Available online at www.sciencedirect.com
ScienceDirect
Journal of Fluorine Chemistry 128 (2007) 1318–1325
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

# Nucleophilic trifluoromethylation of aryl halides with methyl trifluoroacetate

Bernard R. Langlois [a,b,c,d,e,f,*], Nicolas Roques [a,b,c,d,e,f,1]

[a] ICBMS, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, Equipe SERCOF,
43 boulevard du 11 novembre 1918, Villeurbanne F-69622, France
[b] CNRS, UMR 5246, Villeurbanne, F-69622, France
[c] Université de Lyon, Lyon F-69622, France
[d] Université Lyon 1, Lyon F-69622, France
[e] INSA-Lyon, Villeurbanne F-69622, France
[f] CPE Lyon, Villeurbanne F-69616, France

Received 8 May 2007; received in revised form 1 August 2007; accepted 2 August 2007
Available online 7 August 2007

## Abstract

When associated with an alkaline halide, such as cesium fluoride or cesium chloride, and Cu(I) species, methyl trifluoroacetate (MTFA) constitutes a valuable trifluoromethylating agent for substituting aromatic (or heteroaromatic) iodides and bromides. The reaction can be carried out in DMF at 180 °C or, better, in sulfolane which allows he reaction to proceed at a lower temperature (from 140 °C).

*Keywords:* Benzotrifluorides; (Trifluoromethyl)arenes; Methyl trifluoroacetate; Alkaline fluorides; Alkaline chlorides; Trifluoromethylation; Aromatic substitution

## 1. Introduction

Benzotrifluoride and derivatives are currently prepared, especially on the industrial scale, in a two step procedure from the corresponding toluenes, via benzotrichlorides [1], but now, as for other trifluoromethylated compounds [2], an increasing interest is paid to the direct introduction of a trifluoromethyl moiety on aromatic nuclei. This can be done in a radical way, from $CF_3Br$ [3] or alkaline trifluoromethanesulfinates [4], but this technique is not regioselective, or by regioselective nucleophilic substitution of aryl iodides or bromides with (trifluoromethyl)copper(I) species, generated *in situ*. Several methods have been described to produce such species, either under mild conditions from ozone-depleting reagents ($CF_2Br_2$ [5], $CF_3Br$ [6]) or expensive $CF_3I$ [7] and (trifluoromethyl)-trimethylsilane [8], as well as by thermal decarboxylation of alkaline trifluoroacetates in the presence of cuprous iodide [9,16]. The latter technique is the most popular and has been developed on a large scale, but suffers from the fact that, because of their low solubility, alkaline trifluoroacetates must be used in excess (usually five-fold). This drawback becomes more dramatic when scaling up the reaction: as alkaline trifluoroacetates are very hygroscopic, all the ionic reagents must be used in larger excess (up to 10 eq. of $CF_3CO_2M$ and 5 eq. for CuI). Time-consuming azeotropic dehydration of these salts, carried out *in situ* prior trifluoromethylation, allows the excess of reagents to be decreased [10] but, correlatively, increases the mean crystal size of alkaline trifluoroacetates, which become less soluble, that decreases reaction velocity. Such a large amount of salts to be withdrawn constitutes a severe problem on the industrial scale since these salts cannot be recycled in an economical way and, consequently, must be stored, that is not compatible with a sustainable development.

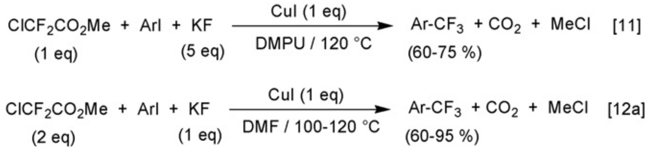
This is the reason why several teams investigated the use of cheap but non-ionic trifluoromethylating agents such as methyl (fluorosulfonyl)difluoroacetate, prepared from tetrafluoroethyl sultone [11]. Then, in the early 1990s, McNeil and Burton [12] and Chen and co-workers [13a] reported, independently and quite simultaneously, a substitutive trifluoromethylation of aryl halides with methyl chlorodifluoroacetate, potassium fluoride

---

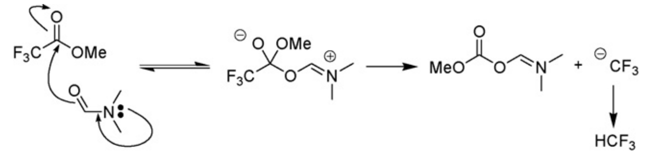
[*] Corresponding author. Tel.: +33 4 72 44 81 63; fax: +33 4 72 43 13 23.
*E-mail address:* bernard.langlois@univ-lyon1.fr (B.R. Langlois).

[1] Present address: Laboratoire Pierre Fabre, 16 rue Jean Rostand, F-81600 Gaillac, France.

0022-1139/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2007.08.001



Scheme 1. Aromatic trifluoromethylation with methyl chlorodifluoroacetate.



Scheme 2. Reaction of DMF and MTFA.

and CuI in apolar aprotic solvents (Scheme 1). This reaction was further extended to methyl bromodifluoroacetate [13b]. Obviously, less salts are used and produced in this technique.

As proposed by Chen et al., the reaction could involve three key steps: first, a Krapcho demethylation of $ClCF_2CO_2Me$ by iodide, followed by decarboxylation of the resulting chlorodifluoroacetate to provide the unstable $^{-}CF_2Cl$ anion which expells $Cl^{-}$ and generates a difluorocarbene, trapped by fluoride. The resulting and unstable trifluoromethyl anion is then stabilized by Cu(I).

Globally, this reaction looks like a formal substitution of chlorine for fluorine in the chlorodifluoromethyl moiety coupled with a Krapcho demethylation with CuI. Consequently, it could be expected that methyl trifluoroacetate (MTFA) and CuI would be also able to act as a trifluoromethylating system under the same conditions, but without addition of fluoride anions. However, substitutive trifluoromethylation of 4-iodoanisole with such a system failed in DMF, even at 180 °C: at this temperature, MTFA was quite completely decomposed (conversion = 90%) and fluoroform was extensively formed (69% *vs.* converted MTFA). The formation of fluoroform has been already reported during aromatic trifluoromethylation using sodium trifluoroacetate and CuI [16]. In this latter case, fluoroform obviously arised from protonation, by protic impurities, of the $^{-}CF_3$ anion resulting from direct decarboxylation of trifluoroacetate. However, in the present study, as no significant amount of intermediate trifluoroacetate has been observed, another process could be envisaged: for example, fluoroform could be issued from DMF and MTFA, through the mechanism proposed in Scheme 2 by analogy with our previous work dealing with the generation of $^{-}CF_3$ from trifluoroacetic esters and nucleophiles [14].

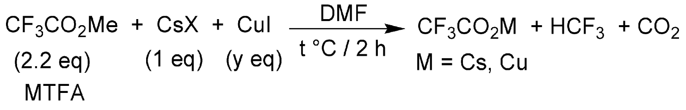
In contrast, under the same conditions, not any reaction occurred when DMF was replaced by sulfolane, which does not exhibit any nucleophilic character. This observation is consistent with the fact that, in the previous experiments, fluoroform could arise from MTFA and DMF, considered as a nucleophile, according to Scheme 2.

## 2. Results and discussion

This unsuccessful experiment prompted us to examine the trifluoromethylating ability of MTFA towards aryl halides, in the presence of copper(I) iodide and cesium halides. First, we studied the behaviour of MTFA, dissolved in DMF, towards CsX (X = F, Cl) alone then towards a mixture of CsX and CuI (Table 1).

Table 1 shows that demethylation of MTFA by CsF began at 70 °C with a significant formation of cesium trifluoroacetate (entry 1). Decarboxylation of this salt started at 130 °C with appearance of fluoroform in the absence of CuI (entries 3 and 7) but without formation of fluoroform in the presence of CuI (entries 5 and 8): as expected, the generated $^{-}CF_3$ was probably stabilized as a copper(I) derivative. At 180 °C, MTFA was completely converted and fluoroform extensively formed, along appreciable amounts of cesium trifluoroacetate (entry 4). It can be noticed that the sum of fluoroform and cesium trifluoroacetate amounts was larger than the quantity of engaged cesium fluoride. This means that fluoroform was not only generated from intermediate cesium trifluoroacetate but also from MTFA and DMF, as previously proposed. Consequently, MTFA will have to be used in excess during the further experiments carried out in DMF. In the absence of CuI, cesium chloride was almost as potent as cesium fluoride at

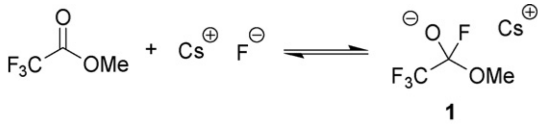
Table 1
Reaction of MTFA with CuI and/or CsX



| Entry | X | *y* (eq.) | *t* (°C) | Conv. MTFA (%)[a] | $CF_3CO_2M$[a] (% *vs.* CsX) | $CHF_3$[a] (% *vs.* CsX) | $CF_3CO_2M + CHF_3$ (% *vs.* CsX)[a] |
|---|---|---|---|---|---|---|---|
| 1 | F | 0 | 70 | 19 | 35 | 0 | 35 |
| 2 | F | 0 | 100 | 21 | 41 | 0 | 41 |
| 3 | F | 0 | 130 | 67.5 | 69 | 23 | 92 |
| 4 | F | 0 | 180 | 100 | 41.5 | 94 | 135.5 |
| 5 | F | 1 | 130 | 62 | [b] | 0 | – |
| 6 | F | 1 | 180 | 100 | [b] | 45.5 | – |
| 7 | Cl | 0 | 130 | 50.5 | 59 | 39.5 | 98.5 |
| 8 | Cl | 1 | 130 | 26 | [b] | 0 | – |

[a] Determined by $^{19}F$ NMR, with $PhOCF_3$ as internal standard, on the crude mixture in the absence of CuI and after filtration on silica gel in the presence of CuI.

[b] Not determined by $^{19}F$ NMR because of traces of paramagnetic Cu(II).



Scheme 3. Adduct between MTFA and fluoride anion.

130 °C (entries 3 and 7), whereas, in the presence of CuI, conversion of MTFA dropped down dramatically with cesium chloride, probably because of an halogen exchange around Cu(I) which generated cesium iodide, which was demonstrated, in an independent experiment, to be inactive for demethylation of MTFA.

If such a high rate of decomposition of MTFA was understandable with cesium chloride, which is completely soluble in DMF at 130 °C, it was surprising that cesium fluoride, which is poorly soluble in DMF, even at 180 °C [15], could provide the same results. Moreover, if chloride can be reasonably assumed to attack MTFA on the soft $sp^3$ carbon center, fluoride, which is a far more harder nucleophile, is more expected to interact with the harder $sp^2$ carbonyl center. Thus, it can be postulated, by analogy with our previous results already mentioned [14], that $F^-$ could form with MTFA a tetrahedric intermediate **1** which could enhance the solubility of CsF and decrease the hardness of the fluoride anion (Scheme 3).

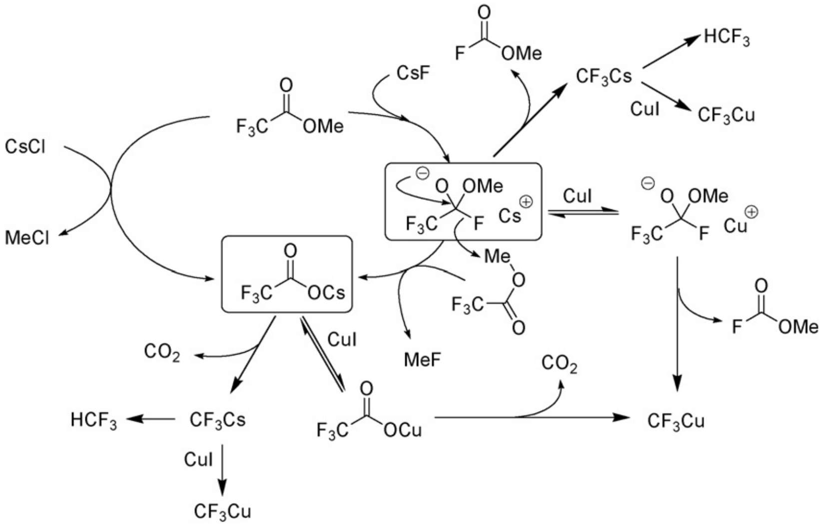
The possibility of such an intermediate led us to imagine that cesium chloride and cesium fluoride could react by two different pathways, CsCl operating through a classical Krapcho mechanism and generating cesium trifluoroacetate, which is further decarboxylated, whereas, from CsF, the $^-CF_3$ anion could be generated from **1** and provide directly fluoroform. However, this latter hypothesis is not consistent with the fact that, when using CsF, both cesium trifluoroacetate and fluoroform were observed. Thus, competitive routes could be proposed (Scheme 4).

These preliminary experiments indicated that "$CF_3Cu$" **3** could be generated from MTFA, CsX and CuI. It was not possible to discriminate between the different species reported in the literature ($CF_3Cu$, $[CF_3CuI]^-$, $[(CF_3)_2Cu]^-$) [5a,b,16] but, as all of them are claimed to be trifluoromethylating agents, we examined the behaviour of the MTFA/CsF/CuI system towards 4-iodoanisole **2a**. No reaction occurred in DMF or sulfolane at 130 °C for 6 h. However, when the trifluoromethylating species **3** were first generated from MTFA, CsF and CuI at 130 °C for 2 h (to minimize the competitive thermal or DMF-mediated decomposition of MTFA), then iodoanisole was added and the whole mixture brought to 180 °C for 4 h, two or three products were formed, depending on the solvent. These compounds resulted from the substitution of the iodine atom by trifluoromethyl, methoxy and dimethylaminocarbonyl groups, the ratio of them depending on the ratio between the reagents (Table 2).

Table 2 indicates that first, conversion of **2a** increased when increasing the excess of MTFA. This could be explained by the fact that, with small excess of TFMA, thermal or DMF-induced decomposition of this reagent competed with aromatic substitution. Second, increasing excess of MTFA strongly decreases the methoxylation process. Third, substitution of iodine for dimethylaminocarbonyl occurred in DMF only but decreased as trifluoromethylation increases. Finally, sulfolane was a more adapted solvent than DMF for trifluoromethylation.

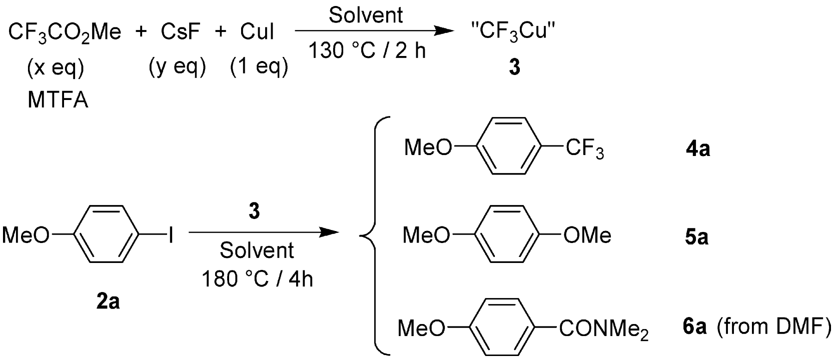
With such a procedure, best trifluoromethylation yields were obtained with a five-fold excess of MTFA and 1 or 2.5 eq. (in sulfolane and DMF, respectively) of cesium fluoride. Indeed, such an excess of MTFA could be a drawback from an economical point of view. However, from an ecological point of view, it must be noticed that the by-products coming from MTFA are essentially gaseous ($CO_2$, $CH_3X$, $HCF_3$), that is not the case during trifluoromethylation with alkaline trifluoroacetates, which generates large amounts of salts that must be stored.

Methoxylation, which occurred at 180 °C and not at 130 °C, was consistent with the formation of the tetrahedral intermediate **1** since methoxide species could not result from a Krapcho process. Indeed, **1** could expell either a fluoride or a methoxide or a trifluoromethyl anion, in the order



Scheme 4. Generation of $^-CF_3$ from MTFA and cesium halides.

Table 2
Two steps one-pot substitution of 4-iodoanisole with MTFA/CsF/CuI



| Entry | *x* (eq.) | *y* (eq.) | Solv.[a] | Conv. ArI (%)[b] | **4a** (%)[c] *vs.* conv. ArI | **5a** (%)[b] *vs.* conv. ArI | **6a** (%)[d] % *vs.* conv. ArI |
|---|---|---|---|---|---|---|---|
| 1[e] | 1.0 | 1.0 | DMF | 42 | 0 | 69 | 0 |
| 2 | 1.0 | 1.0 | Sulfol. | 30 | 23 | 35 | – |
| 3[e,f] | 1.6 | 1.0 | DMF | 37 | 0 | 60 | 0 |
| 4[e] | 3.0 | 1.0 | DMF | 61 | 11 | 2 | 51 |
| 5 | 3.0 | 1.0 | Sulfol. | 56 | 71 | 1–2 | – |
| 6[g] | 5.0 | 1.0 | DMF | 72 | 12 | 5.5 | 35 |
| 7[e] | 5.0 | 1.0 | Sulfol. | 80 | 80 | 4 | – |
| 8 | 5.0 | 2.5 | DMF | 69 | 40.5 | 6 | 14 |

[a] DMF: *N*,*N*-dimethylformamide; Sulfol.: sulfolane.

[b] From $^{1}H$ NMR after filtration over silica gel.

[c] From $^{19}F$ NMR (with $PhOCF_3$ as internal standard) after filtration over silica gel.

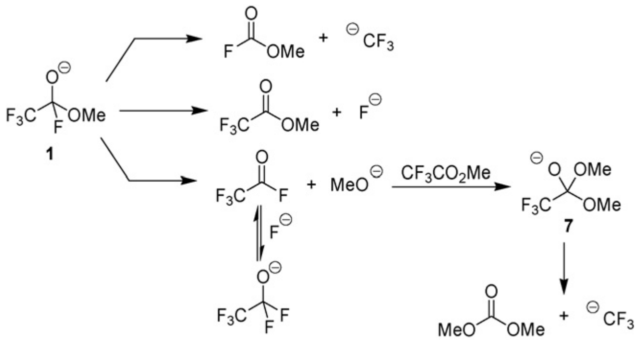
[d] From GC analysis after filtration over silica gel.

[e] Analyses by methods (a–c).

[f] Conv. MTFA = 94%, $HCF_3$ = 38.5% *vs.* MTFA.

[g] Conv. MTFA = 50%, $HCF_3$ = 24% *vs.* MTFA.

C–$CF_3$ > C–F (because of coulombian repulsions) > C–OMe. However, when an excess of MTFA was used, methoxide was probably trapped by MTFA to provide another tetrahedral intermediate **7**, analogous to those reported by us [14] or other teams [17,18]. **7** could be also a source of trifluoromethyl anions (Scheme 5). Thus, an excess of MTFA could not only prevent methoxylation but also increase trifluoromethylation. The qualitative detection of trifluoroacetyl fluoride in the gas phase and dimethyl carbonate in the liquid phase sustained the occurrence of $sp^3$ intermediates **1** and **7**. Concerning trifluoroacetyl fluoride, we verified, from an authentic sample of this compound, that it did not act as a trifluoromethylating agent, under the conditions used for MTFA. However, it probably caused a loss of fluoride since it can trap it, through a known equilibrium, to provide the $CF_3CF_2O^-$ anion (Scheme 5).



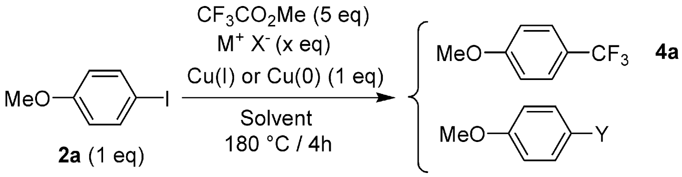
Scheme 5. Terahedral adducts from MTFA.

It is known that, under the action of a base such as fluoride, DMF decomposes into carbon monoxide and dimethylamine [19]. Indeed, these products were detected in the gas phase during our experiments. They could substitute the iodine atom after oxidative addition of Cu(I) in the C–I bond to provide benzamide **6a**. This observation allows us to assume that all the Cu(I) mediated iodine substitutions we observed arose from an oxidative addition/reductive elimination mechanism.

Such side reactions could explain the needed excess of cesium fluoride (2.5 eq.) which, on the other hand, could be solubilized by an excess of MTFA, the latter being also useful to reduce methoxylation and enhance trifluoromethylation.

In all the experiments reported in Table 2, the conversion of aromatic substrate **2a** remained uncomplete and, except in entries 5 and 7, the yield of trifluoromethylated product **4a** *vs.* **2a** was often poor to modest. This could be due to the fact that the trifluoromethylating species, preformed at 130 °C before addition of **2a**, could be too much solvated or aggregated. Indeed, organometallic compounds, especially copper ones, are know to gather into clusters along time; obviously, these clusters are less reactive than the monomeric species. Consequently, the reaction was carried out in one step at 180 °C, in different aprotic polar solvents and in the presence of

Table 3
One step substitution of 4-iodoanisole with MTFA/halides/Cu(I) or Cu(0)



| | MX (*x* eq.) | Solv.[a] | Cu | Conv. ArI[b] (%) | **4a**[c] *vs.* ArI (%) | **4a**[c] *vs.* conv. ArI (%) | ArY[d] *vs.* ArI (*Y*, %) | ArY[d] *vs.* conv. ArI (*Y*, %) |
|---|---|---|---|---|---|---|---|---|
| 1 | CsF (1.0) | DMF | CuI | 100 | 46 | 46 | CONMe$_2$ 37 | CONMe$_2$ 37 |
| 2 | CsF (2.5) | DMF | CuI | 100 | 75 | 75 | CONMe$_2$ 8 | CONMe$_2$ 8 |
| 3 | CsF (2.5) | DMF | CuBr | 96 | 61 | 64 | CONMe$_2$ 11 Br 15 | CONMe$_2$ 11 Br 16 |
| 4 | CsF (2.5) | DMF | Cu(0) | 65 | 14 | 22 | CONMe$_2$ 47 H 4 | CONMe$_2$ 72 H 6 |
| 5 | CsF (2.5) | DMAc | CuI | 60 | 16 | 27 | H 17 | H 28 |
| 6 | CsF (2.5) | NMP | CuI | 97 | 23 | 24 | H 46 | H 47 |
| 7 | CsF (2.5) | DMSO[e] | CuI | 78 | 0 | 0 | SMe 78 | SMe 100 |
| 8 | CsF (2.5) | Sulf. | CuI | 100 | 79 | 79 | – | – |
| 9 | CsCl (1.0) | DMF | CuI | 92 | 60 | 65 | Cl 12 | Cl 13 |
| 10 | CsCl (2.5) | DMF | CuI | 83 | 55 | 66 | Cl 8 | Cl 10 |
| 11 | CsBr (1.0) | DMF | CuI | 79 | 32 | 40 | Br 27 | Br 34 |
| 12 | CsI (1.0) | DMF | CuI | 66 | 46 | 70 | – | – |
| 13 | KF (2.5) | DMF | CuI | 60 | 35 | 58 | CONMe$_2$ 12 | CONMe$_2$ 20 |
| 14 | KI (1.0) | DMF | CuI | 52 | 33 | 63 | – | – |
| 15 | TMAI (2.5) | DMF | CuI | 45 | 25 | 56 | – | – |

[a] DMF: *N*,*N*-dimethylformamide; DMAc: *N*,*N*-dimethylacetamide; NMP: *N*-methylpyrolidinone; DMSO: dimethylsulfoxide; Sulfol.: sulfolane (1,1-dioxo-tetrahydrothiophene); TMAI: tetramethylammonium iodure.

[b] From $^{1}$H NMR after filtration over silica gel.

[c] From $^{19}$F NMR (with PhOCF$_3$ as internal standard) after filtration over silica gel.

[d] From GC analysis after filtration over silica gel.

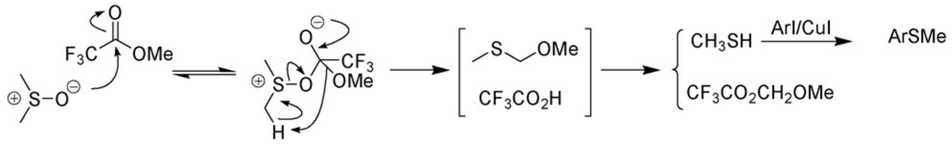
[e] At 130 °C.

different alkaline halides as well as different copper species (Table 3).

Significant differences appeared between the two step procedure (Table 2) and the one step method at 180 °C (Table 3). Best results were obtained in the latter case: trifluoromethylation was more selective since the yield (*vs.* converted **2a**) was up to 75% at 180 °C (Table 3, entry 2), compared to 40.5% for the two step procedure (Table 2, entry 8). Moreover, dimethylaminocarbonylation decreased and methoxylation never occurred at 180 °C. Concerning the solvent, dimethylaminocarbonylation was still observed in DMF but only when alkaline fluorides were used (entries 1–4, 13); with other alkaline chlorides or bromides, substitution of aromatic iodine by the corresponding halide was the main side reaction (entries 9–11). With other *N*,*N*-dialkylated polar aprotic solvents such as DMAc (entry 5) and NMP (entry 6), hydrodeiodination matched trifluoromethylation. In DMSO, selective methylthiolation was only observed (entry 7). As substrate **2a** remained almost unaffected by DMSO at 130 °C in the absence of methyl trifluoroacetate, this substitution could involve the formation of methanethiol from DMSO and MTFA (Scheme 6), by analogy with that already reported from trifluoroacetyl fluoride or carbonyl difluoride [20]. Again, sulfolane appeared at least as efficient as DMF (entry 8 *vs.* entry 2), with the advantage that no side reaction occurred in sulfolane.

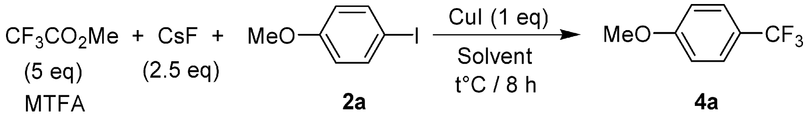
Concerning the copper catalyst, CuBr was slightly less efficient than CuI and metallic copper was poorly selective (entries 2–4). It was also verified that sub-stoichiometric amounts of CuI (0.5 eq.) decreased the conversion of the substrate (35.5%) and the yield of trifluoromethylation (18%).

As far as the alkaline halide was concerned, similar results were obtained with 1.0 or 2.5 eq. of cesium chloride (entries 9, 10) whereas trifluoromethylation selectivity was strongly enhanced when increasing the amount of cesium fluoride (entries 1, 2). Thus, 2.5 eq. of cesium fluoride could be advantageously replaced by 1 eq. of cesium chloride. This difference probably reflects the better solubility of CsCl and/or a difference in mechanisms, as already suggested in Scheme 4. Other cesium halides (CsBr, CsI) delivered lower conversions



Scheme 6. Pummerer-type reaction between MTFA and DMSO.

Table 4
Influence of the temperature



| Entry | Solv. | *t* (°C) | Conv. ArI (%) | **4a** (%) *vs.* ArI | **4a** (%) *vs.* conv. ArI |
|---|---|---|---|---|---|
| 1 | DMF | 180 | 100 | 75 | 75 |
| 2 | DMF | 140 | 13 | 0 | 0 |
| 3 | Sulfol. | 180 | 100 | 79 | 79 |
| 4 | Sulfol. | 160 | 82 | 66 | 80 |
| 5 | Sulfol. | 140 | 77 | 53 | 69 |

than CsCl ($CsCl > CsBr > CsI$), though satisfactory chemoselectivity was obtained with cesium iodide (entries 9, 11, 12). It must be noticed that the less soluble potassium fluoride led to a far lower conversion of **2a** and to a lower selectivity.

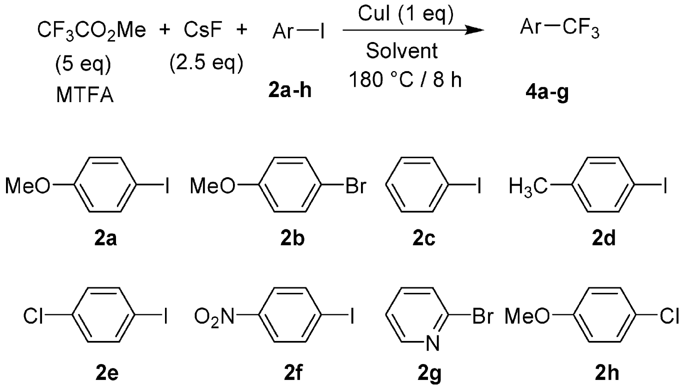
The last parameter studied for the one step trifluoromethylation was temperature, either in DMF or in sulfolane (Table 4).

As already mentioned, DMF and sulfolane were equally suited at 180 °C, but, at 140 °C, DMF was quite inefficient whereas sulfolane remained a useful solvent. As it would be surprising that the relationship between solubility of CsF and temperature should be so different in DMF and sulfolane, we suggest that such a difference could come from a better chelation, by sulfolane, of Cu(I) in cuprous trifluoroacetate, the decarboxylation of which would be facilitated. Nevertheless, despite this activating effect, Cu(I) must be used in a stoichiometric amount, even in sulfolane, though the mechanism usually admitted for copper-mediated aromatic substitution implies Cu(I) as catalyst (Scheme 7). Such a contradiction could be resolved by kinetic considerations: if the oxidative addition rate is far lower than the decarboxylation rate [$k_1$ (or $k'_1$) $\gg k_2$], the unstable $^{-}CF_3$ species accumulate and must be stabilized by equal amounts of Cu(I).

Then, trifluoromethylation with MTFA/CsF/CuI was applied to other aryl halides (Table 5).

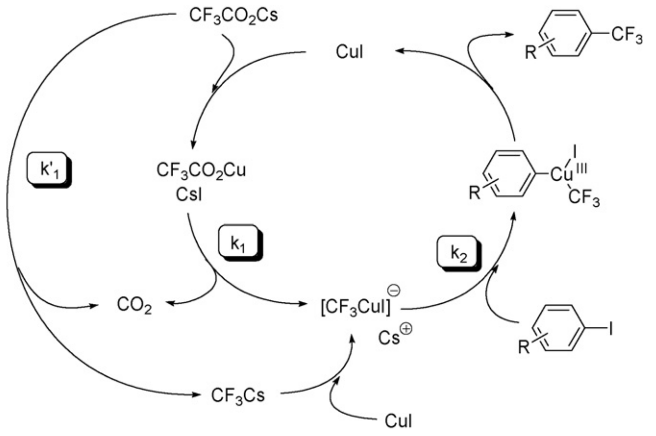
As expected for a copper-mediated aromatic substitution, aryl halides exhibit the following order of reactivity

Table 5
Trifluoromethylation of various aryl halides



| Entry | 2 | Solv. | Conv. ArX (%) | **4** (%)[a] *vs.* Conv. ArX | **4** (%)[a] *vs.* ArX |
|---|---|---|---|---|---|
| 1 | **2a** | DMF | 100 | 75 | 75 |
| 2 | **2a** | Sulfol. | 100 | 79 | 79 |
| 3 | **2b**[b] | DMF | 73 | 56 | 41 |
| 4 | **2c** | DMF | 100 | (69) | (69) |
| 5 | **2d** | DMF | 100 | 65 (71) | 65 (71) |
| 6 | **2e** | DMF | 100 | 50 (82) | 50 (82) |
| 7 | **2f** | Sulfol.[c] | 86 | 62 (63) | 53 (54) |
| 8 | **2g** | DMF | 100 | 42 (45) | 42 (45) |
| 9 | **2h** | Sulfol. | 16 | 0 | 0 |

[a] Isolated yields; in parentheses, crude yield from GC and NMR.
[b] Side formation of **2a** (7% from GC).
[c] At 140 °C.

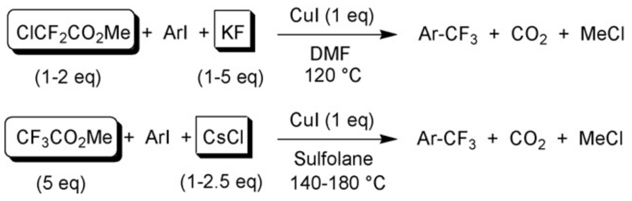


Scheme 7. Mechanism of aromatic trifluoromethylation.

ArI > ArBr ≫ ArCl and, in fact, aryl chloride **2h** was quite completely recovered. As expected also, for a given leaving group, the results were not really influenced by the nature of the aromatic substituent. It can be noticed that the possibility to carry out trifluoromethylation in sulfolane at 140 °C was fruitful in the case of *para*-nitroiodobenzene **2f** since, in DMF, no reaction was observed at 140 °C, trifluoromethylation was poorly selective at 160 °C and extensive decomposition occurred at 180 °C.

Finally, aromatic perfluoroalkylation with different trifluoroacetic or pentafluoropropionic acid derivatives were also briefly evaluated (Table 6), without wishing to study precisely, at the moment, the scope of these reagents.

These experiments demonstrated that trifluoromethylation was more efficient and far more selective with methyl trifluoroacetate than with ethyl trifluoroacetate. This could reflect steric effects governing the attack of fluoride on the carbon in α position to oxygen during the Krapcho reaction. Moreover, ethyl trifluoroacetate could β-eliminate ethylene under the action of fluoride, considered as a strong base in aprotic solvents, as do many ethyl esters in basic medium under heating. Thus, generated HF could consume some fluoride (by formation of $HF_2^-$) or some trifluoromethyl anions (by formation of fluoroform). Of course, the Krapcho process cannot be invoked when trifluoroacetic anhydride was used but, in this case, addition of fluoride on the trifluoroacetyl moiety, followed by elimination, probably led to cesium trifluoroacetate and trifluoroacetyl fluoride (that we demonstrated to be inactive for trifluoromethylation). The fact that trifluoroacetic anhydride acted as a trifluoromethylating agent, under these conditions, comforts our hypothesis of formation of $sp^3$ intermediates, such as **1**, resulting from the attack of $F^-$ on a trifluoroacetyl moiety.



Scheme 8. Comparison of MTFA and MCDFA.

## 3. Conclusion

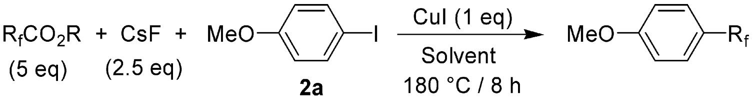
In conclusion, when associated with an alkaline halide (such as cesium fluoride or cesium chloride) and Cu(I) species, methyl trifluoroacetate constitutes a valuable trifluoromethylating agent for substituting aromatic (or heteroaromatic) iodides and bromides. The reaction can be carried out in DMF at 180 °C or, better, in sulfolane which allows the reaction to proceed at a lower temperature (from 140 °C). It can be underlined that methyl trifluoroacetate is more easily available than methyl chlorodifluoroacetate, previously used by Chen and Burton as trifluoromethylating agent, since, on the industrial scale, chlorodifluoroacetic derivatives are usually obtained as by-products in the manufacture of trifluoroacetic derivatives, for example during vapor phase fluorination of trichloroacetyl chloride. Some complementarity can be drawn between our technique and that of Chen and Burton in the sense that we can use methyl trifluoroacetate and alkaline chlorides instead of methyl chlorodifluoroacetate and potassium fluoride (Scheme 8).

## 4. Experimental

Prior to use, solvents were distilled and stored over 3 Å molecular sieves under $N_2$. Other reagents were used as

Table 6

Aromatic perfluoroalkylation with different trifluoroacetic or pentafluoropropionic derivatives



| Entry | $R_f$ | R | Solv. | Conv. ArI (%) | **4** (%) *vs.* ArI |
|---|---|---|---|---|---|
| 1 | $CF_3$ | Me | DMF | 100 | 75 |
| 2[a] | $CF_3$ | Et | DMF | 92 | 26 |
| 3 | $C_2F_5$ | Me | Sulfol. | 100 | 50 |
| 4 | $(CF_3CO)_2O$ | Sulfol. | 59 | 30[b] | |

[a] Same result with CsCl instead of CsF.

[b] Side formation of 1,4-dimethoxybenzene.

received. TLC analyses were carried out on silica gel (Kieselgel 60F 254) deposited on aluminum plates, detection being done by UV (254 nm). Flash-chromatographies were performed on silica gel Geduran SI 60. Unless stated otherwise, NMR spectra were recorded in $CDCl_3$. $^1H$ NMR were recorded at 200 or 300 MHz and $^{13}C$ NMR spectra at 50 or 75 MHz. The substitution pattern of the different carbons were determined by a "DEPT 135" sequence. $^{19}F$ NMR spectra were recorded at 188 MHz. Chemical shifts ($\delta$) are given in ppm *vs*. TMS ($^1H$, $^{13}C$) or $CFCl_3$ ($^{19}F$) used as internal references. Coupling constants are given in hertz. Crude yields were determined by $^{19}F$ NMR *vs*. $PhOCF_3$ ($\delta_F = -58.3$ ppm) used as standard. GC was carried out on an apparatus fitted with a semi-capillary column (length: 15 m, diameter: 0.53 mm, film thickness (DB1): 1 μm) and a catharometric detector. Mass spectrometry, coupled with gas chromatography, was carried out under electron impact at 70 eV.

### *4.1. General procedure*

The solvent (20 mL) and the different reagents were introduced in a 150 mL stainless steel autoclave, designed to be used up to 220 °C and 150 bars. After closing, the vessel was immerged in an oil bath previously brought to the desired temperature and the reaction medium was stirred with a magnetic bar. After reaction, the autoclave was cooled in dry ice and, after degassing, a sample of the crude medium was analyzed by $^{19}F$ NMR (with internal standard) to measure the amount of volatile fluorinated products such as fluoroform or unreacted methyl trifluoroacetate. Then, the reaction mixture was poured on a mixture (60 mL) of water and diethyl ether (1:1). Metallic salts were filtered on Celite and the filtrate was extracted with diethyl ether. The organic phases were gathered, dried over $MgSO_4$ and concentrated under vacuum at room temperature. The liquid residue was analyzed by GC and $^1H$ NMR and the remaining polar aprotic solvent was separated from the aromatic products by a short chromatography over silica gel with a petroleum ether/diethyl ether mixture (95:5) as eluent. Since, all the products were described in the literature, their characteristics were compared to the published data or to an authentic sample when commercially available. For the products which have to be quantified by GC, their retention time was compared to that of an authentic sample and quantification was done by addition of a known quantity of this authentic sample.

## Acknowledgement

The Rhodia Co., is very much acknowledged for granting N. Roques' Ph.D. work.

## References

[1] B.R. Langlois, in: J.C. Tatlow, R.E. Banks, B.E. Smart (Eds.), Fluoro-Organic Chemistry: Principles and Commercial Applications, Plenum Pub. Co., New York, 1994 , pp. 221–235 (Chapter 10).

[2] (a) M.A. McClinton, D.A. McClinton, Tetrahedron 48 (1992) 6555;
(b) B.R. Langlois, T. Billard, Synthesis (2003) 185.

[3] M. Tordeux, B. Langlois, C. Wakselman, J. Chem. Soc., Perkin Trans. I (1990) 2293.

[4] B. Langlois, E. Laurent, N. Roidot, Tetrahedron Lett. 32 (1991) 7525.

[5] (a) D.M. Wiemers, D.J. Burton, J. Am. Chem. Soc. 108 (1986) 832;
(b) M.A. Willert-Porada, D.J. Burton, N.C. Baenziger, J. Chem. Soc., Chem. Commun. (1989) 1633;
(c) D.J. Burton, D.M. Wiemers, J. Am. Chem. Soc. 107 (1985) 5014;
(d) D.J. Burton, Z.Y. Yang, Tetrahedron 48 (1992) 189;
(e) J.H. Clark, M.A. Mc Clinton, R.J. Blade, J. Chem. Soc., Chem. Commun. (1988) 638.

[6] J.M. Paratian, J. Périchon, S. Sibille, J. Chem. Soc., Chem. Commun. (1992) 53.

[7] (a) Y. Kobayashi, I. Kumadaki, Tetrahedron Lett. 47 (1969) 4095;
(b) Y. Kobayashi, K. Yamamoto, I. Kumadaki, Tetrahedron Lett. 42 (1979) 4071.

[8] H. Urata, T. Fuchikami, Tetrahedron Lett. 32 (1991) 91.

[9] (a) N. Yukihisa, H. Takeshi, Japanese Patent 0413651 (1990) (to Daicel Chem. Ind.).
N. Yukihisa, H. Takeshi, Chem. Abstr. 116 (1990) 235232e;
(b) K. Matsui, E. Tobita, M. Ando, K. Kondo, Chem. Lett. (1981) 1719.

[10] J.W. Freskos, Synth. Commun. 18 (1988) 965.

[11] Q.Y. Chen, S.W. Wu, J. Chem. Soc., Chem. Commun. (1989) 705.

[12] J.G. McNeil, D.J. Burton, J. Fluorine Chem. 55 (1991) 225.

[13] (a) D.B. Su, J.X. Duan, Q.Y. Chen, Tetrahedron Lett. 32 (1991) 7689;
(b) J.X. Duan, D.B. Su, Q.Y. Chen, J. Fluorine Chem. 61 (1993) 279.

[14] L. Jablonski, J. Joubert, T. Billard, B.R. Langlois, Synlett (2003) 230.

[15] B. Langlois, L. Gilbert, G. Forat, in: J.R. Desmurs, S. Ratton (Eds.), The Roots of Organic Development, Elsevier, Amsterdam, 1996, pp. 244–292.

[16] G.E. Carr, R.D. Chambers, T.F. Holmes, D.G. Parker, J. Chem. Soc., Perkin Trans. I (1988) 921.

[17] P. Capdevielle, M. Maumy, Tetrahedron Lett. 34 (1993) 1007.

[18] E. Bergman, J. Org. Chem. 23 (1958) 476.

[19] J.A. Riddick, W.B. Bunger, T.K. Sakano, fourth ed., Physical Properties and Methods of Purification, vol. II, Wiley & Sons, 1986.

[20] H.G. Lange, J.M. Shreeve, J. Fluorine Chem. 28 (1985) 219.