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Radical hydrotrifluoromethylation of ynamides:
a route toward β -CF₃ enamides†Wanqiao Huang,[‡] Ruzhong Zhang,[‡] Ruxue Zhang, Jianxin Yu and Mang Wang*

We report here a radical hydrotrifluoromethylation of ynamides to provide an alternative route toward β -CF₃ enamides. By using PhICF₃Cl as the CF₃ reagent and DMF as the H-donor, the reaction occurred smoothly in the presence of NaH at room temperature. Further reduction of the resulting β -CF₃ enamides efficiently delivered β -CF₃ amines. Gram-scale synthesis was conducted to demonstrate the practicability of the method.

Introduction

Molecules containing two powerful functionals, trifluoromethyl and amino, in adjacent positions are valuable targets in drug design and synthetic chemistry.¹ Consequently, great efforts have been focused on the assembly of amino and trifluoromethyl at the *ortho* position.² In this field, the aminotrifluoromethylation of alkenes provides the main and step-economical route toward β -CF₃ amines (Scheme 1A).^{2i,j} On the other hand, enamines have found wide synthetic applications,³ which also encouraged investigations on the vicinal trifluoromethylated enamines. However, to date, there have been limited approaches established for preparing β -CF₃ enamines. Apart from several works on utilizing the amination of pre-synthesized CF₃-containing substrates,⁴ as well as a recent report involving a three-component reaction between trifluorodiazaoethane, aldehydes, and imines,⁵ trifluoromethylation-based methods have been documented to deliver β -CF₃ enamines, including *via* the aminotrifluoromethylation of alkynes (Scheme 1A)⁶ and direct Csp²-H trifluoromethylation of enamines (Scheme 1B).⁷

During our ongoing explorations in the field of trifluoromethylation, an externally coordinated CF₃-containing λ^3 -iodane (PhICF₃Cl)⁸ was synthesized to be used in a set of trifluoromethylative bifunctionalization reactions.⁹ Efficient trifluoromethylative bifunctionalization reactions of alkenes have been developed by our group recently.^{9a-d} In order to extend the synthetic applications of PhICF₃Cl, the trifluoromethylation of alkynes

was investigated in the follow-up work. As a result, when ynamides¹⁰ were chosen as alkyne substrates for the reaction with PhICF₃Cl in DMF, unprecedented β -CF₃ enamides were produced. It provides an alternative and mild route toward β -CF₃ enamides. β -CF₃ amines were obtained by further reduction. Herein, we report a new hydrotrifluoromethylation of ynamides (Scheme 1C).

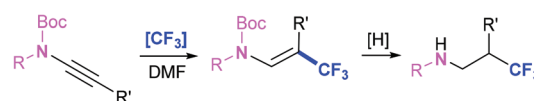
Results and discussion

It was reported that CF₃ radical addition onto *N*-benzoyl ynamides afforded aryltrifluoromethylative cyclization products.¹¹ In order to avoid such possible side reactions, *tert*-butyl ethynyl(phenyl)carbamate **1a** was chosen in our initial attempt to carry out the trifluoromethylation of ynamides using

A. Aminotrifluoromethylation of Alkenes/Alkynes



B. Trifluoromethylation of Enamines

C. Hydrotrifluoromethylation of Ynamides *This Work*

Scheme 1 Trifluoromethylation-based route toward β -CF₃ amines/enamides.

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PhICF₃Cl as the trifluoromethylating reagent. Notably, the hydrotrifluoromethylation product **2a** was obtained in 57% NMR yield, accompanied by **3a** in 36% NMR yield only by stirring a mixture of **1a** and PhICF₃Cl in DMF at room temperature (Table 1, entry 1). DMF was likely the H-donor in such a simple reaction mixture and a radical process was proposed for the formation of **2a**. According to our previous work in which radical trifluoromethylation of alkenes with PhICF₃Cl could not occur at room temperature without the assistance of a reductant,^{9d} ynamide substrate **1a** likely acted as a tertiary amine type electron donor¹² for the generation of the CF₃ radical from PhICF₃Cl. Thus, an additional reductant was used for the above hydrotrifluoromethylation of **1a**. As we hypothesized, the addition of tertiary amines, including triethylamine (TEA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and *N,N*-diisopropylethylamine (DIPEA), could indeed help increase the yield of **2a** a little bit (entries 2–4). Tetrabutylammonium iodide (TBAI) and zinc iodide showed poor performance (entries 5 and 6), and triethylsilane had no obvious influence on this reaction (entry 7). In comparison, NaH was proven to be an optimal reductant, leading to **2a** in 81% NMR yield (entry 8). No **3a** was detected in these cases (entries 2–6 and 8). Solvent screening showed that **2a** could also be obtained in good to moderate yields in *N,N*-dimethylacetamide (DMAc, entry 9), tetrahydrofuran (THF, entry 10) and *N*-methylpyrrolidone (NMP, entry 11). However, dichloromethane (DCM, entry 12) was not suitable for the reaction. The reaction time was then controlled precisely (entries

13–15). It was found that the NMR yield of **2a** was 75% within 2 h (entry 14). Finally, a gram-scale experiment was conducted and **2a** was obtained in 70% isolated yield, which demonstrated the robustness of the protocol (entry 16).

After establishing the optimal conditions for this reaction (Table 1, entry 14), the generality of this protocol was examined by using various kinds of ynamide substrates (Table 2).

First, a series of *N*-phenyl-substituted ynamides were selected and tested in this reaction. We were pleased to see that electronically and sterically distinct substituents at different positions were tolerated, affording the β-CF₃ enamides (**2b–x**) in good yields. Ynamides bearing electron-withdrawing groups, such as halide (**1b–e**, **1q**, **1t**, and **1w**), fluoroalkyl (**1p**) or carbonyl groups (**1k** and **1l**), could all provide the desired products in good yields. Electron-rich substituents like alkyl (**1f–h**, **1j**, **1r**, **1u** and **1v**), aryl (**1i**), and alkoxy/aryloxy (**1m–o**, **1s**, and **1x**) did not have obvious influences on the reactions. Remarkably, enamide **2w** could be generated in 90% yield from the reaction of sterically hindered ynamide **1w**. Secondly, the protecting groups of the ynamides were tested. Both *N*-Ac and *N*-Cbz ynamides were suitable for this reaction although the reactions afforded **2a** and **2aa** in reduced yields under identical conditions. However, *p*-toluenesulfonyl-ynamide **1ab** was not suitable for this reaction. The reaction was complex and the desired product **2ab** was not detected. Next, hydrotrifluoromethylations of *N*-benzyl ynamides were carried out under identical conditions. A series of *N*-benzyl ynamides substituted at different positions were selected and tested in this reaction. It was found that all the tested *N*-benzyl ynamides **1ac–ag** were efficiently transformed into the corresponding products **2ac–ag**. In addition, the enamide product **2ah** could also be generated from *N*-phenylethyl ynamide **1ah** in 70% yield.

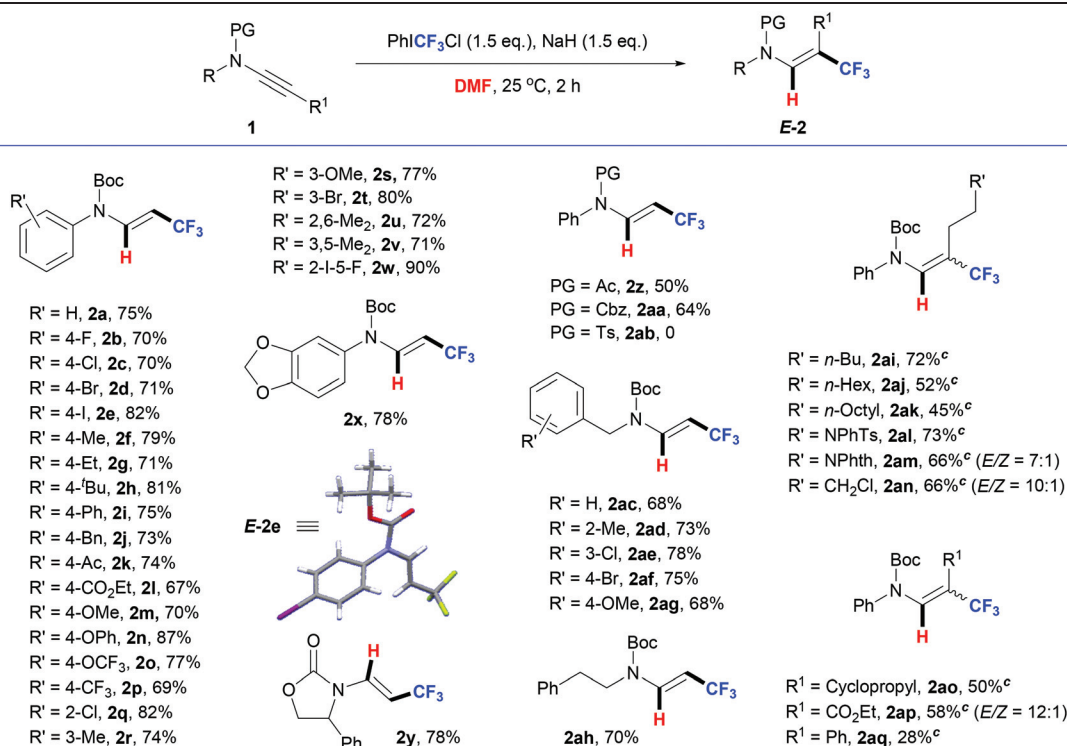
Finally, non-terminal ynamides were synthesized to test the substrate scope. As shown in Table 2, the desired products **2** could be obtained in moderate to good yields when the reaction time was prolonged. Long-chain alkyl- (**1ai–an**), cycloalkyl- (**1ao**) and ester-ynamides (**2ap**) all proved to be suitable for this reaction. In comparison, phenyl substituted ynamide **1aq** delivered **2aq** in 28% yield, along with the generation of regioisomeric isomers.¹³ Note that the hydrotrifluoromethylation of ynamides **1** stereoselectively afforded enamines **2**. Thermodynamically stable *E*-isomeric enamines were obtained as the main products in most cases, which was proved by the X-ray crystal structure of **2e**.¹⁴ In comparison, lower stereoselectivities were observed in some cases, such as **2am**, **2an** and **2ap**, likely caused by the little difference in the thermodynamic stability of the products.

As described above, we have established a novel hydrotrifluoromethylation reaction of ynamides, which provides a trifluoromethylative bifunctionalization pathway to synthesize β-CF₃ enamides. Further transformation of β-trifluoromethyl enamides **2** was investigated to highlight the synthetic potential of the approach. As shown in Table 3, by using silyl hydride as the reductant, reduction/deprotection products **4**, β-CF₃ amines,^{1a,b,15} could be obtained in good to

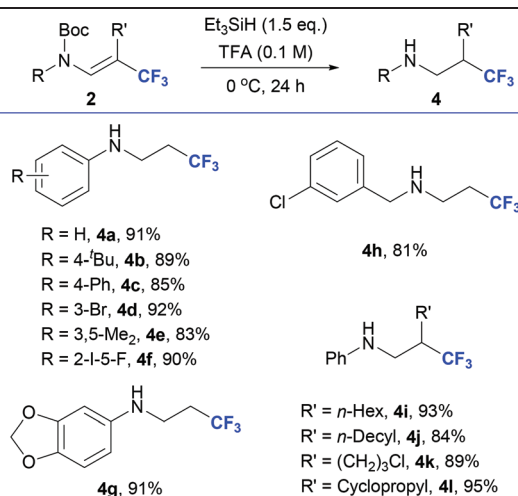
Table 1 Optimization of reaction conditions^a

Entry	Reductant	Solv.	t/h	2a ^b /%	3a ^{c,d} /%
1	—	DMF	12	50	36
2	TEA	DMF	12	61	N.D.
3	DBU	DMF	12	65	N.D.
4	DIPEA	DMF	12	67	N.D.
5 ^e	TBAI	DMF	12	14	Trace
6	ZnI ₂	DMF	12	23	Trace
7	Et ₃ SiH	DMF	12	52	17
8	NaH	DMF	12	81(75) ^f	N.D.
9	NaH	DMAc	12	69	N.D.
10	NaH	NMP	12	52	9
11	NaH	THF	12	54	21
12	NaH	DCM	12	9	Trace
13	NaH	DMF	1	66	N.D.
14	NaH	DMF	2	75(72) ^f	N.D.
15	NaH	DMF	6	72	N.D.
16 ^g	NaH	DMF	2	75(70) ^f	N.D.

^a Reaction conditions: **1a** (0.2 mmol), PhICF₃Cl (1.5 eq.), reductant (1.5 eq.), solvent (2.0 mL), 25 °C, N₂. ^b¹⁹F NMR yield using benzotrifluoride as the internal standard. ^c¹H NMR yield using dibromomethane as the internal standard. ^dN.D. = not detected. ^e80% of **1a** was recovered. ^fIsolated yields of *E*-**2a** are shown in brackets. ^gGram-scale reaction was performed at the 5.5 mmol scale.

Table 2 Substrate scope of hydrotrifluoromethylation of ynamides^{a,b}

^a Reaction conditions: **1** (0.2 mmol), PhICF₃Cl (0.3 mmol, 1.5 eq.), NaH (0.3 mmol, 1.5 eq.), DMF (2.0 mL), 25 °C, N₂, 2 h. ^b Isolated yields of *E-2* unless the *E/Z* ratio is otherwise noted in the brackets. ^c Reaction conditions: 30 °C, 12 h.

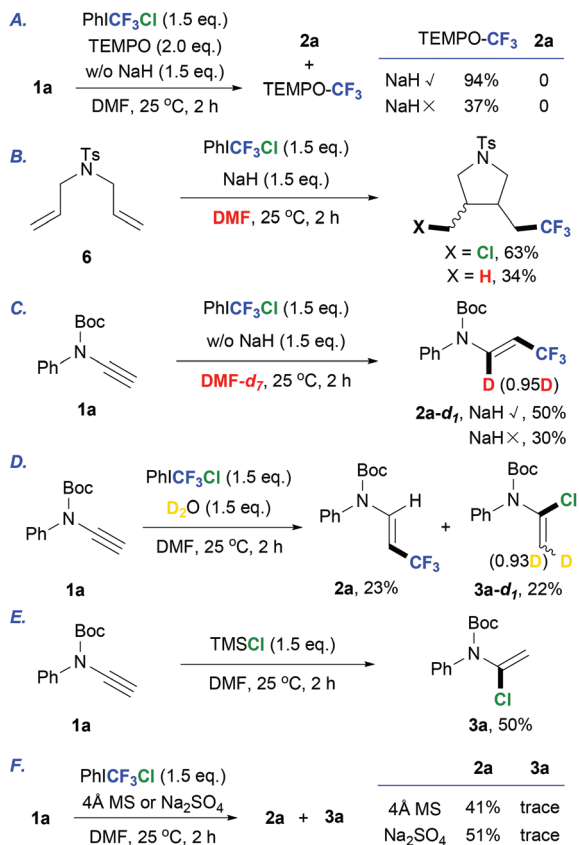
Table 3 Deprotected reduction of β-CF₃ enamines^{a,b}

^a Reaction conditions: **2** (0.1 mmol), Et₃SiH (0.15 mmol, 1.5 eq.), TFA (1.0 mL), 0 °C, N₂, 24 h. ^b Isolated yields of **4**.

excellent yields in the presence of trifluoroacetic acid.¹⁶ β-CF₃ enamides generated from substituted *N*-phenyl ynamides (**1a**, **1h**, **1j**, **1t**, **1v**, **1w**, and **1x**), *N*-benzyl ynamide (**1ae**) and non-terminal ynamides (**1ai**, **1ak**, **1an** and **1ao**), were all suitable

for this reductive deprotection reaction to generate the corresponding β-CF₃ amines **4a–l**.

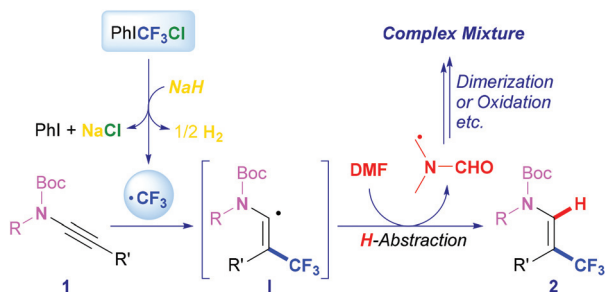
A set of control experiments were conducted to verify the possible reaction mechanism. Radical trapping experiments were carried out under the standard conditions by the addition of 2,2,6,6-tetramethylpiperidine-1-oxide (TEMPO, Scheme 2A). The desired product **2a** could not be obtained in the presence or absence of NaH, which suggested the involvement of a radical process. A radical clock experiment was also conducted by using *N,N*-diallyl-4-methylbenzenesulfonamide under the standard reaction conditions (Scheme 2B). As a result, both chloro-^{9d} and hydro-cyclization products¹⁷ were obtained to demonstrate a radical mechanism. To identify the hydrogen source, deuterated DMF was used in the reaction of **1a**. As shown in Scheme 2C, the reactions were carried out in DMF-*d*₇ with or without NaH, and the deuterated product **2a-d**₁ was obtained, demonstrating an H-abstraction process from the solvent involved in the reaction. No deuterated β-CF₃ enamide was detected when D₂O was added in this reaction (Scheme 2D), which excluded the formation of **2a** via protonation from water; meanwhile, the deuterated chloro-enamide **3a-d**₁ was detected as the background product. To further verify the formation of **3a** from an electrophilic addition of alkynes, we performed an additional reaction of **1a** in DMF using TMSCl as the Cl-source instead of PhICF₃Cl. **3a** was obtained in 50% yield, suggesting that a background reaction



Scheme 2 Control experiments.

existed in our hydrotrifluoromethylation of ynamides **1**. This experimental result indicated that NaH may also help in the removal of water from the reaction mixture, which is beneficial for inhibiting the formation of byproducts **3**. Further investigations on the role of NaH were carried out by the reaction of **1a** and PhICF₃Cl in the presence of desiccants without NaH (Scheme 2F). As a result, the formation of **3a** was inhibited, but the yield of **2a** was still moderate. These experimental results showed that NaH not only acted as a water removal reagent but also assisted in the radical hydrotrifluoromethylation of ynamides.

According to the literature^{12c,18} and experiment results, a plausible mechanism is proposed as described in Scheme 3.



Scheme 3 A plausible radical mechanism.

PhICF₃Cl is reduced by NaH to release the trifluoromethyl radical, which is added to substrate **1** immediately to generate alkenyl radical intermediate **I**. Meanwhile, iodobenzene and hydrogen¹⁹ are generated, respectively, suggesting that NaH acts as a reductant of PhICF₃Cl through an electron transfer pathway. An H-atom-abstraction of **I** from the solvent DMF subsequently occurred and gave the hydrotrifluoromethylation product **2**. In this case, it is proposed that the *N*-methyl-H of DMF is abstracted²⁰ by the electrophilic trifluoromethylated radical **I**, which is supported by the fact that good transformations could also be obtained in either DMAc or NMP (Table 1, entries 9 and 10). The generated DMF-based carbon radical would further undergo dimerization, oxidation, hydrolysis, or other processes, resulting in the formation of mixed products.²¹ Note that although this proposed mechanism is preferred, other plausible H-abstraction processes or reaction mechanisms cannot be ruled out at this stage.

Conclusions

In conclusion, by using PhICF₃Cl as the trifluoromethyl source, the hydrotrifluoromethylation of ynamides was achieved successfully, in which a series of β-CF₃ enamides were synthesized efficiently. The mild and transition-metal free reaction conditions, the good functional group tolerance and the capability to be performed at the gram scale make this method valuable and practical. Control experiments proved that the reaction occurred *via* a radical process, which is a new achievement in the field of underexplored free radical reactions of ynamides.

Author contributions

W. Huang and R. Z. Zhang performed the experiments and co-wrote the ESI.† W. Huang wrote the initial draft of this manuscript. R. X. Zhang and J. Yu helped in preparing several substrates. Prof. M. Wang conceived the project and concept reviewed the manuscript. All authors read and contributed to the revisions and approved the final version to be published.

Conflicts of interest

There are no conflicts to declare.

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