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Short Communication

Synthesis of trifluoromethyl moieties by late-stage copper (I) mediated nucleophilic fluorination

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ABSTRACT

The nucleophilic fluorination of bromodifluoromethyl derivatives mediated by the complex $(PPh_3)_3CuF$ is described. Under the reaction conditions, different trifluoroacetates, trifluoroketones, trifluoroarenes and trifluoroacetamides were obtained in good yields.

1. Introduction

The introduction of a fluorine atom into a moiety can considerably affect the physicochemical properties of bioactive molecules. In particular, the trifluoromethyl group (CF_3) is an important substituent in medicinal chemistry that is widely represented in drugs and druglike molecules [1]. Late-stage introduction of fluorine into organic compounds has kept the attention of synthetic organic chemists in the last years due to the applicability of the artificial ^{18}F isotope in positron emission tomography (PET) [2–4]. While an enormous amount of new fluorination reactions have been developed [5], late-stage nucleophilic introduction of fluorine still remains as a challenge [2]. This could be attributed to the decreased nucleophilicity of the fluoride anion due to its high solvation energy [6]. For this reason the use of harsh reaction conditions including high temperatures [7] (>140 °C) and/or activators are usually required [8–11]. This difficulty is accentuated when the nucleophilic fluorination is desired at a fluorinated carbon center. The presence of one or two fluorine atoms in the carbon center will hinder such substitution owing to the electrostatic effect of the current fluorine substitution [18].

The $(PPh_3)_3CuF$ complex was reported for the first time in 1970 [12] and it is considered to be the closest related compound to Cu(I)F [13,14]. Although $(PPh_3)_3CuF$ has been used as intermediate in the synthesis of the well-known trifluoromethylating agent $(PPh_3)_3CuCF_3$ [15], its reactivity as nucleophilic fluorinating agent has not been studied in detail. To the best of our knowledge, there are only two reports in this context. First, the group of Konovalov reported the synthesis of 1-fluoro-2-nitrobenzene from 1-bromo-2-nitrobenzene using $(PPh_3)_3CuF$ [16]. Another paper was published by the Szabó group on regio- and stereoselective nucleophilic fluorination of allyl chlorides using the same $(PPh_3)_3CuF$ complex, showing the promising properties of this complex as a nucleophilic fluorine source [17].

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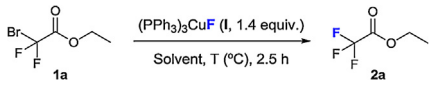
Table 1
Screening of reaction conditions.[a]



Entry	Solvent	Temperature (°C)	Conversion (%)[b]
1	$CDCl_3$	40	<1
2	$CDCl_3$	80	5
3	THF	80	11
4	1,4-Dioxane	80	11
5	Toluene	80	3
6	DMF	80	69
7	DMF	100	90

[a] Reaction conditions: **1a** (0.1 mmol), solvent (0.3 mL), dissolved and heated in the corresponding solvent and temperature under an argon atmosphere for 2.5 h.
[b] Conversion determined by ^{19}F NMR spectroscopy from the reaction crude.

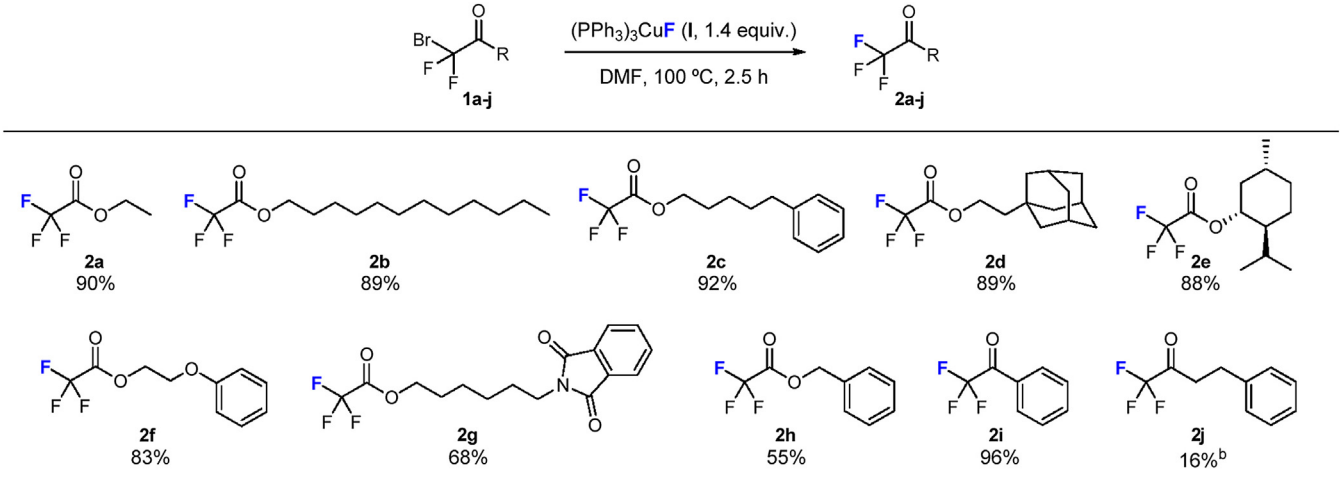
In this paper we present a new late-stage nucleophilic fluorination process for the synthesis of trifluoromethyl moieties (CF_3). This method is based on the halogen exchange reaction between the corresponding difluorobromomethyl derivative (R-CF_2Br) and the easily available copper (I) complex $(PPh_3)_3CuF$.

2. Results and discussion

Our initial investigation started with the transformation of a model substrate, ethyl 2-bromo-2,2-difluoroacetate (**1a**) into the corresponding trifluoroacetate (**2a**) using the $(PPh_3)_3CuF$ complex **I** (Table 1). First, we screened different solvent and temperatures. When $CDCl_3$ was used as solvent, low conversions were observed at 40 or 80 °C (Table 1, entries 1 and 2). The use of more polar solvents, such as THF or 1,4-dioxane, gave similar results and 11% of conversion was observed for both solvents (Table 1, entries 3 and 4). The use of the non-polar solvent toluene did not improve the conversion (Table 1, entry 5). Notably, the conversion of the reaction was increased up to 69% at 80 °C for 2.5 h when using DMF as solvent (Table 1, entry 6). When increasing the temperature from 80 to 100 °C the reaction proceed with a 90% conversion (Table 1, entry 7).

With these results in hand, we investigated the scope of the reaction (Scheme 1). All trifluoromethylated products obtained in the fluorination reactions with $(PPh_3)_3CuF$ were relatively unpolar and by consequence difficult to separate from PPh_3 (arising from the decomposition of the Cu-F complex). Thus, even after careful purification the product samples usually contained varying amounts of PPh_3. Hence, for practical reasons and because this is not a problem for a possible PET application due to the use of HPLC purifications, the yields provided in Scheme 1 were determined by ^{19}F NMR using an internal standard. All products were prepared by alternative methods and fully characterized (see Experimental Section 4.8) before being identified by ^{1}H and ^{19}F NMR spectroscopy in the crude reaction mixtures. Different bromodifluoroacetates with alkyl chains (**1a–d**) were well tolerated in the reaction, yielding the corresponding trifluoroacetates **2a–d** in excellent yields (89–92%). Substrates containing bulky substituents as **1e**, derived from (−)-menthol, also gave excellent results (88% yield). Substrates with phenoxy or *N*-phthalimide substituents (**1f–g**) gave the corresponding trifluoroacetates (**2f–g**) in good yields (83% and 68%, respectively). Only in the case of the benzyl derivative **1h** the yield was diminished to 55%, due to the formation of by products in the reaction mixture. We obtained an excellent yield in the fluorination of 2,2,2-bromodifluoroketone **1i** (96%). However, the enolyzable 2,2,2-bromodifluoroketone **1j** provided low yield of the product **2j** in a complex mixture of decomposition products.

Next, we turned our attention to the nucleophilic fluorination of benzylic positions with the purpose of synthesizing trifluoromethyl arenes in a late-stage fashion (Table 2). For this particular reaction, we found that there was no single solvent suitable for all tested substrates. For the *p*-Ph substituted substrate **3a**, a 93% was obtained using $CDCl_3$ at 70 °C (Table 2, entry 1). With this promising result in hand, we focused our attention into more challenging substrates such as electron deficient arenes [8,9,18]. When a *p*-CN group was incorporated in the substrate (**3b**), only 25% was obtained using toluene at 120 °C (Table 2, entry 2). Substrates bearing a *p*-Br or *p*-OCF_3 substituent gave moderate yields, 49% and 40%, respectively using 1,2-dichloroethane at 100 °C (Table 2, entries 3 and 4). Substrates with the strong electron-withdrawing groups *p*-CF_3 and *p*-CF_2Br (**3e** and **3f**, respectively) yielded the corresponding trifluoromethyl arenes



Scheme 1. Substrate scope of trifluoroacetates and trifluoroketones.[a]
[a]Reaction conditions (unless otherwise noted): **1a–j** (0.1 mmol), DMF (0.3 mL), heated at the 100 °C under an argon atmosphere for 2.5 h. Yield determined by ^{19}F NMR spectroscopy using 2,2,2-trifluorotoluene as internal standard. [b]Using $CDCl_3$ at 70 °C.