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A Convenient Synthesis of Monofluorobutene Derivatives

Noritada Matsuo* and Andrew S. Kende†
Sumitomo Chemical Co., Ltd., Takarazuka Research Center, 4-2-1 Takatsukasa, Takarazuka, Hyogo 665
†Department of Chemistry, University of Rochester, Rochester, N. Y., 14627, USA
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Synopsis. (*Z*)-1,4-Dibromo-1,1,2-trifluoro-2-butene (**2a**) reacts regioselectively with sodium benzenesulfinate and triethyl phosphite respectively to yield the (*Z*)-isomers of 3,4,4-trifluoro-4-bromo-2-butenyl phenyl sulfone (**3**) and diethyl (*Z*)-4-bromo-3,4,4-trifluoro-2-butenylphosphonate (**6**). These could easily be transformed to a variety of polyfunctional monofluoroalkene derivatives.

The introduction of fluorine into organic molecules often gives rise to enhancement of biological activity. There are various biologically active compounds containing a monofluoroalkene moiety,[1)] in spite of the scarcity of simple, general methodology for the stereoselective synthesis of monofluoroalkene compounds.[2)]

We have previously reported the versatile transformations of 1,1,2-trifluoro-1,3-butadiene (**1**) to a variety of functionalized monofluoroalkene compounds.[2)]

Our continuing interest in monofluoroalkene syntheses from the diene **1** has prompted us to explore the utility of (*Z*)-1,4-dibromo-1,1,2-trifluoro-2-butene (**2a**), easily obtained by bromination of the diene **1**.[3)]

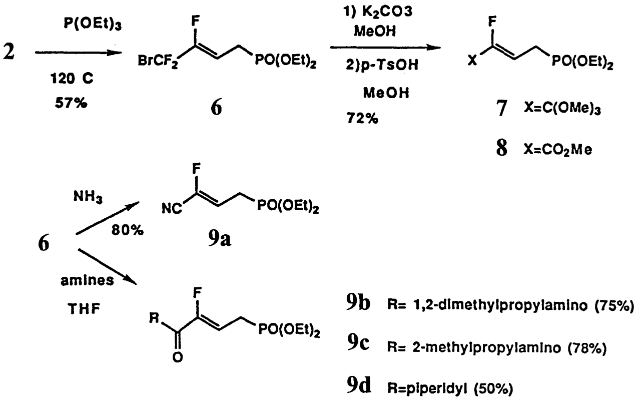
In this paper we describe easier formation of C4 monofluoroalkene intermediates.

Bromination of the diene **1** in dichloromethane at −10 °C gave the mixture of (*Z*)-1,4-adduct **2a** and 1,2-adduct **2b** (**2a**:**2b**=2:1). The 1,2-adduct **2b** spontaneously rearranged into the (*Z*)-1,4-adduct **2a** at room temperature. The dibromide **2a** was reacted with sodium benzenesulfinate in *N,N*-dimethylformamide to give the sulfone **3** in 60% yield. The sulfone **3** underwent rapid transformation in methanolic potassium carbonate at room temperature to give in high yield the known (*Z*)-orthoester **4**, which we have previously converted[2)] to monofluoro-chrysanthemic acid derivative **5**.[4)]

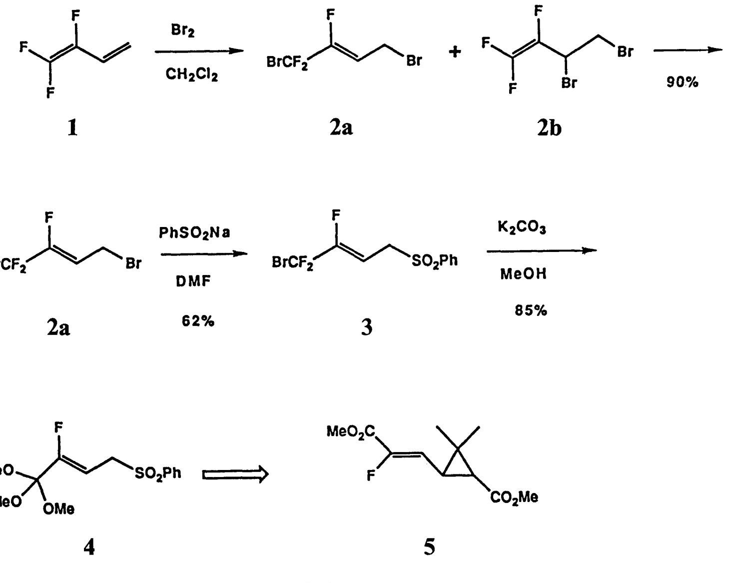
On the other hand, the dibromide **2a** reacted with triethyl phosphite to obtain the Horner–Emmons type reagent **6**. This phosphonate was transformed to the known methyl ester **8** via the orthoester **7** by reaction with methanolic potassium carbonate at room temperature, followed by mild hydrolysis in methanol with a catalytic amount of *p*-toluenesulfonic acid.

In addition, the nitrile **9a** and various amide derivatives **9b, c, d** were easily obtained by reacting with ammonia and corresponding amines in tetrahydrofuran respectively.

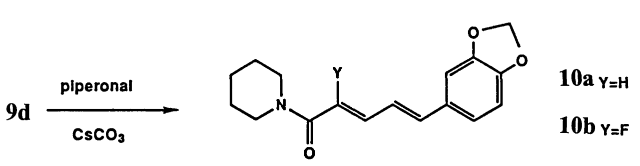
The piperidide compound **9d** was transformed to the (2*Z*,4*E*)-2-fluoro analog **10b**[2)] of the known insecticide piperine **10a** in high yield by reaction of the phospho-



Scheme 2.



Scheme 1.



Scheme 3.

nate **9d** with piperonal in 2-propanol in the presence of cesium carbonate. Enhancement of the insecticidal activity was observed by introduction of a fluorine atom at 2 position. The details of the insecticidal activity will soon be published elsewhere.

In conclusion, by use of the 1,4-bromine adduct **2a** of 1,1,2-trifluorobutadiene **1**, important and versatile (*Z*)-monofluorobutene synthons **3** and **6** were readily obtained and these were transformed to various biologically important monofluoroalkene compounds.

Experimental

All the melting points are uncorrected. IR spectra were measured on a Hitachi Model 270-30 spectrometer. ^{1}H and ^{19}F NMR spectra were recorded on a Hitachi R-90 spectrometer in CDCl$_3$ solution, using Me$_4$Si as an internal standard in ^{1}H NMR and CFCl$_3$ as an external standard in ^{19}F NMR. MS spectra were recorded on a Hitachi DF/GC/MS M-80.

(*Z*)-1,4-Dibromo-1,1,2-trifluoro-2-butene (2a). To a solution of 12.9 g (119 mmol) of 1,1,2-trifluoro-1,3-butadiene in dichloromethane (150 ml) at 0 °C was slowly added 15.5 g of bromine (97 mmol). The resulting mixture was stirred for one hour at 0 °C. The mixture was poured into ice-water, and the liquid was extracted twice with dichloromethane. The organic layers were combined, washed once with brine, and then dried over anhydrous magnesium sulfate. Evaporation of solvent gave a mixture of 1,4-adduct **2a** and 1,2-adduct **2b** as a yellow oil, (**2a**:**2b**=2:1). The 1,2-adduct **2b** rearranged to the 1,4-adduct completely on standing for one day at room temperature. This was purified by distillation to give 21.9 g (84.3%) of (*Z*)-1,4-dibromo-1,1,2-trifluoro-2-butene (**2a**) as a clear oil, bp 65 °C (20 mmHg, 1 mmHg=133.322 Pa); ^{1}H NMR δ=3.96 (dq, 2H), 5.76 (dt, 1H); ^{19}F NMR δ=−57.5 (d, *J*=18.6), −125.4 (dt, *J*=28. 9, 18.6). 1,2-adduct **2b**: ^{1}H NMR δ=3.73 (m, 2H), 4.83 (dm, 1H, *J*=27); ^{19}F NMR δ=−98.0, −115.2, −187.5.

(*Z*)-4-Bromo-3,4,4-trifluoro-2-butenyl Phenyl Sulfone (3). To a solution of 3.1 g (11.6 mmol) of (*Z*)-1,4-dibromo-1,1,2-trifluoro-2-butene **2a** in 20 ml of *N*,*N*-dimethylformamide was added 2.8 g (14 mmol) of sodium benzenesulfinate. The reaction mixture was stirred for 15 h at room temperature. The contents of the flask were poured into a large excess of ice-water, and the liquid was extracted twice with ethyl acetate. The organic layers were combined, washed once with brine, and then dried over anhydrous magnesium sulfate. Evaporation of solvent gave a yellow liquid which was chromatographed on silica gel (30% ethyl acetate in hexane) to give 2.3 g (60%) of (*Z*)-4-bromo-3,4,4-trifluoro-2-butenyl phenyl sulfone as a yellow oil; ^{1}H NMR δ=3.9 (dq, 2H), 3.6 (dt, 1H), 7.4—8.0 (m, 5H); ^{19}F NMR δ=−122.39 (dt, *J*=18.6, 31), −57.58 (d, *J*=18.6).

(*Z*)-3-Fluoro-4,4,4-trimethoxy-2-butenyl Phenyl Sulfone (4). Potassium carbonate (3.8 g, 27.5 mmol) was added to a solution of 2.3 g (7 mmol) of 4-bromo-3,4,4-trifluoro-2-butenyl phenyl sulfone in 20 ml of methanol at room temperature. The resulting mixture was stirred for 12 h at room temperature. The reaction was diluted with 100 ml of diethyl ether. The contents of the flask were filtered and the white solid was washed with excess diethyl ether. The ether solution was evaporated in vacuo to give 1.8 g (85%) of the crude 3-fluoro-4,4,4-trimethoxy-2-butenyl phenyl sulfone as an oil. The physical properties were identical with those we previously reported;[2] ^{1}H NMR δ=3.1 (s, 9H), 4.0 (d, 2H, *J*=9), 5.5 (dt, 1H, *J*=9,33), 7.5—7.9 (m, 5H); ^{19}F NMR δ=−120.5 (d, *J*=31.1). This could be used for the next reaction without further purification.

Diethyl (*Z*)-4-Bromo-3,4,4-trifluoro-2-butenylphosphonate (6). Triethyl phosphite (6.8 g, 41.0 mmol) was added to (*Z*)-1,4-dibromo-1,1,2-trifluoro-2-butene (10.0 g, 37.3 mmol). The mixture was stirred for 10 h at 120 °C over distilling off ethyl bromide formed. The reaction mixture was distilled to obtain 6.9 g (57%) of diethyl (*Z*)-4-bromo-3,4,4-trifluoro-2-butenylphosphonate as a colorless oil; bp 96—98 °C (1 mmHg); IR (neat) 1258, 1024 cm^{-1}; ^{1}H NMR δ=2.67 (ddd, 2H), 4.1 (m, 6H), 5.57 (m, 1H); ^{19}F NMR δ=−126.97 (m), −56.44 (dd, *J*=20.7, 4.1); MS *m*/*z* 324 (M-1), 326 (M+1).

Diethyl (*Z*)-3-Fluoro-3-methoxycarbonyl-2-propenylphosphonate (8). Potassium carbonate (10.2 g, 73.9 mmol) was added to a solution of 6.0 g (18.5 mmol) of diethyl 4-bromo-3,4,4-trifluoro-2-butenylphosphonate in 50 ml of methanol at room temperature. The resulting mixture was stirred for 12 h at room temperature. After removal of solvent in vacuo, the residue was partitioned between 100 ml of diethyl ether and 50 ml of water. The ether layer was washed once with brine. Evaporation of the solvent gave a clear oil. Methanol (20 ml) and *p*-toluenesulfonic acid (50 mg) were added to this oil and the resulting solution was stirred for 0.5 h at room temperature. The reaction mixture was poured into water and the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo followed by distillation gave 3.4 g (72%) of diethyl (*Z*)-3-fluoro-3-methoxycarbonyl-2-propenylphosphonate[5] as a colorless oil; bp 125 °C (0.55 mmHg); IR (neat) 1746, 1682, 1256 cm^{-1}; ^{1}H NMR δ=1.30 (t, 6H), 2.73 (ddd, 2H), 3.8 (s, 3H), 4.1 (m, 4H), 6.13 (dq, 1H); ^{19}F NMR δ=−127.8 (dd, *J*=31, 12.4); MS *m*/*z* 254 (M^{+}).

Diethyl (*Z*)-3-Cyano-3-fluoro-2-propenylphosphonate (9a). Diethyl (*Z*)-4-bromo-3,4,4-trifluoro-2-butenylphosphonate (1.0 g, 3.1 mmol) was stirred with ammonia (15 mmol) in 10 ml of tetrahydrofuran at 0 °C for 1 h and then stirred for 12 h at room temperature. The reaction mixture was poured into ice-cooled 5% aqueous hydrochloric acid and the mixture was extracted three times with ethyl acetate after saturation of the solution with sodium chloride. The combined organic layers were washed successively with 5% sodium hydrogencarbonate solution and brine, and then dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by purification with preparative TLC (hexane–ethyl acetate=1:1) gave 0.54 g (80%) of 3-cyano-3-fluoro-2-propenylphosphonate as a colorless oil: IR (neat) 2240 cm^{-1}; ^{1}H NMR δ=1.3 (t, 6H), 2.76 (ddd, 2H), 4.12 (dq, 4H), 5.81 (m, 1H); ^{19}F NMR δ=−122.34 (dd, *J*=12.4, 31); MS *m*/*z* 221 (M^{+}).

Diethyl (*Z*)-3-[(1,2-Dimethylpropyl)carbamoyl]-3-fluoro-2-propenylphosphonate (9b). 1,2-Dimethylpropylamine (0.94 g, 10.2 mmol) was added to a solution of 1.0 g (3.1 mmol) of diethyl (*Z*)-4-bromo-3,4,4-trifluoro-2-butenylphosphonate in 10 ml of tetrahydrofuran at 0 °C. The resulting mixture was stirred for 1 h at 0 °C and 12 h at room temperature. The reaction mixture was poured into ice-cooled 5% aqueous hydrochloric acid and the mixture was extracted three times with ethyl acetate after saturation of the solution with sodium chloride. The organic layers were combined, washed successively with 5% sodium hydrogencarbonate solution and brine, and then dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by purification with preparative TLC (hexane–ethyl acetate=1:1) gave 0.71 g (75%) of diethyl

(*Z*)-3-[(1,2-dimethylpropyl)carbamoyl]-3-fluoro-2-propenylphosphonate as a clear oil: IR (neat) 1662 cm^{-1}; ^{1}H NMR δ=0.90 (d, 6H), 1.12 (d, 3H), 1.31 (t, 6H), 2.72 (ddd, 2H), 4.10 (dq, 4H), 5.7—6.4 (m, 1H); ^{19}F NMR δ=−131.08 (m, 12.4, 33); MS *m*/*z* 309 (M$^+$).

Diethyl (*Z*)-3-[(2-Methylpropyl)carbamoyl]-3-fluoro-2-propenylphosphonate (9c). (*Z*)-4-Bromo-3,4,4-trifluoro-2-butenylphosphonate (1.0 g, 3.1 mmol) was allowed to react with 2-methylpropylamine (0.74 g, 10.2 mmol) in tetrahydrofuran according to the same procedure as **9b** to give 0.71 g (78%) of (*Z*)-diethyl 3-*N*-(2-methylpropyl)carbamoyl-3-fluoro-2-propenylphosphonate: IR (neat) 1664 cm^{-1}; ^{1}H NMR δ=0.92 (d, 6H), 1.30 (t, 3H), 2.72 (ddd, 2H), 3.15 (t, 2H), 4.10 (dq, 4H), 5.7—6.4 (m, 1H); ^{19}F NMR δ=−131.28 (m); MS *m*/*z* 295 (M$^+$).

Diethyl (*Z*)-3-Piperidinocarbonyl-3-fluoro-2-propenylphosphonate (9d). Diethyl (*Z*)-4-Bromo-3,4,4-trifluoro-2-butenylphosphonate (1.0 g, 3.1 mmol) was allowed to react with piperidine (1.02 g, 12 mmol) in tetrahydrofuran according to the same procedure as **9b** to give 0.48 g (50%) of diethyl (*Z*)-3-piperidylcarbonyl-3-fluoro-2-propenylphosphonate: IR (neat) 1646 cm^{-1}; ^{1}H NMR δ=1.26 (t, 3H), 1.6 (bs, 6H), 2.68 (ddd, 2H), 3.45 (bs, 4H), 4.06 (dq, 4H), 5.2—5.9 (m, 1H); ^{19}F NMR δ=−115.3 (dd, *J*=12.4, 35.1); MS *m*/*z* 307 (M$^+$).

1-[(2*Z*,4*E*)-2-Fluoro-5-[3,4-(methylenedioxy)phenyl]-2,4-pentadienoyl]piperidine (10b). To a solution of 479 mg (1.56 mmol) of diethyl (*Z*)-3-piperidinocarbonyl-3-fluoro-2-propenylphosphonate and 257 mg (1.72 mmol) of piperonal in 5 ml of 2-propanol at 0 °C was added 1017 mg (3.02 mmol) of cesium carbonate under a nitrogen atmosphere. The reaction mixture was stirred for 3 h at 0 °C and 12 h at 20 °C. The reaction mixture was poured into ice-water and the liquid was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. Evaporation of solvent gave the crude crystalline product (0.5 g). This was purified by recrystallization from hexane and ethyl acetate (3:1) to obtain 359 mg (76%) of 1-[(2*Z*,4*E*)-2-fluoro-5-[3,4-(methylenedioxy)phenyl]-2,4-pentadienoyl]-piperidine as white crystals: Mp 97.5—98.0 °C; ^{1}H NMR δ=1.62 (m, 6H), 3.53 (m, 4H), 5.95 (s, 2H), 6.39 (dd, 1H, *J*=10, 33), 6.62 (d, 1H, *J*=16), 6.75 (d, 1H, *J*=8), 6.84 (dd, 1H, *J*=10, 16), 6.87 (d, 1H, *J*=8), 6.98 (s, 1H); MS *m*/*z* 303 (M$^+$). Found: C, 67.22; H, 6.11; N, 4.66%. Calcd for $C_{17}H_{18}FO_3N$: C, 67.29; H, 5.99; N, 4.62%.

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