Trifluoromethylation of aromatic compounds *via* Kolbe electrolysis in pure organic solvent. Study on laboratory and pilot scale

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The present study investigates the conditions of trifluoromethylation of various aromatic compounds *via* the Kolbe oxidation of trifluoroacetic acid. The preparative electrolyse conditions were first optimized on the laboratory scale using the trifluoromethylation of benzonitrile in acetonitrile solutions as a model case. Sodium or pyridinium trifluoroacetates were tried as a source of trifluoromethyl radicals, the partial neutralization of trifluoroacetic acid by pyridine provided the best yield of trifluoromethylbenzonitrile (46%). The trifluoromethylation of the other aromatic compounds such as acetophenone, benzaldehyde and nitrobenzene led to yields slightly lower than those observed in the case of benzonitrile. The trifluoromethylation of benzonitrile was then studied in a commercially available flow cell. Yields were consistent with those obtained on the laboratory scale.

Preparation of trifluoromethyl-substituted organic compounds has attracted increasing attention because of interesting biomedical and biochemical applications.[1] To achieve trifluoromethylation of aromatic compounds, various chemical methods are available, among them are the conversion of a methyl group to a trifluoromethyl group,[2] the use of trifluoromethyl copper[3–6] and the generation of trifluoromethyl radicals from precursors.[7–10] Electrochemical methods can be used to generate nucleophilic trifluoromethyl species from CF_3Br or CF_3I [11,12] or trifluoromethyl radicals by the oxidation of trifluoroacetic acid by Kolbe electrolysis.

The Kolbe reaction is commonly understood as the coupling of the alkyl chain of a carboxylate $RCOO^-$ to synthesize the dimer R_2 or the cross-coupling product[13] R^1–R^2 from a mixture of two carboxylates. In these cases, high current (densities equal or greater than 250 mA cm^{-2}) allow the formation of coupling products because of a high radical concentration at the electrode surface; electrolyses are generally carried out in aqueous or methanol–water solutions in a weakly acidic medium (2–30% of the carboxylic acid is deprotonated by a mineral base). However, the anodically generated radicals, $R^\cdot$, can be trapped by various unsaturated acceptors, commonly olefinic compounds. In this case current densities lower (10 to 100 mA cm^{-2}) than those required for dimerization are applied, which also prevent the oxidation of the acceptor. Kolbe electrolysis of trifluoroacetic acid has been performed for coupling the CF_3 group to various electron-deficient olefins[14–22] and acetylenic compounds[23,24] in acetronitrile–water media.

Because of the poor adsorption of trifluoroacetates[25] (compared to water or oxygen) on the electrode surface, very low yields of C_2F_6 are obtained in an aqueous medium: the production of dioxygen is the main process that occurs at the electrode. In constrast, the use of acetonitrile as the major solvent, stable at the high potential, allows trifluoromethyl radicals to be produced in good yield (in this medium, at $E \geqslant 2.7$ V *vs.* SCE, C_2F_6 represents 65–80% of the products[26]). A small quantity of water is generally added to increase the conductivity of the solution. On account of the poor adsorption of trifluoroacetates and trifluoromethyl radicals and because of its stability at high anodic potentials,[27] platinum is generally used as the electrode material on the laboratory scale. When trifluoromethyl radicals are added to olefinic double bonds, the main products are bistrifluoromethylated and trifluoromethylated dimerization compounds. Yield and selectivity depend on the nature of the substituents on the C=C bond, on the current density and the reaction temperature.[28] To the best of our knowledge, Grinberg *et al.* were the first to use Kolbe electrooxidation for trifluoromethylation of aromatic compounds.[29,30] By focusing their study on the mechanism of this reaction (under classical conditions, see above), they showed that aromatic trifluoromethylation is promoted by the adsorption of the arene on the anode surface and that the trifluoromethylation is competitive with the aromatic oxidation in the range of potentials at which trifluoromethyl radicals are generated.

The aim of our work was to investigate the trifluoromethylation of various aromatic compounds *via* Kolbe electrolysis under conditions compatible with an industrial process. First of all, we have studied preparative conditions in acetonitrile solutions on the laboratory scale and we have chosen benzonitrile as the model substrate. In the attempt to improve the yields of trifluoromethybenzonitrile, we have shown that an organic base give better results than sodium hydroxide; optimized conditions were applied to other aromatic compounds bearing electron-withdrawing groups. Secondly, we have promoted the trifluoromethylation of benzonitrile in a flow cell, using a technique of experimental planning, in view of scale-up to the pilot plant.

Experimental

The reagents were commercial trifluoroacetic acid (Fluorochem 98%), sodium trifluoroacetate (Fluorochem 98%), acetonitrile (SDS 99.8%), pyridine (Acros 99%), PhCN (Aldrich GC 99%), $PhCOCH_3$ (Aldrich 99%), PhCHO (Acros 98%), $PhNO_2$ (Acros 99%), PhCl (Acros 98%) and $PhCH_3$ (Acros 98%); these were used as received.

For electrochemical investigations, voltammograms were obtained on an EGG Model 273A potentiostat. Auxiliary and working electrodes were platinum and potentials were referenced to the saturated calomel electrode (SCE). Before measurement, acetonitrile solutions were purged with pure argon to remove oxygen.

On the laboratory scale, for a typical preparative electrolysis, the reaction was carried out in an undivided cell (25 cm^3) equipped with two platinum cylindrical grids as electrodes. The anode ($L \times l = 6 \times 4$ cm) surrounded the cathode, which was placed in the middle of the cell. The solution was a mixture of acetonitrile (18 ml), trifluoroacetic acid (TFA, 50 mmol), pyridine (40 mmol) and after good stirring of the solution, benzonitrile (2.5 mmol). The electrolysis was performed at room temperature under a constant-current intensity (30 mA $\leqslant I \leqslant$ 500 mA) until 1 F per mol TFA of electricity was engaged.

The flow cell was a parallel plate reactor (FM01® electrolyser from ICI) equipped with commercial platinum foil anode and platinum electroplated cathode (titanium substrate, 16 × 4 cm). No turbulance promoter was added and the electrodes were separated just by a cell gasket (3 mm thick). The cell was connected to a tank (500 ml) by PTFE tubing. The temperature and the flow of the solution were controlled. The operating procedure for electrolysis was the same as the one used on the laboratory scale.

Aromatic products were quantified in solution by gas chromatography (DB5 MS, 30 m) by comparison with authentic samples. The nature of the products was confirmed by mass spectroscopy (Varian 3400 CX/Saturn 2000).

Results and discussion

Study of trifluoromethylation of aromatic compounds on the laboratory scale

Use of sodium hydroxide. Sodium trifluoroacetates have been commonly used as a source of $CF_3^{\cdot}$ radicals. Therefore, the first preparative electrolyses were carried out in an aqueous acetonitrile (H_2O–acetonitrile = 1 : 8)–TFA (2 mol L^{-1}) solution with NaOH (0.4 mol L^{-1}) as base. Benzonitrile (PhCN) was considered as model. Trifluoromethylbenzonitrile was obtained but also small amounts of bistrifluoromethylated aromatics and traces of trifluoromethoxybenzonitrile.

$$\mathrm{PhCN} \xrightarrow{CF_3^{\cdot}} CF_3\text{–}C_6H_4\text{–}CN + (CF_3)_2\text{–}C_6H_3\text{–}CN + \text{other products}$$

The ratio of ortho, meta and para isomers of trifluoromethylbenzonitrile obtained (o : m : p = 46 : 18 : 36) was the same for all experiments. This ratio is consistent with the free radical nature of the reaction.

As explained in the experimental section, we followed the decrease of benzonitrile and increase of trifluoromethylbenzonitrile until 1 F per mol TFA of electricity was consumed. Fig. 1 shows the typical evolution of the concentration of these compounds. Depending on the initial amount of PhCN, the concentration of trifluoromethylbenzonitrile either reaches a maximum value, as observed on Fig. 1, or else increases until the PhCN is fully consumed.

We present the results of our experiments either at the maximum point mentioned above, when it exists, or at the end of the electrolysis in the other cases. The chemical yields (R_{CF3t}) of trifluoromethylbenzonitrile obtained (see Table 1) were quite modest and can be explained by the relatively poor reactivity of electrophiles like $CF_3^{\cdot}$ toward benzonitrile. The highest conversion rates of PhCN were obtained for the lowest concentration of aromatic or for the highest current intensity applied.

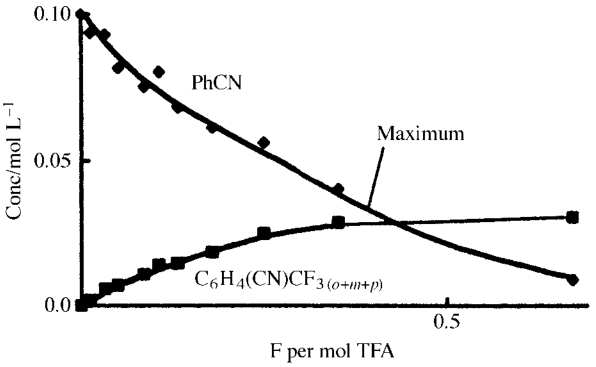

Fig. 1 Electrolysis in acetonitrile–water (8 : 1)–NaOH (0.4 mol L^{-1})–TFA (2 mol L^{-1}) solution, [PhCH] = 0.1 mol L^{-1}, chromatographic analysis.

The selectivity of the reaction (expressed by X_{CF3t}) represents the amount of benzonitrile consumed that leads to trifluoromethylbenzonitrile. At a high intensity value, X_{CF3t} does not seem to depend on benzonitrile concentration (comparison of entries 1 *vs.* 3 or 2 *vs.* 4 in Table 1), whereas variation of intensity at a fixed aromatic concentration seems to have a more significant influence on X_{CF3t} (comparison of entries 1 *vs.* 2 or 4 *vs.* 5). Thus comparisons allow to define an optimal ratio between [PhCN] and intensity value. As a particularity, in entry 5 of Table 1 ([PhCN] = 0.1 mol L^{-1}, $I = 30$ mA), the byproduct trifluoromethoxybenzonitrile $CF_3O\text{–}C_6H_4\text{–}CN$, accounts for one-third of the converted PhCN. This is the maximum amount of this product that we have observed. We can suppose that O_2 is responsible for the production of this by-product, as Smertenko *et al.*[31] have demonstrated.

Use of pyridine. In order to perform preparative electrolyses in acetonitrile exempt of water, we have considered the neutralization of trifluoroacetic acid with an organic base. As we can see on Fig. 2, oxidation of pyridinium salt (curve *b*) occurs in the same range of potentials as sodium trifluoroacetate (curve *c*), that is, at a potential higher than 2.4 V (pyridine does not exhibit any voltammetric signal within the potential range). The addition of benzonitrile to an acetonitrile–TFA solution containing pyridine does not lead to any other oxidation peaks (data not shown).

As expected, there was no production of trifluoromethoxybenzonitrile during electrolyses performed in acetonitrile–TFA (2 mol L^{-1})–pyridine–PhCN solutions, whereas GC-MS analysis showed many products resulting from multitrifluoromethylation of the aromatic ring. Trifluoromethylbenzonitrile production reaches a maximum in all the experiments and results of electrolyses are reported at this point. Results reported in Table 2 show that the yield of the reaction of trifluoromethylation is strongly dependent on both the intensity and concentration, of pyridine. The increase of the base concentration and consequently the increase of the trifluoroacetate concentration, probably promote the adsorption of the trifluoroacetates at the anode surface. This adsorption is competitive with the adsorption of

Table 1 Electrolysis in acetonitrile–water (8 : 1)–NaOH (0.4 mol L^{-1})–TFA (2 mol L^{-1}) solutions

Entry	[PhCN] /mol L^{-1}	I /mA	T_c(PhCN)[a] /%	X_{CF3t}[b] /%	R_{CF3t}[c] /%
1	0.5	500	50	32	16
2	0.5	100	28	42	12
3	2	500	14	36	5
4	0.1	100	60	50	30
5	0.1	30	15	36	5

[a] Conversion rate of benzonitrile. [b] Yield of trifluoromethylbenzonitrile (sum of ortho, meta and para isomers) based on benzonitrile consumed. Isomer ratio o : m : p (%) is 46 : 18 : 36. [c] Chemical yield $R_{CF3t} = T_c \times X_{CF3t}$.

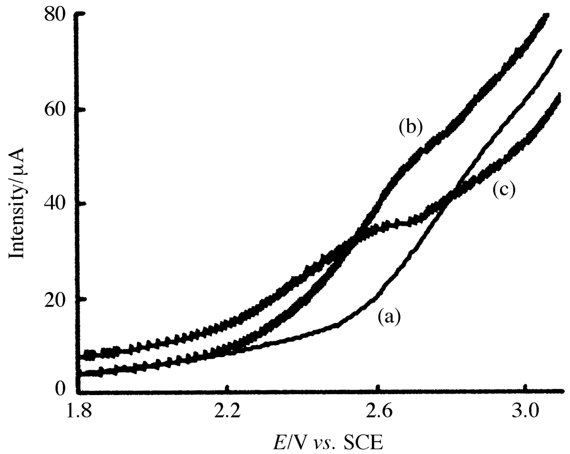

Fig. 2 Oxidation of trifluoroacetates in acetonitrile–NBu_4BF_4 (0.1 mol L^{-1}) solution; linear sweep voltammetry, scan rate = 0.1 V s^{-1}, Pt electrode ($S = 0.2$ mm^2): (*a*) [TFA] = 0.04 mol L^{-1}, (*b*) [TFA] = 0.04 mol L^{-1} + [Py] = 0.04 mol L^{-1}, (*c*) [TFANa] = 0.02 mol L^{-1}. Curve (*a*) is identical when there is no TFA in solution.

Table 2 Electrolysis in acetonitrile–TFA (2 mol L^{-1})–pyridine solutions

[Py] /mol L^{-1}	[PhCN] /mol L^{-1}	I /mA	T_c(PhCN)[a] /%	X_{CF3t}[b] /%	R_{CF3t}[c] /%
0.4	0.1	100	70	33	23
1.6	0.1	200	58	38	22
1.6	**0.1**	**38**	**70**	**65**	**46**
1.6	0.3	38	52	70	36
2.0	0.1	39	60	65	39

[a] Conversion rate of benzonitrile. [b] Yield of trifluoromethylbenzonitrile (sum of ortho, meta and para isomers) based on benzonitrile consumed. [c] Chemical yield $R_{CF3t} = T_c \times X_{CF3t}$.

Table 3 Electrolysis of different aromatic compounds in acetonitrile–TFA (2 mol L^{-1})–pyridine (1.6 mol L^{-1}) solution, aromatic concentration of 0.1 mol L^{-1}

Aromatic	T_c(ArH)[a] /%	X_{CF3t}[b] /%	R_{CF3t}[c] /%	Isomer ratio (o : m : p)/%
PhCOCH	90	40	36	63 : 12 : 25
PhCHO	66	52	34	48 : 14 : 38
$PhNO_2$[d]	70	0	0	
$PhNO_2$[e]	70	14	10	42 : 58 (m + p)

[a] Conversion rate of aromatic. [b] Yield of trifluoromethylated aromatic (sum of ortho, meta and para isomers) based on aromatic consumed. [c] Chemical yield $R_{CF3t} = T_c \times X_{CF3t}$. [d] Production of $PhNH_2$, PhN=NPh, $C_6H_4(CF_3)NH_2$ (GC-MS analysis). [e] Electrolysis in a two-compartment cell (sintered glass diaphragm).

aromatics.[14] Results show that intensity must be kept at low values to obtain the best selectivity of the reaction and avoid further trifluoromethylation. Yields of trifluoromethylbenzonitrile are highest for the lower concentration of aromatic substrate. Under the best conditions, the yield of trifluoromethylbenzonitrile is equal to 46%.

We have selected the optimal conditions for the trifluoromethylation of benzonitrile ([TFA] = 2 mol L^{-1}, [pyridine] = 1.6 mol L^{-1}, $I = 38$ mA, [aromatic] = 0.1 mol L^{-1}) to perform the trifluoromethylation of other aromatic compounds bearing withdrawing groups such as acetophenone, benzaldehyde and nitrobenzene. Although these aromatic compounds are more easily reducible than PhCN, the concentration of aromatics with regard to the TFA concentration and the current intensity used allowed us to perform the electrolysis without the use of a diaphragm.

As shown in Table 3, yields are slightly lower than those obtained from PhCN since 35% of the trifluoromethyl compound are obtained for benzaldehyde or acetophenone. From nitrobenzene, only poor yields of trifluoromethylnitrobenzene were observed, provided that we used a divided cell (Table 3, last entry); otherwise products resulting from the reduction of $PhNO_2$ (anilines or azoxybenzene) are mainly observed. In the case of the use of aromatics bearing electrodonating groups such as chlorobenzene and toluene, these oxidation conditions lead to trifluoroacetoxylated derivatives [$C_6H_4(Cl)–OCOCF_3$ and $PhCH_2–OCOCF_3$].

Study of trifluoromethylation of benzonitrile on the pilot scale

In a second set of experiments, we have studied the trifluoromethylation of benzonitrile in a commercially available flow cell. This reactor is specially designed to perform electrosyntheses extrapolation to an industrial scale. In view of the laboratory scale studies, a platinum coated titanium anode was used. Experimental conditions were defined according to an experimental design (Hadamard matrix, MODDE software) based on the data obtained on the laboratory scale. This experimental planning usually allows one to extract a maximum of information from the collected data in a delimited number of experimental runs and to find the optimal conditions for the trifluoromethylbenzonitrile electrosynthesis. Thus, experimental factors that have been changed *simultaneously* were: trifluoroacetic acid concentration [TFA], initial ratio of base to TFA [pyridine]/[TFA], benzonitrile concentration [PhCN], flow rate of electrolyte (*d*), current intensity (*I*) and temperature (*T*). For each parameter considered, two limiting values were defined. The experiments performed and the results obtained are presented in Table 4.

As we can see (entry 4, Table 4), the highest chemical yield (R_{CF3t}) is 28% and the highest selectivity (X_{CF3t}) is 50%. This result is close to that we have observed on the laboratory scale. The Hadamard matrix used to describe these results seems to show that such a chemical yield is the highest that can be expected in the experimental domain explored (within the two limiting values for each experimental parameter). During our experiments, the major problem we have encountered was the corrosion of the anode. This is mainly due to the dissolution of titanium as shown by concentrations of Ti cation observed in solution (chromatographic measurement). The lifetime of the anode is defined by the point at which the anode potential decreases to around 1 V *vs.* SCE. At this

Table 4 Electrosynthesis of trifluoromethylbenzonitrile in a flow cell

Entry	[PhCN] /mol L^{-1}	[TFA] /mol L^{-1}	[Py] /[TFA]	d /L mol^{-1}	I /A	T /°C	R_{CF3t} /%
1	0.3	2	0.35	1	1.0	40	15
2	0.3	4	0.35	0.6	0.3	40	13
3	0.3	4	0.65	0.6	1.0	20	11
4	0.1	4	0.65	1	0.3	40	28
5	0.3	2	0.65	1	0.3	20	20
6	0.1	4	0.35	1	1.0	20	4
7	0.1	2	0.65	0.6	1.0	40	20
8	0.1	2	0.35	0.6	0.3	20	8

potential, the electrochemical process that occurs is mainly titanium corrosion. This point is reached after 480 working hours.

Conclusion

While the trifluoromethylation reaction *via* Kolbe electrolysis is usually carried out in aqueous organic solutions, this study proposes the use of pyridine as a base to generate trifluoroacetate anions and promote the trifluoromethylation of aromatic compounds in a non-aqueous medium. Among various aromatics bearing electron-withdrawing groups, benzonitrile gives the best yields of trifluoromethylated products.

Study of the trifluoromethylation of benzonitrile in a flow cell shows that this reaction can be easily extrapolated from the laboratory scale to the pilot scale. However, corrosion of anodic material is observed, mainly due to titanium dissolution in non-aqueous trifluoroacetic acid solutions.

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