Stereoselective introduction of a trifluoromethyl allylic group

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(Received May 2, 1992; accepted July 29, 1992)

Abstract

High regio- and stereo-selective introduction of a trifluoromethyl group in various unsaturated systems is described. The key step is the treatment of 1,1-difluoro-1-alken-3-ols with (diethylamino)sulphur trifluoride (DAST) to give 1,1,1-trifluoro-2-alkenes.

During the past few years, trifluoromethylated organic molecules have drawn much attention due to their unique biological properties and a considerable effort has been devoted to the development of new synthetic routes to these fluorinated compounds [1]. The replacement of hydrogen atoms by fluorine atoms in biological molecules causes only a small steric perturbation but leads to major changes in hydrophobicity and polarity of the hydrocarbon chain [2].

In a previous publication, we have described an efficient method for the incorporation of a trifluoromethylated group in an allylic position [3]. Herein, we report its application to the synthesis of various products such as alkenes (**1**, **2**, **3**), styrenes (**5**, **6**, **7**), enynes (**8**), dienes (**4**, **9**, **10**) and trienes (**11**). Our procedure is based on two key steps (Scheme 1); an initial reaction between difluorovinyl-lithium, prepared *in situ* with difluoroethylene and s-BuLi, and various carbonyl compounds A leads to the allylic β,β-difluorinated alcohols B for which we have previously described the preparation [4]. Secondly, the intermediate alcohols B are attacked by DAST [(diethylamino)sulphur trifluoride] via an $S_{N2'}$ substitution reaction of a hydroxy moiety by fluoride, to afford the corresponding trifluorinated compounds C with high regio- and stereo-selectivity (if $R^2 = H$, only one isomer is obtained). A similar mechanism has been described previously for other nucleophilic attacks, such as that by a hydride [5] or by halogenides [6].

The treatment of the carbonyl derivatives A with 2,2-difluorovinyl-lithium, quantitatively prepared *in situ* from 1,1-difluoroethylene and s-BuLi in THF

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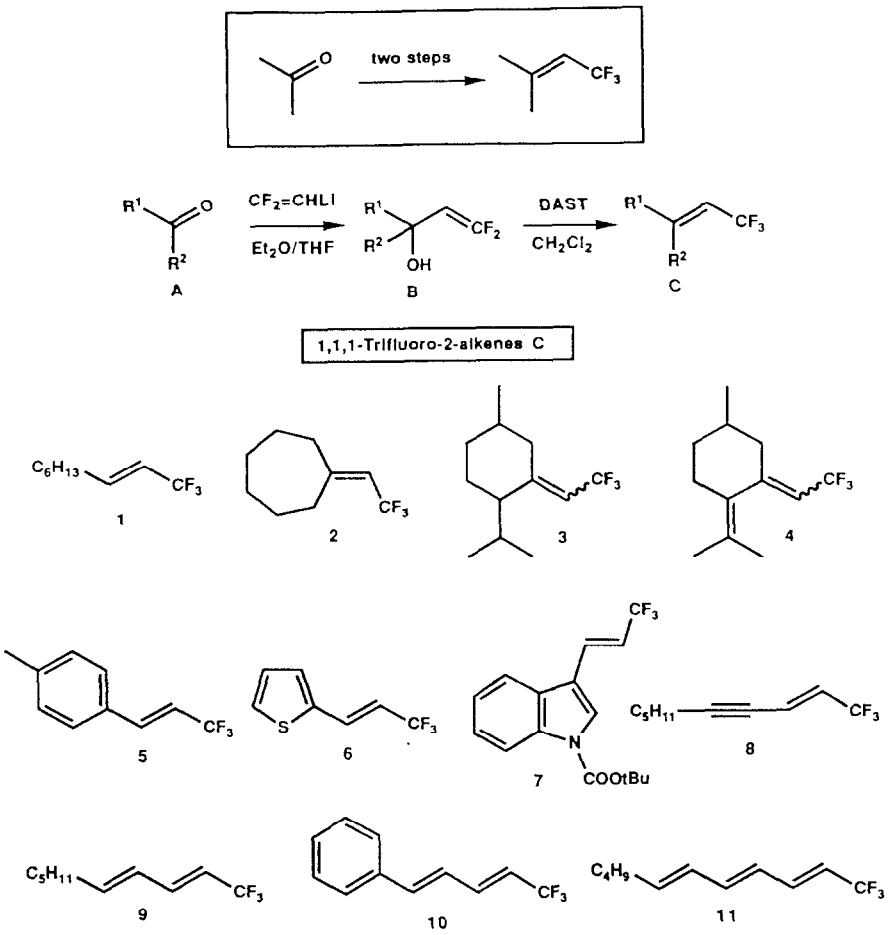
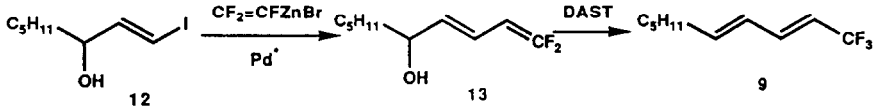
0022-1139/93/$6.00



Scheme 1.

and Et_2O (80:20) at -100 °C, leads to the alcohols B. The latter are relatively unstable and should be used quickly, due to their tendency to undergo a rapid allylic migration to yield α-unsaturated acid fluorides. To the intermediate alcohols (1 equiv.) was added DAST (1 equiv.) in CH_2Cl_2 at -70 °C to afford the trifluorinated products C which may be distilled or recrystallized. The overall yields for the two steps were of the order of 50–60%.

Moreover, we have shown that the trifluorinated product **9** may also be prepared starting from the dienol **13** by an analogous substitution reaction with DAST (Scheme 2). The intermediate dienol is easily obtained by a palladium-catalyzed cross-coupling reaction between the iodoalkene **12** [7] and difluorovinylzinc bromide [8]. The overall yield and the chemical and stereoselective purities of **9** were similar to those obtained by the first route.



Scheme 2.

All the products were characterized via their spectral properties (IR, NMR) and their stereoisomeric and chemical purities were evaluated by gas chromatographic analyses.

In conclusion, this route appears to be a general and highly regioselective method for the introduction of a trifluoromethyl group into various unsaturated systems; this reaction has allowed us to prepare products of very high stereoisomeric and chemical purities, with good overall yields and in only a few steps from readily available starting materials.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Varian VXR 300 and a Jeol GSX 400 spectrometer $CDCl_3$; δ(ppm) from TMS, J(Hz) and ^{19}F NMR spectra on a Jeol FX 90 spectrometer $CDCl_3$; δ(ppm) from $CFCl_3$, J(Hz). Infrared spectra were measured on a Perkin-Elmer 397 spectrometer (neat, cm^{-1}). Gas chromatographic analyses were performed on a Carlo Erba model 2900 instrument equipped with fused silica polar capillary column (25 m WCOT FFAP, 0.32 id, H_2 carrier gas, flow 25 ml min^{-1}, 1.2 bar).

Preparation of the intermediate alcohols B

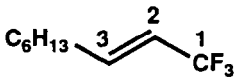
To a solution of $F_2C{=}CH_2$ (4 g, 62.5 mmol) in THF (80 ml) and Et_2O (20 ml) was added 50 mmol of s-BuLi in cyclohexane at -100 °C. The reaction mixture was stirred at -90 °C for 20 min, and then a solution of the carbonyl compound A (40 mmol) in Et_2O (10 ml) was added at -100 °C. After 30 min at -90 °C, the temperature was raised to 0 °C (20 min). The solution was then hydrolyzed by addition of H_2SO_4 solution (1 N) and extracted with Et_2O. The organic phase was successively washed with saturated aqueous solutions of $NaHCO_3$ and NaCl and dried over $MgSO_4$. After evaporation of the solvents, the corresponding alcohol was obtained.

Preparation of the trifluorinated products C

DAST (2.5 ml, 20 mmol) was added over 5 min at -70 °C to a solution of crude alcohol B (prepared from 20 mmol of the carbonyl compound) in CH_2Cl_2 (25 ml). After 15 min at -60 °C, the temperature was allowed to warm up to 0 °C (15 min). The reaction mixture was hydrolyzed by H_2O (30 ml) at 0 °C and extracted with Et_2O. The organic phase was successively washed with saturated aqueous solutions of $NaHCO_3$ and NaCl. It was then

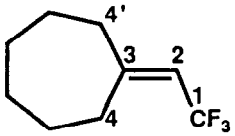
dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was filtered through a small column packed with silica (eluting with pentane). The solvent was evaporated and the residue was distilled or recrystallized to afford the trifluorinated product C.

(*E*)-1,1,1-Trifluoro-2-nonene (**1**):



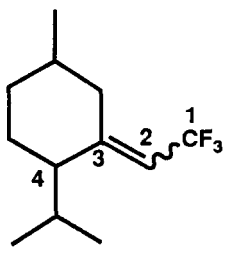
B.p. 42 °C/10 Torr, (*E*) steric purity (⩾99%). IR (cm^{-1}): 2920; 2850; 1810; 1740; 1675; 1645; 1460; 1315; 1270; 1120; 965; 670. ^{19}F NMR δ: −64.6 (m) ppm. ^1H NMR δ: 0.9 (t, 3H); 1.3 (m, 6H); 1.4 (m, 2H); 2.15 (m, 2H); 5.60 (dqt, H-2); 6.38 (dtq, H-3) ppm; $J_{H(2)-H(3)} = 15.95$ Hz, $J_{H(2)-F} = 6.6$ Hz, $J_{H(3)-H(4)} = 6.6$ Hz, $J_{H(3)-F} = 2.2$ Hz, $J_{H(2)-H(4)} = 1.65$ Hz. ^{13}C NMR δ: 14.1; 22.8; 28.3; 29.0; 31.7; 31.9; 118.8 (q, C-2, $J = 32.9$ Hz); 123.5 (q, C-1, $J = 268.6$ Hz); 141.0 (q, C-3, $J = 6.7$ Hz) ppm.

2-Cycloheptylidene-1,1,1-trifluoroethane (**2**):



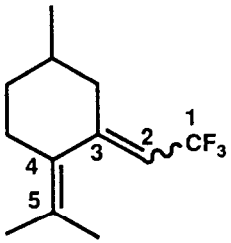
B.p. 52–54 °C/10 Torr. IR (cm^{-1}): 2920; 2850; 1715; 1660; 1440; 1375; 1270; 1100; 685. ^{19}F NMR δ: −57.6 (d, $J = 9.2$ Hz) ppm. ^1H NMR δ: 1.5–1.7 (m, 8H); 2.3 (m, 2H-4'); 2.5 (m, 2H-4); 5.42 (qt, H-2) ppm; $J_{H(2)-F} = 8.8$ Hz, $J_{H(2)-H(4')} = 1.2$ Hz. ^{13}C NMR δ: 27.1; 28.6; 29.4; 29.8; 31.2; 38.3; 114.9 (q, C-2, $J = 33.6$ Hz); 124.2 (q, C-1, $J = 270.6$ Hz); 157.8 (q, C-3, $J = 6.0$ Hz) ppm.

2-*p*-Menthanylidene-1,1,1-trifluoroethane (**3**):



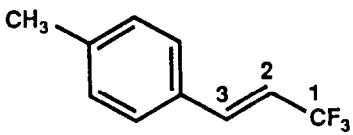
B.p. 76–78 °C/10 Torr. Two isomers (*Z* and *E*): 80/20. Chemical purity ≈90%. IR (cm^{-1}): 2950; 2860; 1660; 1630; 1450; 1375; 1330; 1265; 1210; 1110; 860; 695. ^{19}F NMR δ: −55.8 (d, $J = 6.1$ Hz, 80%); −56.4 (d, $J = 9.2$ Hz, 20%) ppm. ^1H NMR δ: 0.9–1.0 (3d, 9H); 1.0–2.0 (m, 8H); 2.54, 2.57, 2.60 and 2.63 (4s, H-4); 5.39 (q, H-2) ppm; $J_{H(2)-F} = 8.8$ Hz. ^{13}C NMR δ: Major isomer: 19.4; 20.4; 21.7; 26.8; 26.9; 31.4; 33.0; 36.6; 51.2; 112.0 (q, C-2, $J = 33.1$ Hz); 124.0 (q, C-1, $J = 271.5$ Hz); 156.9 (q, C-3, $J = 5.5$ Hz). Minor isomer: 112.6 (q, C-2, $J = 33.1$ Hz); 123.5 (q, C-1, $J = 272.1$ Hz); 157.9 (q, C-3, $J = 5.6$ Hz) ppm.

2-*p*-Menthenylidene-1,1,1-trifluoroethane (**4**):



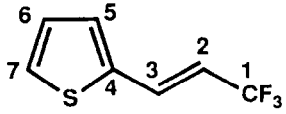
B.p. 75 °C/10 Torr. Two isomers (*Z* and *E*): 80/20. Chemical purity ≈80% (this product contained two non-separable fluorinated impurities). IR (cm^{-1}): 3060; 2910; 1715; 1655; 1450; 1270; 1190; 1110; 925. ^{19}F NMR δ: −56.7 (d, J=9.2 Hz, 80%); −61.1 (d, J=6.1 Hz, 20%) ppm. ^{1}H NMR δ: Major isomer: 5.29 (q, H-2, $J_{H(2)-F}$=8.8 Hz). Minor isomer: 5.37 (q, H-2, $J_{H(2)-F}$=8.2 Hz) ppm. ^{13}C NMR δ: Major isomer: 21.7; 21.8; 22.0; 30.3; 34.0; 35.0; 39.4; 114.2 (q, C-2, J=33.0 Hz); 123.8 (q, C-1, J=272.1 Hz); 133.4 (s, C-5); 146.5 (s, C-4); 154.0 (q, C-3, J=5.5 Hz) ppm.

(*E*)-3-*p*-Tolyl-1,1,1-trifluoro-2-propene (**5**):



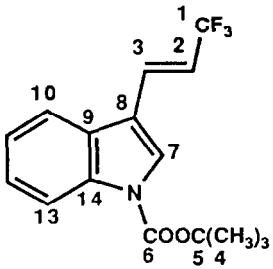
F.p. 58 °C (pentane), (*E*) steric purity (⩾99%). IR (in CCl_4) (cm^{-1}): 3020; 2920; 1660; 1610; 1510; 1330; 1310; 1270; 1120; 970; 665. ^{19}F NMR δ: −63.6 (d, J=6.1 Hz) ppm. ^{1}H NMR δ: 2.35 (s, 3H); 6.14 (dq, H-2); 7.11 (dq, H-3); 7.19 (d, 2H); 7.34 (d, 2H) ppm; $J_{H(2)-H(3)}$=16.1 Hz, $J_{H(2)-F}$=6.6 Hz, $J_{H(3)-F}$=2.0 Hz. ^{13}C NMR: δ: 20.8; 114.5 (q, C-2, J=33.6 Hz); 123.7 (q, C-1, J=268.6 Hz); 127.2 (s); 129.3 (s); 130.5 (s); 137.4 (q, C-3, J=6.7 Hz); 140.0 (s) ppm.

(*E*)-3-Thienyl-1,1,1-trifluoro-2-propene (**6**):



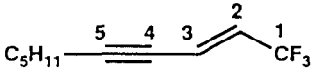
B.p. 64 °C/10 Torr, (*E*) steric purity (⩾99%). IR (cm^{-1}): 3100; 1655; 1365; 1295; 1270; 1205; 1120; 1040; 955; 870; 810; 700. ^{19}F NMR δ: −63.6 (d, J=6.1 Hz) ppm. ^{1}H NMR δ: 5.98 (dq, H-2); 6.99 (dd, H-6); 7.12 (d, H-5); 7.21 (dq, H-3); 7.29 (d, H-7) ppm; $J_{H(2)-H(3)}$=15.8 Hz, $J_{H(2)-F}$=6.7 Hz, $J_{H(6)-H(7)}$=4.9 Hz, $J_{H(5)-H(6)}$=3.2 Hz, $J_{H(3)-F}$=1.6 Hz. ^{13}C NMR δ: 115.1 (q, C-2, J=34.5 Hz); 124.3 (q, C-1, J=269.8 Hz); 128.4 (s, C-5); 128.7 (s, C-6); 130.8 (s, C-7); 131.3 (q, C-3, J=7.1 Hz); 138.8 (s, C-4) ppm.

(*E*)-3-(1-t-Butoxycarbonyl-3-indolyl)-1,1,1-trifluoro-2-propene (**7**):



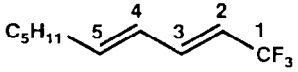
F.p. 71 °C (pentane), (*E*) steric purity (⩾99%). IR (cm^{-1}): 3140; 2960; 1740; 1660; 1450; 1365; 1230–1270; 1080–1150; 960; 740. ^{19}F NMR δ: −63.8 (d, J=6 Hz) ppm. ^{1}H NMR δ: 1.65 (s, 9H-4); 6.30 (dq, H-2); 7.26 (dq, H-3 $J_{H(2)-H(3)}$=16.5 Hz, $J_{H(2)-F}$=6.6 Hz, $J_{H(3)-F}$=2.2 Hz); 7.33 and 7.39 (2ddd, H-11 and H-12, J=8.2 Hz, J=7.7 Hz, J=1.1 Hz); 7.76 (d, 1H, J=7.7 Hz); and 8.20 (d, 1H, J=8.2 Hz (H-10 and H-13)); 7.8 (s, H-7) ppm. ^{13}C NMR δ: 28.1 (s, C-4); 84.6 (s, C-5); 115.2 (q, C-2, J=33.1 Hz); 115.3; 115.6; 119.7; 123.5; 123.8 (q, C-1, J=268.4 Hz); 125.3; 127.6; 127.7; 129.4 (q, C-3, J=6.7 Hz); 136.1; 149.1 (s, C-6) ppm.

(*E*)-1,1,1-Trifluoro-2-decene-4-yne (**8**):



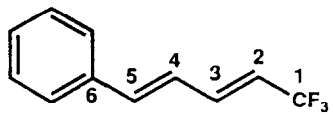
B.p. 63 °C/10 Torr, (*E*) steric purity (⩾99%). IR (cm^{-1}): 2920; 2860; 2210; 1805; 1740; 1640; 1460; 1370; 1300; 1260; 1120; 1040; 950; 870; 655. ^{19}F NMR δ: −65.0 (m) ppm. ^{1}H NMR δ: 0.9 (t, 3H); 1.35 (m, 4H); 1.55 (m, 2H); 2.34 (t, 2H); 5.96 (dq, H-2); 6.26 (dq, H-3) ppm; $J_{H(2)-H(3)}$=15.9 Hz, $J_{H(2)-F}$=6.7 Hz, $J_{H(3)-F}$=2.3 Hz. ^{13}C NMR δ: 14.1; 19.7; 22.5; 28.4; 31.4; 76.4; and 99.3 (2s, C-4 and C-5); 120.4 (q, C-3, J=7.9 Hz); 123.6 (q, C-1, J=270.6 Hz); 127.3 (q, C-2, J=33.7 Hz) ppm.

(*E*,*E*)-1,1,1-Trifluoro-2,4-decadiene (**9**):



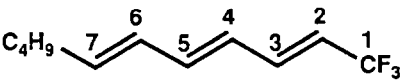
B.p. 66–67 °C/10 Torr, (*E*,*E*) steric purity (⩾99%). IR (cm^{-1}): 2920; 2850; 1720; 1660; 1630; 1460; 1270; 1110; 985; 855; 675. ^{19}F NMR δ: −63.7 (d, J=6.1 Hz) ppm. ^{1}H NMR δ: 0.9 (t, 3H); 1.3 (m, 4H); 1.4 (m, 2H); 2.14 (q, 2H); 5.57 (dq, H-2); 6.00 (dt, H-5); 6.07 (dd, H-4); 6.71 (ddq, H-3) ppm; $J_{H(2)-H(3)}$=15.6 Hz, $J_{H(4)-H(5)}$=15.3 Hz, $J_{H(3)-H(4)}$=9.3 Hz, $J_{H(2)-F}$=6.9 Hz, $J_{H(5)-H(6)}$=5.8 Hz, $J_{H(3)-F}$=2.0 Hz. ^{13}C NMR δ: 14.2; 22.9; 29.0; 31.9; 33.2; 116.8 (q, C-2, J=33.6 Hz); 124.2 (q, C-1, J=267.8 Hz); 127.5 (s, C-5); 138.3 (q, C-3, J=6.7 Hz); 143.4 (s, C-4) ppm.

(*E*,*E*)-5-Phenyl-1,1,1-trifluoro-2,4-pentadiene (**10**):



F.p. 35 °C (pentane), (*E,E*) steric purity (⩾99%). IR (in CCl_4) (cm^{-1}): 3030; 1650; 1500; 1450; 1355; 1275; 1235; 1110; 1000; 865; 690. ^{19}F NMR δ: −63.4 (m) ppm. ^1H NMR δ: 5.76 (dq, H-2); 6.71 (dd, H-4); 6.78 (d, H-5); 6.88 (ddq, H-3); 7.25–7.45 (m, 5H) ppm; $J_{H(4)-H(5)} = 15.4$ Hz, $J_{H(2)-H(3)} = 15.1$ Hz, $J_{H(3)-H(4)} = 8.9$ Hz, $J_{H(2)-F} = 7.0$ Hz, $J_{H(3)-F} = 1.7$ Hz. ^{13}C NMR δ: 118.9 (q, C-2, $J = 33.9$ Hz); 124.2 (q, C-1, $J = 269.6$ Hz); 125.5 (s, C-5); 127.7 (s); 129.5 (s); 129.6 (s); 136.5 (s, C-6); 138.2 (q, C-3, $J = 7.0$ Hz); 140.0 (s, C-4) ppm.

(*E,E,E*)-1,1,1-Trifluoro-2,4,6-undecatriene (**11**):



B.p. 88–90 °C/10 Torr, (*E,E,E*) steric purity (⩾99%). IR (cm^{-1}): 3020; 2950; 2920; 2860; 1650; 1635; 1600; 1355; 1300; 1270; 1100; 995; 860; 680. ^{19}F NMR δ: −63.6 (d $J = 6.1$). ^1H NMR δ: 0.9 (t, 3H); 1.2 (m, 4H); 2.15 (q, 2H); 5.63 (dq, H-2); 5.89 (dt, H-7); 6.11 (2dd, H-4 and H-5); 6.43 (dd, H-6); 6.74 (ddq, H-3) ppm; $J_{H(2)-H(3)} = 15.4$ Hz, $J_{H(5)-H(4)} = 15.4$ Hz, $J_{H(7)-H(6)} = 14.8$ Hz, $J_{H(6)-H(5)} = 11.0$ Hz, $J_{H(4)-H(3)} = 11.0$ Hz, $J_{H(2)-F} = 7.1$ Hz, $J_{H(7)-H(8)} = 7.1$ Hz, $J_{H(3)-F} = 1.7$ Hz. ^{13}C NMR δ: 13.9; 22.3; 31.1; 32.6; 116.9 (q, C-2, $J = 33.1$ Hz); 123.6 (q, C-1, $J = 268.4$ Hz); 126.2 (s); 129.4(s); 137.6 (q, C-3, $J = 7.4$ Hz); 140.0 (s); 140.1 (s) ppm.

Acknowledgements

The authors thank Prof. J. F. Normant and C. Descoins for helpful discussions. This work was supported by INRA and CNRS. We are indebted to Atochem for a generous gift of $CF_2=CH_2$.

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