


 Cite this: *RSC Adv.*, 2025, **15**, 3273

A facile synthesis of CF_3 -containing iminoisobenzofurans *via* copper-catalyzed oxygen trifluoromethylation–cyclization of *o*-vinyl-*N*-alkylamide[†]

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Received 9th November 2024
 Accepted 13th December 2024

DOI: 10.1039/d4ra07978g

rsc.li/rsc-advances

A copper-catalyzed oxygen trifluoromethylation of *o*-vinyl-*N*-alkylamide using Togni reagent as the trifluoromethyl precursor is demonstrated for the efficient synthesis of trifluoromethyl-containing iminoisobenzofurans. Preliminary mechanistic studies indicate that free radicals are involved in this process. The advantages of this approach include relatively mild reaction conditions and good functional group tolerance.

Introduction

Isobenzofurans are significant heterocyclic compounds that serve as a crucial reaction intermediate in the synthesis of numerous natural products and bioactive compounds.^{1–3} Notably, in recent years, iminoisobenzofurans, which are a crucial example of isobenzofurans,^{4,5} have emerged as highly attractive synthetic target compounds. The feasibility of traditional metal-catalyzed synthesis methods for these compounds, such as Pt- and Ag-/Au-catalyzed intramolecular cyclization of *o*-alkynylbenzamides and *o*-alkynylbenzohydroxamic acid derivatives, has been proven by many previous works.^{6,7} Based on these attempts, photo-induced cyclization and electrochemical reactions have also been realized for the synthesis of iminoisobenzofurans. For example, Lei *et al.* developed a mild and efficient electrochemical cyclization method for olefin amides, yielding benzamide, oxazoline, and iminoisobenzofuran compounds in high yields. Notably, the team discovered that this synthesis method operates effectively without the need for external oxidants or metal catalysts, thereby offering a novel approach for the preparation of iminoisobenzofurans. A similar synthetic approach was introduced for radical cascade cyclization of olefinic amides and diselenides, generating more than 40 examples of iminoisobenzofurans.⁸ Guo *et al.* exploited the regioselective and chemoselective *O*-cyclization or *N*-cyclization of olefin amides and diselenides to develop a new selenide imine isobenzofuran or isoindole *via* solar photocatalysis,

facilitating the aerobic synthesis of indolones.⁹ Zhu *et al.* demonstrated a photo-induced construction approach to generate sulfonamidylated iminoisobenzofurans and benzoxazines *via* mild and metal-free synthesis by reacting 2-vinylbenzamides with *N*-(2-vinylphenyl) amides.¹⁰ Xiao *et al.* prepared diversely functionalized CF_3 -containing iminoisobenzofurans through a visible-light-induced photocatalytic radical addition/cyclization reaction, with satisfactory substrate scope and functional group tolerance.¹¹ The aforementioned results demonstrate an advancement in the synthesis methods for iminoisobenzofurans. However, they also highlight several challenges associated with organic electrochemistry and photocatalytic synthesis, including slow reaction rates, high economic costs, and difficulties in controlling reaction conditions.¹² Consequently, the development of novel catalysts for the synthesis of iminoisobenzofurans, building upon traditional synthesis methods, remains a valuable area for further investigation.

Trifluoromethyl groups (CF_3) play an increasingly vital role in the fields of pharmaceuticals and agrochemicals owing to their unique structural motifs. They have a direct impact on the permeability, lipophilicity, and metabolic stability of the corresponding organic products.^{13–15} Consequently, in recent years, the incorporation of CF_3 groups into organic molecules, particularly through the C-trifluoromethylation reaction, has become a prominent area of interest for researchers.¹⁶ Togni reagents, which are two trifluoromethyl-modified organic hypervalent iodine compounds, serve as effective electrophilic trifluoromethylation agents. They not only react with a variety of nucleophiles to facilitate efficient electrophilic trifluoromethylation but are also compatible with numerous sensitive functional groups, thereby broadening their applicability.^{17–19} Copper salts and their complexes serve as

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† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4ra07978g>

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effective catalysts in the synthesis of a wide range of natural and synthetic compounds. Over the years, their efficacy has gained widespread recognition. In copper-catalyzed coupling reactions, particularly those that facilitate the formation of intramolecular oxy-trifluoromethylations, copper salts or complexes in various oxidation states are integral to the catalytic process.^{20–23} For instance, Buchwald *et al.* obtained cyclic lactones/ethers with satisfactory yields *via* Cu-catalyzed oxy-trifluoromethylations of unactivated alkenes.²⁴ Building upon this foundation, the researchers further investigated the bifunctional trifluoromethylation of alkenes, specifically focusing on the amino-trifluoromethylation reaction, which simultaneously generates C–CF₃ and C–N bonds. Notably, the intramolecular aminotri fluoromethylation reaction facilitates the construction of N-heterocycles through intramolecular cyclization, initiated by the trifluoromethylation of amine alkenes or alkynes. The resulting compounds have garnered significant interest from researchers as potential new agricultural chemicals.^{25,26} In 2016, Wang reported a copper-catalyzed aminotri fluoromethylation of *o*-vinyl-*N* alkoxyamide with the Togni reagent towards the synthesis of CF₃-containing lactams.²⁷ In addition, as for CF₃-iminoisobenzofuran development, the exploration of efficient, green and mild synthesis methods is still challenging.

Based on the free radical addition/cyclization mechanism of alkenes, we designed an efficient synthetic method for CF₃-containing iminoisobenzofurans, utilizing the Togni reagent as a CF₃ source and a copper salt as the catalyst. This approach offers the advantage of employing a non-noble metal catalyst, while its reaction conditions are characterized by their simplicity, mildness, and efficiency.

Results and discussion

Optimization for the synthesis of iminoisobenzofurans

Initially, Togni's reagent (**2a**) was chosen as a CF₃ radical precursor to verify the feasibility of the reaction, as shown in Table 1. Our investigation began by reacting CuI, 1,10-phenanthroline (phen), and CH₃CN at 50 °C under a nitrogen atmosphere (Table 1, entry 1), resulting in the successful synthesis of the target product **3a** with a yield of 52%.

For the proposed reaction conditions, parameters such as the metal catalyst, ligand, solvent, and temperature were systematically examined (Table 1). In entry 2, a higher yield of **3a** (56%) was achieved without the addition of phen as the ligand reagent, indicating that the ligand was not essential for this reaction. Other copper metal catalysts were tested under the same conditions, with CuBr·Me₂S demonstrating the highest effectiveness (entries 2–12). Adjusting the temperature, by increasing and decreasing it, did not yield satisfactory results (entries 13–15). Among the solvents screened, CH₃CN provided the most favorable yield (entries 16–19). Additionally, it was confirmed that the inert atmosphere (N₂) was crucial for achieving high reaction efficiencies. Encouraged by these findings, a reaction was conducted using *N*-(*tert*-butyl)-2-(1-phenylvinyl)benzamide (**1a**), Togni's reagent (**2a**), and CuBr·Me₂S in CH₃CN under a nitrogen atmosphere at 50 °C (oil

Table 1 Optimization of the reaction conditions^a

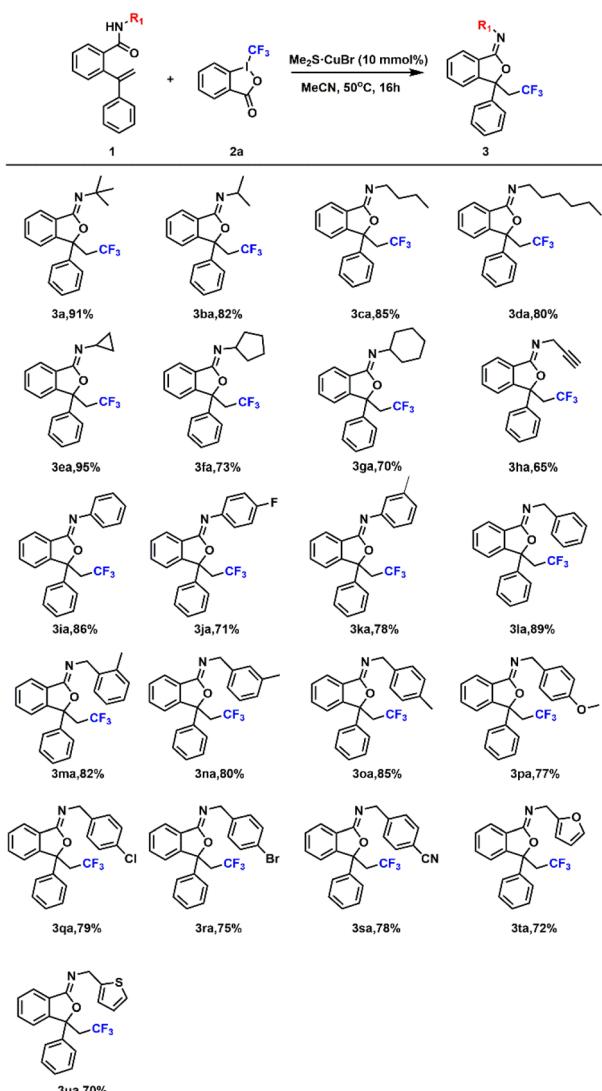
Entry	[Cu]	Ligand	Solvent	T (°C)	Yield ^b (%)
1	CuI	Phen	CH ₃ CN	50	52
2	CuI	—	CH ₃ CN	50	56
3	—	Phen	CH ₃ CN	50	0
4	—	—	CH ₃ CN	50	0
5	CuBr	—	CH ₃ CN	50	48
6	Cu ₂ O	—	CH ₃ CN	50	83
7	CuBr ₂	—	CH ₃ CN	50	68
8	[(CH ₃ CN) ₄ Cu]PF ₆	—	CH ₃ CN	50	57
9	C ₅ H ₃ CuO ₂ S	—	CH ₃ CN	50	45
10	CuBr·Me ₂ S	—	CH ₃ CN	50	91
11	CuOAc	—	CH ₃ CN	50	53
12	CuCl	—	CH ₃ CN	50	56
13	CuBr·Me ₂ S	—	CH ₃ CN	r. t.	40
14	CuBr·Me ₂ S	—	CH ₃ CN	40	80
15	CuBr·Me ₂ S	—	CH ₃ CN	60	88
16	CuBr·Me ₂ S	—	THF	50	42
17	CuBr·Me ₂ S	—	DCE	50	36
18	CuBr·Me ₂ S	—	MeOH	50	51
19	CuBr·Me ₂ S	—	1,4-Dioxane	50	41

^a Reaction conditions: *N*-(*tert*-butyl)-2-(1-phenylvinyl)benzamide (**1a**) (0.2 mmol), Togni's reagent (**2a**) (0.22 mmol), CuBr·Me₂S (0.02 mmol), CH₃CN (1 mL), 50 °C, N₂, and 16 h. ^b Isolated yields. THF, tetrahydrofuran; DCE, and 1,2-dichloroethane.

bath), resulting in a high yield of 91% for the target product **3a** (entry 10).

On the basis of determining the optimal reaction conditions, the practicability of this method was discussed. We first explored amides **1** with different substituents on the N atom, as shown in Table 2. Reactions involving amide substrates with alkyl groups (*tert*-butyl, isopropyl, *n*-butyl and *n*-hexyl) were investigated with accepted yields (Table 2, **3a**–**3da**), and it was revealed that steric hindrance could affect the yield. Moreover, amide substrates bearing large steric hindrance groups (cyclopropanyl, cyclopentanyl and cyclohexanyl) could be obtained with good yields (Table 2, **3ea**–**3ga**). Next, substituents with phenyl afforded better yields than alkynyl (Table 2, **3ha** and **3ia**). The good electron supply and conjugation properties of phenyl may have a positive effect on the yield of the product **3**. Therefore, we varied the substituents on phenyl to demonstrate this effect. The position of the methyl substituent on the phenyl group has little effect on the yield of the product (Table 2, **3ma** and **3oa**), but the yield of the product will decrease if the electron-withdrawing group is used as the phenyl-substituted group (Table 2, **3pa** and **3sa**). In general, irrespective of whether aliphatic substituents or electron-absorbing substituents were used, the yields of the above products are all acceptable. Even when heterocycles (furan and thiophene) are used as

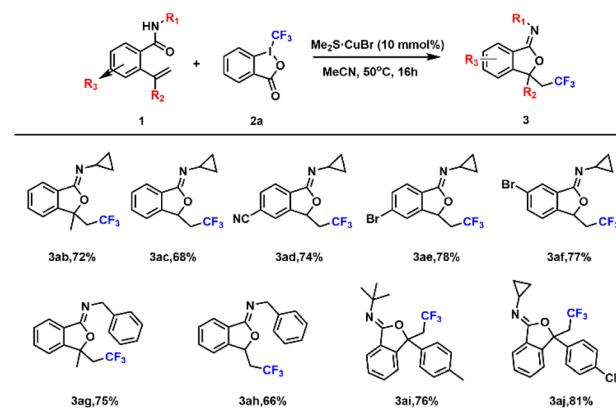


Table 2 Synthesis of 3a–3ua ^a ^b

^a Reaction conditions: *N*-2-(1-phenylvinyl)benzamide (1) (0.2 mmol), Togni's reagent (2a) (0.22 mmol), CuBr·Me₂S (0.02 mmol), CH₃CN (1 mL), 50 °C, N₂, 16 h. ^b Isolated yields.

substituents (Table 2, 3ta and 3ua), the method is still applicable.

The types and positions of the substituted iminoisobenzofurans were discussed in Table 3, and all the compounds provide acceptable yields. Reactions of cyclopropyl-substituted amides proceeded smoothly (Table 3, 3ab–3af), providing products in satisfactory yields, and the introduction of an electron-donating group (Me) could increase the yields of the products (Table 3, 3ab and 3ac). When an electron-drawing group such as –CN and –Br was present on the phenyl, the yields of the products could be improved, and the position of the electron-withdrawing group has little effect on the yield (Table 3, 3ad–3af). It is worth mentioning that the introduction of large steric groups (benzyl, tertiary butyl, phenethyl and

Table 3 Synthesis of 3ab–3aj ^a ^b

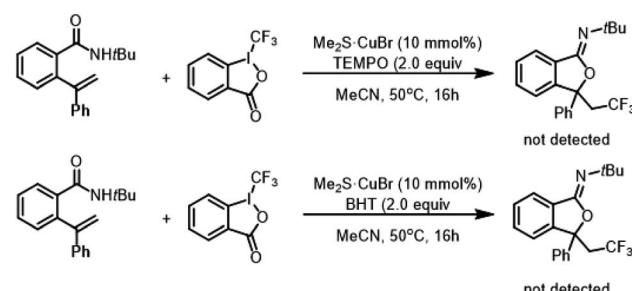
^a Reaction conditions: *N*-2-(1-phenylvinyl)benzamide (1) (0.2 mmol), Togni's reagent (2a) (0.22 mmol), CuBr·Me₂S (0.02 mmol), CH₃CN (1 mL), 50 °C, N₂, and 16 h. ^b Isolated yields.

chlorobenzene) can offer corresponding products with higher yields (Table 3, 3ag and 3aj), demonstrating the universality of this reaction.

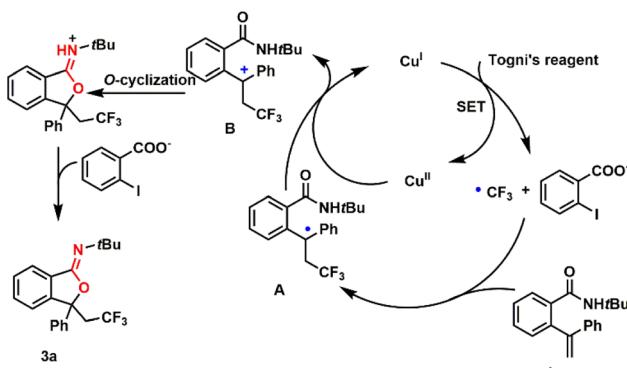
Proposed mechanism for the synthesis of iminoisobenzofuran

To gain insights into the potential pathway of copper-catalyzed oxytrifluoromethylation, we conducted a radical inhibition experiment (Scheme 1). In this standard reaction, the presence of 2.0 equivalents of radical scavengers, such as 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT), led to the complete absence of CF₃-containing iminoisobenzofuran formation. These findings suggest that the reaction proceeds through radical species.

Based on the observations and literature reports, a plausible mechanism for this copper-catalyzed oxytrifluoromethylation was illustrated in Scheme 2. A single electron transfer (SET) between Cu^I and Togni's reagent generated the reactive CF₃ radical. Subsequently, the CF₃ radical attacked the C=C bond of substrate 1a, resulting in the formation of intermediate A, which was then oxidized by Cu^{II} to yield the benzylic carbocation B. Finally, an intramolecular nucleophilic attack followed by deprotonation led to the formation of the desired product 3a.



Scheme 1 Radical inhibition experiments.



Scheme 2 Proposed mechanism.

Experimental

In a typical synthesis of CF_3 -containing iminoisobenzofurans, *N*-(*tert*-butyl)-2-(1-phenylvinyl)benzamide (**1a**) (0.2 mmol, 1.0 equiv.), **2a** (0.22 mmol, 1.1 equiv.) and 0.02 mmol of $\text{CuBr} \cdot \text{Me}_2\text{S}$ (10 mmol%) were dissolved in MeCN (1 mL). Thereafter, the mixture was stirred at 50 °C under an N_2 atmosphere in the oil bath for 16 hours. Upon completion of the reaction, as indicated by thin-layer chromatography, the reaction mixture was concentrated using rotary evaporation. The resulting products were then purified *via* silica column chromatography, generally employing a solvent mixture of 50–70% petroleum ether in dichloromethane.

Conclusions

In summary, we developed a new method to directly synthesize various CF_3 -containing iminoisobenzofurans using Cu-catalyzed oxygen trifluoromethylation of *N*-alkylamide under mild and green reaction conditions. By further expanding the substrate range, we obtained 30 substrates and conducted mechanistic studies. The reported method opens up a new path for the green and mild preparation of iminoisobenzofurans.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Author contributions

Shuo Gao: investigation, data curation, and methodology. Qiwang Zhou: investigation and data curation. Zilin Liu: data curation. Kaiyuan Zhang: writing – original draft. Di Yang: supervision and writing – review & editing. Zhenhua Zhang: writing – review & editing, supervision, funding acquisition, and conceptualization.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank the Natural Science Foundation of Shandong Province (ZR2022QB182, ZR2022QB254).

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