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A Facile and Practical Synthesis of 1-Aryl-3,3,3-trifluoropropynes

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Synopsis. A facile and practical method for the synthesis of $ArC{\equiv}CCF_3$ is described which involves (1) conversion of aldehydes ArCHO into $ArCH{=}CClCF_3$ with 1,1,1-trichloro-2,2,2-trifluoroethane, zinc powder, and acetic anhydride in one-pot and (2) dehydrochlorination with sodium *t*-butoxide or sodium amide/*t*-butyl alcohol.

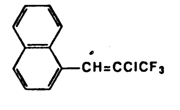
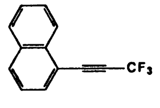
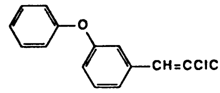
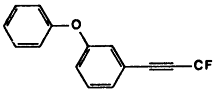
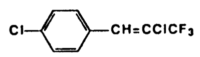
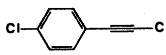
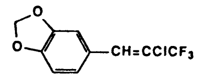
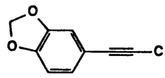
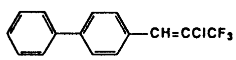
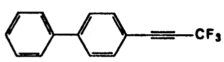
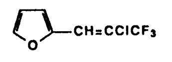
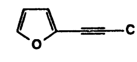
In view of rapidly growing role of organofluorine compounds particularly in material and pharmaceutical science, synthesis of organofluorine compounds is becoming more and more important.[1] Introduction of fluorine and polyfluoroalkyl groups to organic molecule at the late stage of the synthesis often encounters technical and economical problems.[2,3] Use of fluorine-containing building blocks[2] is the alternative approach to the synthesis of organofluorine compounds. Of various trifluoromethyl-substituted building blocks, 1-aryl-3,3,3-trifluoropropynes, which were studied previously with structural interest,[4] have recently been attracting much attention from polymer chemists,[5] organometallic chemists,[6] and synthetic chemists[7] as well as pharmaceutical scientists.[8] Synthetic methods of this type of acetylenes reported so far are classified into four categories: (1) Bromination of trifluoromethylethenes followed by double dehydrobromination,[9] (2) thermal decomposition of triphenylphosphonium trifluoroacetylmethylylides,[8] (3) palladium-mediated coupling reaction of 3,3,3-trifluoropropyne with iodoarenes,[5] and (4) trifluoromethylation of stannylacetylenes.[10] The method (1) is chronologically the first one but suffers restricted application, since we failed to apply the procedure to an acetylene of higher boiling points, e.g. 1-(1-naphthyl)-3,3,3-trifluoropropyne. The second one is suitable only for laboratory-scale synthesis. The third method apparently have practical advantage, but trifluoropropyne should be generated in situ from a relatively expensive precursor.[11] The last one is of no practical use. We report herein a readily accessible two-step entry for the synthesis of 1-aryl-3,3,3-trifluoropropynes.

$$RCHO + CCl_3CF_3 \longrightarrow \underset{\mathbf{1}}{RCH{=}CClCF_3} \longrightarrow \underset{\mathbf{2}}{RC{\equiv}CCF_3}$$

Results and Discussion

Aldehydes RCHO are readily transformed to olefins $RCH{=}CClCF_3$ (**1**) by the one-pot reaction which employs 1,1,1-trichloro-2,2,2-trifluoroethane, zinc powder, and acetic anhydride.[12] Dehydrochlorination of the olefins should give rise to the desired acetylenes $RC{\equiv}CCF_3$ (**2**). We studied various bases to effect the *β*-elimination. Tertiary amines and lithium amides were totally ineffective. Potassium *t*-butoxide gave fair amount of the acetylenes. Changing the counter ion to sodium or employing a reagent derived from sodium amide and *t*-butyl alcohol was found to be highly effective. Various olefins of $RCH{=}CClCF_3$ were treated with the sodium amide/*t*-butyl alcohol system. Although the olefins which have R = aliphatic or alicylic were either recovered unchanged or decomposed, those having aryl groups gave excellent yields of acetylenes. Results are listed in Table 1.

Table 1. Dehydrochlorination of **1**

Run	Olefin	Product	Yield/%[a]
1			90[b]
2			91[c]
3			51[d]
4			77[e]
5			81[c] 95[f]
6			60[g]

a) Isolated yields after distillation unless otherwise stated. b) The reaction was carried out in 0.78 mmol scale. c) The reaction was carried out in 2 mmol scale. d) The reaction was carried out in 0.46 mmol scale. e) The reaction was carried out in 1 mmol scale. f) The reaction was carried out in 0.01 mol scale. g) Estimated by ^{19}F NMR with 1,3,5-trichloro-2,4,6-trifluorobenzene as an internal standard. This reaction was carried out in 2 mmol scale.

In addition to 3,3,3-trifluoropropynyl-substituted carbocyclic aromatics (Runs 1—5), a furan derivative (Run 6) is now accessible. Our strategy is based on two-carbon elongation of ArCHO by using inexpensive reagents and thus find wide practical application.

Experimental

Boiling points were measured by use of Büchi Kugelrohor or Glass Tube Oven (Shibata) and are given in °C/Torr(1 Torr=133.322 Pa). ^1H NMR spectra (tetramethylsilane as an internal standard) were obtained with a Hitachi R-90H or Varian EM-390 spectrometer and ^{19}F NMR spectra (trichlorofluoromethane as an internal standard) with a Hitachi R-20B spectrometer. IR data were recorded with a JASCO A-202 spectrometer. MS spectra (70 eV) were recorded with a Hitachi RMU-6MC machine. Sodium amide was purchased from Yoneyama Chem. Ind. and used directly. Benzene and *t*-butyl alcohol were freshly distilled before use over benzophenone ketyl and calcium hydride respectively. The chlorotrifluoromethyl substituted olefins **1** were prepared through a modified procedure of our previous publication.[12]

2-Chloro-3,3,3-trifluoro-1-(1-naphthyl)propene. To a *N,N*-dimethylformamide (DMF) (20 ml) solution of 1-naphthalenecarbaldehyde (3.12 g, 20.0 mmol) were added 1,1,1-trichloro-2,2,2-trifluoroethane (2.84 ml, 24.0 mmol) and zinc powder (1.44 g, 22.0 mmol), and the mixture was stirred at room temperature for 1 h and at 50 °C for 24 h before treatment with acetic anhydride (3 ml) and zinc powder (2.62 g, 40 mmol). The resulting mixture was stirred at 50 °C for 2 h, poured to 10% hydrochloric acid (100 ml) and extracted with diethyl ether (100 ml×3 times). The ethereal extract was washed with sat sodium hydorgencarbonate (50 ml) aq solution and then with sat sodium chloride aq solution (50 ml×twice) and dried over magnesium sulfate. Filtration and concentration followed by distillation in vacuo gave the desired olefin (3.2 g, 62% yield) as a colorless oil. Bp 89 °C (bath temp)/0.3 Torr; ^{1}H NMR ($CDCl_3$) δ=7.3—7.6 (m, 3H), 7.7—7.9 (m, 4.5H); ^{19}F NMR ($CDCl_3$-$CFCl_3$) δ=69.0 (s) for (*Z*)-isomer, 62.2 (s) for (*E*)-isomer, intensity ratio (*Z*):(*E*)=7:1. IR (neat) 3060, 1640, 1285, 1260, 180, 1160, 1140, 960, 800, 770 cm^{-1}; MS *m/z* (rel intensity) 256 (48, M$^+$), 221 (100), 201 (74), 152 (79). Found: C, 60.93; H, 3.34%. Calcd for $C_{13}H_8ClF_3$: C, 60.84; H, 3.14%.

2-Chloro-3,3,3-trifluoro-1-(2-furyl)propene. To furfural (1.66 ml, 20.0 mmol) dissolved in DMF (20 ml) were added 1,1,1-trichloro-2,2,2-trifluoroethane (2.85 ml, 24 mmol) and zinc powder (1.44 g, 22 mmol), and the resulting mixture was stirred at 50 °C for 4 h. Acetic anhydride (3.0 ml, 27 mmol) and zinc powder (2.62 g, 40 mmol) were added to the mixture at 0 °C, and the whole was stirred at 50 °C for 1 h and then at 50 °C for 18 h. After workup as above, the ether solvent was stripped off by atmospheric distillation through 10 cm-Vigreux column. Final distillation afforded the title olefin (2.12 g, 54% yield) as a colorless oil. Bp 60 °C (bath temp)/20 Torr. ^{1}H NMR ($CDCl_3$) δ=6.55 (dd, 1H), 7.13 (dd, 1H), 7.22 (s, 1H) for the (*Z*)-isomer, 6.47 (dd, 1H), 6.69 (d, 1H), 6.94 (s, 1H), 6.49 (d, 1H) for the (*E*)-isomer, (*Z*):(*E*)=6:1. ^{19}F NMR ($CDCl_3$-$CFCl_3$) δ=69.0 (s) for (*Z*)-isomer, 63.0 for (*E*)-isomer; IR (neat) 3160, 3070, 2950, 1650, 1480, 1290, 1180, 1140, 1020, 970, 880, 742 cm^{-1}; MS *m/z* (rel intensity) 196 (100, M$^+$), 167 (27), 133 (31), 113 (17), 99 (16), 83 (10), 63 (20). Found: C, 42.77; H, 1.84%. Calcd for $C_7H_4ClF_3O$: C, 42.78; H, 2.05%.

1-(1-Naphthyl)-3,3,3-trifluoropropyne. A Typical Procedure for Dehydrochlorination of 1. A benzene (1 ml) solution of 2-chloro-1-(1-naphthyl)-3,3,3-trifluoropropene (0.20 g, 0.78 mmol) and *t*-butyl alcohol (0.5 ml) was added to sodium amide (0.22 g, 5.2 mmol) suspended in benzene (2 ml), and the mixture was heated to reflux for 5 h. The reaction mixture was poured to 10% hydrochloric acid (10 ml) and extracted with ether (20 ml×3). The combined ethereal extract was washed with aq sodium hydrogencarbonate solution (20 ml×2) and dried over magnesium sulfate. Filtration, concentration under reduced pressure followed by preparative TLC (silica gel, hexane) afforded 1-(1-naphthyl)-3,3,3-trifluoropropyne (0.156 g, 90% yield) and the recovered starting material (3%). The acetylene showed bp 95 °C (bath temp)/0.7 Torr; ^{1}H NMR ($CDCl_3$) δ=7.20—7.90 (m, 6H), 8.10—8.20 (m, 1H); ^{19}F NMR ($CDCl_3$-$CFCl_3$) δ=49.5 (s); IR (neat) 3800, 2250, 1400, 1315, 1260, 1205, 1140, 800, 770 cm^{-1}; MS *m/z* (rel intensity) 220 (100, M$^+$), 201 (48), 170 (28), 150 (10), 85 (14). Found: C, 70.85; H, 3.31%. Calcd for $C_{13}H_7F_3$: C, 70.91; H, 3.20%.

1-(1-Naphthyl)-3,3,3-trifluoropropye. An Alternative Procedure with Sodium *t*-Butoxide. Sodium *t*-butoxide was prepared by heating a mixture of sodium amide (0.29 g, 74 mmol), benzene (2 ml), and *t*-butyl alcohol (0.7 ml) at reflux temperature for 1 h. 2-Chloro-1-(1-naphthyl)-3,3,3-trifluoropropene (0.26 g, 1.0 mmol) dissolved in benzene (1 ml) was added, and the mixture was heated to reflux for 5 h. Workup as above followed by purification by TLC gave the desired acetylene (161 mg, 73% yield) and the starting material (9%).

Other acetylenes in Table 1 were prepared by the typical procedure and showed following physical properties.

1-(3-Phenoxyphenyl)-3,3,3-trifluoropropyne: Bp 140 °C (bath temp)/1.5 Torr; ^{1}H NMR ($CDCl_3$): δ=6.93—7.40 (m); ^{13}C NMR ($CDCl_3$): δ=75.9 (q,$J_{C\text{-}CF_3}$=52.6 Hz), 85.9 (sextet, *J*=6.4 Hz), 114.8 (q,J_{CF_3}=256.9 Hz), 119.5 (d), 119.8 (d), 121.3 (d), 127.2 (d), 121.8 (d), 124.2 (d), 127.0 (d), 130.0 (d), 130.1 (d), 156.1 (s), 157.7 (s); ^{19}F NMR ($CDCl_3$-$CFCl_3$) δ=50.3 (s); IR (KBr) 3100, 3050, 2260, 1580, 1490, 1325, 1203, 1140, 695, 685 cm^{-1}; MS *m/z* (rel intensity) 262 (100, M$^+$), 165 (42), 94 (5), 77 (56), 51 (39). Found: C, 68.76; H, 3.36%. Calcd for $C_{15}H_8F_3O$: C, 68.97; H, 3.09%.

1-(4-Chlorophenyl)-3,3,3-trifluoropropyne: Bp 60 °C (bath temp)/5 Torr (lit[8] 64 °C/44 Torr); ^{1}H NMR ($CDCl_3$) δ=7.32 (d, 2H), 7.48 (d, 2H); ^{19}F NMR ($CDCl_3$-$CFCl_3$) δ=50.3 (s); IR (neat) 2940, 2870, 2260, 1598, 1495, 1325, 1310, 1130—1180, 1105, 1085, 1015, 870, 830, 750, 530 cm^{-1}; MS *m/z* (rel intensity) 204 (100, M$^+$), 185 (32), 169 (64), 154 (16), 99 (11), 74 (11), 50 (11).

1-(3,4-Methylenedioxyphenyl)-3,3,3-trifluoropropyne: Bp 95 °C (bath temp)/5 Torr; ^{1}H NMR ($CDCl_3$): δ=6.00 (s, 2H), 6.75 (d, 1H), 6.90 (α, 1H), 7.70 (dd, 1H); ^{13}C NMR ($CDCl_3$): δ=74.4 (q, $J_{C\text{-}CF_3}$=52.3 Hz), 86.8 (sextet, $J_{C\text{-}CF_3}$=6.0 Hz), 101.8 (t), 108.8 (d), 111.5 (s), 111.9 (d), 115.0 (q, J_{CF_3}=256.4 Hz), 128.0 (d), 147.7 (s), 150.1 (s); ^{19}F NMR ($CDCl_3$-$CFCl_3$) δ=49.5 (s); IR (neat) 2920, 2250, 1500, 1440, 1315, 1240, 1180, 1140, 1100, 1040, 930, 860, 810, 610, 540 cm^{-1}; MS *m/z* (rel intensity) 214 (100, M$^+$), 195 (14), 156 (12), 106 (9), 87 (27). Found: C, 56.05; H, 2.56%. Calcd for $C_{10}H_5F_3O_2$: C, 56.09; H, 2.35%.

1-(2-Furyl)-3,3,3-trifluoropropyne: Boiling point of this compound could not be measured as it distilled with low-boiling solvents. Its analytical sample was obtained by preparative GLC. ^{1}H NMR ($CDCl_3$) δ=6.47 (dd, 1H), 6.92 (d, 1H), 7.53 (d, 1H); ^{13}C NMR ($CDCl_3$) δ=80.3 (q, $J_{C\text{-}CF_3}$=53.3 Hz), 111.4 (d), 114.9 (q, J_{CF_3}=257.5 Hz), 120.1 (d), 128.4 (s), 133.4 (q, *J*=1.9 Hz), 146.1 (d); ^{19}F NMR ($CDCl_3$-$CFCl_3$) δ=51.0 (s); IR (neat) 3150, 2260, 2240, 1300, 1220, 1190, 1150, 1010 cm^{-1}; MS *m/z* (rel intensity) 160 (100, M$^+$), 141 (25), 131 (29), 106 (14), 81 (39), 78 (29), 63 (65). Found: C, 52.30; H, 1.82%. Calcd for $C_7H_3F_3O$: C, 52.52; H, 1.89%.

1-(4-Phenylphenyl)-3,3,3-trifluoropropyne. A Procedure for Gram-Order Synthesis. Sodium amide (2.73 g, 0.07 mol) was added to a benzene (50 ml) solution of 2-chloro-1-(4-phenylphenyl)-3,3,3-trifluoropropene (2.82 g, 0.01 mol) under an argon atmosphere. To the resulting mixture was added *t*-butyl alcohol (6.64 ml, 0.07 mol) at room temperature. The mixture immediately turned to thick under slightly exothermal evolution of ammonia. Benzene (30 ml) was added to facilitate stirring, and the whole was stirred for 2 h before treatment with 10% hydrochloric acid (100 ml). The organic layer was separated, and the aqueous layer was extracted with ether (50 ml×2). The combined organic layer was washed with sat sodium hydrogencarbonate aq solution (50 ml×2) and dried over sodium sulfate. Concentration followed by column chromatography (silica gel, hexane) afforded the title acetylene (2.34 g, 95% yield) as colorless solid. Mp 87 °C; ^{1}H NMR ($CDCl_3$): δ=7.30—7.60 (m); ^{13}C NMR ($CDCl_3$): δ=76.3 (q, $J_{C\text{-}CF_3}$=52.9 Hz), 86.6 (m), 114.0 (q, J_{CF_3}=256.6 Hz), 117.2 (m), 127.1 (d), 127.2 (d), 128.3 (d), 129.0 (d), 132.9(d), 139.6 (s), 143.7 (s); ^{19}F NMR ($CDCl_3$-$CFCl_3$) δ=49.9 (s); IR (KBr) 3100, 3050, 2270, 2200, 1530, 1490, 1410, 1330, 1220, 1170, 1120—1140, 875, 848, 767, 720, 690 cm^{-1}; MS *m/z* (rel intensity) 246 (100, M$^+$), 227 (10), 196 (5), 176 (7), 123 (5). Found: C, 72.90; H, 3.59%. Calcd for $C_{15}H_9F_3$: C, 73.17; H, 3.68%.

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