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Preliminary Note

Generation of trifluoromethylcopper from chlorodifluoroacetate

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Abstract

In the presence of fluoride ion, methyl chlorodifluoroacetate undergoes halide ion-promoted decarboxylation to give trifluoromethide which can be trapped with cuprous iodide. The resulting trifluoromethyl copper reagent has been observed spectroscopically and can be trapped with aryl iodides to give the corresponding trifluoromethylaromatic compound.

Pharmaceutical and agricultural chemicals that contain trifluoromethyl groups have been the subject of increased research activity in recent years [1, 2]. Concomitant with these applications have been increased efforts to develop inexpensive yet efficient trifluoromethylating agents with particular emphasis focused on the *in situ* generation and coupling of trifluoromethyl copper with aryl halides.

Several years ago we developed a novel preparation of trifluoromethyl cadmium and zinc reagents from difluorodihalomethanes [3]. Subsequent work extended this reaction to the *in situ* formation and capture of CF_3Cu [4]. Mechanistically, organometallic formation involved the generation of difluorocarbene, capture of the carbene with fluoride to give trifluoromethide, and finally reaction of trifluoromethide with metal halide to afford the trifluoromethyl organometallic [3].

$$[:CF_2] + F^- \rightleftharpoons [CF_3]^-$$

$$[CF_3]^- + MX_2 \longrightarrow CF_3MX + (CF_3)_2M$$

$$(M = Zn, Cd)$$

Later, Chen and Wu utilized this mechanistic approach to form CF_3Cu from methyl fluorosulphonyldifluoroacetate [5] and fluorosulphonyldifluoromethyl iodide [6].

An alternative source of difluorocarbene is methyl chlorodifluoroacetate. We have previously shown that this ester readily decomposes in the presence

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of the lithium chloride/HMPA or KF/18-crown-6 complexes to generate difluorocarbene [7]. Hence, if this ester decomposition is carried out with alkali metal fluorides in the presence of copper(I) salts, trifluoromethyl copper should be formed.

$$CF_2ClCO_2CH_3 + CuI \xrightarrow[\text{solvent, heat}]{KF} CF_3Cu$$

via

$$CF_2ClCO_2CH_3 + X^- \longrightarrow CH_3X + CO_2 + [:CF_2] + Cl^-$$

(X=I or F)

$$[:CF_2] + F^- \rightleftharpoons [CF_3{}^-] \xrightarrow{CuI} CF_3Cu \text{ or } [CF_3CuI]^-$$

We wish to report that treatment of methyl chlorodifluoroacetate with excess potassium fluoride in the presence of 1 equiv. cuprous iodide and 1 equiv. of an aryl iodide in HMPA or DMPU at 120 °C gives good yields of the trifluoromethyl-substituted aromatic compound.

Table 1 presents typical examples of this methodology.

The operational details of the experimental procedure for the preparation of the trifluoromethyl aromatic compounds are as outlined below. 3.2 g (20 mmol) methyl chlorodifluoroacetate, 10 ml DMPU, 3.8 g (20 mmol) cuprous iodide, and 5.8 g (100 mmol) dry potassium fluoride were charged into a 100 ml one-necked round-bottom flask equipped with a magnetic stir-bar, septum port with septum and condenser topped with a nitrogen inlet. Iodobenzene, 4.1 g (20 mmol), was added via a syringe and the mixture heated to 120 °C for 4 h. The organic contents of the flask were removed under vacuum and the resulting mixture poured into water. The organic layer was separated, dried over 4 Å molecular sieves and distilled under reduced pressure to give 1.85 g (62%) of 1,1,1-trifluorotoluene, b.p., 50 °C/25 mmHg, 99% GLPC purity; ^{19}F NMR: $\delta -63$ ppm (s).

TABLE 1

Preparation of 1,1,1-trifluoromethyl aromatics

$$CF_2ClCO_2CH_3 + KF\text{ (excess)} + CuI + \xrightarrow[\text{DMPU, heat}]{KF,} ArCF_3$$

ArI	$ArCF_3$	Isolated yield(%)[a]
PhI	$PhCF_3$	62
o-$CH_3C_6H_4I$	o-$CH_3C_6H_4CF_3$	52
m-$CF_3C_6H_4I$	m-$CF_3C_6H_4CF_3$	76
o-$NO_2C_6H_4I$	o-$NO_2C_6H_4CF_3$	64[b]
p-$CH_3C_6H_4I$	p-$CH_3C_6H_4CF_3$	73

[a] Products were identified by comparison to previously prepared samples [4].

[b] ^{19}F NMR yield based on $PhCF_3$ as an internal standard.

When the reaction was carried out in the absence of iodobenzene, CF_3Cu was detected spectroscopically at -29.2 ppm (^{19}F NMR) in low yield ($< 10\%$). Similar reactions in DMF with iodobenzene gave lower yields (40%) of 1,1,1-trifluorotoluene and the formation of pentafluoroethyl copper was detected spectroscopically.

Addition of potassium iodide in an attempt to accelerate the dealkylation of the ester did not appear to significantly increase the rate of formation of the trifluoromethyl-substituted products.

This approach provides an alternative methodology to other *in situ* routes for the formation and capture of trifluoromethyl copper with aryl halides. The advantage of this method is the availability of an inexpensive, easily handled precursor. The methodology described above further supports our earlier mechanistic proposal for the formation of trifluoromethyl organometallics via a difluorocarbene intermediate.

Additional studies will focus on the scope of this trifluoromethylation reaction and optimization of this procedure.

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