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2-Bromo-3,3,3-trifluoropropene: a facile trifluoromethylacetylene anion synthon

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Abstract

The introduction of trifluoromethylacetylene units into organic compounds has been further studied and extended. The direct reaction of two equivalents of Lithium Diisopropylamide with 2-bromo-3,3,3-trifluoropropene gave lithium trifluoromethylacetylide, the anion of which was trapped in greater than 90% overall yield with a variety of electrophiles.

Keywords: Trifluoromethylacetylene; 2-Bromo-3,3,3-trifluoropropene; Organic compounds

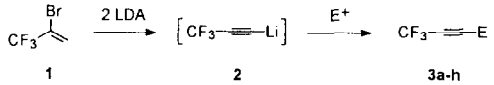
1. Introduction

Fluorinated organometallic reagents are of general interest as synthetic intermediates for introducing a fluorinated unit into organic compounds [1,2]; many of these products possess enhanced biological and physiological activity [3,4]. The trifluoromethylethyne moiety is particularly useful since it can undergo a range of subsequent transformations, and can be introduced via the corresponding organolithium [5], Grignard [6] or organozinc reagent [7,8]. The usual precursor to these useful organometallic species is trifluoromethylacetylene; a gas which, although commercially available, is expensive and difficult to prepare and handle [9]. To the best of our knowledge, the only reported preparations of metal trifluoromethylacetylides which do not involve handling trifluoromethylacetylene gas are: (i) trifluoropropynyl zinc reagents prepared from 1,1,1-trifluoro-perchloropropane or 3,3,3-trifluoro-1,1,2-trichloropropene [10], which have low reactivities [7]; and (ii) Ishihara et. al.'s [11] preparation of fluoroalkyl substituted propargyl alcohols from the fluoride ion catalyzed reaction of 1H-F-1-alkenephosphonates with silyl enol ethers. For trifluoromethyl substituted propargyl alcohols, only low yields were obtained; and the method required a multiple-step sequence. Because of the gap in the literature of a satisfactory trifluoromethylacetylene synthon, we decided to investigate the use of 2-bromo-3,3,3-trifluoropropene (**1**) for this purpose. When the planned work was completed and we had succeeded in our aim, Yamazaki and his co-workers [12] published an article along the same lines as our concept. We can confirm their work and we now present our independent results which give a variety of additional examples.

2. Results and discussion

We confirm that the use of 2-bromo-3,3,3-trifluoropropene (**1**) affords a convenient and high yielding method to introduce a trifluoromethylethynyl moiety into a range of organic substrates. Trifluoropropynyl lithium (**2**) was prepared in high yield in THF at −78°C by the reaction of 2-bromo-3,3,3-trifluoropropene (**1**) with two equivalents of lithium diisopropylamide. Compound **1** is a liquid which was easily and economically prepared in high yield from commercially available materials, according to literature procedures [5,13] (Scheme 1).

The Japanese group utilized nine aldehydes and two ketones as electrophiles in their work: all of which gave excellent yields. In our case, two additional aldehydes and three additional ketones were used, as well as three of the same carbonyl compounds as used by the Japanese group; the expected addition products **3a–h** were formed in 90–98% isolated yields (see Table 1). One difference between ours and the Japanese experimental procedure is the addition sequence: we added LDA to the solution of compound **1** in



Scheme 1.

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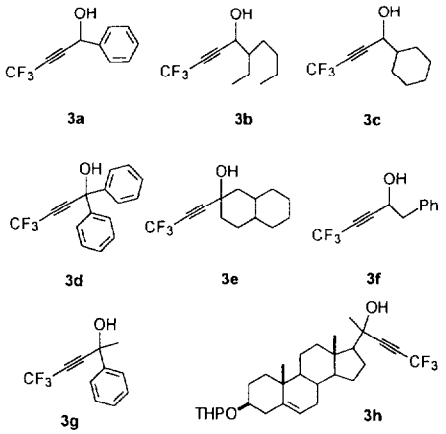
THF, while they added the precooled THF solution of compound **1** to a THF solution of LDA. Evidently, both methods afford the products in excellent yield.

The structures of the products **3a–h** were supported by IR and NMR spectra. For compound **3a**, a strong signal was found at 2277 cm^{-1} in its IR spectrum, which indicates the presence of a triple bond; three quartet carbon signals were found in the ^{13}C NMR spectrum, because of coupling between carbon and fluorine. For novel structures (**3b**, **3d**, **3e**, **3h**) and the known compounds (**3c**, no NMR results previously reported [11]), microanalyses were obtained to confirm the structures. For the other known compounds (**3a**, **3f**, **3g**), the NMR data obtained are in agreement with literature data (Scheme 2).



Scheme 2.

Reported preparation of **2** by deprotonation of trifluoromethylacetylene and reactions with a variety of ketones gave the expected adducts in only 25–70% yield [5]. Alternatively, reported yields of trifluoropropargyl alcohols were only 34–45% [11] when trifluoromethylacetylene was prepared in situ from fluorinated alkenephosphonates and reacted with aldehyde equivalents. Thus the present method represents a much more efficient procedure than those currently available.

In conclusion, we agree with the conclusion [12] of the Japanese group that lithium trifluoromethylacetylide can be prepared cheaply and easily from 2-bromo-3,3,3-trifluoropropene, and the reagent thus formed gives much higher yields of adducts than when it is formed by other literature methods.

3. Experimental section

3.1. General

The 2-bromo-3,3,3-trifluoropropene (**1**) was prepared according to literature methods [5], all other materials were obtained commercially and used without purification. Melting points were determined on a Kofler hot stage apparatus without correction. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 300 MHz spectrometer [δ in ppm from tetramethylsilane (0 ppm), $CDCl_3$ (77.0 ppm) and fluorotrichloromethane (0 ppm) for ^{1}H, ^{13}C and ^{19}F NMR, respectively, positive for downfield shifts] in $CDCl_3$. Column chromatography was carried out using 230–400 mesh silica.

3.2. Preparation of Lithium Trifluoromethylacetylide and Addition to Electrophiles; General Procedure

LDA (7.3 mL of 1.5 M solution in cyclohexane) was added slowly with stirring to a solution of 2-bromo-3,3-trifluoropropene (0.96 g, 5.5 mmol) in dry THF (20 mL) at −78 °C. The resulting red/black solution was stirred at this temperature for a further 10 min. The electrophile (5 mmol dissolved in 5 mL dry THF) was added dropwise over several minutes, and the pale yellow solution was stirred at −78 °C for a further hour, then allowed to warm to room temperature. The reaction mixture was poured into saturated aqueous ammonium chloride and extracted with diethyl ether. The organic phase was dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting oil was purified by column chromatography on silica gel. The yields and microanalytical data for these reactions are reported in Table 1.

Table 1
Yields and Characterization of Compounds **3a–h**

Product	Isolated yield (%)	Literature yield (%)	Ref.	Microanalysis: Found C	Found H	Formula	Calcd C	Calcd H
3a	95	83	[14]	-	-	$C_{10}H_7F_3O$	-	-
3b	96	-	-	59.51	7.93	$C_{11}H_{17}F_3O$	59.45	7.71
3c	90	45	[11]	58.06	6.55	$C_{10}H_{13}F_3O$	58.25	6.35
3d	98	-	-	69.57	3.97	$C_{16}H_{11}F_3O$	69.55	4.02
3e	92	-	-	63.16	6.74	$C_{13}H_{17}F_3O$	63.38	6.96
3f	93	61	[15]	-	-	$C_{11}H_9F_3O$	-	-
3g	92	69	[5]	-	-	$C_{11}H_9F_3O$	-	-
3h	95	-	-	70.29	8.51	$C_{29}H_{41}F_3O_3$	70.42	8.35

3.3. 1-Phenyl-4,4,4-trifluorobut-2-yn-1-ol (3a) [14]

yellow oil; ^{1}H NMR δ 2.62 (br s, 1H), 5.52 (s, 1H), 7.38–7.45 (m, 3H) and 7.47–7.51 (m, 2H); ^{13}C NMR δ 63.7, 73.3 (q, J = 53.0 Hz), 86.4 (q, J = 6.1 Hz), 114.1 (q, J = 257.5 Hz), 126.6, 128.9, 129.2 and 137.8; ^{19}F NMR δ −51.1 (d, $J_{H\text{-}F}$ = 2.5 Hz).

3.4. 5-Ethyl-1,1,1-trifluoronon-2-yn-4-ol (3b)

yellow oil; ^{1}H NMR (mixture of two diastereoisomers) δ 0.75–0.90 (m, 6H), 1.15–1.60 (m, 9H), 2.80 (br s, 1H) and 4.45 (br s, 1H); ^{13}C NMR (mixture of two diastereoisomers, peaks for minor isomer in square brackets) δ 11.3 [11.2], 13.9 [13.8], 22.4 [22.3], 22.9 [22.8], 28.9 [28.8], 29.3 [29.2], 45.4, 63.4, 72.7 (q, J = 53.1 Hz), 87.8 (q, J = 5.5 Hz) and 114.2 (q, J = 257.0 Hz); ^{19}F NMR δ -51.0 (s).

3.5. 1-Cyclohexyl-4,4,4-trifluorobut-2-yn-1-ol (3c) [12]

light yellow oil; ^{1}H NMR δ 1.0–1.36 (m, 5H), 1.58–1.75 (m, 2H), 1.76–1.90 (m, 4H), 2.38 (br s, 1H) and 4.26 (dq, $J_{H\text{-}H}$ = 6.1 Hz, $J_{H\text{-}F}$ = 2.9 Hz, 1H); ^{13}C NMR δ 25.8, 26.1, 28.0, 28.3, 43.4, 66.5, 72.8 (q, J = 51.8 Hz), 87.3 (q, J = 6.1 Hz) and 114.1 (q, J = 255.8 Hz); ^{19}F NMR δ -50.6 (d, $J_{H\text{-}F}$ = 2.8 Hz).

3.6. 1,1-Dihenyl-4,4,4-trifluorobut-2-yn-1-ol (3d)

white microcrystals, mp 54–56 °C; ^{1}H NMR δ 2.80 (br s, 1H), 7.25–7.40 (m, 6H) and 7.45–7.50 (m, 4H); ^{13}C NMR δ 73.9 (q, J = 53.1 Hz), 74.2, 89.2 (q, J = 6.7 Hz), 114.3 (q, J = 258.2 Hz), 125.9, 128.5, 128.6 and 142.5; ^{19}F NMR δ -50.8 (s).

3.7. 2-(3,3,3-trifluoro-1-propynyl)-2-decalinol (3e)

white needles, mp 65–67°C; ^{1}H NMR (mixture of isomers) δ 2.26 (br s, 1H) and 0.73–2.06 (m, 16H); ^{13}C NMR (mixture of isomers) δ 21.0, 25.5, 26.0, 26.2, 26.3, 28.7, 28.8, 30.8, 31.0, 32.8, 33.1, 33.2, 33.5, 34.2, 34.3, 34.5, 36.7, 38.9, 39.3, 40.0, 42.2, 46.2, 67.0, 69.3, 70.0, 72.3 (q, J = 53.0 Hz), 90.6 (m) and 114.7 (q, J = 257.0 Hz); ^{19}F NMR δ -50.5 (s) [-50.6 (s), minor isomer].

3.8. 5,5,5-Trifluoro-1-phenylpent-3-yn-2-ol (3f) [15]

light yellow oil; ^{1}H NMR δ 2.60 (br s, 1H), 3.03 (d, J = 6.3 Hz, 2H), 4.60 (br s, 1H) and 7.24–7.38 (m, 5H); ^{13}C NMR δ 42.8, 62.4, 72.8 (q, J = 52.0 Hz), 87.2 (q, J = 6.3 Hz), 114.0 (q, J = 256.0 Hz), 127.4, 128.6, 129.7 and 135.1; ^{19}F NMR δ -51.1 (s).

3.9. 5,5,5-Trifluoro-2-phenyl-3-pentyn-2-ol (3g)

white microcrystals, mp 71–72 °C [lit. value [5] 71–73 °C]; ^{1}H NMR δ 1.81 (s, 3H), 3.87 (br s, 1H), 7.25–7.36 (m, 3H) and 7.52 (d, J = 8.0 Hz, 2H); ^{13}C NMR δ 32.0, 69.7, 72.0 (q, J = 52.5 Hz), 90.1 (q, J = 5.9 Hz), 114.4 (q, J = 256.0 Hz), 124.6, 128.4, 128.6 and 143.1; ^{19}F NMR δ -50.8 (s).

3.10. 3β-(Tetrahydropyranyloxy)-23,23,23-trifluorochol-5-en-22-yn-20(R,S)-ol (3h):

white needles, mp 164–165 °C; ^{1}H NMR (mixture of two diastereoisomers) δ 0.85 (s, 3H), 0.95 (s, 3H), 1.10–1.25 (m, 2H), 1.35–2.10 (m, 26H), 2.25–2.32 (m, 2H), 3.36–3.50 (m, 2H), 3.82–3.90 (m, 1H), 4.64–4.68 (m, 1H) and 5.30–5.35 (m, 1H); ^{13}C NMR (mixture of two diastereoisomers) δ 13.2, 19.3, 19.9, 20.8, 24.1, 24.9, 25.5, 27.9, 31.2, 31.3, 31.4, 31.7, 31.8, 36.7, 37.2, 40.0, 40.2, 43.3, 50.0, 56.1, 59.9, 62.7, 70.9, 73.1 (q, J = 52.0 Hz), 75.9, 91.1 (q, J = 7.6 Hz), 96.6, 114.2 (q, J = 257.0 Hz), 121.2 and 141.2; ^{19}F NMR δ -50.9 (s) [-50.7 (s), minor isomer].

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