An Efficient Electrochemical Trifluoromethylation of Aromatic Halides with Bromotrifluoromethane and a Sacrificial Copper Anode

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The electrochemical cross-coupling of bromotrifluoromethane with aromatic or heteroaromatic iodides and bromides is successfully achieved in a one-compartment electrolysis cell fitted with a sacrificial copper anode.

Since the pioneer work of McLoughlin[1] and Kobayashi,[2] trifluoromethylcopper has been recognized as a convenient reagent for coupling with aromatic and heteroaromatic halides. Various methods have been proposed to provide access to this species, including reaction of CF_3I[2] or CF_2Br_2[3] with metallic copper, pyrolysis of copper trifluoroacetate,[4] CuF-induced decomposition of CF_3SiR_3[5], and metathesis reactions from cadmium,[6] or mercury[7] species. Little work has been done with the cheap but poorly reactive CF_3Br.[8]

In the course of our work on the use of sacrificial anodes in organic electrosynthesis,[9] we found that a copper anode enabled CF_3Cu species to be formed from CF_3Br. Electrolyses were performed in a one-compartment cell, fitted with a copper anode and a stainless steel cathode, under constant-current conditions, in dimethylformamide (DMF) as solvent. The addition of complexing agents such as triphenylphosphine, tributylphosphine, 2,2′-bipyridine (bpy) or tetramethylethylenediamine (tmeda) was found to be necessary to avoid the precipitation of copper(I) bromide. These ligands may also complex the organocopper species which exhibited ^{19}F NMR signals in the δ 25–35 (*vs.* $CFCl_3$) region and were able to couple, upon heating, with various halides.

We first developed a two-step procedure, involving CF_3Cu formation by electrolysis of the CF_3Br solution, and coupling, upon warming, with the subsequently added halide.

A typical procedure was as follows: freshly distilled DMF (35 ml), Bu_4NBr (1 mmol) as supporting electrolyte, and triphenylphosphine (20 mmol) were introduced in the electrolysis cell[9] fitted with a condenser, a copper anode (0.8 cm diameter, immersed to 2 cm) and a stainless steel grid as the cathode (20 cm^2 area). The cell was immersed in a cold bath (-15 °C) and CF_3Br was bubbled through the solution. A constant current of 0.3 A was passed for 6 h (6500 C).† 4-Iodoanisole (10 mmol) was then introduced in the cell, the solution was flushed with argon and the cell was heated in an oil bath (90 °C) during 3 h. It was then allowed to cool overnight. Hydrolysis (50 cm^3 HCl, 2 mol dm^{-3}) and decantation of the solid ($CuBr{\cdot}PPh_3$ complex) were followed by pentane extraction (3 × 50 ml). The solvent was distilled off. Chromatography on silica gel (70–230 mesh) with pentane as eluent gave 7.5 mmol of trifluoromethylanisole. The main by-product was 4-bromoanisole; traces of anisole and the corresponding biaryl and 4-pentafluoroethylanisole were detected.

Results involving various ligands are presented in Table 1. Lower yields were obtained with amines than with phosphines, the main by-product in these cases being the hydrogenation product. As expected, an aromatic iodide was more reactive than a bromide, and the presence of an electron-attracting group such as cyano or nitro favoured the coupling reaction. With the strongly electron-withdrawing nitro group, even a chloride could react with moderate yield.

In some experiments, both aromatic halide and CF_3Br were introduced at the beginning of the electrolysis. The aromatic halide did not react during the electrolysis and the coupling reaction started only on heating. This prompted us to develop a one-step procedure, with the electrolysis performed at 90–100 °C, under pressure. A cylindrical stainless steel or brass autoclave (140 ml volume) was used, and the inner surface served as the cathode. A copper rod, disposed along the axis, was the anode.

A typical procedure was as follows: freshly distilled DMF (40 ml) and tmeda (12 ml, 80 mmol), Bu_4NBr (1 mmol) and 4-bromobenzonitrile (20 mmol) were introduced in the autoclave. CF_3Br was charged under a pressure of 3 bar. The electrolysis (0.3 A) began at room temperature for 20 min. The gas was then purged, the autoclave was refilled (3–6 bar,‡ and put in an oil bath progressively heated to 95 °C. The pressure rose to 10–15 bar. The electrolysis, monitored by GC of aliquots, was stopped when 70% of the bromobenzonitrile

Table 1 Coupling reaction of aromatic halides with electrogenerated CF_3Cu[a]

ArX (mmol)	Ligand (mmol)	ArCF$_3$ (%)[b]
4-Iodoanisole (10)	tmeda (100)	50[c]
4-Iodoanisole (10)	bpy (50)	67[c]
4-Iodoanisole (10)	PBu_3 (20)	92
4-Iodoanisole (10)	PPh_3 (20)	75[d]
4-Bromoanisole (10)	PBu_3 (20)	15[d]
4-Bromobenzonitrile (10)	PPh_3 (20)	72
4-Bromonitrobenzene (10)	PPh_3 (20)	70
4-Chloronitrobenzene (10)	PBu_3 (20)	55[d]
4-Chloronitrobenzene (10)	tmeda (100)	Trace[c]
Ethyl 4-bromobenzoate (5)	PBu_3 (20)	52[d]
Methyl 2-bromobenzoate (5)	PBu_3 (20)	98
2-Bromopyridine (10)	PBu_3 (20)	90
2-Bromopyridine (10)	tmeda (100)	98

[a] For experimental conditions, see text. [b] GC yield. [c] Main by-product ArH. [d] Large amounts of the starting halide were recovered.

Table 2 Electrochemical cross-coupling between aromatic halides and CF_3Br[a]

ArX (mmol)	ArCF$_3$[b] (%)
4-Iodoanisole (20)	90
1-Iodonaphthalene (20)	98
4-Bromobenzonitrile (20)	91
3,5-Dichlorobromobenzene (10)	70[c]
Ethyl 4-bromobenzoate (10)	56
Methyl 2-bromobenzoate (10)	54
4-Bromochlorobenzene (10)	32[c]
4-Bromoanisole (10)	32
2-Bromoanisole (20)	32
3-Bromoanisole (20)	23
4-Bromonitrobenzene (10)	98
4-Chlorobenzonitrile (10)	3
2-Bromopyridine (20)	95
3-Bromopyridine (20)	98
3-Bromoquinoline (20)	98
2-Bromothiophene (5)	88[d]

[a] For experimental conditions, see text. [b] GC yield. [c] Only bromine was substituted. [d] A *ca.* 50 : 50 mixture of 2- and 3-trifluoromethylthiophene was obtained.

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† About 30 mmol of CF_3Br may be reduced (2 F mol^{-1}).

‡ The weight gain of the autoclave is around 7.5–15 g (50–100 mmol of CF_3Br).

had been consumed (7 h, 7600 C, 3.9 F mol^{-1}). Heating was maintained for a further 2 h. After cooling, the solution was poured into 100 ml of 2 mol dm^{-3} HCl, and extracted with pentane (3 × 50 ml). The solvent was distilled off, and the crude product was chromatographed over silica gel (pentane as eluent). 4-Trifluoromethylbenzonitrile (18.2 mmol) was obtained, contaminated by benzonitrile (0.9 mmol) and 4-pentafluoroethylbenzonitrile (0.9 mmol).

Curiously, in this one-step procedure, the yield of coupling product was better with tmeda than with triphenylphosphine. Little hydrogenation product was formed, compared to the two-step procedure. Results, all obtained with tmeda as ligand, are reported in Table 2.

Excellent yields of coupling product were obtained from aromatic iodides and heteroaromatic bromides. Aromatic bromides, unless deactivated by donor substituents, still give useful yields. However, our efforts to increase the yield in the most unfavourable cases, either by raising the temperature or extending the electrolysis time, resulted mainly in the formation of pentafluoroethyl and heptafluoropropyl derivatives.

In comparison to the usual organometallic methods leading to trifluoromethylcopper, this electrochemical technique based on the use of a copper sacrificial anode has two advantages; it allows the use of CF_3Br as starting material, instead of the expensive CF_3I, and coupling with a large variety of aromatic or heteroaromatic halides is achieved under mild conditions, with reasonable yields. Work is in progress to characterize the CF_3Cu complexes by their ^{19}F NMR spectra, and to determine the electrochemical mechanism of their formation.

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