Electroreductive Coupling of Trifluoromethylarenes with Electrophiles: Synthetic Applications

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The electroreductive coupling of trifluoromethylarenes with carbon dioxide, acetone, or *N,N*-dimethylformamide is achieved with good yields by electrolysis in an undivided cell fitted with a sacrificial anode.

Molecules bearing an $ArCH_2$ group (Ar = aromatic), such as arylacetic acids and related compounds, are used in pharmaceutical or agrochemical fields. The presence of two fluorine atoms on the benzylic carbon is expected to modify the biological activity and the potential interest of these fluorosubstituted compounds is then evident. Unfortunately, methods allowing the synthesis of these $ArCF_2$ derivatives are scarce and inconvenient,[1] since trifluoromethylarenes ($ArCF_3$) fail to provide suitable organometallic species as intermediate reagents.

We have found a one-step electrochemical method for preparing $ArCF_2$ branched molecules from trifluoromethylbenzenes in good yields.

The electrochemical reduction of trifluoromethylbenzenes has been reported to lead mainly to the corresponding toluenes.[2] In some cases, however, a stepwise electroreduction affording a mixture of fluorotoluenes is observed.[3] On the other hand, we have previously described an electrosynthetic procedure using sacrificial metallic anodes (M) and allowing the electroreductive coupling of organic halides with electrophilic reagents (E) such as carbon dioxide,[4,5] carbonyl compounds,[6] or *N*,*N*-dimethylformamide (DMF).[7] The

Table 1. Electrosyntheses from trifluoromethylbenzene derivatives.

$ArCF_3$	Electrophile	Anode	Isolated product	Yield (%)
$PhCF_3$	CO_2	Mg	(**1**) $PhCF_2CO_2Me$	65
$4\text{-}FC_6H_4CF_3$	CO_2	Mg	(**2**) $4\text{-}FC_6H_4CF_2CO_2Me$	70
$PhCF_3$	Me_2CO	Mg	(**3**) $PhCF_2CMe_2OH$	40
$PhCF_3$	Me_2CO	Al	(**3**) $PhCF_2CMe_2OH$	80
$4\text{-}FC_6H_4CF_3$	Me_2CO	Al	(**4**) $4\text{-}FC_6H_4CF_2CMe_2OH$	55
$PhCF_3$	DMF	Mg	(**5**) $PhCF_2CH(OCOMe)_2$	62
$4\text{-}FC_6H_4CF_3$	DMF	Mg	(**6**) $4\text{-}FC_6H_4CF_2CH(OCOMe)_2$	58

synthetic interest of $ArCF_2$ derivatives prompted us to investigate the behaviour of trifluoromethylarenes under the same conditions. We now report our first results concerning the electrosynthesis of some difluorobenzyl compounds according to equations (1) and (2).

$$M \rightarrow M^{n+} + ne \quad \text{at the anode} \quad (1)$$

$$ArCF_3 + 2e + E \rightarrow ArCF_2\,E^- + F^- \quad \text{at the cathode} \quad (2)$$

The electrolyses were carried out at room temperature in DMF containing $ArCF_3$ (0.5 M) and Bu_4NBr (4×10^{-2} M) as supporting electrolyte. The undivided cell, fitted with a stainless steel grid as the cathode and a magnesium or aluminium rod as the anode has been described elsewhere.[5] A constant current (0.1 A dm^{-2}) was supplied until the charge reached 2.2 electron-mol per mol of $ArCF_3$.

For electrocarboxylation experiments, a magnesium anode was used and carbon dioxide was bubbled at atmospheric pressure through the solution. Solvent evaporation, treatment of the residue with methanol and sulphuric acid, and addition of water followed by diethyl ether extraction yielded the acid in the form of the methyl esters (**1**) and (**2**) (Table 1).†

Coupling with acetone involved addition of the acetone as a co-solvent (10% v/v). Better results were obtained with aluminium rather than magnesium as the anodic material. Solvent evaporation and hydrolysis with aqueous HCl followed by diethyl ether extraction gave the α,α-difluorobenzyldimethyl carbinols (**3**) and (**4**) which were purified by chromatography on silica gel (Table 1).†

For the electroformylation, DMF acts as both solvent and reagent. A magnesium anode was used and the cathode was coated with an electrolytic deposit of cadmium which proved to increase the yields of aldehydes obtained from electroreduction of organic halides.[7] The electrolytic solution was poured into acetic anhydride then added to a small amount of conc. HCl and pyridine. The mixture was allowed to react overnight. Hydrolysis with aqueous HCl followed by pentane extraction afforded the diacetates (**5**) and (**6**) which were purified by chromatography on silica gel (Table 1).†

In conclusion, this electrolytic process offers an easy and efficient synthetic route, *via* a convenient one-stage reaction, to valuable $ArCF_2$ branched molecules from the corresponding trifluoromethylbenzenes and various CO containing electrophiles.

We thank the S.N.P.E. (Société Nationale des Poudres et Explosifs) for financial support.

Received, 12th April 1989; Com. 9/01506J

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† *Selected spectroscopic data*: (**1**) ^1H n.m.r. (60 MHz; $CDCl_3$) δ 3.73 (s, 3H), 7.4 (m, 5H); ^{19}F n.m.r. ($CDCl_3$) δ 103.54 (s); *m/z* (70 eV) 186 (M^+, 9.7%), 127 ($M^+ - CO_2Me$, 100%). (**2**) ^1H n.m.r. (60 MHz; $CDCl_3$) δ 3.83 (s, 3H), 7.36 (m, 4H); ^{19}F n.m.r. ($CDCl_3$) δ 102.14 (s, 2F), 108.74 (m, 1F); *m/z* (70 eV) 204 (M^+, 7.5%), 145 ($M^+ - CO_2Me$, 100%). (**3**) ^1H n.m.r. (60 MHz; $CDCl_3$) δ 1.23 (s, 6H), 2.23 (s, 1H disappears with D_2O), 7.42 (m, 5H); ^{19}F n.m.r. ($CDCl_3$) δ 108.94 (s); *m/z* (70 eV) 186 (M^+, 2.3%), 127 ($M^+ - CMe_2OH$, 18.5%) (**4**) ^1H n.m.r. (60 MHz; $CDCl_3$) δ 1.28 (s, 6H), 2.59 (s, 1H disappears with D_2O), 7.3 (m, 4H); ^{19}F n.m.r. ($CDCl_3$) δ 108.14 (s, 2F), 110.04 (m, 1F); *m/z* (70 eV) 185 ($M^+ - F$, 3.8%), 145 ($M^+ - CMe_2OH$, 4.2%), 59 ($M^+ - F\,C_6H_4CF_2$, 100%). (**5**) ^1H n.m.r. (60 MHz; $CDCl_3$); δ 2.05 (s, 6H), 7.2 (t, 1H), 7.5 (m, 5H); ^{19}F n.m.r. ($CDCl_3$) δ 111.5 (d, J_{F-H} 6.8 Hz). (**6**) ^1H n.m.r. (60 MHz; $CDCl_3$) δ 2.05 (s, 6H), 6.9—7.7 (m, 5H); ^{19}F n.m.r. ($CDCl_3$) δ 110.5 (m, 1F), 111.0 (dd, 2F, J_{F-H} 7 Hz).