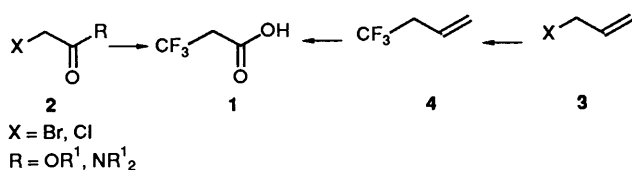# Trifluoromethylation of Aliphatic Halogen Compounds

Jean-Philippe Bouillon, Christian Maliverney, Robert Merényi and Heinz G. Viehe *
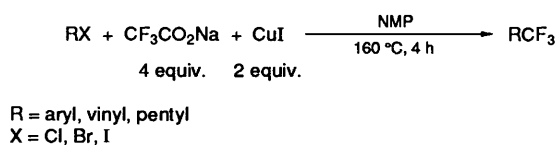*Laboratoire de Chimie Organique, Place L. Pasteur, 1, B-1348 Louvain-la-Neuve, Belgium*

Aryl, heteroaryl or vinyl halides can be trifluoromethylated using CF_3CO_2Na–CuI. With alkyl iodides, however, the method fails, yielding trifluoroacetyl esters instead. Allylic halogens can be substituted with Burton's reagent, obtained from dihalogenodifluoromethane *via* CF_3CdHal and transmetallation with CuI. A new access to trifluoropropionic acid is thereby found. Prop-2-ynyl bromide produces trifluoromethylallene. Attempts at trifluoromethylation of bromoacetate with CF_3CO_2Na–CuI in NMP (*N*-methyl-2-pyrrolidone) solution led to formation of the trifluoroacetoxy derivative and of a formal adduct of hexafluoroacetone to the α position of NMP.

In comparison with trifluoroacetic acid chemistry, that of its homologue, 3,3,3-trifluoropropionic acid **1** is much less accessible.[1–6] We have recently reported on the synthesis and reactions of the related new C_3 trifluoro-lactic and -pyruvic thioamides.[7] Here we describe attempts at new trifluoromethylations for the direct or indirect preparation of **1** starting from either halogenoacetates **2**, or the corresponding amides, or from allylic halides **3** with subsequent oxidation of 4,4,4-trifluorobutene **4** (Scheme 1).

2   1   4   3

X = Br, Cl
R = OR¹, NR¹₂

Scheme 1

Of the two methods of trifluoromethylation, the first stemmed from former work by Carr *et al.*,[8] based on the report by Matsui *et al.*[9] on the trifluoromethylation of halogenoaromatic compounds extended to halogenovinyl and halogenoalkyl derivatives. It involves the *in situ* reaction of a formal equivalent of the trifluoromethyl anion generated when sodium trifluoroacetate is thermally decomposed in aprotic dipolar solvents such as *N*-methylpyrrolidone (NMP) in the presence of cuprous iodide (Scheme 2).

$$RX + CF_3CO_2Na + CuI \xrightarrow[160\ °C,\ 4\ h]{NMP} RCF_3$$

4 equiv.   2 equiv.

R = aryl, vinyl, pentyl
X = Cl, Br, I

Scheme 2

The yields are generally excellent and are hereby confirmed for halides with aryl, heteroaryl or vinyl substituents. However, the former report on the synthesis of 1,1,1-trifluorohexane[8] **5** is now recognized as erroneous, producing instead pentyl trifluoroacetate **6** (Scheme 3). Heptyl and nonyl iodide also
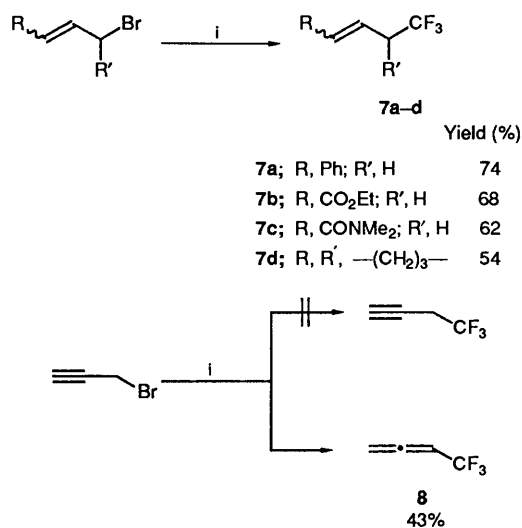
5
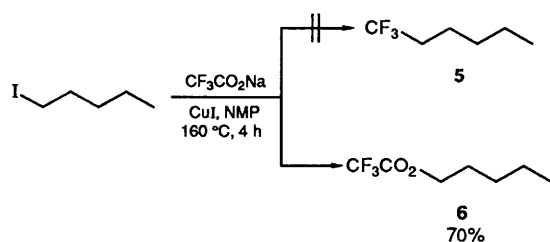
6
70%
Scheme 3

produced the respective trifluoroacetates in 53 and 42% yield, instead of trifluoroalkanes.[10] Apparently the nucleophilic substitution with iodoalkanes is faster than the decarboxylation of copper trifluoroacetate.

The second approach to trifluoromethylation using a trifluoromethyl copper reagent was described by Burton and involves the reaction of dihalogenodifluoromethane with either metallic zinc or cadmium in *N*,*N*-dimethylformamide (DMF), followed by transmetallation with CuI.[11,12] Allyl chloride can also be substituted in high yield at room temperature (Scheme 4).

70%
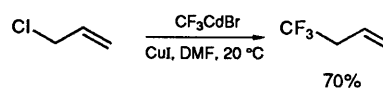
Scheme 4

This method is now found to be applicable also to secondary allylic bromides and to bromo-crotonate or -amide, whereas prop-2-ynyl bromide produces by S_N2'-substitution the known trifluoromethyl propadiene **8**, in analogy to reactions observed recently by Burton[13] and Hung[14] (Scheme 5).

7a–d

Yield (%)

7a; R, Ph; R', H   74
7b; R, CO₂Et; R', H   68
7c; R, CONMe₂; R', H   62
7d; R, R', —(CH₂)₃—   54

8
43%

Scheme 5 *Reagents and conditions:* i, CF_3CdBr, CuI, DMF, 20 °C

Since halogenoacetates are formally heteroallylic systems, trifluoromethylation using the CF_3CdBr–CuI method was attempted, but only traces of product were obtained, as evidenced by ^{19}F NMR spectroscopy. The CF_3CO_2Na–CuI method in NMP also failed, producing mainly the trifluoroacetoxyacetate **9**, as well as an unexpected formal aldol adduct of the solvent to hexafluoroacetone **10** (Scheme 6). It could be
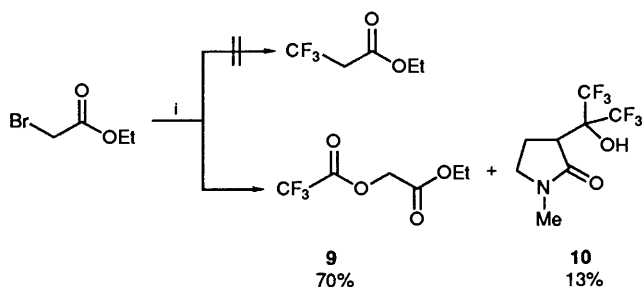
Scheme 6 *Reagents and conditions:* i, CF₃CO₂Na, CuI, NMP, 160 °C, 4 h

shown that this adduct was formed from the alkyltrifluoro-acetate intermediate, since it was detected by ¹⁹F NMR spectroscopy in the crude mixture of the reaction of pentyl iodide (which has given pentyl trifluoroacetate **6**).

Octyl trifluoroacetate also was allowed to react with CF₃CO₂Na–CuI–NMP to give the same adduct **10**, as shown by ¹⁹F NMR spectroscopy. A second step involves [CF₃Cu], but it may react following both routes of Scheme 7.
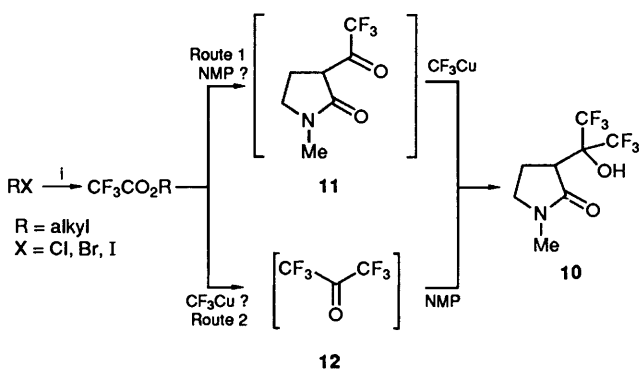
Scheme 7 *Reagents and conditions:* i, CF₃CO₂Na, CuI, NMP, 160 °C, 4 h

Experimental evidence for route 1 is that, 3-trifluoroacetyl-NMP **11** furnished 15% yield of **10** when treated with CF₃CO₂Na–CuI. For route 2, that hexafluoroacetone **12** reacted with NMP–CuI at 160 °C, as shown by NMR spectroscopy.

Since halogenoacetates could not yet be trifluoromethylated in substantial yields a route from allyl bromide, *via* trifluoro-propionic acid **1**, to the *N,N*-dimethylamide **13** was established according to Scheme 8.
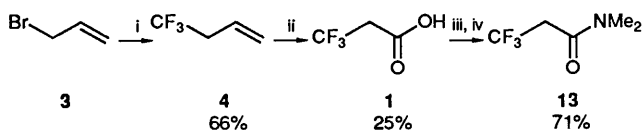
Scheme 8 *Reagents and conditions:* i, CF₃CdBr, CuI, DMF, 20 °C; ii, KMnO₄, crown ether (18-6), benzene, 20 °C; iii, SOCl₂, CH₂Cl₂; iv, NHMe₂, DMAP, CHCl₃

Experimental

M.p.s were taken using a Dr. Tottoli apparatus and are uncorrected. B.p.s were estimated using a Kugelrohr apparatus. IR and mass spectra were measured on a Perkin-Elmer 1710 and a Finnigan Mat TSQ70 apparatus, respectively. ¹H, ¹⁹F and ¹³C NMR spectra were recorded in a CDCl₃ solution on a Varian WXR or a Varian Gemini 200 spectrometer. TMS (Me₄SiCl) is the internal reference for ¹H and ¹³C spectra, and CFCl₃ for ¹⁹F spectra. Chemical shifts are in ppm on the δ scale and coupling constants *J* are given in Hz. The following

abbreviations are used: s singlet, d doublet, t triplet, q quartet, qt quintet and m multiplet.

Matsui Reaction with Pentyl Iodide: Pentyl Trifluoroacetate **6**.—A mixture of pentyl iodide (10 mmol), sodium trifluoro-acetate (4 equiv.) and copper iodide (2 equiv.) in anhydrous NMP (8 cm³) was heated to 160 °C during 4 h. After cooling, the volatile components were removed under reduced pressure and rectified at normal pressure with a horizontal distillation apparatus, to give pentyl trifluoroacetate **6** (0.85 g, 46%); b.p. 122 °C/740 mmHg; ν_{max}/cm⁻¹ 2935, 2880, 1770 (CF₃CO₂), 1460, 1300, 1175 and 745; δ_F −75.7 (s); δ_H 0.83 (3 H, t, *J* 7.6), 1.3–1.4 (4 H, m), 1.76 (2 H, qt, *J* 6.9) and 4.35 (2 H, t, *J* 6.1); δ_C decoupled 13.5, 21.9, 27.4, 27.6, 68.2, 114.6 (q, $^1J_{C,F}$ 286.3) and 157.7 (q, $^2J_{C,F}$ 42.0); *m/z* 113 (M⁺ − C₅H₁₁, 2%), 99, 95, 71 (C₅H₁₁) and 69.

Matsui Reaction with Ethyl Bromoacetate: Ethyl Trifluoro-acetoxyacetate **9** *and* 3-(1-*Hydroxy*-2,2,2-*trifluoro*-1-*trifluoro-methylethyl*)-1-*methyl*-2-*pyrrolidone* **10**.—Analogously, the same mixture with ethyl bromoacetate (10 mmol) was heated at 160 °C during 4 h. After cooling, it was diluted with diethyl ether (100 cm³), hydrolysed (aqueous NH₄Cl) and filtered through Celite. The organic layer was washed (aqueous NaCl), dried (MgSO₄) and evaporated. The crude product was distilled horizontally (50 °C/0.3 mmHg) to give the acetate **9**, as a clear colourless liquid (1.4 g, 70%), and an orange solid, which recrystallised from pentane as colourless needles (0.35 g, 13%) and analysed as the hexafluoro compound **10**.

Compound **9**: ν_{max}/cm⁻¹ 2965, 2860, 1800, 1765, 1440, 1390, 1360, 1230, 1140, 965 and 775; δ_F −75.4 (s); δ_H 1.19 (3 H, t, *J* 7.1), 4.24 (2 H, q, *J* 7.1) and 4.82 (2 H, s); *m/z* 200 (M⁺), 172, 155, 128, 99 and 69.

Compound **10**: m.p. 73 °C (pentane) (Found: C, 36.4; H, 3.4; N, 5.15. C₈H₉F₆NO₂ requires C, 36.23; H, 3.42; N, 5.28%; ν_{max}/cm⁻¹ 3100, 2945, 2920, 1655, 1500, 1410, 1270, 1190, 1155, 950 and 740; δ_F −72.6 (q, *J* 9.0) and −78.3 (q, *J* 9.1); δ_H 2.30 (2 H, m), 2.92 (3 H, d, *J* 0.9), 3.02 (1 H, t, *J* 10.0), 3.41 (2 H, dd, *J* 8.7 and 4.9) and 8.32 (1 H, s); δ_C 19.9 (t, $^1J_{C,H}$ 135.6), 29.9 (q, $^1J_{C,H}$ 139.7), 39.3 (d, $^1J_{C,H}$ 130.3), 47.2 (t, $^1J_{C,H}$ 144.5), 77.0 (m), 122.2 (q, $^1J_{C,F}$ 287.1), 123.3 (qd, $^1J_{C,F}$ 290.2 and $^3J_{C,H}$ 8.8) and 173.4 (s); *m/z* (M⁺), 246, 196, 97 and 69.

General Procedure for Trifluoromethylation of Allylic Brom-ides.—Burton's reagent, CF₃CdBr, was prepared in DMF following the reported procedure[11] to give a 1 mol dm⁻³ solution. This solution (1.5 equiv.) was added dropwise at −78 °C to a mixture of an allylic bromide and copper iodide (1 equiv.) in DMF (1 × 10⁻³ mol dm⁻³). The reaction mixture was warmed to room temperature and stirred during several hours; it was then diluted with diethyl ether, hydrolysed with aqueous NH₄Cl and filtered through Celite. The organic layer was washed with brine, dried (MgSO₄) and evaporated. The crude product was purified by chromatography (for **7a,c**) or by distillation (for **7b,d**).

4,4,4-*Trifluoro*-1-*phenylbut*-1-*ene* **7a**. With cinnamyl bromide (1.97 g, 10 mmol) the *title compound* **7a** was obtained as a colourless liquid (1.37 g, 74%) (Found: C, 64.6; H, 5.05. C₁₀H₉F₃ requires C, 64.51; H, 4.87%); ν_{max}/cm⁻¹ 3086, 3030, 2932, 1681, 1600, 1499, 1450, 747 and 694; δ_F −67.2 (t, $^3J_{F,H}$ 10.6); δ_H 2.94 (2 H, qdd, $^3J_{H,F}$ 10.6, 7.3 and 1.4), 6.8 (1 H, dt, *J* 15.9-*trans* configuration, 7.3), 6.56 (1 H, d, *J* 15.9), 7.3 (5 H, m); δ_C decoupled 37.3 (q, $^2J_{C,F}$ 30.0), 117.1 (q, $^3J_{C,F}$ 3.7), 126.2 (q, $^1J_{C,F}$ 272.2), 126.5, 128.1, 128.7, 136.4 and 136.8; *m/z* 186 (M⁺, 58%), 149, 117, 111, 91 and 77.

Ethyl 5,5,5-*trifluoropent*-2-*enoate* **7b**. With ethyl 4-bromobut-2-enoate (1.93 g, 10 mmol) the *title compound* **7b** was obtained

as a pale yellow liquid (1.15 g, 68%); b.p. 83 °C (Found: C, 45.9; H, 5.0. $C_7H_9F_3O_2$ requires C, 46.16; H, 4.98%); v_{max}/cm^{-1} 3440, 1729, 1670, 1296, 1039 and 720; δ_F −66.0 (t, $^3J_{F,H}$ 10.4); δ_H 1.30 (3 H, t, J 7.1), 3.01 (2 H, qdd, $^3J_{H,F}$ 10.4, 7.2 and 1.5), 4.2 (2 H, q, J 7.1), 6.06 (1 H, d, J 15.7-*trans* configuration), 6.83 (1 H, dt, J 15.7 and 7.2); δ_C decoupled 13.4, 36.1 (q, $^2J_{C,F}$ 30.8), 60.3, 125.1 (q, $^1J_{C,F}$ 277.2), 127.6, 134.7 (q, $^3J_{C,F}$ 3.6) and 165.1; m/z 182 (M$^+$, 26%), 113, 95, 90, 86, 73 and 67.

5,5,5-*Trifluoro*-N,N-*dimethylpent-2-enamide* **7c**. With 4-bromo-N,N-dimethylbut-2-enamide (1.92 g, 10 mmol) **7c** was obtained as a colourless liquid (1.12 g, 62%); b.p. 56 °C/0.5 mmHg; v_{max}/cm^{-1} 2934, 1670, 1641, 1398 and 714; δ_F −66.1 (t, $^3J_{F,H}$ 10.0); δ_H 3.0 (8 H), 6.50 (1 H, d, J 15.4-*trans* configuration), 6.72 (1 H, dt, J 15.4 and 7.7); δ_C decoupled 35.1, 36.3 (q, $^2J_{C,F}$ 30.3), 36.8, 124.9 (q, $^1J_{C,F}$ 272.0), 126.6, 131.2 (q, $^3J_{C,F}$ 3.6) and 166.3; m/z 181 (M$^+$, 57%), 112, 98 and 72.

3-*Trifluoromethylcyclohexene* **7d**. With 3-bromocyclohexene (1.62 g, 10 mmol) **7d** was obtained as a colourless liquid (0.82 g, 54%); b.p. 66 °C; v_{max}/cm^{-1} 3038, 2939, 2876, 2841, 1243, 986 and 910; δ_F −73.2 (d, $^3J_{F,H}$ 9.3); δ_H 1.5–1.9 (2 H, m), 2.16 (1 H, m), 2.83 (1 H, m), 3.2 (1 H, m), 5.63 (1 H, m) and 6.0 (1 H, m); δ_C decoupled 20.0, 21.6 (q, $^3J_{C,F}$ 2.5), 24.2, 39.8 (q, $^2J_{C,F}$ 26.9), 120.4 (q, $^3J_{C,F}$ 3.3), 127.4 (q, $^1J_{C,F}$ 279.6) and 132.4; m/z 150 (M$^+$, 38%), 130, 81 and 69.

4,4,4-*Trifluorobuta*-1,2-*diene* **8**. Unlike compounds **7**, 4,4,4-trifluorobuta-1,2-diene **8** was directly distilled out of the reaction mixture *in vacuo* (20 mmHg). With prop-2-ynyl bromide (2.98 g, 25 mmol) a liquid with very low boiling point was obtained (1.17 g, 43%); b.p. 17 °C; NMR spectra were measured in a sealed tube; δ_F −61.4 (m); δ_H 5.32 (2 H, m) and 5.50 (1 H, m); δ_C 81.4 (td, $^1J_{C,H}$ 171.4 and $^3J_{C,H}$ 6.3), 85.0 (dqm, $^1J_{C,H}$ 177.5 and $^2J_{C,F}$ 39.1), 122.4 (qm, $^1J_{C,F}$ 269.6) and 208.7 (m, $^3J_{C,F}$ 5.9).

Preparation of 3,3,3-*Trifluoro*-N,N-*dimethylpropanamide* **13**.—As described by Burton,[11] allyl bromide (6.05 g, 50 mmol) was treated with CF_3CdBr (75 mmol) in DMF to give the 4,4,4-trifluorobut-1-ene **4** (3.63 g, 66%). Compound **4** was oxidized with potassium permanganate *via* a reported procedure[15] (in benzene solution at room temperature with about 1% 18-crown-6 as catalyst) to give 3,3,3-trifluoropropionic acid **1** (1.06 g,

25%). After chlorination (SOCl$_2$) and amination with dimethylamine in the presence of 4-(N,N-dimethylamino)-pyridine, the desired product **13** was obtained as a colourless liquid (0.21 g, 71%); b.p. 123–125 °C; v_{max}/cm^{-1} 2978, 2938, 2876, 1659, 1403, 1279, 927, 837 and 730; δ_F −63.1 (t, $^3J_{F,H}$ 10.7); δ_H 3.07 (3 H, s), 3.15 (3 H, q, $^6J_{H,F}$ 1.5) and 3.25 (2 H, q, $^3J_{H,F}$ 10.7); δ_C decoupled 36.6, 37.6, 52.9 (q, $^2J_{C,F}$ 29.8) 117.4 (q, $^1J_{C,F}$ 294.2) and 163.1 (q, $^3J_{C,F}$ 4.2); m/z 155 (M$^+$, 10%), 111, 103, 83 and 72.

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