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1-Bromo-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene: synthesis and electrophilic reactivity

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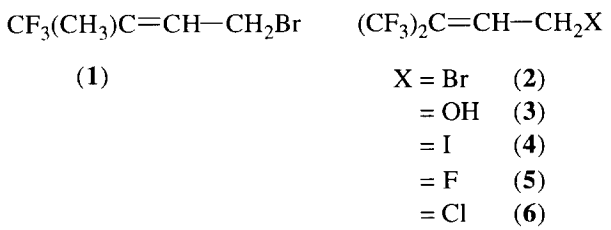
Abstract

A two-step synthesis of 1-bromo-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene in 35% overall yield is reported starting from commercially available hexafluoroacetone. The electrophilic reactivity of this new compound towards various nucleophilic reagents has been studied. Substitution products or ones arising from allylic rearrangement are obtained depending on the nature of the nucleophile.

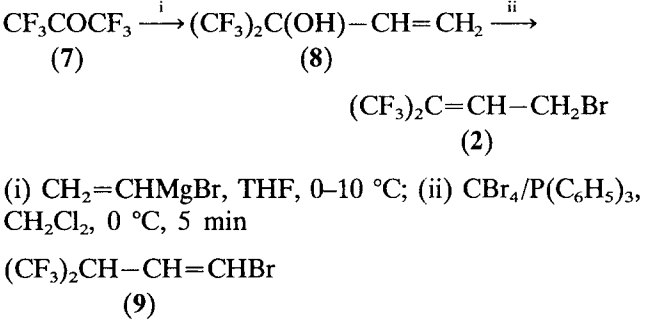
Keywords: Bromotrifluoro(trimethyl)but-2-ene; Synthesis; Electrophilic reactivity; NMR spectroscopy; IR spectroscopy; Mass spectrometry

1. Introduction

During the course of our studies on the fluorinated analogues of prenyl derivatives we have described the synthesis of 1-bromo-3-(trifluoromethyl)but-2-ene (**1**) (Scheme 1) and studied its use as a synthon for introducing the trifluorinated prenyl group in more elaborate molecules [1]. Bis-trifluorinated (hexafluorinated) prenyl derivatives are also useful compounds. For example, the replacement of the prenyl unit in Lapachol by the hexafluorinated unity enhances the antitumoural activity [2]. It is therefore of interest to have accessible a readily available hexafluoroprenyl building block such as provided by compounds **2–6** (Scheme 1). Only a few reports have appeared in the literature on this kind of compound. 4,4,4-Trifluoro-3-(trifluoromethyl)but-2-en-1-ol (**3**) has been used for the synthesis of a modified chrysanthemic acid [3] while the iodide derivative **4**, prepared by the action of potassium iodide on the brosylate derived from alcohol **8** (Scheme 2) has been used for the synthesis of the fluorinated Lapachol [2]. The fluoride analogue **5** has been synthesized by fluorination of **8** with sulfur tetrafluoride with a view to preparing fluorine-containing polymers [4]. The 1-bromo-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene compound **2**, which has not yet been described, appears to be a good synthon; it is probably more stable than the iodide and much more reactive than the fluoride. We report here its two-step synthesis starting from commercially available hexafluoroacetone. This new synthon has been used as an electrophile in substitutions giving two kinds of compounds depending on the nature of the nucleophiles employed.



Scheme 1.



Scheme 2.

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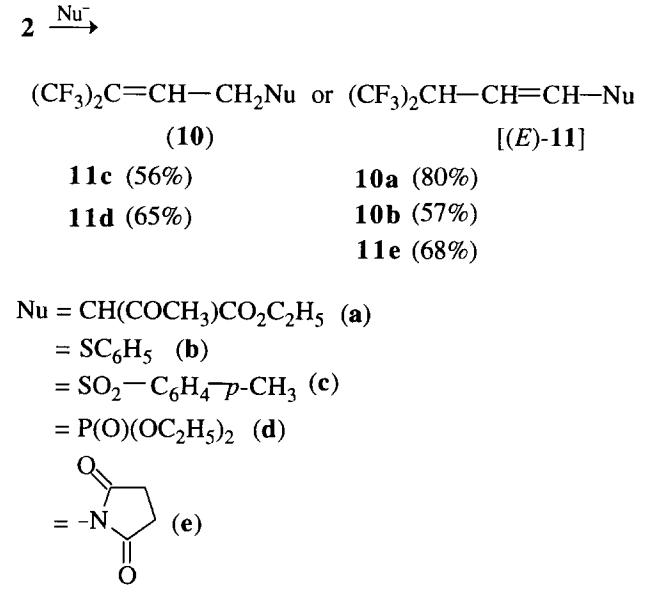
2. Results and discussion

The alcohol **8** was prepared by condensation of hexafluoroacetone (**7**) on vinylmagnesium bromide using the method described by Rutner [2] and was obtained in 70% yield as a 1:1 azeotropic mixture with tetrahydrofuran (Scheme 2). Attempts to remove the tetrahydrofuran from the mixture by distillation over concentrated sulfuric acid [5], as has been described for 1,1,1-trifluoro-2-(trifluoromethyl)but-3-yn-2-ol [6], were unsuccessful in our hands. Treatment of alcohol **8** with a carbon tetrabromide/triphenylphosphine mixture in dichloromethane at 0 °C gave 1-bromo-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene (**2**) in 51% yield as a 1:1 azeotropic mixture with tetrahydrofuran. The overall yield of this two-step synthesis was 35% based on the hexafluoroacetone employed.

It is necessary to carefully control the length of the reaction and the temperature of the same. An increase in either led to the formation of the chloride **6** which could not be separated from **2**. When diethyl ether (the usual solvent for this transformation) was employed, a mixture of two bromides was obtained, i.e. that expected (**2**) and **9**. To avoid the use of tetrahydrofuran, we considered preparing bromide **2** from the reported allylic alcohol 4,4,4-trifluoro-3-(trifluoromethyl)but-2-en-1-ol (**3**) [3], but all attempts to repeat the preparation described for this alcohol were unsuccessful in our hands [7].

Bromide **2** was then used as the electrophile in various substitution reactions (Scheme 3). Substitution products or those arising from allylic rearrangements were formed depending on the nature of the nucleophile. With the sodium salt of ethyl acetoacetate and sodium thiophenoxide, the expected compounds **10a** and **10b** were isolated in 56% and 65% yield, respectively. With sodium *p*-toluenesulfinate in methanol, compound **10c** was not obtained; instead compound **11c** was isolated in 80% yield. The same double-bond migration was observed when bromide **2** was treated with triethylphosphite or the sodium salt of *N*-succinimide. In this way, compounds **11d** and **11e** were obtained in 57% and 68% isolated yield, respectively. In all cases only the (*E*)-isomer **11** was formed.



Scheme 3.

The allylic shift **10**→**11** probably arises from the mesomeric effect of the substituents (sulfone, phosphonate, succinimide) leading to the more stable compounds **11**. This transposition, which has not been observed in the condensation reactions of bromide **1** [1], demonstrates the increase in allylic proton acidity when a second trifluoromethyl group is present in these prenyl derivatives.

3. Experimental details

^{1}H NMR (200.13 MHz) spectra were recorded on a Bruker AC-200e FT spectrometer and ^{19}F NMR (56.4 MHz) on a Varian EM36OL instrument. NMR chemical shifts (δ in deuterochloroform) are reported in ppm, positive downfield from tetramethylsilane for ^{1}H and negative upfield from trichlorofluoromethane for ^{19}F. IR spectra were obtained on a Perkin-Elmer 1420 spectrophotometer. Preparative gas chromatography was performed on a Shimadsu GC 8A apparatus equipped with a 2.5 m SE-30 column. Melting points were measured using a Mettler FP61 instrument. Exact mass measurement and elemental analyses were performed by the Service d'Analyses, Université Pierre et Marie Curie, Paris.

The ether employed was diethyl ether. Brine was a saturated aqueous sodium chloride solution. Hexafluoroacetone was purchased from Aldrich-Chimie.

Nucleophilic substitutions were conducted using a 1:1 azeotropic mixture of bromide **3** and tetrahydrofuran. The weights reported are those for the azeotropic mixture while the molar numbers quoted are those for the bromide.

3.1. 1-Bromo-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene (2)

Triphenylphosphine (16.3 g, 0.054 mol) was added rapidly with stirring to a mixture of tetrabromomethane (20.6 g, 0.0465 mol) and 1,1,1-trifluoro-2-(trifluoromethyl)but-3-en-2-ol (8.26 g, 0.0376 mol, 1:1 tetrahydrofuran azeotrope) in dichloromethane (80 ml) at 0 °C with stirring. After addition was complete the mixture was stirred for a further 5 min and then water (30 ml) was added. After decanting, the aqueous layer was extracted with dichloromethane (2×30 ml). The organic

layer was subjected to rapid bulb-to-bulb distillation under vacuum (0.2 mmHg) without heating. The distillate was dried over $MgSO_4$. After filtration, the solvent was distilled off using an efficient column. The residue was distilled in a Spaltrohr Fischer apparatus to give 1-bromo-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene (**2**) as a 1:1 azeotropic mixture with THF (6.3 g, 51% yield calculated from ^1H NMR spectrum), b.p. 96–98 °C. ^1H NMR δ: 4.1 (d, 2H, $J=8.8$ Hz); 6.82 (t, 1H, $J=8.8$ Hz) ppm. ^{19}F NMR δ: −58.85 (q, 3F, $J=7.5$ Hz); −66.81 (q, 3F, $J=7.5$ Hz) ppm. IR (CCl_4) ν (cm^{-1}): 2960; 2880; 2840; 1800; 1780; 1660; 1630; 1450; 1380; 1300; 1220; 1160; 1130; 1090; 1050; 900. HR–MS: Calc. for $C_5H_3BrF_6$, 255.9322. Found, 255.9321.

3.2. 1-Chloro-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene (6)

This compound was obtained when the reaction time was longer or the temperature was higher than 0 °C and was isolated by means of preparative gas chromatography (80 °C). ^1H NMR δ: 4.27 (d, 2H, $J=7.4$ Hz); 6.75 (t, 1H, $J=7.4$ Hz) ppm. ^{19}F NMR δ: −58.85 (q, 3F, $J=7.5$ Hz); −66.81 (q, 3F, $J=7.5$ Hz) ppm. IR (CCl_4) ν (cm^{-1}): 3010; 1670; 1380; 1310; 1260; 1220; 1060; 1030. Analysis: Calc. for $C_5H_3ClF_6$ (212.515): C, 28.26; H, 1.42%. Found: C, 28.14; H, 1.35%.

3.3. 1-Bromo-4,4,4-trifluoro-3-(trifluoromethyl)but-1-ene (9)

This compound was prepared when ether was used instead of dichloromethane and was isolated by preparative gas chromatography (70 °C). Only the (*E*)-isomer was obtained. ^1H NMR δ: 3.56 (2×qd, 1H, $J=8.1$, 9.9 Hz); 6.1 (dd, 1H, $J=13.8$, 9.9 Hz); 6.64 (d, 1H, $J=13.8$ Hz) ppm. ^{19}F NMR δ: −67.4 (d, $J=8.1$ Hz) ppm.

3.4. Ethyl 2-acetyl-6,6,6-trifluoro-5-(trifluoromethyl)hex-4-enoate (10a)

To a 60% sodium hydride dispersion in mineral oil (0.216 g, 0.0054 mol) washed with pentane (2×5 ml), ethyl acetoacetate (1.15 ml, 0.009 mol) in dry THF (15 ml) was added dropwise at room temperature under an inert atmosphere. Then 1-bromo-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene (1.45 g, 0.0043 mol) was added quickly and the mixture refluxed for 12 h. After cooling to 0 °C, 2% hydrochloric acid (30 ml) was added, the aqueous solution decanted off and extracted with ether (3×30 ml), the organic layer washed with brine (2×50 ml) and dried over $MgSO_4$. After filtration, the solvents were evaporated (20 mmHg). The residue was chromatographed on silica using petroleum ether/ethyl acetate (85:15, v/v) as eluent to afford ethyl 2-acetyl-6,6,6-trifluoro-5-(trifluoromethyl)hex-4-enoate (**10a**) (0.74 g, 0.0024 mol, 56%) as a colourless oil. ^1H NMR δ: 1.23 (t, 3H, $J=7$ Hz); 2.23 (s, 3H); 2.79–2.89 (m, 2H); 3.54 (t, 1H, $J=6.8$ Hz); 4.16 (q, 2H, $J=7$ Hz); 6.67 (t, 1H, $J=7.6$ Hz) ppm. ^{19}F NMR δ: −58.5 (q, 3F, $J=4.9$ Hz); −64.3 (q, 3F, $J=4.9$ Hz) ppm. IR (CCl_4) ν (cm^{-1}): 2960; 2920; 1730; 1710; 1670; 1630; 1390; 1350; 1230; 1200; 1150; 1090. HR–MS: Calc. for $C_{11}H_{12}F_6O_3$, 306.06906. Found, 306.06907.

3.5. 1-Thiophenoxy-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene (10b)

1-Bromo-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene (**2**) (1 g, 0.003 mol) was added dropwise to a suspension of freshly prepared sodium thiophenoxide (0.792 g, 0.006 mol) in benzene (5 ml) under an inert atmosphere. The mixture was stirred at 40 °C for 5 h. Ether (10 ml) was added, then saturated calcium carbonate (10 ml). After decanting, the aqueous layer was extracted with ether (3×20 ml). The organic solution was washed with brine (3×40 ml) and dried over $MgSO_4$. After filtration, the solvents were evaporated under vacuum (20 mmHg). The residue was chromatographed on silica using petroleum ether as eluent to afford 1-thiophenoxy-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene (**10b**) (0.56 g, 0.00195 mol, 65%) as a colourless oil. ^1H NMR δ: 3.65 (d, 2H, $J=7.4$ Hz); 6.08 (t, 1H, $J=7.4$ Hz); 7.03–7.42 (m, 5H) ppm. ^{19}F NMR δ: −57.87 (q, 3F, $J=6$ Hz); −64.05 (q, 3F, $J=6$ Hz) ppm. IR (CCl_4) ν (cm^{-1}): 3060; 3000; 1660; 1570; 1470; 1430; 1380; 1350; 1310; 1260; 1220; 1150; 1090; 1050; 1020. HR–MS: Calc. for $C_{11}H_8F_6S$, 286.0250. Found, 286.0249.

3.6. (E)-1-p-Toluenesulfonyl-4,4,4-trifluoro-3-(trifluoromethyl)but-1-ene (11c)

Sodium *p*-toluenesulfinate (0.538 g, 0.006 mol) was added as one portion to 1-bromo-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene (**2**) (1 g, 0.003 mol) in methanol (5 ml). The mixture was stirred at room temperature for 1 h. Ether (10 ml) was added followed by water (20 ml). After decanting, the aqueous layer was extracted with ether (3×10 ml). The organic solution was washed with saturated sodium bicarbonate (40 ml) and brine (40 ml). After drying over $MgSO_4$ and filtration, the solvents were evaporated under vacuum (20 mmHg). The solid residue was recrystallized from 95% ethanol to give (*E*)-1-*p*-toluenesulfonyl-4,4,4-trifluoro-3-(trifluoromethyl)but-1-ene (**11c**) (0.79 g, 0.0024 mol, 80%) as white crystals, m.p. 69.3 °C. ^1H NMR δ: 1.95 (s, 3H); 2.8 (m, 1H); 6.41 (d, 1H, $J=15.2$ Hz); 6.81 (d, 2H, $J=8$ Hz); 6.91 (dd, 1H, $J=15.2$, 9 Hz); 7.78 (d, 2H, $J=8$ Hz) ppm. ^{19}F NMR δ: −66.88 (d, $J=7$ Hz) ppm. IR (CCl_4) ν (cm^{-1}): 3020; 2960; 2920; 1590; 1490; 1440; 1400; 1340; 1290; 1260; 1220; 1150; 1140; 1080. Analysis:

Calc. for $C_{12}H_{10}F_6O_2S$ (332.228): C, 43.38; H, 3.03%. Found: C, 43.56; H, 3.10%.

3.7. (E)-Diethyl(4,4,4-trifluoro-3-(trifluoromethyl)but-1-enyl)phosphonate (11d)

A mixture of 1-bromo-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene (**2**) (1 g, 0.003 mol) and triethylphosphite (0.47 ml, 0.0027 mol) was heated to 140 °C in a total condensation/variable take-off type column until all the bromoethane had distilled. After cooling, the residue was chromatographed on silica using dichloromethane/ethyl acetate (90:10, v/v) as eluent to afford (*E*)-diethyl(4,4,4-trifluoro-3-(trifluoromethyl)but-1-enyl)-phosphonate (**11d**) (0.48 g, 0.0015 mol, 57%) as a colourless oil. ^{1}H NMR δ: 1.39 (t, 6H, J=7.5 Hz); 3.73 (m, 1H, J=8.9 Hz); 4.17 (dq, 4H, J=7.5 Hz); 6.24 (t, 1H, J=16.7 Hz); 6.62 (ddd, 1H, J=8.9, 16.7, 20.9 Hz) ppm. ^{19}F NMR δ: −68.6 (d, J=7 Hz) ppm. IR (CCl_4) ν (cm^{-1}): 2960; 2915; 2885; 1670; 1430; 1380; 1350; 1310; 1245; 1170; 1110; 1040; 1020; 955. Analysis: Calc. for $C_9H_{16}F_6O_3P$(314.122): C, 34.41; H, 4.17%. Found: C, 34.71; H, 4.31%.

3.8. (E)-N-(4,4,4-trifluoro-3-(trifluoromethyl)but-1-enyl)succinimide (11e)

1-Bromo-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene (**2**) (1 g, 0.003 mol) was added to a mixture of succinimide (0.45 g, 0.003 mol), potassium carbonate (0.23 g, 0.00165 mol) and 18-crown-6 (3 mg) in toluene (5 ml). The mixture was heated to 110 °C for 3 h. Water (10 ml) was then added and, after decantation, the aqueous layer was extracted with ether (3×20 ml). The organic solution was washed with brine (3×20 ml) and dried over $MgSO_4$. After filtration, the solvents were evaporated under vacuum (20 mmHg). The residue was chromatographed on silica using dichloromethane/ethyl acetate (80:20, v/v) as eluent affording (*E*)-*N*-(4,4,4-trifluoro-3-(trifluoromethyl)but-1-enyl)succinimide (**11e**) (0.56 g, 0.002 mol, 68%) as white crystals, m.p. 125.1 °C. ^{1}H NMR δ: 2.73 (s, 4H); 3.87 (m, 1H, J=7.6, 9.5 Hz); 6.65 (dd, 1H, J=14.8, 9.5 Hz); 6.85 (d, 1H, J=14.8 Hz) ppm. ^{19}F NMR δ: −61.6 (d, J=7.6 Hz) ppm. IR (CCl_4) ν (cm^{-1}): 2950; 1720; 1650; 1370; 1340; 1290; 1260; 1230; 1210; 1180; 1140; 1090. Analysis: Calc. for $C_9H_7F_6NO_2$ (221.144): C, 48.87; H, 4.56%. Found: C, 48.79; H, 4.49%.

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