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Water-promoted regio-selective trifluoromethylation of vinyl conjugated diazoacetates†

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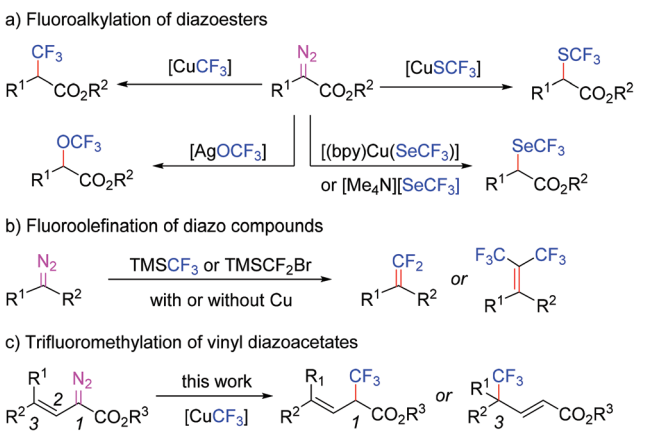
An efficient trifluoromethylation reaction of vinyldiazoacetates under mild reaction conditions was depicted. Pre-generated $CuCF_3$ was used as a trifluoromethylation reagent and water acted as both a promoter and proton source. The reaction is compatible with a broad scope of functional groups and easy to scale-up. The wide functional group tolerance of the reaction enables further synthetic manipulation of the products.

Introduction

Fluorinated organic compounds often show improved metabolic stability, lipophilicity and bioavailability compared to their non-fluorinated analogues.[1] Therefore, they are useful motifs in pharmaceuticals, agrochemicals and materials science.[2] Moreover, fluorinated functional groups are usually used as versatile surrogates in many indispensable transformations.[3] The trifluoromethyl group is a representative fluorinated moiety used to decorate molecules; in this regard, its installation has aroused a great deal of interest.[3,4] Therefore, numerous synthetically useful approaches have been developed to constitute C–CF_3 bonds, while the increasing demand for diverse trifluoromethylated compounds still needs to be met.[5]

Diazo compounds are well-established carbene precursors, which proved to be effective in the incorporation of fluorine into molecules.[6–12] Previously, we developed a water-promoted trifluoromethylation of diazo esters using pre-generated $CuCF_3$ as a trifluoromethylating agent.[7a] In that work, we found that water played a crucial role in activating $CuCF_3$ by dissociating redundant ligands (I^-), as well as a proton source to quench the reaction intermediate. Considering the merit of reaction efficacy, this protocol has been successfully applied to trifluoromethylthiolation,[8] trifluoromethoxylation,[9] trifluoromethylselenolation,[10] *gem*-difluoroalkenylation,[11] *etc.* (Scheme 1). Despite its synthetic potential, the substrate scope is mainly limited to aryl/alkyl diazo esters, and/or diaryl diazomethanes. It intrigued our interest in exploring variable synthetically convertible functionalities to demonstrate the prowess for further manipulation. The displacement of aryl/alkyl groups with a vinyl group while preserving the ester group renders operationally stable donor–acceptor alkenyl conjugated diazo esters and enables their further modulation.[13,14] Nevertheless, since the allylic carbene tends to undergo conjugative isomerisation, a plausible 1,3-selective trifluoromethylation may occur, leading to increased complexity.[14] Herein, we report our discovery on the trifluoromethylation of vinyl diazoacetates.



Scheme 1 Fluoroalkylation and olefination of diazo compounds.

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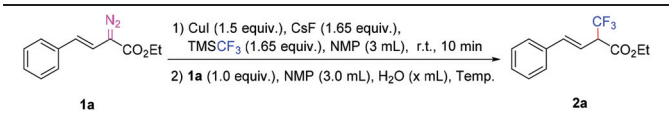
Results and discussion

To test the feasibility of the trifluoromethylation of vinyl-conjugated diazoacetates, we embarked on the investigation by virtue of previously reported conditions. Ethyl phenylethenyl diazoacetate (**1a**) was chosen as a model substrate, pre-generated $CuCF_3$ (from CuI, $TMSCF_3$ and CsF 1/1.1/1.1) was used as a trifluoromethylation reagent, and *N*-methylpyrrolidone (NMP) was used as the solvent. To our disappointment, when 44 equivalents of H_2O (1/15 to NMP in volume)[7a] were added, no desired product was observed. We quickly realized that the substrate is less reactive than phenyl diazoacetate, a popularly used substrate in previous work.[7–12] Then, we attempted to increase the quantity of H_2O and were excited to observe the desired product **2a** on adding 1/6 H_2O (in volume to NMP, *vide infra*), although in only 6% yield (Table 1, entry 5), while smaller quantities of H_2O resulted in no desired reaction at all (Table 1, entries 2–4). When H_2O 1/5 to NMP in volume was used, the yield increased steeply to 54% (Table 1, entry 6). Whereas when 1/4 of H_2O was used, the yield was slightly lower than when 1/5 of H_2O was used; this is probably owing to the fast decomposition of $CuCF_3$ in the presence of excessive amounts of water (Table 1, entry 7).[7a] Further optimization showcased that shortening the reaction time to 3 h resulted in the highest yield of 89% (Table 1, entries 7–10), which indicated that the product would decompose with extended reaction time, while 1.5 h does not drive the reaction completely to the end (Table 1, entry 11). It was confirmed by ^{19}F NMR that by extending the reaction time over 3 h, more side-products were observed. Notably, improving the reaction temperature and using DMF instead of NMP rendered inferior results (Table 1, entries 12 and 13). It is worth mentioning that the trifluoromethylation occurred solely on the carbenic carbon in all cases, and no 3-trifluoromethylation product was detected.

Table 1 Screening of the reaction conditions[a]



1a 2a

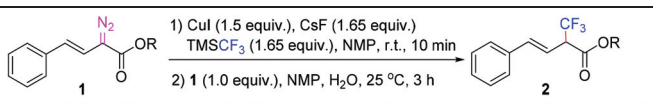
Entry	Time (h)	Temp. (°C)	H_2O/NMP (V/V)	Yield[b] (%)
1	12	25	1 : 15	0
2	12	25	1 : 20	0
3	12	25	1 : 12	0
4	12	25	1 : 10	0
5	12	25	1 : 6	5
6	12	25	1 : 5	54
7	12	25	1 : 4	39
8	8	25	1 : 5	60
9	5	25	1 : 5	64
10	3	25	1 : 5	89 (82)
11	1.5	25	1 : 5	59
12	3	40	1 : 5	41
13[c]	3	25	1 : 5	72

[a] Reaction conditions: **1a** (0.5 mmol), CuI (0.75 mmol), CsF (0.825 mmol), and $TMSCF_3$ (0.825 mmol). [b] Yields were determined by ^{19}F NMR with $PhOCF_3$ as an internal standard. [c] DMF was used as a solvent.

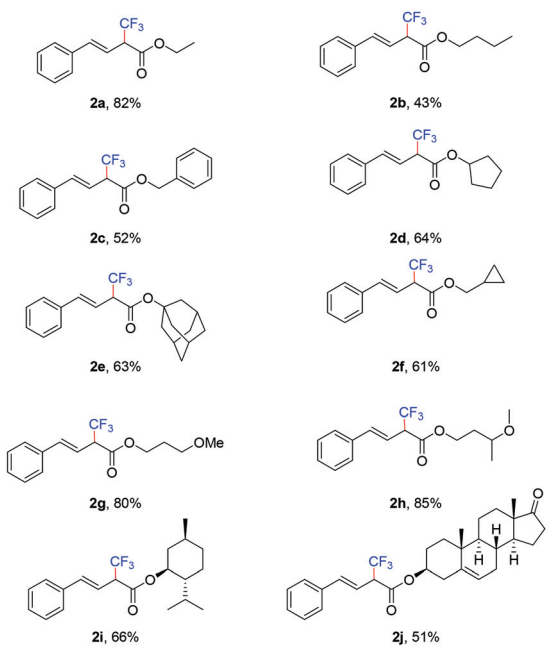
With the optimized conditions in hand (Table 1, entry 10), we examined the generality of this trifluoromethylation reaction using various vinyl diazoacetates, and moderate to high yields could be obtained (Table 2). Elongating the ester alkyl chain, or using cyclic alcohol esters resulted in a slight yield drop, which was probably caused by the steric hindrance from the ester moiety. This current reaction is different from the previous trifluoromethylation of α-diazo esters (Table 2, **2a**–**2j**).[7a] The substrate bearing the cyclopropyl group was well tolerated under standard reaction conditions, and none of the ring-opened side-products were detected (Table 2, **2f**). When substrates with ether groups were employed, the ether groups were kept intact, and good yields were obtained (Table 2, **2g** and **2h**). When vinyl diazoacetates derived from L-menthol and dehydroepiandrosterone were subjected to the standard conditions, the reactions worked smoothly to give 66% and 51% yield, respectively (Table 2, **2i** and **2j**).

Encouraged by the above results, we continued to study vinyl diazoacetates with diverse substituents on the vinyl moiety (Table 3). The aryl vinyl diazoacetates bearing alkyl, methoxy, and halogen substituents on the aromatic ring reacted smoothly to afford the trifluoromethylation products in medium to good yields (Table 3, **4a**–**4l**). The methyl and methoxy substituents at the *ortho*-, *meta*-, or *para*-position of the aryl ring only slightly influenced the product yields

Table 2 Trifluoromethylation of phenylvinyl diazoacetates[a]

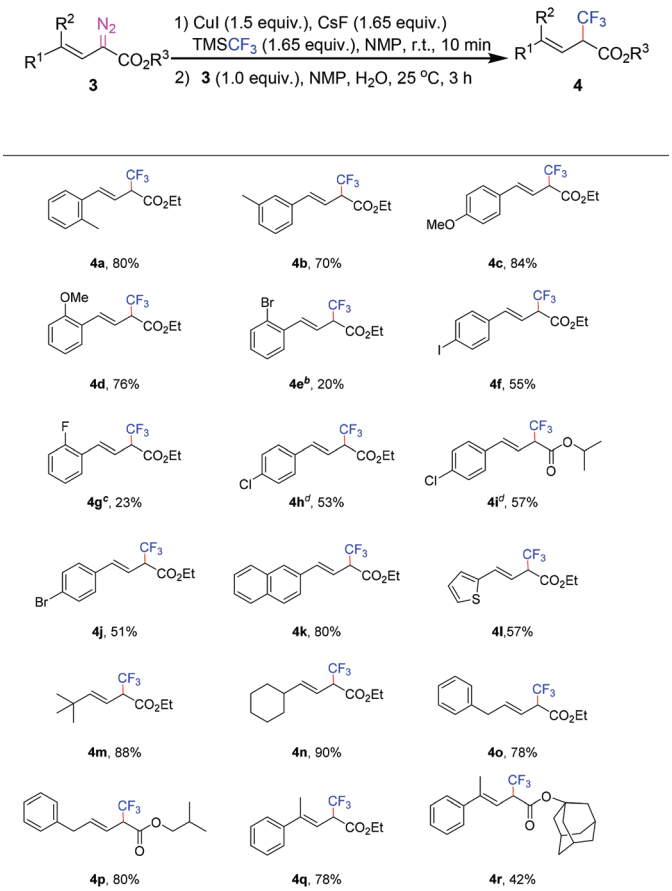


1 2



[a] Unless otherwise noted, reactions were performed on a 0.5 mmol scale by adding **1** and water to the pre-generated $CuCF_3$/NMP solution. Yields refer to isolated products.

Table 3 Trifluoromethylation of vinyl diazoacetates by altering the substituents on the vinyl moiety[a]

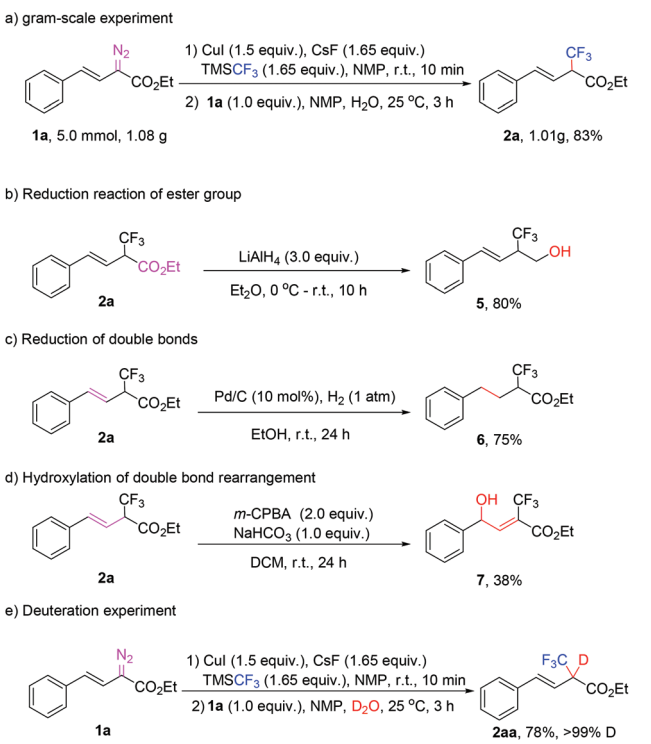


[a] Unless otherwise noted, reactions were performed on a 0.5 mmol scale by adding **3** and water to the pre-generated "$CuCF_3$". Yields refer to the isolated yields of analytically pure products. [b] The reaction was performed at 35 °C and the reaction time was 7 h. [c] The reaction was performed at 35 °C and the reaction time was 5 h. [d] The reaction was performed at 35 °C.

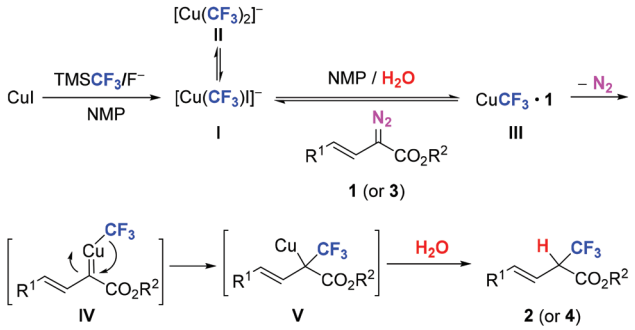
(Table 3, **4a–4d**), while the halogen substituents at the *ortho*-position of the aryl ring afforded lower yields than those at the *para*-position (Table 3, **4e–4j**). It is worth noting that halogen substituents fluoro, chloro, bromo and iodo are all compatible under the reaction conditions (Table 3, **4e–4j**), and no carbon–halogen bond cleaved products were observed. Moreover, the thiophenyl group was well tolerated, and a moderate yield of 57% was obtained (Table 3, **4l**). Intriguingly, when alkyl or benzyl substituted vinyl diazoacetates were subjected to standard reaction conditions, excellent product yields could be obtained (Table 3, **4m–4p**), perhaps owing to the improved stability of vinyl diazoacetates with less π-conjugation, which differentiates the current trifluoromethylation from the previous hydroboronation.[13] The aforementioned results intrigued our interest in testing more complicated substrates; to our delight, trisubstituted vinyl diazoacetates **3q** and **3r** afforded the corresponding products **4q** and **4r** in 78% and 42% yield, respectively (Table 3, **4q** and **4r**). By comparison, the lower yield of **4r** than **4q** is probably ascribed to the combined steric effect of both substituents on vinyl and ester moieties.

To further explore the practicability of the reaction, a gram scale experiment using **1a** as the substrate was performed under standard conditions, and the reaction worked smoothly to afford **2a** in 83% yield (Scheme 2(a)). Moreover, reduction of the ester with $LiAlH_4$ and the vinyl group with Pd/C–H_2 was carried out successfully to give 80% and 75% yield, respectively (Schemes 2b and c). Unexpectedly, when **2a** was exposed to *m*-CPBA oxidation, the normal epoxidation product was not detected, instead a double bond-hydroxylation induced isomerisation product **7** was obtained in 38% yield (Scheme 2(d)). To clarify the importance of water, we also conducted a D_2O-mediated reaction, and the deuterium substituted product was obtained in 78% yield, which indicated that water not only acts as a promoter, but also as a proton source (Scheme 2(e)).[15]

Based on the experimental results, a plausible mechanism was proposed as shown in Scheme 3. Compared to previous work,[7a,15] the primary difference was that the reactivity of substrates used in this work was generally lower than that of the previously used ones, which indicates that more water was essential to promote the reaction. The reaction was initiated by pre-generated $CuCF_3$, which existed as an equilibrium of (trifluoromethyl)copper species **I** and **II** *via* ligand redistribution on copper. Then, water was added to promote iodide anion dissociation of $CuCF_3$ to increase its reactivity, subsequently forming a diazo compound coordinated complex **III** in the presence of diazo compound **1** (or **3**). Complex **III** underwent nitrogen gas extrusion to form trifluoromethylcopper–carbene



Scheme 2 Practicability of the reaction.



Scheme 3 Proposed reaction mechanism.

intermediate **IV**, and migration of CF_3 to the carbenic carbon atom of **IV** resulted in intermediate **V**. It was then hydrolysed to afford product **2** (or **4**).

Conclusions

In summary, we described an efficient trifluoromethylation reaction of vinyl diazoacetates; the vinyl moiety enables further synthetic manipulation of the products. In comparison with the reaction of phenyl diazoacetates, vinyl diazoacetates require more water as a promoter. The reaction is not sensitive to the steric effect and showcases robust functional group tolerance. Moreover, the gram scale experiment showed no yield drop at all. Interestingly, conventional reductive operation affords the corresponding reduced products, while oxidation with *m*-CPBA results in a double bond migration hydroxylated product. Replacement of H_2O with D_2O afforded a deuterated product with a similar yield, demonstrating the role of H_2O as both a promoter and proton source.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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