1-Bromo-3-trifluoromethylbut-2-ene: synthesis and electrophilic reactivity

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Abstract

A three-step synthesis of 1-bromo-3-trifluoromethylbut-2-ene in 54% overall yield is reported starting from 1,1,1-trifluoroacetone. The electrophilic reactivity of this compound towards various nucleophiles has been studied. Thus, for example, condensation with the sodium salt of diethyl malonate gave ethyl 2-carboethoxy-5-trifluoromethylhex-4-enoate in 66% yield.

Introduction

There continues to be a great interest in the selective synthesis of fluorinated compounds, in particular those involving easily prepared fluorinated building blocks [1]. Since prenyl derivatives are useful synthons, for example in the terpene field [2], it is attractive to obtain their fluorinated analogues.

Only two trifluorinated prenyl derivatives have been reported to date. 3-Trifluoromethylbut-2-en-1-ol has been used in studies of the prenyltransferase mechanism [3], in the synthesis of fluorinated analogues of vitamin E [4] and of the insect growth regulator KK-42 [5]. 1-Chloro-3-trifluoromethylbut-2-ene has been used in the synthesis of pyrimidopurinediones for anti-inflammatory activity studies with a yield limited to 22% [6].

To our knowledge, the more reactive bromide has not yet been described although it could be a valuable building block for introducing the trifluorinated prenyl group. We report here an easy three-step synthesis of 1-bromo-3-trifluoromethylbut-2-ene (**4**) in 54% overall yield starting from 1,1,1-trifluoroacetone and we illustrate the use of this new synthon in nucleophilic substitutions to obtain various compounds **5**, generally in fair yield.

Results and discussion

The alcohol **3** was prepared as described by Dale Poulter and Satterwhite [3] (Scheme 1). Condensation of 1,1,1-trifluoroacetone (**1**) with carbo-

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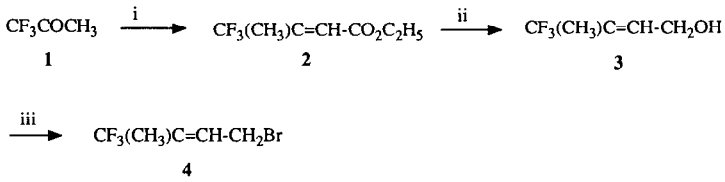
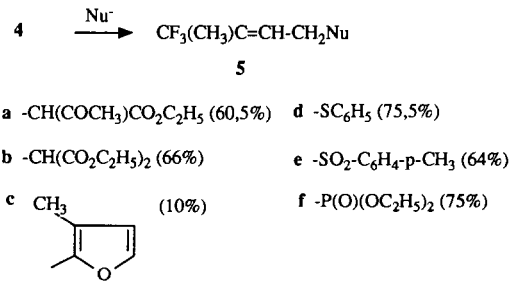


1 2 3 4

Scheme 1. i,$(C_6H_5)_3P{=}CH{-}CO_2C_2H_5$, ether, r.t., 18 h; ii, $LiAlH_4$, ether, 0 °C; iii, PBr_3, ether, 0 °C, 2 h.



Scheme 2.

ethoxymethylenetriphenylphosphorane following Dull's procedure [7] gave ethyl 3-trifluoromethylbut-2-enoate (**2**) as a mixture of (*E*)- and (*Z*)-isomers (95:5). The ester **2** was reduced with lithium aluminium hydride at 0 °C to 3-trifluoromethylbut-2-en-1-ol which was also obtained as a mixture of (*Z*)- and (*E*)-isomers in the same ratio.

Treatment of alcohol **3** with phosphorus tribromide in diethyl ether at 0 °C gave 1-bromo-3-trifluoromethylbut-2-ene (**4**) in 68% yield as a 96:4 mixture of (*E*)- and (*Z*)-isomers. In this last step, the solvent must be slowly distilled in an efficient apparatus, because of the volatility of bromide **4**. The overall yield from 1,1,1-trifluoroacetone was 54%. The assignment of the stereochemistry was based on an analysis of the ^1H and ^{19}F NMR spectra as for esters **2** [8]. The chemical shift of the vinylic proton is lower in the (*Z*)-isomer than in the (*E*)-isomer (respectively 5.9 and 6.3 ppm).

The bromide **4** [as a 96:4 mixture of (*E*)- and (*Z*)-isomers] was then allowed to react with various nucleophiles (Scheme 2). Thus condensation with the sodium salt of diethyl malonate in tetrahydrofuran gave **5b** in 66% yield. Sulphur and phosphorus derivatives were also prepared. Phenyl sulphide (**5d**) was obtained in 75.5% yield from sodium phenyl sulphide and the phosphonate **5f** was obtained in 75% yield from triethylphosphite. In cases **a** and **b** (see Scheme 2), 2 equiv. of nucleophile was necessary to reduce the yield of the disubstituted by-product from 21% to 3%.

For example, in order to obtain a trifluorinated terpene analogue, we condensed **4** with 2-lithio-3-methylfuran [9]. The trifluorinated analogue of *Rose Furan* (**5c**) was isolated in only 10% yield (25% estimated by analysis of the ^{19}F NMR spectrum of the crude material). No substitution occurred

with sodium azide and potassium cyanide irrespective of the solvent and the reaction temperature, e.g. tetrahydrofuran, dimethylformamide, dimethylsulphoxide and from room temperature to reflux. These three last examples demonstrate the reduced reactivity of bromide **4** compared to its hydrogenated analogue, the prenyl bromide. An inverted trifluoromethyl effect was previously deduced from the comparative reactivities of γ-trifluoromethylallyl and crotyl chlorides [10, 11]. Pegolotti and Young [10] found their surprising observation difficult to explain owing to destabilization of the partial positive charge in the transition state by the trifluoromethyl group.

In all cases, analysis of the ^{19}F NMR spectra of the crude materials showed only the existence of the (*E*)-isomer. No competitive S_N2 reaction was observed in any case. Work is now in progress to study the nucleophilic reactivity of compound **5d–f**.

Experimental

^1H NMR (200.13 MHz) spectra were recorded on a Bruker AC 200e Fourier-transform spectrometer and ^{19}F NMR (56.4 MHz) on a Varian EM360L instrument. NMR chemical shifts δ in deuterochloroform are reported in ppm, positive downfield from tetramethylsilane for ^1H and negative upfield from trichlorofluoromethane for ^{19}F. IR spectra were obtained on a Perkin-Elmer 1420 spectrophotometer. Exact mass measurement and elemental analyses were performed by the Service de Microanalyses, Université P. et M. Curie, Paris.

Ether was diethyl ether. THF and ether (dry) were distilled over sodium just before use. Brine was a saturated aqueous sodium chloride solution. 1,1,1-Trifluoroacetone was purchased from Aldrich-Chimie.

1-Bromo-3-trifluoromethylbut-2-ene (4)

Phosphorus tribromide (3.4 ml, 35.7 mmol) was added dropwise to a solution of 3-trifluoromethylbut-2-en-1-ol (5 g, 35.7 mmol) in ether (50 ml) at 0 °C. After stirring at this temperature for 2 h, the reaction mixture was poured on to ice and extracted with ether (2×30 ml). The organic layer was successively washed with 5% aqueous $NaHCO_3$ (30 ml) and brine (2×30 ml), and dried over $MgSO_4$. The solvent was carefully distilled off and the residue was distilled to give 1-bromo-3-trifluoromethylbut-2-ene (**4**) as a colourless liquid (4.96 g, 24.4 mmol, 68%), b.p. 112 °C. ^1H NMR δ:1.5 (s, (*Z*)-isomer, 4%) and 1.8 (s, (*E*)-isomer, 96%)(3H); 3.9 (d, 2H, J=8.8 Hz); 5.9 (t, J=8.8 Hz, (*Z*)-isomer) and 6.3 (s, 3H, (*E*)-isomer)(1H) ppm. ^{19}F NMR δ: −62.6 (s, (*Z*)-isomer); −71 (s, (*E*)-isomer) ppm. IR (CCl_4) ν: 2960; 2920; 2840; 1670; 1540; 1440; 1350; 1300; 1245; 1200; 1170; 1150; 1120; 1080; 1060; 1000 cm^{-1}. Analysis: Calcd. for $C_5H_6BrF_3$ (203.006): C, 29.58; H, 2.98%. Found: C, 29.63; H, 2.95%.

Ethyl 2-acetyl-5-trifluoromethylhex-4-enoate (5a)

To a 60% sodium hydride dispersion in mineral oil (1.182 g, 32 mmol), washed with pentane (2×5 ml) under an inert atmosphere, was added dry

THF (60 ml) followed by dropwise addition of ethyl acetoacetate (7.53 ml, 59 mmol) at room temperature. The mixture was then refluxed and 1-bromo-3-trifluoromethylbut-2-ene (6 g, 29.5 mmol) was added rapidly. The resulting solution was stirred under reflux for 10 h. After cooling, the reaction was quenched with 2% hydrochloric acid (50 ml) and extracted with ether (3×50 ml). The combined organic layer was washed with brine and dried over anhydrous sodium sulphate. After removal of the solvent (20 mmHg), the residue was distilled bulb to bulb (15 mmHg) to give an oil. Distillation of the latter using a spinning-band apparatus (Perkin-Elmer M-131T) under reduced pressure (15 mmHg) gave ethyl 2-acetyl-5-trifluoromethylhex-4-enoate (**5a**) as a colourless liquid (4.51 g, 17.88 mmol, 60.5%), b.p. 114 °C/15 mmHg. ^{1}H NMR δ: 1.2 (t, 3H, J=7.05 Hz); 1.73 (s, 3H); 2.19 (s, 3H); 2.57 (br. t, 2H, J=7.33 Hz); 3.47 (t, 1H, J=7.33 Hz); 4.15 (q, 2H, J=7.05 Hz); 5.95 (t×m, 1H, J=7.4 Hz) ppm. ^{19}F NMR δ: −67.5 (s) ppm. IR (CCl_4) ν: 2980; 1740; 1710; 1680; 1635; 1440; 1380; 1240; 1220; 1195; 1175; 1125 cm^{-1}. Analysis: Calcd. for $C_{11}H_{15}F_3O_3$ (252.23): C, 52.38; H, 5.99%. Found: C, 52.53; H, 6.16%.

*Ethyl 2-carboethoxy-5-trifluoromethylhex-4-enoate (**5b**)*

This compound was prepared by the same method as for **5a** using the following amounts of materials: 60% sodium hydride dispersion in mineral oil (0.59 g, 14.8 mmol), diethyl malonate (4.48 ml, 29.4 mmol), 1-bromo-3-trifluoromethylbut-2-ene (3 g, 14.7 mmol) and dry THF (20 ml), giving after distillation ethyl 2-carboethoxy-5-trifluoromethylhex-4-enoate (**5b**) as a colourless liquid (2.76 g, 9.7 mmol, 66%), b.p. 82–83 °C/15 mmHg. ^{1}H NMR δ: 1.2 (t, 6H, J=7.1 Hz); 1.74 (s, 3H); 2.64 (br. t, 2H, J=7.45 Hz); 3.36 (t, 1H, J=7.45 Hz); 4.13 (q, 4H, J=7.1 Hz); 5.96 (t×m, 1H, J=7.45 Hz) ppm. ^{19}F NMR δ: −67.8 (s) ppm. IR (CCl_4) ν: 2985–2865; 1745; 1724; 1670; 1460; 1435; 1360; 1330; 1305; 1255; 1220; 1170; 1115 cm^{-1}. Analysis: Calcd. for $C_{12}H_{17}F_3O_4$ (282.21): C, 51.06; H, 6.07%. Found: C, 51.23; H, 5.92%.

*3-Methyl-2-(3-trifluoromethylbut-2-enyl)furan (**5c**)*

2,2′-Di(3-methylfuryl)mercury prepared following literature methods [9] (2.1 g, 5.79 mmol) in dry ether (5 ml) was added dropwise to a suspension of 15% lithium sand in hexane (0.4 g, >50% excess) in dry ether (5 ml) at −20 °C. This mixture was stirred at −20 °C for 1 h, then allowed to warm to room temperature and stirred again for 30 min. The solution of the organolithium compound was forced by argon pressure through a sintered glass disc into a second reaction vessel kept at −20 °C. 1-Bromo-3-trifluoromethylbut-2-ene (1.23 g, 6.06 mmol) in dry ether (5 ml) was added dropwise. After stirring at room temperature for 3 h, the mixture was cooled and 2% hydrochloric acid (20 ml) was added. The solution was extracted with ether (3×20 ml) and the organic layer was washed with brine to pH=5, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica using CH_2Cl_2/petroleum ether (40:60, v/v)

as eluent affording an orange coloured oil which was then distilled in a Kügelrohr apparatus to give 3-methyl-2-(3-trifluoromethylbut-2-enyl)furan (**5c**) (0.12 g, 0.58 mmol, 10%) as a colourless oil having an unpleasant smell, b.p. 110 °C/13 mmHg. ^{1}H NMR δ: 1.93 (s, 3H); 2.03 (s, 3H); 3.47 (br. d, 2H, J=7.05 Hz); 6.21–6.33 (m, with doublet at 6.25, 2H, C*H*=C(CH$_3$)CF$_3$ and C*H*=CH–O, J=1.66 Hz); 7.3 (d, 1H, J=1.66 Hz) ppm. ^{19}F NMR δ: −69.98 (s) ppm. IR (CCl_4) ν: 3170; 2970; 2920; 2890; 2860; 1670; 1460; 1320; 1170; 1120; 1060 cm^{-1}. HRMS: Calcd. for $C_{10}H_{11}F_3O$, 204.0717. Found, 204.0714.

*1-Phenylsulphide-3-trifluoromethylbut-2-ene (**5d**)*

1-Bromo-3-trifluoromethylbut-2-ene (3 g, 14.7 mmol) was added dropwise, under an inert atmosphere, to a suspension of freshly prepared sodium phenyl sulphide (3.9 g, 16.8 mmol) in benzene (90 ml). The resulting solution was stirred at room temperature for 5 h. Celite (5 g) was added, the mixture filtered through a sintered glass (No. 2) equipped with glass wool and the cake washed with benzene (2×30 ml). The solvent was evaporated (20 mmHg) and the residue distilled under reduced pressure (0.7 mmHg) to give 1-phenylsulphide-3-trifluoromethylbut-2-ene (**5d**) (2.59 g, 11.16 mmol, 75.5%), b.p. 73 °C/0.7 mmHg. ^{1}H NMR δ: 1.46 (s, 3H); 3.44 (br. d, 2H, J=7.8 Hz); 6.08 (t×m, 1H, J=7.8 Hz); 7.28 (m, 5H) ppm. ^{19}F NMR δ: −68.3 (s) ppm. IR (CCl_4) ν: 3060–2820; 1670; 1570; 1540; 1470; 1430; 1350; 1305; 1175; 1115; 1060 cm^{-1}. Analysis: Calcd. for $C_{11}H_{11}F_3S$ (232.267): C, 56.88; H, 4.77%. Found: C, 56.75; H, 4.82%.

*1-p-Toluenesulphonyl-3-trifluoromethylbut-2-ene (**5e**)*

Sodium *p*-toluenesulphinate (0.96 g, 5.38 mmol) was added, in one portion, to 1-bromo-3-trifluorobut-2-ene (0.5 g, 2.46 mmol) in methanol (5 ml). This mixture was refluxed for 24 h, then cooled to room temperature, diluted with water (20 ml) and extracted with ether (3×20 ml). The organic layer was washed with saturated sodium bicarbonate (100 ml) and brine (2×100 ml). After drying over anhydrous sodium sulphate, the solvent was evaporated (20 mmHg). The crude white solid was recrystallized from 95% ethanol to give 1-*p*-toluenesulphonyl-3-trifluoromethylbut-2-ene (**5e**) (0.44 g, 1.6 mmol, 64%), m.p. 107.2 °C. ^{1}H NMR δ: 1.18 (s, 3H); 2.39 (s, 3H); 3.8 (d, 2H, J=8.05 Hz); 6 (t×m, 1H, J=8.1 Hz); 7.3 (d, 2H, J=8.15 Hz); 7.67 (d, 2H, J=8.15 Hz) ppm. ^{19}F NMR δ: −69 (s) ppm. IR (CCl_4) ν: 3020; 2960; 2920; 2850; 1670; 1590; 1490; 1440; 1400; 1350; 1320; 1300; 1230; 1180; 1165; 1140; 1120; 1080; 1060 cm^{-1}. Analysis: Calcd. for $C_{12}H_{13}F_3O_2S$ (278.28): C, 51.79; H, 4.71%. Found: C, 51.82; H, 4.76%.

*Diethyl (3-trifluoromethylbut-2-enyl)phosphonate (**5f**)*

1-Bromo-3-trifluoromethylbut-2-ene (2 g, 9.8 mmol) and triethylphosphite (1.23 g, 7.3 mmol) were heated at 140 °C using a total condensation/variable take-off type column until all the bromoethane had distilled. After cooling, the mixture was distilled to afford diethyl (3-trifluoromethylbut-2-

enyl)phosphonate (**5f**) (1.92 g, 7.38 mmol, 75%), b.p. 135 °C/18 mmHg. ^{1}H NMR δ: 1.25 (t, 6H, J=7.3 Hz); 1.76 (d, 3H, J=3.08 Hz); 2.65 (d×d, 2H, J=7.5 Hz); 4.05 (d×q, 4H, J=7.3 Hz); 6.06 (br. d×t, 1H, J=6.3 Hz) ppm. ^{19}F NMR δ: −68.6 (d, J=5.64 Hz) ppm. IR (CCl_4) ν: 2960; 2915; 2885; 1670; 1430; 1380; 1350; 1310; 1245; 1170; 1110; 1040; 1020; 955 cm^{-1}. Analysis: Calcd. for $C_9H_{16}F_3O_3P$ (260.128): C, 41.55; H, 6.20%. Found: C, 41.72; H, 6.19%.

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