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Synthesis of trifluoromethyl-containing isoindolinones from tertiary enamides *via* a cascade radical addition and cyclization process†

Hui Yu,* Mingdong Jiao, Xiaowei Fang and Pengfei Xuan

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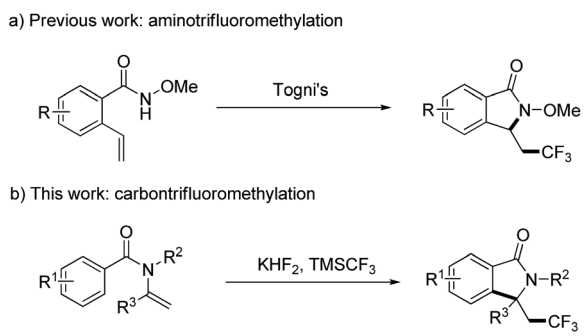
A radical trifluoromethylation reaction of tertiary enamides was investigated and trifluoromethyl-containing isoindolinones were prepared under mild conditions. Using $TMSCF_3$ as a radical source, $PhI(OAc)_2$ as an oxidant and KHF_2 as an additive, tertiary enamides were converted to isoindolinones *via* a cascade addition and cyclization process in moderate to good yields.

In recent years, trifluoromethyl-containing azaheterocycles have attracted much attention for their potential application in the fields of pharmaceutical and agricultural chemistry.[1] Thus, lots of efforts have been devoted to the synthesis of trifluoromethyl azaheterocycles,[2] and among these developed methods, radical cascade addition and cyclization has emerged as a remarkable strategy due to its unique properties such as economy and high efficiency. Unsaturated amides are commonly used substrates for this type of transformation, which could be attacked by a CF_3 radical followed by intramolecular C–O, C–N, or C–C bond formation to give different kinds of trifluoromethyl azaheterocycles. Fu reported a metal-free trifluoromethylation of *N*-allyamides with CF_3SO_2Na for the synthesis of trifluoromethyl-containing oxazolines *via* oxytrifluoromethylation.[3] In the presence of copper salts, *N*-acyl-2-allylaniline could be converted to trifluoromethylated indolines in moderate to good yields *via* aminotrifluoromethylation process.[4] With Togni's reagent,[5] $TMSCF_3$,[6] CF_3SO_2Na,[7] CF_3SO_2Cl[8] and other reagents[9] as the CF_3 source, α, β-unsaturated amides, tosyl amides, or imides underwent a tandem conversion to give trifluoromethyl-containing oxindoles or isoquinoline-1,3-diones by trifluoromethylation/arylation reaction. On the other hand, as a special type of unsaturated amide containing an active double bond, enamide also exhibited excellent reactivity in radical reactions.[10] In fact, trifluoromethylation of enamides has already been investigated, and in most cases trifluoromethylated alkenes were obtained as the main products.[11] To the best of our knowledge, the radical trifluoromethylation and cyclization of enamide still remains undeveloped.

Isoindolinones are important *N*-heterocyclic compounds necessary in organic and pharmaceutical chemistry, and these compounds are used widely as anticoagulants and tranquilizers such as aristolactam, pagoclone, and zopiclone.[12] To introduce a CF_3 group into isoindolinones, Wang and co-workers explored a convenient way to the synthesis of trifluoromethyl-containing isoindolinones by radical aminotrifluoromethylation (Scheme 1a),[13] but this transformation only occurred for *N*-methoxylbenzamides, and in case of *N*-alkylbenzamides trifluoromethylated alkenes were obtained as the major products. 1,1-disubstituted terminal alkenes were also not suitable substrates because of the competition between O-trapping and N-trapping process. Thus, development a new method for the synthesis of trifluoromethyl-containing isoindolinones is still in demand. Here in, as a continuation of our efforts on the radical modification of amide derivatives,[14] we wish to present our work on the synthesis of trifluoromethyl-containing isoindolinones using enamides as the start materials by radical carbon trifluoromethylation (Scheme 1b).

Initially, *N*-*n*-butyl-*N*-(2-propenyl) benzamide **1a** was chosen as the model substrate to optimize the reaction conditions of this radical carbontrifluoromethylation process. As shown in Table 1, the reaction of **1a** with $TMSCF_3$ (4.0 equiv.) was firstly



Scheme 1 Synthesis of trifluoromethyl-containing isoindolinones.

School of Chemical Science and Engineering, Shanghai Key Lab of Chemical Assessment and Substainability, Tongji University, 1239 Siping Road, Shanghai, 200092, P. R. China. E-mail: yuhui@tongji.edu.cn; Fax: +86 21 65981097; Tel: +86 21 65981097

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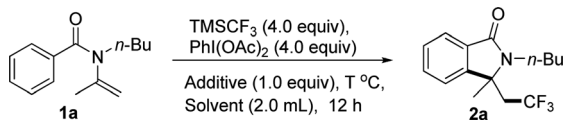
examined in CH_3CN with $PhI(OAc)_2$ (4.0 equiv.) as the oxidant and NaF (1.0 equiv.) as the additive at 80 °C under N_2 atmosphere. 12 hours later, all the start material disappeared monitored by TLC and the desired product **2a** was isolated in 15% yield with *N*-*n*-butyl benzamide isolated as the main byproduct (Table 1, entry 1). When KF and CsF was used instead of NaF, the desired product **2a** was obtained in 35% and 38% yield respectively (Table 1, entries 2 and 3). To our delight, when bifluoride was used as the additive, the yield of **2a** could be improved significantly, and KHF_2 gave better result than $NaHF_2$ and NH_5F_2 (Table 1, entries 4–6). Changing the solvent to CH_3CN, CH_2Cl_2 or toluene resulted in the formation of **2a** in only 0–32% yields (Table 1, entries 7–9). Increasing the reaction temperature to 100 °C or decreasing the reaction temperature to 60 °C and room temperature led to lower yield of **2a** (Table 1, entries 10–12). Another commercial oxidant $PhI(OCOCF_3)_2$ (4.0 equiv.) was also tested but to give poor yield of **2a** (Table 1, entry 13). When the amount of $TMSCF_3$ and $PhI(OAc)_2$ was reduced to 3.0 equiv., only 62% yield of **2a** could be isolated (Table 1, entry 14). The amount of KHF_2 was increased to 1.5 equiv. or decreased to 0.5 equiv. also caused lower yield of **2a** (Table 1, entry 15). Finally, 1.0 equiv. of NaOAc was added to the reaction but the yield of **2a** was not improved (Table 1, entry 16). On the basis of these results, entry 5 represents the best conditions.

Under the optimized reaction conditions, the scope of substrates was investigated with results summarized in Table 2. For substrates with methyl group substituted at different positions on the benzoyl moiety of **1a**, no significant steric hindrance was observed (Table 2, **2b–e**). Substrates with electron-withdrawing group also gave satisfied yields (Table 2, **2f–k**). Interestingly, 2,4-dichloro benzoyl substrate gave the desired product **2j** in 36% yield accompanied with the 2-dechlorination product **2g** in the same yield (Table 2, **2j**). 1-Naphthoyl substrate underwent a smooth reaction to afford the product in 60% yields (Table 2, **2l**). Changing the substituted group on the nitrogen from *n*-butyl to other alkyl groups also gave the corresponding product in moderate yield (Table 2, **2m–o**). Substrates with different substituents on the inner side of double bond also gave the desired products in moderate yields, including a spiro product **2r** (Table 2, **2p–r**). For substrate with phenyl group on the double bond, no desired product could be found due to the increased steric hindrance, and trifluoromethylated alkene **2s** was furnished in 66% yield (Table 2, **2s**).

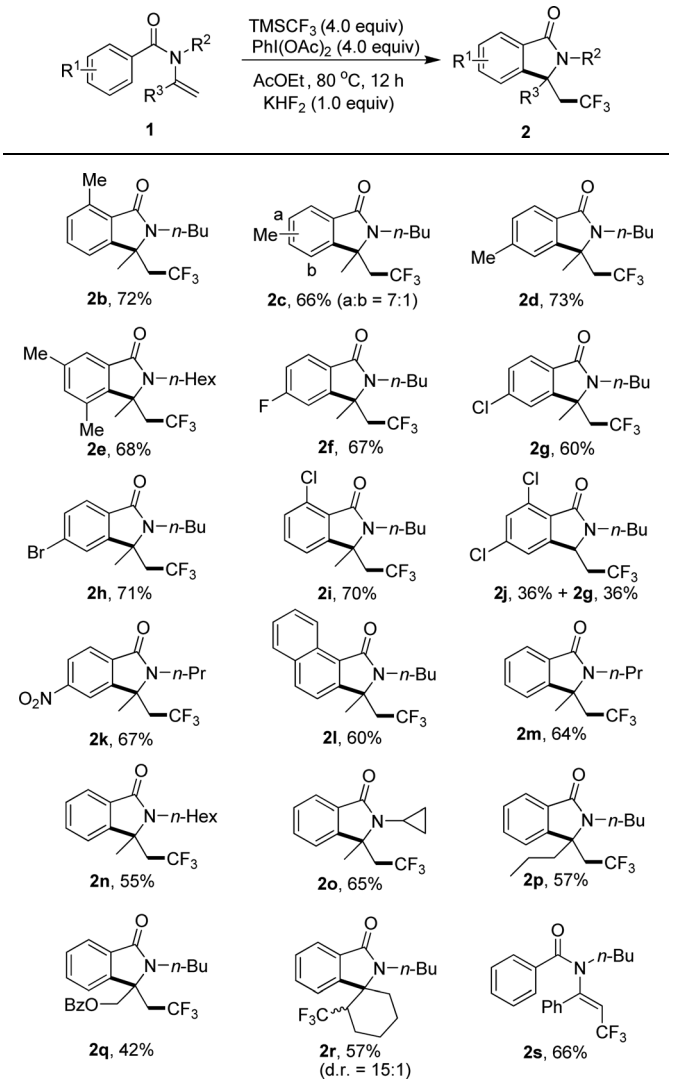
Table 1 Screening conditions[a]



Entry	Additive (0.3 equiv.)	Solvent (2 mL)	Temp. (°C)	Yield of **2a**[b] (%)
1	NaF	EtOAc	80	15
2	KF	EtOAc	80	38
3	CsF	EtOAc	80	35
4	$NaHF_2$	EtOAc	80	52
5	KHF_2	EtOAc	80	75
6	NH_5F_2	EtOAc	80	40
7	KHF_2	CH_3CN	80	21
8	KHF_2	CH_2Cl_2	80	32
9	KHF_2	Toluene	80	Trace
10	KHF_2	EtOAc	100	61
11	KHF_2	EtOAc	60	43
12	KHF_2	EtOAc	r.t.	NR
13	KHF_2	EtOAc	80	37[c]
14	KHF_2	EtOAc	80	62[d]
15	KHF_2	EtOAc	80	58[e], 47[f]
16	KHF_2	EtOAc	80	73[g]

[a] The reaction was carried out on 0.2 mmol scale in a sealed tube under N_2. [b] Isolated yield. [c] $PhI(OCOCF_3)_2$ (4.0 equiv.) was used as the oxidant. [d] Reaction carried out with $PhI(OAc)_2$ (3.0 equiv.) and $TMSCF_3$ (3.0 equiv.). [e] With 1.5 equiv. KHF_2. [f] With 0.5 equiv. KHF_2. [g] 1.0 equiv. NaOAc was added.

Table 2 Scope of substrates[a,b]



[a] The reaction was performed with **1** (0.2 mmol), KHF_2 (0.2 mmol), $TMSCF_3$ (0.8 mmol), $PhI(OAc)_2$ (0.8 mmol) in EtOAc (2.0 mL) under N_2 at 80 °C for 12 h in a sealed tube. [b] Isolated yields.

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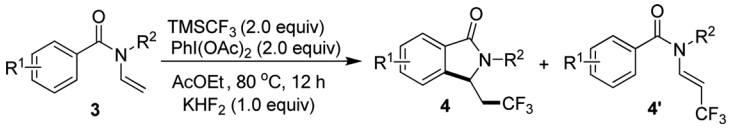
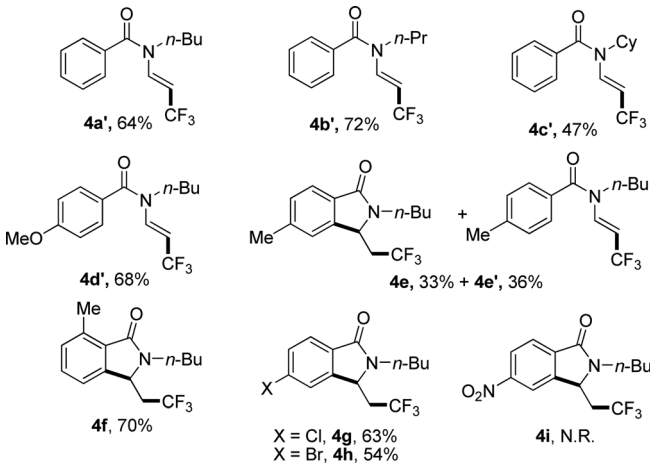
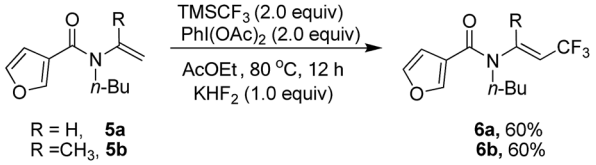
Table 3 Synthesis of the peroxide products[a,b]



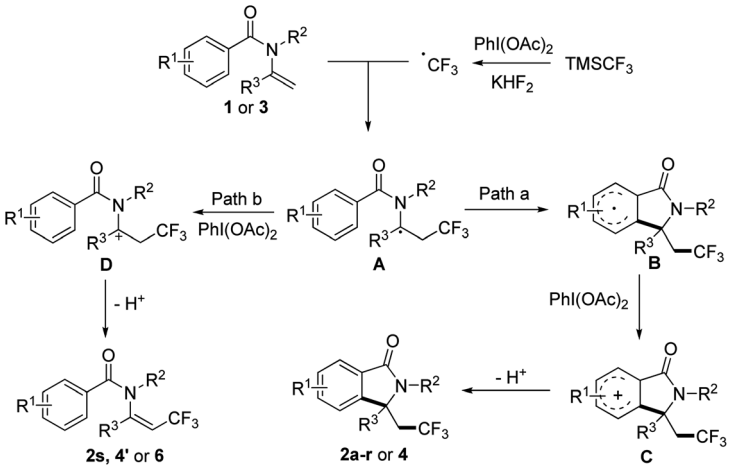


[a] The reaction was performed with **3** (0.2 mmol), KHF_2 (0.2 mmol), $TMSCF_3$ (0.8 mmol), $PhI(OAc)_2$ (0.8 mmol) in EtOAc (2.0 mL) under N_2 at 80 °C for 12 h in a sealed tube. [b] Isolated yields.



Scheme 2 . Results of heterocyclic substrate **5a** and **5b**.

When *N*-*n*-butyl-*N*-(2-vinyl) benzamide **3a** was subjected to the reaction conditions, no isoindolinone was observed, and the main product was trifluoromethylated alkene (Table 3, **4a′**). Changing the *N*-protecting group to *n*-propyl or cyclohexyl also caused the formation of trifluoromethylated alkenes (Table 3, **4b′–4c′**). It seemed that the substituents on the benzoyl group had significant influence on the reaction result. For example, substrate with methoxy group on the *para* position of the benzoyl moiety still gave trifluoromethylated alkene as the main product (Table 3, **4d′**), but substrate with methyl group on the *para* position led to a mixture of trifluoromethylated alkene and isoindolinone (Table 3, **4e**/**4e′**). However, substrate with methyl group on the *ortho* position or halides on the *para* position of the benzoyl group gave only isoindolinones as the main products (Table 3, **4f–4h**). Substrate with NO_2 on the *para* position displayed low reactivity and no reaction occurred (Table 3, **4i**).



Scheme 3 Possible mechanism.

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Heterocyclic substrate such as **5a** and **5b** was also examined, but no cyclization product could be found and trifluoromethylated alkene **6a** and **6b** was obtained as the only product (Scheme 2).

To gain insights into the reaction mechanism, a control experiment was carried out to elucidate the mechanism. When 1.0 equiv. TEMPO was added to the reaction, the yield of **2a** decreased significantly to 15%, which indicated the possibility of a radical pathway. Based on the control experimental result and the previous investigation on aryltrifluoromethylation of alkenes, plausible mechanism for our methodology is proposed in Scheme 2. In the presence of KHF_2, $TMSCF_3$ reacted with $PhI(OAc)_2$ to generate CF_3 radical, then the CF_3 radical attacked enamide **1** or **3** affording radical intermediate **A**. Depending on the structure of the substrate, intermediate **A** would be converted to trifluoromethyl-containing isoindolinone or trifluoromethylated alkene according to different pathways as followed: (path a) intramolecular cyclization of **A** gave the resulting radical **B** with an aryl ring, which was oxidized to intermediate **C** then underwent deprotonation to give rise to the final product **2a–r** or **4**; (path b) **A** was oxidized to intermediate **D** then underwent elimination to give trifluoromethylated alkene **2s**, **4′** or **6** (Scheme 3).

Conclusions

In conclusion, we have demonstrated a simple, facile approach to trifluoromethyl-containing isoindolinones by radical addition and cyclization of enamides with moderate to good yields under mild conditions. KHF_2 was found crucial for this cyclization process and further investigation into the mechanism is currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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