF (3 mL) at -78 °C, acetophenone (180 mg, 1.5 mmol) was added under nitrogen atmosphere at -78 °C in 5 min. The solution was stirred for 1 h at -78 °C and then a solution of 1 (230 mg, 1.0 mmol) in THF (2 mL) was added. After being stirred for 1 h at -78 °C, the solution was poured into saturated aqueous NaCl solution (15 mL) and extracted with AcOEt (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (2 : 1 hexane : AcOEt) to give 6 as a colorless solid (230 mg, 66 % yield): mp 119-121 °C; IR (KBr) 1686, 1335, 1152 cm^{-1}; ^1H NMR δ 1.93-1.99 (4 H, m), 3.19 (1 H, dd, J = 14.4, 9.8 Hz), 3.30-3.70 (7 H, m), 3.72-3.84 (1 H, m), 7.44-8.00 (5 H, m); ^{13}C NMR δ 26.0, 35.1 (q, J = 28 Hz), 36.3 (q, J = 2 Hz), 47.4 (q, J = 2 Hz), 48.0, 127.0 (q, J = 279 Hz), 128.5, 129.1, 134.0, 136.5, 195.8; ^{19}F NMR δ -65.2 (d, J – 10 Hz); MS (CI) *m/z* 350 ($M + H^+$). Anal. Calcd for $C_{15}H_{18}F_3NO_3S$: C, 51.57; H, 5.19; N, 4.01. Found: C, 51.40; H,5.10 ; N, 4.01.

1-[2-(Benzylamino)-3,3,3-trifluoropropylsulfonyl]pyrrolidine 7. To a solution of 1 (230 mg, 1.0 mmol) and benzylamine (118 mg, 1.1 mmol) in THF (3 mL) at 0 °C was added NaH (60 % oil dispersion, 60 mg, 1.5 mmol) under nitrogen atmosphere. After being stirred for 3 h at 80 °C, the solution was poured into saturated aqueous NaCl solution (20 mL) and extracted with AcOEt (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (2 : 1 hexane : AcOEt) to give 7 as a yellow oil (96 mg, 58 % yield): R_f 0.46 (2 : 1 hexane : AcOEt); IR (neat) 1263, 1152, 1127 cm^{-1}; ^1H NMR δ 1.79-1.98 (4 H, m), 2.16 (1 H, br s), 3.06 (1 H, dd, J = 14.2, 9.8 Hz), 3.24 (1 H, dd, J = 14.2, 2.4 Hz), 3.29-3.42 (4 H, m), 3.75 (1 H, dqd, J = 9.8, 6.8, 2.4 Hz), 3.92 (1 H, d, J = 12.6 Hz), 4.03 (1 H, d, J = 12.6 Hz), 7.24-7.40 (5 H, m); ^{13}C NMR δ 25.9, 47.8, 47.9, 53.0, 56.0 (q, J = 29 Hz), 126.0 (q, J = 283 Hz), 127.8, 128.9, 128.9, 139.1; ^{19}F NMR δ -75.5 (d, J = 7 Hz); MS (CI) *m/z* 337 ($M + H^+$). Anal. Calcd for $C_{14}H_{19}F_3N_2O_2S$: C, 49.98; H, 5.69; N, 8.33. Found: C, 50.08; H,5.98 ; N, 7.98.

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