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Copper-Mediated Deuterotrifluoromethylation of α-Diazo Esters

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A copper-mediated deuterotrifluoromethylation of *α*-diazo esters under the promotion of deuterium oxide (D_2O) has been developed for the synthesis of deuterium-labeled trifluoromethyl compounds. This deuterotrifluoromethylation reaction is of broad scope and can afford the deuterated products with higher than 99% isotopic purity. Moreover, the results of this investigation also provide some experimental evidences to support our previously proposed trifluoromethylation mechanism.

Keywords copper, trifluoromethylation, deuterium, diazo compounds

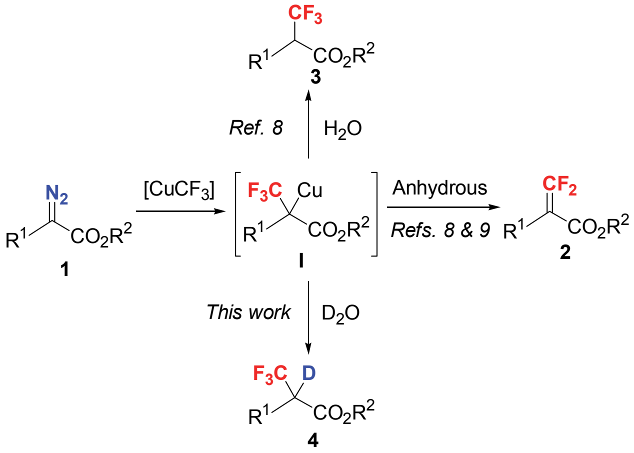
Introduction

Fluorine-containing organic molecules are widely applied in pharmaceuticals, agrochemicals and functional materials due to their improved lipophilicity, metabolic stability and bioavailability endowed by the unique fluorine atom.[1] As one of the most common fluorinated moieties, trifluoromethyl group (CF_3) is frequently used in pharmaceutical and agrochemical research to enhance the bioactivity of organic molecules.[2] Exploring new methods for introducing CF_3 into organic molecules is remarkably one of the hotspots in modern organic chemistry. Recently, many breakthroughs on the Cu- and Pd-catalyzed/mediated trifluoromethylation of aromatic carbons have been achieved.[3] However, transition-metal-assisted trifluoromethylation of aliphatic carbons is less developed.[4]

Isotopic substitution can be used to determine the mechanism of a chemical reaction via the kinetic isotope effect.[5] Isotopic labeled compounds, are often used as isotope tracer in medical diagnostics, age-determination of radioisotope-containing materials, quantifying proteins, *etc*.[6] The late-stage introduction of isotopes is often based on isotope-exchanging method, which always gives impure isotope labeled chemicals.[7]

Previously, we reported a Cu-mediated trifluoromethylation of *α*-diazo esters (Scheme 1).[8] The mechanism investigation suggested that the reaction involves a migratory insertion of carbene ligand into trifluoromethyl-copper bond, giving an *α*-trifluoromethyl-*α*-copper ester intermediate **I**. There are two reaction pathways for the further transformation of intermediate **I**: (i) *β*-fluoride elimination under anhydrous conditions to give 1,1-difluoroalkenes **2**;[8,9] and (ii) protonation in the presence of water to afford *α*-trifluoromethylesters **3**.[8] When a trifluoromethylthiocopper reagent was used, the corresponding hydrotrifluoromethylthiolation can also be achieved.[10] To expand the synthetic application of this copper promoted trifluoromethylation and to find more evidences to support our proposed mechanism, we investigated the capturing of intermediate **I** with other agents. Herein, we report copper-mediated deuterotrifluoromethylation of *α*-diazo esters under the promotion of deuterium oxide (D_2O) (Scheme 1).

Scheme 1 Reaction of $CuCF_3$ with diazo esters



Results and Discussion

In previous work, we developed two methods for the trifluoromethylation of *α*-diazo esters with pre-regener-

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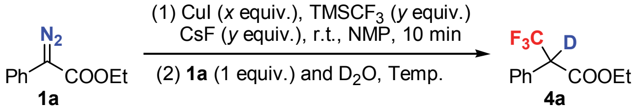
ated "CuCF$_3$" reagent (prepared from CuI/TMSCF$_3$/CsF in a ratio of 1.0 ∶ 1.1 ∶ 1.1).[8] One is the added CuI-promoted reaction (with adventitious water as the proton source), and the other is the added water promoted reaction. At the outset of this work, to probe the formation of trifluoromethylated organocopper intermediate **I**, D$_2$O was used to quench the CuI-promoted trifluoromethylation reaction, and a 18% yield of deuterated product **4a** was obtained (Scheme 2, Eq. 1).[11] However, we soon realized that intermediate **I** can readily undergo protonation by water, the deuterated product **4a** may be generated from the H-D exchange of the original formed product **3a** under the action of the unreacted CuCF$_3$, which served as a base. To test the possibility of H-D exchange, pure deuterated **4a** was subjected to the standard conditions of water-promoted trifluoromethylation reaction.[8] Interestingly, the H-D exchange indeed took place; however, only a conversion of about 80% was observed (Scheme 2, Eq. 2). When non-deuterated compound **3a** was subjected to the H-D exchange reaction conditions, a similar conversion was observed (Eq. 3). These results indicate that the H-D exchange can take place under the standard trifluoromethylation conditions, and the deuteration yield is only moderate due to the equilibrium reaction.

Since the trifluoromethylated organocopper intermediate **I** in our reaction system could not be observed or trapped by various other electrophiles such as allyl bromide, iodine, diphenyl disulfide, and *α*,*β*-unsaturated compounds,[12] to verify the formation of this intermediate during the trifluoromethylation, we performed the added D$_2$O-promoted reaction. Initially, 0.2 mmol scale starting material **1a** and 0.5 mL solvent NMP were used, and a randomly selected amount of D$_2$O (90 equiv.) was used to test the viability of the reaction. Gratifyingly, the reaction proceeded smoothly to give the desired deuterated product in 36% yield with higher than 99% purity (Table 1, Entry 1). However, reducing the amount of D$_2$O to 1 equiv. is inferior to the reaction (Table 1, Entry 2). Because the viscosity of D$_2$O is larger than H$_2$O, we envisioned that a higher temperature may promote the reaction. Indeed we found that raising the temperature to 40 ℃, the yield increased dramatically from 36% to 68% when 90 equiv. of D$_2$O were used as the promoter (Table 1, Entry 3). Further optimization of the reaction conditions showed that a 75% yield can be achieved by using 100 equiv. of D$_2$O as promoter (Table 1, Entries 4—8). More interestingly, simply increasing the concentration of the starting material **1a** can improve the yield to 89% (Table 1, Entry 9). Further screening the quantity of D$_2$O showed that **4a** could be obtained in a yield as high as 96% when 60 equiv. of D$_2$O was used (Table 1, Entries 9—12).

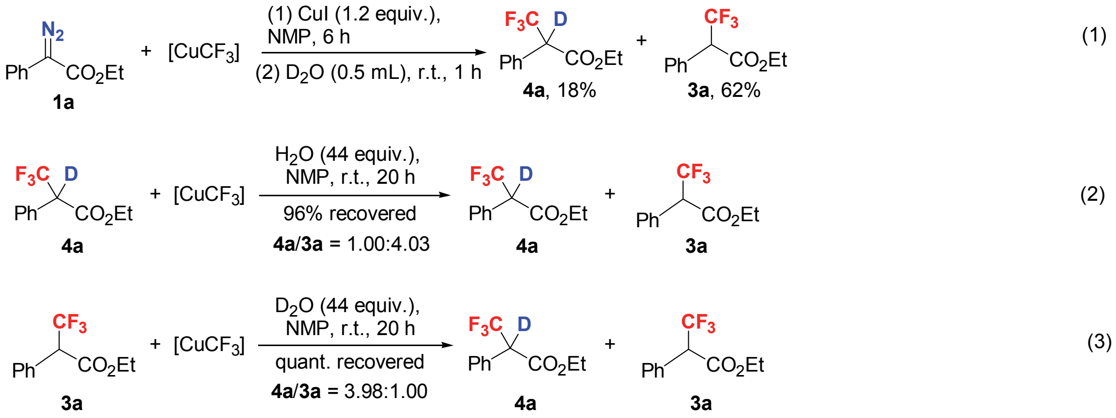
Table 1 Optimization of the reaction conditions[a]



Entry[b]	D$_2$O (equiv.)	Temp./℃	Time/h	Yield[c]/%
1	D$_2$O (90)	r.t.	15	36
2	D$_2$O (1)	r.t.	65	11
3	D$_2$O (90)	40	15	68
4	D$_2$O (50)	40	14	37
5	D$_2$O (100)	40	16	75
6	D$_2$O (120)	40	16	69
7	D$_2$O (220)	40	16	52
8	D$_2$O (100)	40	11	75
9	D$_2$O (40)	40	11	89
10	D$_2$O (60)	40	11	96
11	D$_2$O (80)	40	11	93
12	D$_2$O (100)	40	11	90

[a] All reactions were performed by adding **1a** and additive into the pre-generated "CuCF$_3$". [b] Entries 1—8 were performed on 0.2 mmol sacle (x=1.5, y=1.8) in NMP (3 mL+3 mL) under N$_2$ atmosphere; Entries 9—12 were performed on 0.5 mmol sacle (x=1.5, y=1.65) in NMP (3 mL+3 mL) under N$_2$ atmosphere. [c] The yields were determined by ^{19}F NMR with PhCF$_3$ as an internal standard.

Scheme 2 H-D exchange experiments of *α*-trifluoromethyl esters



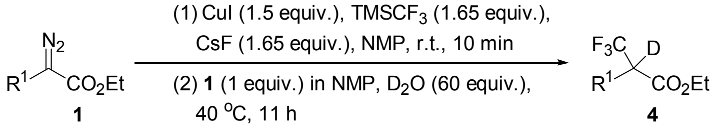
With the optimized reaction conditions in hand (Table 1, Entry 10), we further investigated the versatility of the deuterotrifluoromethylation reaction with diversely substituted α-diazo esters, the results were summarized in Table 2. The reaction was of similar functional group tolerance and electronic effect with previously reported hydrotrifluoromethylation.[8] For example, there occurred no aromatic trifluoromethylation when the aryl ring was substituted by halogens (F-, Cl-, Br) (Table 2, **4g**—**4m**, **4t**, and **4u**), and the substituents on the *orth*-, *meta*-, or *para*-position of the phenyl group had no significant influence on the yields (Table 2, **4b**—**4m**). Similarly, the electron-donating groups substituted on the phenyl groups, afforded better yields than electron-deficient ones (Table 2, **4c**—**4m**). Due to the competitive β-H elimination of Cu-carbene intermediate, the benzyl substituted diazo esters rendered comparably lower yield than phenyl substituted ones (Table 2, Entries **4n**—**4t**). The aliphatic substituted diazo esters gave good yields similar to previous reported hydrotrifluoromethylation (Table 2, Entries **4u**—**4w**).[8]

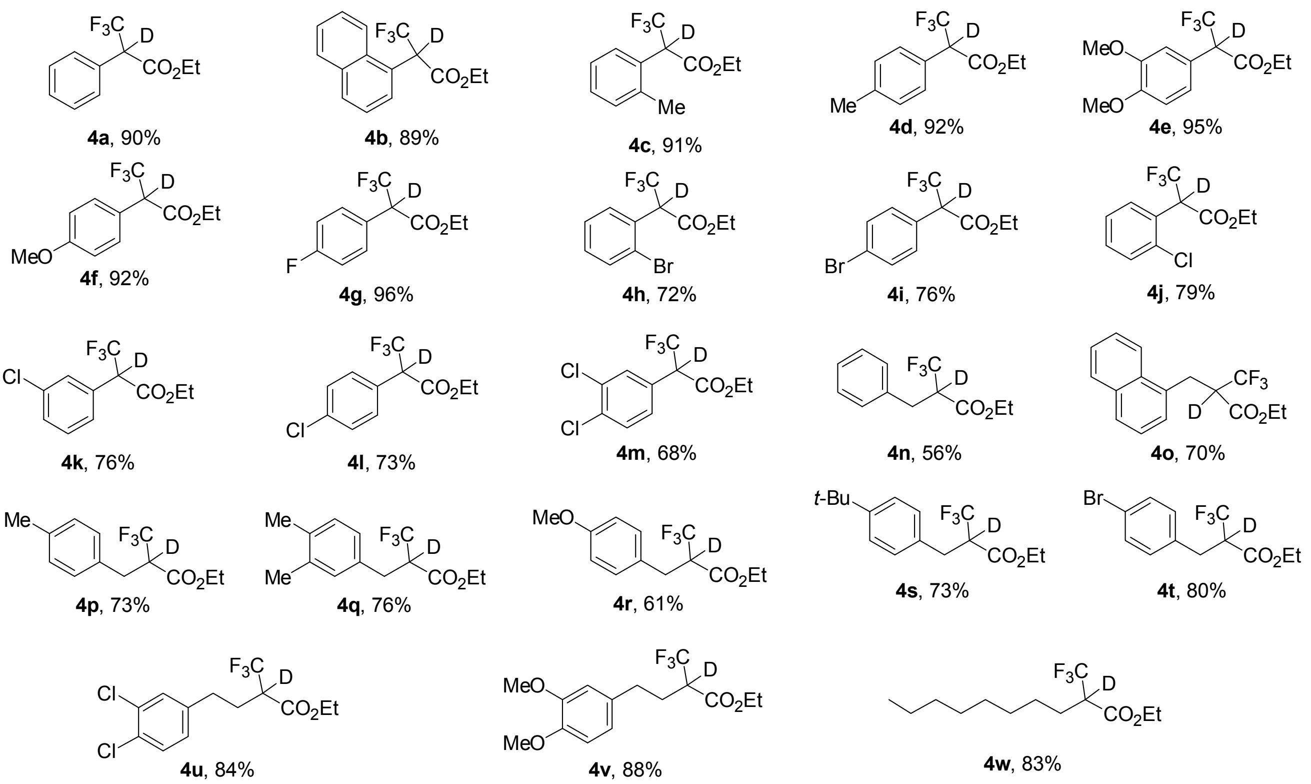
According to the results that the deuterotrifluoromethylation products were produced in high yields and purities higher than 99%, we confirmed the formation of intermediate **I** (see Scheme 1). Compared with the H-D exchange reaction (see Eqs 1 and 3), the high isotope purities of **4** in this reaction probably arise from the avoidance of adventitious water, which prevents the competitive hydrotrifluoromethylation reaction. Moreover, compared with previously reported hydrotrifluoromethylation, this D_2O-promoted deuterotrifluoromethylation required more D_2O than H_2O, and higher reaction temperature, probably due to the higher viscosity of D_2O than H_2O, and the isotope effect of water used to hydrolyze the intermediate **I**.[8]

Conclusions

In conclusion, we have developed a D_2O-promoted deuterotrifluoromethylation reaction, which can be used to synthesize isotopically pure α-deuterium-α-trifluoromethyl esters. The highly pure deuterated products are potentially useful for mechanistic research and other isotope-involved applications. Compared to previously reported water-promoted hydrotrifluoromethylation, this deuterotrifluoromethylation is of similar electronic effect. Moreover, the results of this investigation also provide some experimental evidences to support our previously proposed trifluoromethylation mechanism.

Table 2 Deuterotrifluoromethylation of α-diazo esters[a]





[a] All reactions were performed on 0.5 mmol scale by adding **1** and D_2O into the pre-generated $CuCF_3$. Yields given refer to isolated yields of the analytically pure products.

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Experimental

Typical procedures for D_2O-promoted deuterotrifluoromethylation of α-diazo esters (Table 2)

In a glovebox, to an oven-dried 25-mL Schlenk tube equipped with a stir bar were added CuI (143 mg, 0.75 mmol) and CsF (125 mg, 0.825 mmol). Then the Schlenk tube was sealed with a septum and brought to the bench. $TMSCF_3$ (117 mg, 0.825 mmol) in NMP (3 mL) was added via syringe. After stirring at room temperature for 10 min, ethyl 2-diazo-2-phenylacetate (**1a**) (95 mg, 0.5 mmol) in NMP (3 mL) was added, then D_2O (0.54 mL, 30 mmol) was added. The resulting mixture was heated to 40 ℃ and stirred under N_2 atmosphere for 11 h. After the addition of 5—10 mL HCl (1 mol/L), the mixture was extracted with Et_2O (15 mL×3). The combined organic layer was washed with H_2O (20 mL ×2), then brine (20 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel (petroleum ether/AcOEt, 30∶1, *V*/*V*) to afford **4a** (105 mg, 90% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ: 7.45—7.40 (m, 5H), 4.34—4.18 (m, 2H), 1.26 (t, J=6.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$) δ: 67.5 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ: 166.2, 129.4, 129.2, 128.9, 123.8 (q, J=280.4 Hz), 62.0, 13.8; IR (film) ν: 3068, 2986, 1748, 1453, 1369, 1262, 1198, 1166, 1052, 700 cm^{-1}; MS (EI, *m*/*z*): 233 (M^+, 32.39), 160 (100.00). HRMS (EI): exact mass calcd for $C_{11}H_{10}DF_3O_2$ (M^+): 233.0774, found 233.0779.

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