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Copper-Catalyzed Trifluoromethylation/Cyclization of Alkynes for Synthesis of Dioxodibenzothiazepines

Zi-Qi Zhang, Yi-Hao Xu, Jing-Cheng Dai, Yan Li, Jie Sheng, and Xi-Sheng Wang*

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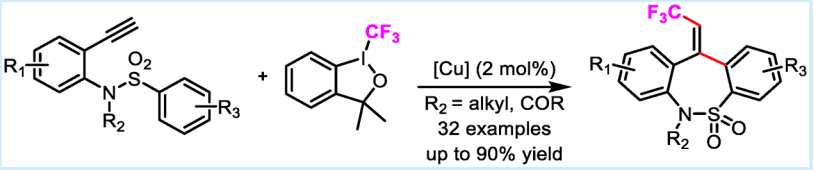


ABSTRACT: A facile and efficient approach for the synthesis of the CF_3-containing dioxodibenzothiazepines has been developed via copper-catalyzed trifluoromethylation/cyclization of alkynes utilizing a radical relay strategy. This method has demonstrated low catalyst loading, high regiocontrol, and broad scope under mild conditions. Good compatibility for the N-protecting group, gram-scale experiment, and further derivation of product prove the versatility of this transformation.

Sulfonamides are undisputed relevant targets for drug design due to their exhibited antithyroid, antibacterial, anti-inflammatory, anticancer, diuretic, antihypertensive, hypoglycemic, and anticonvulsant properties.[1] As a special class of 7-membered cyclic sulfonamide, the dioxodibenzothiazepine skeleton is one of the most important structures existing in sulfonamide drug molecules such as the commercial antidepressant drugs tianeptine and zepastine. What's more, other compounds bearing the 7-membered sulfonamide moieties have also exhibited biological activity, such as anticancer (farnesyltransferase inhibitor) (Figure 1).[2] Compared to the open-chain sulfonamides, efficient synthetic methods to construct such 7-membered cyclic sulfonamides are still limited.[3] For example, palladium-catalyzed direct C−H functionalization using aryl halides[3g−k] or an intramolecular oxidative C−H coupling reaction of two C(sp^2)−H bonds[3h] has been developed as a practical approach to 7-membered cyclic sulfonamides, but only cyclic sulfonamides embedded with biaryls are applicable to these protocols (Scheme 1a). The traditional methods to make 7-membered cyclic sulfonamides are normally based on the Friedel−Crafts acylation strategy,

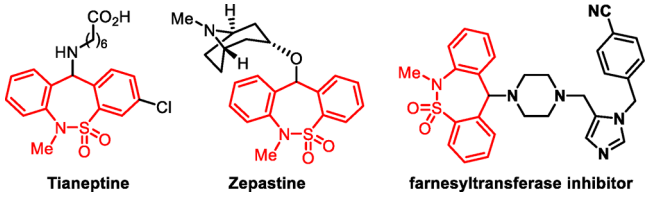
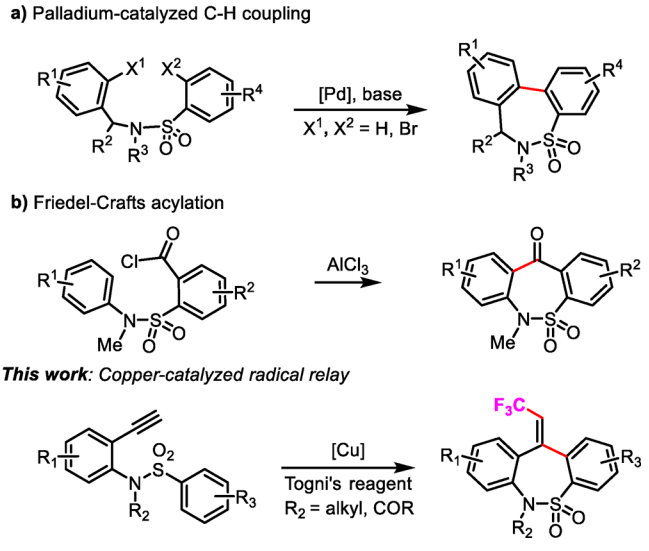


Figure 1. Selected biologically active compounds containing the dioxodibenzothiazepine skeleton.

Scheme 1. Approaches to 7-Membered Cyclic Sulfonamides



but it requires more than seven steps, which in turn reduces the yield and the efficiency (Scheme 1b).[2,3a]

Usually, the radical cyclization reactions have the advantages of high regioselectivity and efficiency.[4] Particularly, as an

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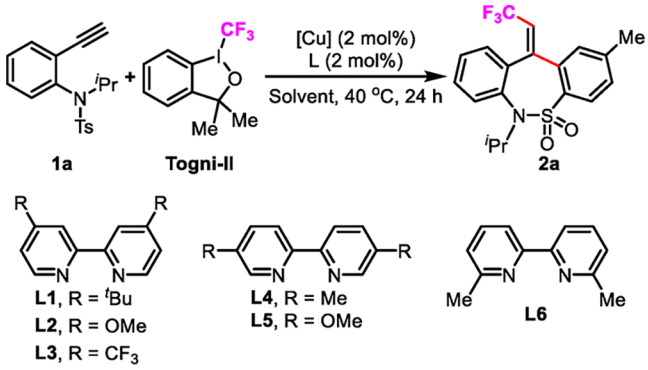
excellent radical acceptor, alkynes could be utilized for facile construction of complex functional molecules because of the high activity of the *in situ* formed vinyl radical, which could induce further cascade reactions.[5,6] We assumed that a rapid and efficient access to 7-membered cyclic sulfonamides might be gained by direct intramolecular radical addition to the aromatic ring of a vinyl radical intermediate. Considering that only limited examples were reported for the synthesis of dibenzazepines via an electrochemical[7] or photocatalytic protocol[8] using this strategy, this tactic needs further development to complement the current methodologies in organic synthesis. As part of our interest in the construction of 7-membered rings,[9] as well as the fact that the incorporation of CF_3 into organic molecules could obviously enhance the lipophilicity, metabolic stability, and bioavailability,[10] we report a novel and facile approach to synthesize dioxodibenzothiazepines via copper-catalyzed trifluoromethylation/cyclization of terminal alkynes by radical relay. This strategy features low catalyst loading, marvelous regio- and stereoselectivity, broad scope, and mild conditions. The efficient incorporation of trifluoromethyl group during this process enabled an applicable synthetic tactic to construct CF_3-containing intermediates for further elaboration in organic synthesis.

We commenced our initial investigation with *N*-(2-ethynylphenyl)-*N*-isopropyl-4-methylbenzenesulfonamide (**1a**) used as the pilot substrate and Togni-II reagent as the trifluoromethylating reagent in the presence of a catalytic amount of CuI (2 mol %) and L_1 (2 mol %) in DMF at 40 °C. The desired product **2a** was afforded in 44% yield after 24 h. A general screening of multifarious copper salts using L_1 as the ligand was conducted subsequently (entries 1−5, Table 1; for details, see the Supporting Information (SI)), which indicated that CuI was still the optimal choice for this reaction with the best yield. Normally used nitrogen-containing ligands with various steric hindrance and electrical properties were next screened (entries 6−10, Table 1; for details, see the SI). To our delight, the electron-rich ligand 5,5′-dimethoxy-2,2′-bipyridine (L_5) could improve the yield of **2a** to 65% (entry 9, Table 1). Solvents were then investigated and exerted a great effect on this reaction; DMF remains the best choice (entries 11 and 12, Table 1; for details, see the SI, Table S4). To increase the yield further, we attempted to add some additives to the system. The addition of extra 1.0 equiv $NaHCO_3$ as a base into the reaction system resulted in a slight decrease in the yield (entry 13), while the H_2O could increase the yield of **2a** to 74% (entry 14). We believe that the addition of water significantly reduces the side reactions,[11] thereby increasing the yield of the product. As only 5% yield of **2a** detected, AcOH had been demonstrated not to be a good additive in this catalytic system (entry 15). It is noteworthy that the prestirring time of catalyst and ligand has a tremendous influence on the reaction efficiency (Table S8, for details, see the SI). Furthermore, prolonging the reaction time to 36 h could furnish the desired product **2a** with even higher yield (88% isolated yield, entry 16, Table 1). It is worth mentioning that only *E*-alkenes were observed in all these reactions.

With the optimized reaction conditions in hand, the scope of this radical cyclization was then elucidated by the preparation of a variety of dioxodibenzothiazepines (Scheme 2). A number of arylalkynes **1** with *para*-, *meta*-, as well as *ortho*-substituted groups (R_3) on the aromatic ring attached to sulfonyl were efficiently cyclized to furnish the desired products **2** with good to excellent yields (**2a**−**2n**). It should be noted that the

Table 1. Optimization of Conditions[a]



entry	[Cu]	L	solvent	yield[b] (%)
1	CuI	L_1	DMF	44
2	CuBr	L_1	DMF	33
3	CuCl	L_1	DMF	27
4	$CuCl_2$	L_1	DMF	16
5	$Cu(OAc)_2$	L_1	DMF	20
6	CuI	L_2	DMF	37
7	CuI	L_3	DMF	6
8	CuI	L_4	DMF	60
9	CuI	L_5	DMF	65
10	CuI	L_6	DMF	30
11	CuI	L_5	CH_3CN	9
12	CuI	L_5	DCM	8
13[c]	CuI	L_5	DMF	55
14[d]	CuI	L_5	DMF	74
15[e]	CuI	L_5	DMF	5
16[d,f]	CuI	L_5	DMF	90 (88)
17[d,g]	CuI	L_5	DMF	80

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), Togni-II (0.3 mmol, 1.5 equiv), [Cu] (2 mol %), L (2 mol %), DMF (2.0 mL), 40 °C, 24 h, under N_2. [b]Yield was determined by ^{19}F NMR using $PhOCF_3$ as internal standard, isolated yield in parentheses. [c]$NaHCO_3$ (1.0 equiv). [d]H_2O (1.0 equiv). [e]AcOH (1.0 equiv). [f]36 h. [g]48 h.

electrical properties of the substituents have a significant effect on the reaction. A *para*-electron-donating group delivered products in a slightly lower yield (**2j**), while *para*-electron-withdrawing groups such as trifluoromethyl and cyano can be transformed into the corresponding products in good yields (**2h**,**i**). Intriguingly, *meta*-methyl-substituted substrate **1k** afforded **2k** and **2k′** as cyclization products with 1:1 selectivity in 76% yield in total. *Ortho*-substituted groups delivered products in a slightly lower yield under the general method but could be further increased to moderate yield by increasing the catalyst loading to 3% and replacing the ligand with 6% DMAP (**2l**,**m**). In particular, *ortho*-bromine-substituted substrate **1m** afforded the product **2m** with an *E*/*Z* selectivity of 7:1, while *o*-chlorine-substituted one gave the *E* product **2l** only, which indicated that the steric hindrance might play an important role for the regiocontrol. Notably, the dimethyl-substituted substrate **1n** could be well tolerated with moderate yield (75%, **2n**). The investigation of substituent (R_1) effects of the arylalkyne ring indicated that electron-donating groups such as alkyl (**2o**, **2v**) and methoxy (**2s**) groups, weak electron-withdrawing groups such as fluoro (**2p**, **2w**), chloro (**2q**, **2x**), and bromo (**2r**, **2y**), and strong electron-withdrawing groups such as esters (**2t**, **2z**) and cyano (**2u**) could also be compatible with our standard conditions. The absolute configuration of **2p** was confirmed by X-ray diffraction (for

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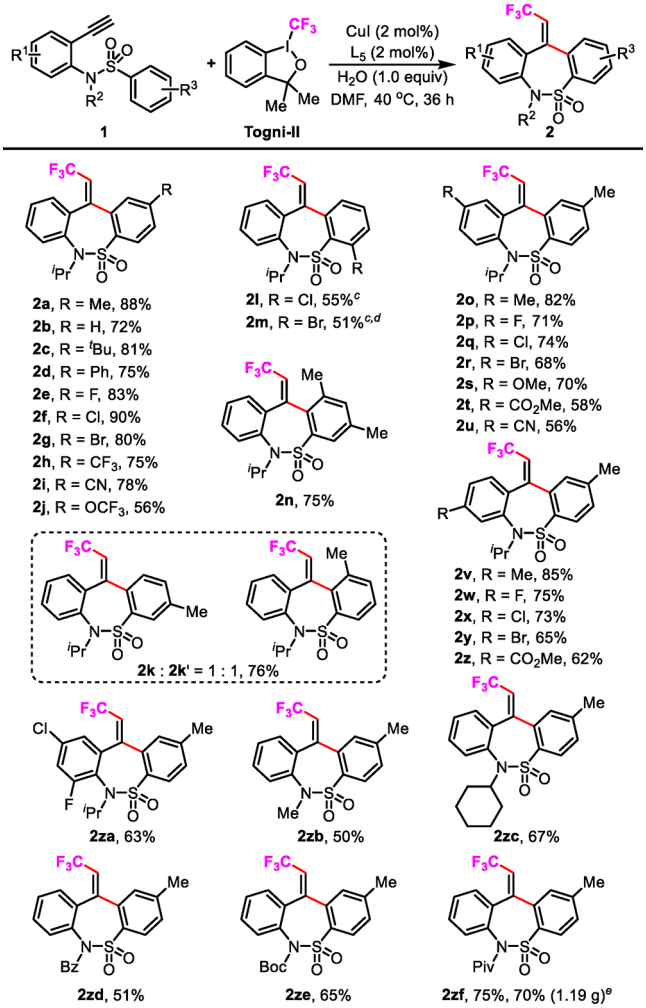
Scheme 2. Substrate Scope[a,b]

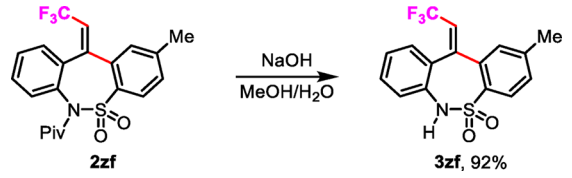


[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), Togni-II (1.5 equiv), CuI (2 mol %), L_5 (2 mol %), H_2O (1.0 equiv), DMF (2.0 mL), 40 °C, 36 h, under N_2. [b]Isolated yield. [c]CuI (3 mol %), DMAP (6 mol %), H_2O (1.0 equiv), DMF (2.0 mL), 40 °C, 36 h, under N_2. [d]E/Z = 7:1. [e]Gram-scale synthesis.

details, see the SI). Similarly, electron-rich substrates could afford the higher yields compared with the electron-deficient substrates, which implied the electronic properties had an impact on reaction efficiency. The protocol was also effective for alkyne bearing both fluoro and chloro groups on the aryl ring to furnish the desired product **2za** with 63% yield. Additionally, N-protecting groups were next evaluated. As an analogue of drug molecules tianeptine and zepastine, *N*-methyl-protected substrate was also compatible with this transformation (**2zb**), albeit in a lower but still acceptable yield. Other N-protecting groups such as cyclohexyl (**2zc**), Bz (**2zd**), Boc (**2ze**), and Piv (**2zf**) were also amenable to this catalytic system, which suggested the versatility of this method. It should be mentioned that the ring-closure reaction occurs preferentially on the aromatic ring attached to the sulfone group rather than the one located on the Bz group (**2zd**). To demonstrate the utility of the cascade cyclization, a gram-scale reaction of **1zf** with Togni-II reagent was carried out, and the reaction gave rise to product **2zf** with slightly lower yield (70%, 1.19 g).

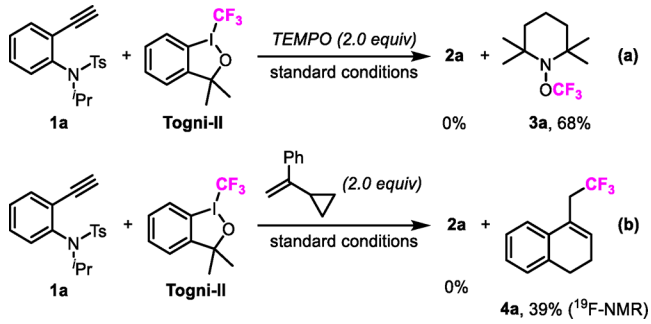
Further transformation of **2zf** was carried out in a methanol/H_2O solution of sodium hydroxide at room temperature for 12 h (Scheme 3). As expected, the pivaloyl group cleaved reaction of **2zf** occurred to give deprotected amine **3zf** in an excellent yield of 92%.

Scheme 3. Further Derivation



To gain further insight into the reaction mechanism, 2.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was subjected to the standard conditions shown in entry 16, Table 1. As a result, dioxodibenzothiazepine **2a** could not be detected, and the radical-trapping product **3a**[12] of the trifluoromethyl radical by TEMPO was afforded in 62% NMR yield (Scheme 4a). Furthermore, the addition of (1-

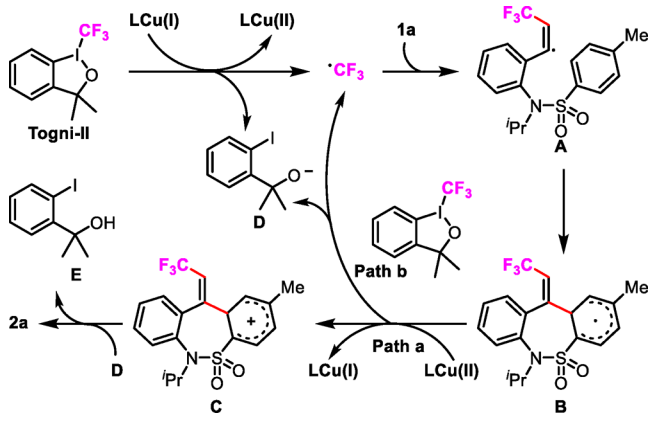
Scheme 4. Mechanistic Studies



cyclopropylvinyl)benzene, a normally used radical clock, to the standard reactions furnished the known product **4a**[13] in 39% NMR yield (Scheme 4b). Both observations clearly demonstrated that this reaction initiated from the attack of *in situ* generated trifluoromethyl radical to the terminal alkyne.

On the basis of the above observations and previous reports,[7,8] the plausible mechanism of this reaction is then proposed (Scheme 5). Initially, CF_3 radical is generated via a single electron transfer (SET) process from Cu(I) species to

Scheme 5. Proposed Mechanism



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Togni-II reagent, accompanied by the formation of the anion species **D** and Cu(II) species. Then the CF_3 radical is fleetly trapped by the terminal alkyne **2a** to afford the vinyl radical **A**, followed by intramolecular addition of **A** for the formation of the radical intermediate **B**. A single electron oxidant of the radical intermediate **B** by Cu(II) species regenerates Cu(I) species and affords the cation intermediate **C**, which furnishes the desired product **2a** along with **E** after the following deprotonation under the promotion of the anion species **D** (path a). Meanwhile, another possible pathway cannot be excluded, in which the cation intermediate **C** may generate by direct single electron transfer (SET) from the radical intermediate **B** to Togni-II reagent with the generation of the anion species **D** and CF_3 radical to enter the next catalytic cycle (path b).

In conclusion, we have developed a novel, facile, and efficient approach for the synthesis of dioxodibenzothiazepines via copper-catalyzed trifluoromethylation/cyclization of arylalkynes utilizing Togni's reagent as the trifluoromethyl source. This method features low catalyst loading, marvelous regio- and stereoselectivity, broad scope, and mild conditions. This radical relay tactic offers a reliable manner for the functionalization of arylalkynes and thus paves a potential path for the facile synthesis of CF_3-containing antidepressant drugs. Further investigations on novel radical-involved cascade cyclization of arylalkynes for efficient construction of complex functional molecules in single step are still underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00344.

Experimental procedures, spectral and analytical data, copies of ^1H, ^{13}C NMR spectra for new compounds (PDF)

Accession Codes

CCDC 2005999 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Xi-Sheng Wang − *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China*; orcid.org/0000-0003-2398-5669; Email: xswang77@ustc.edu.cn

Authors

Zi-Qi Zhang − *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China*

Yi-Hao Xu − *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China*

Jing-Cheng Dai − *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China*

Yan Li − *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China*

Jie Sheng − *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00344

Notes

The authors declare no competing financial interest.

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