Coupling of fluoroform with aldehydes using an electrogenerated base

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Trifluoromethylated alcohols are easily obtained in a one pot electroreaction in which cathodic reduction of iodobenzene generates a strong base which deprotonates fluoroform, inducing its coupling with aldehydes.

Fluorinated molecules and particularly trifluoromethylated compounds are widely used in the pharmaceutical or agrochemical fields, and much effort has been devoted to establishing improved methods for the introduction into organic substrates of fluoro or trifluoromethyl groups.

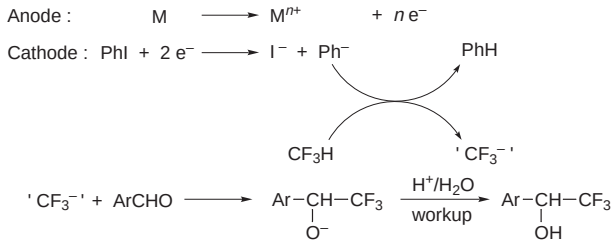
The most common reactants used to achieve trifluromethylation reactions[1] are organometallic compounds, *e.g.* CF_3Cu[2] and CF_3ZnX[3] (X = CF_3, Br, I *etc.*) or the Ruppert reactant CF_3SiMe_3.[4] These compounds are themselves generally prepared from CF_3I or CF_3Br. The electroreduction of CF_3Br is also a convenient method to obtain trifluoromethylated derivatives.[5]

Fluoroform CF_3H is a side product of fluoroorganic chemistry which is not utilised in organic synthesis. Compared to halofluorocarbons, this gas has low toxicity and is not an ozone depleting agent, although it is a powerful greenhouse gas and thus not a useful refrigerant. The use of CF_3H in organic chemistry is a real challenge which could turn an environmental liability into a commercial opportunity. One hindrance is the low reactivity of CF_3H, which is a very weak acid; its pK_a has been estimated to be in the range of 25–28.[6]

Concerning CF_3H as a source of trifluoromethyl anion, the only chemical method reported used strong bases such as Bu^tOK[7] or $MeSOCH_2K$.[8] An electrochemical procedure, which involves an electrogenerated base obtained by electroreduction of pyrrolidone, has also been described.[7] These reactions allow the synthesis of trifluoromethylated alcohols from aldehydes or ketones *via* a low temperature (−50 °C) two step procedure. The solvent DMF seems to play an important role, trapping the CF_3^- anion and giving a tetrahedral intermediate which is the actual trifluoromethylating agent.[8]

We have previously shown that the reduction of aromatic halides such as PhI or PhBr at a cathode covered with an electrolytic deposit of cadmium generates a strong base able to deprotonate weakly acidic molecules, inducing a coupling reaction with electrophilic compounds.[9] The present work is devoted to the extension of this technique to the case of fluoroform, which can then be coupled with aromatic aldehydes under very simple and mild conditions.

The experiments were conducted as a one-step procedure. To DMF was added Bu_4NBF_4 (4×10^{-2} mol l^{-1}) as a supporting electrolyte, an aromatic aldehyde ArCHO (0.5 mol l^{-1}) as the electrophile and iodobenzene (0.5–1.5 mol l^{-1}) as the probase. The solution, maintained at 5–10 °C, was supplied in CF_3H *via* slow bubbling at normal pressure.

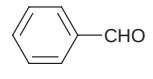
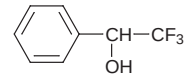
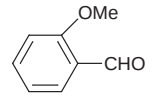
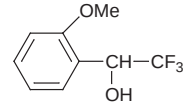
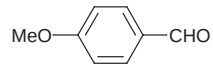
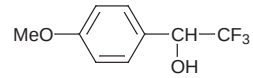
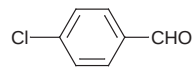
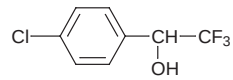
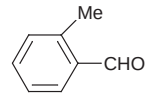
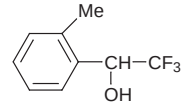
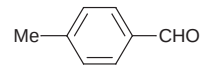
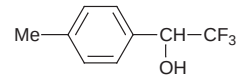
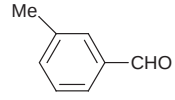
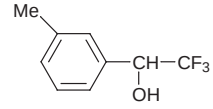
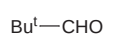
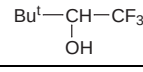


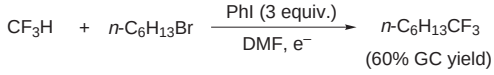
Scheme 1

The undivided electrochemical cell has been described elsewhere.[10] The electrolyses were carried out at constant current (1 A dm^{-2}) using a sacrificial magnesium or aluminium anode and a nickel grid cathode freshly coated with a small deposit of cadmium obtained by electroreduction of $CdBr_2$.[9]

We observed that the reaction required an excess of probase and electricity to achieve full conversion of ArCHO. For example, when the electrolysis was conducted in solutions containing PhCHO and PhI (1 : 1), there was 30–40% residual benzaldehyde after the iodobenzene had been consumed. This is probably due to side reactions involving Ph^- and/or CF_3^-, which were not identified. Consequently, all syntheses were performed in the presence of excess iodobenzene (2–3 equiv.) allowing complete transformation of the aromatic aldehyde. Trifluoromethylated alcohols were obtained upon standard workup (solvent evaporation and acidic hydrolysis) and re-

Table 1 Electrogenerated base mediated coupling of fluoroform with aldehydes

Aldehyde	Product	Yield (%)
		71
		12
		73
		51
		53
		76
		66
		46

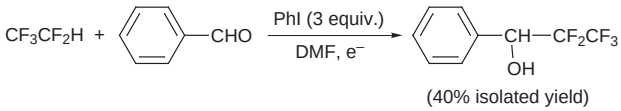


Scheme 2

covered in a pure form by suitable extraction and chromatography on silica gel, and characterised by mass, ^{1}H NMR and ^{19}F NMR analysis.

The reaction pathway corresponds to that shown in Scheme 1. Our results, presented in Table 1, show that various aromatic aldehydes yield the corresponding trifluoromethylated alcohols in moderate to good yields. A limitation of this one-pot reaction is that the aldehyde cannot be more easily reduced than the probase PhI. Indeed, when starting from easily reducible compounds, *e.g.* *o*-, *m*- or *p*-(α,α,α-trifluoromethyl)-benzaldehyde, the sole product recovered is the corresponding pinacol. This would also explain the low yield obtained from 2-methoxybenzaldehyde (see Table 1), for which a large amount of pinacol was detected. For aliphatic aldehydes, we achieved success only with pivalaldehyde, as enolizable compounds mainly gave aldolisation products.

Our method is also suitable for the trifluoromethylation of alkyl halides. (Scheme 2). Finally, we have also proved that



Scheme 3

fluorocarbons other than fluoroform can be used. One example is the coupling of pentafluoroethane with benzaldehyde (Scheme 3).

Notes and References

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1 D. J. Burton and Z. Y. Yan, *Tetrahedron*, 1992, 48, 189; M. A. McClinton and D. A. McClinton, *Tetrahedron*, 1992, **48**, 6555.
2 Y. Kobayashi, K. Yamamoto and I. Kumadai, *Tetrahedron Lett*., 1979, **42**, 4071; Y. Kobayashi, K. Yamamoto, T. Asai, M. Nakano and I. Kumadai, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2755; Y. Kobayashi and I. Kumadai, *J. Chem. Soc., Perkin Trans. 1*, 1980, 661; J. M. Paratian, S. Sibille and J. Périchon, *J. Chem. Soc. Chem. Commun*., 1992, 53.
3 W. Tyrra and D. Nauman, *J. Prakt. Chem*., 1996, **338**, 283.
4 P. Ramaiah, R. Krishnamurti and G. K. S. Prakash, *Org. Synth.*, 1995, 232.
5 J. M. Paratian, E. Labbe, S. Sibille, J. Y. Nédélec and J. Périchon, *Denki Kagaku*, 1994, **62**, 1129.
6 K. J. Klabunde and D. J. Burton, *J. Am. Chem. Soc*., 1972, **94**, 5985.
7 T. Shono, M. Ishifune, T. Okada and S. Kashimura, *J. Org. Chem.*, 1991, **56**, 2.
8 B. Folléas I. Marek, J. F. Normant and L. S. Jalmes, *Tetrahedron Lett.*, 1998, **39**, 2973.
9 R. Barhdadi, J. Gal, M. Heintz and M. Troupel, *J. Chem. Soc., Chem. Commun.*, 1992, 50; R. Barhdadi, B. Simsen, M. Troupel and J. Y. Nédélec, *Tetrahedron*, 1997, **53**, 1721.
10 J. Chaussard, J. C. Folest, J. Y. Nédélec, S. Sibille, J. Périchon and M. Troupel, *Synthesis*, 1990, 2, 369.

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