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Year: 2023

Version: Published version

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Chemistry–A European Journal
Research Article
doi.org/10.1002/chem.202203729
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A Copper-Catalyzed Interrupted Domino Reaction for the Synthesis of Fused Triazolyl Benzothiadiazine-1-oxides

Renè Hommelsheim,[a] Sandra Bausch+,[a] Arjuna Selvakumar+,[a] Mostafa M. Amer,[a, b] Khai-Nghi Truong ,[c] Kari Rissanen,[c] and Carsten Bolm*[a]

In memory of Rolf Huisgen

Abstract: Copper(I)-catalyzed domino reactions of 2-azido sulfoximines with 1-iodoalkynes yield fused triazolyl-containing benzothiadiazine-1-oxides. The protocol features the synthesis of two fused heterocyclic rings in one step with good to excellent yields and a broad functional group tolerance. Detailed mechanistic investigations indicate that a copper π-complex initiates a cycloaddition and oxidative C–N coupling reaction sequence. The results suggest an interrupted domino process involving an iodinated triazole as a key intermediate.

Introduction

Heterocycles are most important in organic chemistry. Due to their unique chemical and biological properties,[1] they find widespread applications in medicinal chemistry[2] and crop protection.[3] In 2021, an analysis of the FDA-approved drugs showed that about 82% of these drugs contained a heterocyclic motif which highlights their importance in daily life.[4] In particular, nitrogen- and sulfur-containing heterocycles show broad activities as antidepressant, anticancer, or antiviral drugs.[5] Thus, new synthetic methods for heterocyclic scaffolds are highly demanded.

Among the nitrogen-containing heterocycles, 1,2,3-triazoles have attracted tremendous interest in the development of bioactive compounds as pharmacophores or bioisosteres for several functional groups.[6] Moreover, they have been studied as functional coatings in material science.[7] 1,2,3-Triazoles are readily accessible by copper(I)-catalyzed azide-alkyne cycloadditions (CuAAC),[8] which are formal Huisgen 1,3-dipolar cycloadditions.[9] These reactions represent the most common example for click chemistry,[10] the development of which was recently awarded with the Nobel Prize in Chemistry 2022.[11] Noteworthy, internal alkynes do not undergo CuAAC processes and, consequently, 1,4,5-trisubstituted triazoles are inaccessible by this route. Therefore, several protocols have been devolved to further modify 1,4-disubstituted 1,2,3-triazoles to access fully functionalized 1,4,5-trisubstituted motifs.[12] In this context, domino or cascade reactions have proven to be elegant strategies to achieve complex and fused skeletons.[13] For example, Fokin and co-workers developed a CuAAC process with azides and 1-iodoalkynes to yield 5-iodo-substituted triazoles.[14] Then, however, a second transformation was required to introduce other functionalities by exchange of the halo group. A direct access of 1,4,5-trisubstituted-triazoles can be obtained by an interrupted CuAAC process in which the nucleophilic Cu(I)-triazole intermediate is intercepted with added electrophiles.[15] Along these lines, Xu and co-workers developed a protocol for the synthesis of 5-hetero-functionalized triazoles.[15a] Trapping the Cu(I)-triazole intermediate by nucleophiles under oxidizing conditions proved to be more challenging, and only a few reports are known.[16]

In recent years, sulfoximines and their related heterocycles have attracted wide interest in the development of novel active pharmaceutical ingredients and crop protection agents.[17] With a small hydrophilic and potentially stereogenic group in combination with the possibility of introducing a wide range of substituents at the nitrogen and the sulfur atom, sulfoximines can be structurally highly diverse. In addition, the sulfoximidoyl moieties can act as both hydrogen bond acceptor and donor (in the case of *N*H free sulfoximines), which allows a fine-tuning of physicochemical properties affecting bioactivities.[17a,18] For modulating such properties, *N*-functionalizations of sulfoximines are important.[19] Those also include several cycloaddition reactions leading to *N*-tetrazolyl and *N*-triazolyl sulfoximine derivatives.[16c,20]

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202203729

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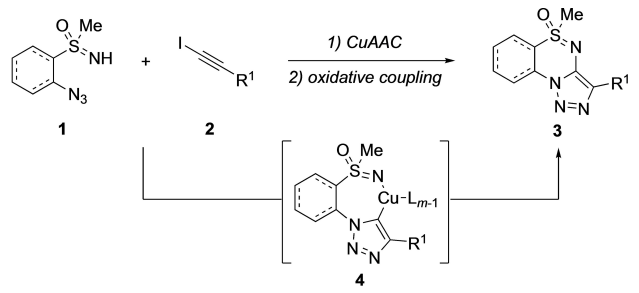
Based on our work on sulfoximidoyl-containing heterocycles[21] and inspired by the work of Latyshev and coworkers,[22] we became interested in combining such ideas and make use of them for synthesizing fused benzothiadiazine-1-oxides **3** (Scheme 1). These heterocycles are analogues of sultams,[23] which are investigated as bioactive compounds and functional materials.[24] We hypothesized that CuAAC reactions of 2-azido sulfoximines **1** with 1-iodoalkynes **2** followed by an intramolecular oxidative coupling would give direct access to motifs **3** via copper species **4**.

Results and Discussion

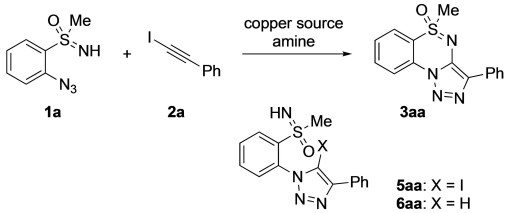
The investigation was initiated by developing a synthetic approach for 2-azido sulfoximines **1**. Pleasingly, these compounds could readily be accessed by direct oxyamination of the corresponding azido sulfides in good to excellent yields even on gram-scale (for details, see the Supporting Information).[25]

With a range of azido sulfoximines **1** in hand, their behavior in click reactions was studied. The initial work was carried out with azido sulfoximine **1a**[26] and iodoalkyne **2a** as model substrates (Table 1, entry 1). Under the classical conditions for CuAAC reactions[14] with a combination of copper(I) iodide (10 mol%) and triethylamine (2 equiv.), a complex product mixture resulted including the normal cycloaddition product **5aa** and its dehalogenated analogue **6aa**.[27] In addition, to our delight, our initial hypothesis (comp. Scheme 1) was confirmed and tricyclic product **3aa** resulting from the intended domino reaction was obtained too albeit only in 6% yield.



Scheme 1. Synthesis of benzo[e][1,2,4]thiadiazine 1-oxides **3** by a copper(I)-catalyzed azide-alkyne cycloaddition and consecutive oxidative coupling.

Table 1. Summary of the optimization of the reaction conditions.[a]



Entry	CuI [mol%]/Cu [mol%]	Amine	Solvent	Yield [%][b]
1	10/0	NEt_3	THF	6
2	10/20	NEt_3	THF	24
3	20/20	NEt_3	THF	61
4	30/20	NEt_3	THF	79
5	30/20	DIPEA	THF	54
6	30/20	TMEDA	THF	24
7	30/20	NEt_3	H_2O	30
8	30/20	NEt_3	Toluene	46
9	30/20	NEt_3	DCM	88
10	30/20	NEt_3	DCM	87[c]

[a] Reaction conditions: CuI, Cu, amine (0.8 mmol, 2 equiv.), THF (1.0 mL), rt, 20 min; then, **1a** (0.4 mmol), **2a** (0.4 mmol), 50 °C, 12 h. [b] Yields after column chromatography. [c] Use of 0.5 mL of DCM.

Aiming at a continuous reactivation of the catalytic species,[22] elemental copper (20 mol%) was added to the aforementioned combination of copper iodide and NEt_3 in the next experiment. Under these conditions, the yield of **3aa** improved to 24% (Table 1, entry 2).[28] With successive increase in the amount of copper(I) iodide from 10 mol% to 30 mol% (Table 1, entries 2–4) the yield of **3aa** increased up to 79%.[29] Substituting triethylamine by diisopropylethylamine (DIPEA) or tetramethylethylendiamine (TMEDA) led to a decrease in yield of **3aa** (Table 1, entries 4–6). Among the solvents THF, toluene, water and DCM, the latter proved optimal, providing tricycle **3aa** in 88% yield (Table 1, entries 4, 7–9). Finally, the solvent amount was reduced (from 1 mL to 0.5 mL of DCM on a 0.4 mmol scale) which had no effect on the yield of **3aa** but simplified the product isolation (Table 1, entry 10).[30] Besides the parameter variations shown in Table 1, other factors including the types of copper salts, ligands, solvents, temperature, etc. were investigated and the respective results are shown in the Supporting Information.[31]

With the optimal reaction conditions in hand, the substrate scope was studied next (Scheme 2). First, 2-azido sulfoximine **1a** was reacted with a range of aryl-substituted iodoalkynes (**2a**–**2l**), affording the corresponding products (**3aa**–**3al**) in good to high yields (76%–87%). In this series, iodoalkynes with both electron-donating (**3ad**) and electron-deficient (**3af**) groups were well tolerated, revealing no electronic effect on the yield of the corresponding product. The only exception was 4-nitro substituted iodoalkyne **2g**, which resulted in a complex product mixture and attempts to isolate **3ag** remained unsuccessful.

Comparing the results for **3ab** (86%), **3ah** (72%), and **3ak** (73%) stemming from reactions of **1a** with 4-, 3-, and 2-tolyl-substituted iodoalkynes **2b**, **2h**, and **2k**, respectively, suggested a stereoelectronic effect induced by the methyl substituent. This trend, however, remained unconfirmed in the series of fluoro-substituted products **3ae**, **3aj** and **3al**, which were isolated in yields of 84%, 65%, and 85%, respectively. The reaction of 2-(iodoethynyl)-naphthalene (**2m**) proceeded well giving **3am** in 95% yield. While the reaction of pyridyl-substituted iodoalkyne **2n** remained unsuccessful, iodoalkyne **2o** reacted smoothly yielding the thienyl-substituted product **3ao** in 74% yield. Aliphatic iodoalkynes **2p**–**2s** reacted well, and the corresponding tricyclic products **3ap**–**3as** were isolated in 71%–81% yield. Iodoalkynes **2t** and **2u** bearing a terminal hydroxyl or a trimethylsilyl group, respectively, proved incompatible. To further demonstrate the robustness of the developed domino reaction protocol, a sulfoximidoyl- containing derivative of ethinylestradiol, a commercially available contraceptive, was targeted (Scheme 2).[32] For this purpose, ethinyles-

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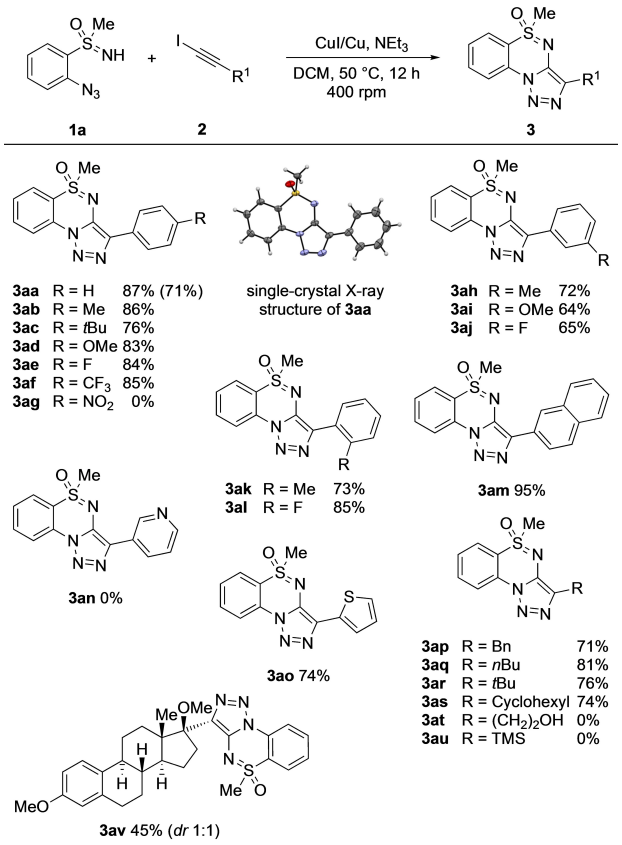
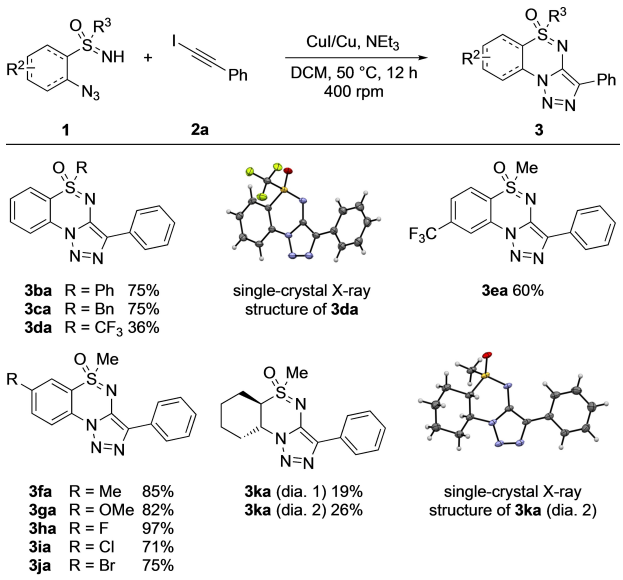


Scheme 2. Substrate scope for the synthesis of tricyclic sulfoximidoyl containing triazoles **3** with respect to iodoalkynes **2**. Reaction conditions: CuI (0.12 mmol), Cu (0.08 mmol), NEt_3 (0.8 mmol), DCM (0.5 mL), rt, 20 min; then, **1a** (0.4 mmol), **2** (0.4 mmol), 50 °C, 12 h. Yields after column chromatography. In parentheses: result of a gram-scale (5.0 mmol) experiment (see Supporting Information for details).



Scheme 3. Substrate scope for the synthesis of tricyclic sulfoximidoyl containing triazoles **3** with respect to 2-azido sulfoximines **1**. Reaction conditions: CuI (0.12 mmol), Cu (0.08 mmol), NEt_3 (0.8 mmol), DCM (0.5 mL), rt, 20 min.; then, **1** (0.4 mmol), **2a** (0.4 mmol), 50 °C, 12 h. Yields after column chromatography. In the reactions providing **3ea** and **3ka**, a solution of **1** in DCM (0.5 mL) was added.

tradiol was converted into its iodo derivative **2v**, which reacted smoothly with sulfoximine **1a** providing the desired derivative **3av** in 45% yield as a 1:1 mixture of its diastereomers. Upscaling the reaction of **1a** and **2a** to 5.0 mmol gave **3aa** in 71% yield. The molecular structure of compound **3aa** was verified by single crystal X-ray crystallography (Scheme 2).[26]

Continuing the investigation of the substrate scope, various azido sulfoximines (**1b**–**1k**) were evaluated in reactions with iodoalkyne **2a** (Scheme 3). Applying *S*-aryl-*S*-phenyl and benzyl-substituted azido sulfoximines **1b** and **1c**, respectively, provided the corresponding products **3ba** and **3ca** in 75% yield. The reaction of the highly electron-deficient *S*-aryl-*S*-trifluoromethyl-substituted sulfoximine **1d** afforded the desired product **3da** as well, although in low yield (36%). These results indicate a strong influence of the electronic properties of the *S*-bonded substituents on the outcome of the reaction. Differently substituted *S*-aryl-*S*-methyl azido sulfoximines (**1e**–**1j**) were well tolerated giving the corresponding products (**3ea**–**3ja**) in good to excellent yields. In addition, the formation of **3ka** derived from aliphatic azido sulfoximine **1k** and **2a** was tested. To our delight, both afore isolated diastereomers of **1k** (for details see the Supporting Information) led to the desired products (**3ka** dia. 1 and **3ka** dia. 2), although in yields of only 19% and 26%, respectively.

The solid-state molecular structures of compounds **3ba**–**3da** and **3ka** were verified by single crystal X-ray crystallography (Scheme 3).[26]

Mechanistic Studies

To gain more insights into the mechanism of the reaction sequence, several control reactions and mechanistic experiments were performed (Scheme 4). In general, two fundamentally different pathways for the domino process appeared plausible: a) an *N*-alkynylation and consecutive cycloaddition or b) a cycloaddition and oxidative C–N coupling pathway.

First, the possible *N*-alkynylation mechanism[33] was evaluated by studying the model reaction of *N*H-sulfoximine **7** with iodoalkyne **2a** under the optimal reaction conditions (Table 1, entry 10). Analyzing the crude reaction mixture by NMR spectroscopy showed no indication for the formation of the corresponding *N*-alkynylation product **8** (Scheme 4A), which suggested the *N*-alkynylation and consecutive cycloaddition pathway to be unlikely. The presence of the homocoupling product **9** indicated the involvement of a copper σ-acetylide complex,[34] which is a commonly proposed intermediate in the CuAAC chemistry of terminal alkynes.[35] All of these data were in favor of a cycloaddition as the first step of the reaction sequence. To find support for this hypothesis, the reaction of azido sulfoximine **1a** with copper acetylide **10**, which proved to be an efficient catalyst for the CuAAC reaction of iodoalkynes,[36] was tested. Applying a stoichiometric amount of **10** in the

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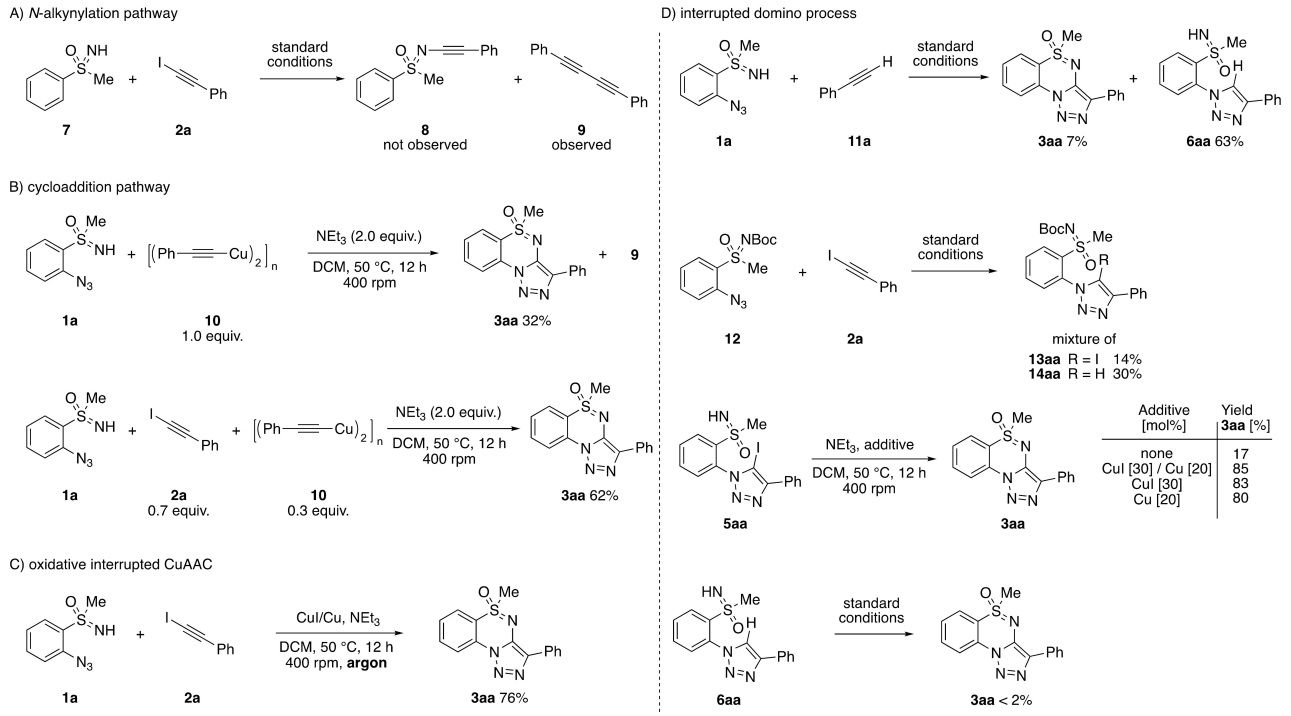
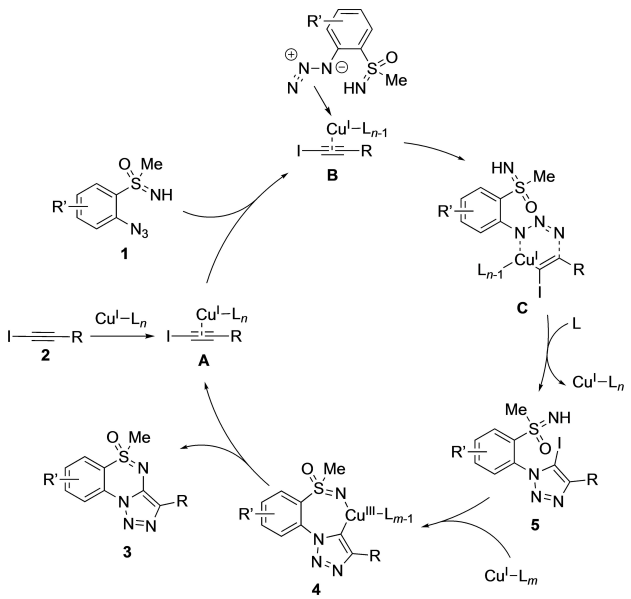


Scheme 4. Experimental mechanistic investigations: A) possible *N*-alkynylation pathway, B) cycloaddition pathway, C) oxidative interrupted CuAAC, D) interrupted domino process.

reaction with **1a** afforded tricyclic product **3aa** in 32% yield (and homocoupling product **9** as by-product; Scheme 4B).[37] In order to confirm the catalytic role of the proposed copper σ-acetylide complex, iodoalkyne **2a** (0.7 equiv.) was mixed with copper phenylacetylide (**10**, 0.3 equiv.) in the absence of additional copper salts (Scheme 5B). To our delight, product **3aa** was observed in 62% yield,[38] supporting the hypothesis that a cycloaddition initiated the domino reaction process under the chosen conditions.



Scheme 5. Proposed catalytic cycle for the copper catalyzed domino reaction.

Although the main reaction path was thereby affirmed, the results raised additional questions. Fokin and co-workers had suggested the reaction to proceed either via a σ-acetylide complex with a Cu(I) triazole intermediate or through the activation of the iodoalkyne by a copper π-complex involving a cyclic vinylidene-type transition state.[14] The first scheme was disfavored because the Cu(I) triazole complex, resulting from σ-acetylide pathway, was expected to be highly sensible to protic sources,[39] which was experimentally not the case as the formation of the iodinated triazoles was even observed in water as solvent.[14] Moreover, several experimental and computational studies revealed substantial differences between the CuAAC mechanism of terminal alkynes and the one with iodoalkynes, which favored the formation of a copper π-complex.[40] In light of this background, we focused our attention on the sequence of the ring closure reaction and C–N bond formation. Again, two mechanisms were possible: a) a trapping of a potential Cu(I) triazole intermediate by the nucleophilic *N*H sulfoximine under oxidative conditions and b) an interrupted domino process involving an iodinated triazole as the key intermediate. The latter would then react in an oxidative C–N coupling or a base-mediated nucleophilic substitution to form the tricyclic product.

With the aim to distinguish between these two pathways, the following experiments were performed: First, the role of dioxygen was targeted because it could be involved in a

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trapping of a potential Cu(I)-triazole intermediate under standard conditions.

Carrying out the model reaction of sulfoximine **1a** and iodoalkyne **2a** under an inert (argon) atmosphere (Scheme 4C) gave **3aa** in 76% yield, showing that dioxygen had only a negligible effect on the product formation. Next, if a potential Cu(I)-triazole intermediate was trapped directly, the use of a non-iodinated alkyne should also lead to the formation of the tricyclic product. This path was excluded by applying phenyl acetylene (**11a**) in the reaction with azido sulfoximine **1a**, which gave **3aa** in only trace amounts (Scheme 4D). In addition, CuAAC product **6aa** was formed in 63% yield. In conclusion, an oxidative trapping of the Cu(I)-triazole intermediate by the nucleophilic *N*H-sulfoximine as described by Song and co-workers appears unlikely.[16c] In contrast, our data indirectly suggest the absence of a Cu(I)-triazole intermediate, and we therefore assume that a π-complex is involved in the CuAAC process.

As noted in the optimization of the reaction conditions, product **3aa** was formed in combination with small amounts of iodinated triazole **5aa** and its dehalogenated analogue **6aa**. For studying the potential of those by-products as intermediates in an interrupted domino process, we consequently aimed at preparing and isolating **5aa** and **6aa** in larger quantities as pure products. This was achieved by performing the reaction of Boc-protected azido sulfoximine **12** with iodoalkyne **2a** under the aforementioned optimized reaction conditions. In this manner, an inseparable 1.0:2.2 mixture of the Boc-protected triazoles **13aa** and **14aa** was obtained in 44% yield. Subsequent deprotection with TFA afforded triazoles **5aa** and **6aa**, respectively.[41] Having those compounds in hand, a metal-free cyclization starting from iodinated triazole **5aa** was tested first. Accordingly, **5aa** was treated with NEt_3 in DCM, and as a result, **3aa** was obtained in 17% yield indicating that a nucleophilic substitution was possible but that it played only a minor role in the product formation process (Scheme 4D).[22] Strong evidence for a metal-catalyzed oxidative C–N coupling as the main reaction pathway was then found using a combination of CuI and Cu powder (as in Table 1, entry 10), which afforded **3aa** from **5aa** in 85% yield. Applying combinations of CuI and NEt_3 or Cu powder and NEt_3 afforded **3aa** in 83% and 80% yield, respectively (Scheme 4D). As expected from the result of the control reaction using phenyl acetylene (**11a**), dehalogenated triazole **6aa** gave only traces of **3aa** when subjected to the standard reaction conditions (Scheme 4D).

On the basis of our findings and previous studies,[14,40] we postulate the mechanistic cycle depicted in Scheme 5. In the first step, iodoalkyne **2** reacts with the active copper species to form a copper π-complex **A** which after complexation of azide **1** forms complex **B**. This complex undergoes a cycloaddition reaction through a cyclic vinylidene-type transition state **C**, as proposed by Fokin and co-workers[14] to form 5-iodo-triazole **5** as a key intermediate. The interrupted domino process is then continued by an oxidative C–N coupling of compound **5** to yield the desired product **3** after reductive elimination from intermediate **4**.[42,43]

Conclusion

In summary, we developed a copper-catalyzed domino reaction leading to fused triazolyl-containing benzothiadiazine-1-oxides. The protocol features a broad substrate scope with high functional group tolerance affording the corresponding heterocycles in good to excellent yields. The applicability of this protocol was demonstrated by the synthesis of an ethinylestradiol analogue. Detailed experimental mechanistic studies suggest that the domino reaction is initiated by a copper-catalyzed cycloaddition reaction through a copper π-complex. A consecutive oxidative coupling of the iodinated triazole as a key intermediate completes the catalytic cycle and affords the observed product.

Experimental Section

Experimental procedure for the synthesis of 2-azido sulfoximines 1: 2-Azido sulfoximines **1** were synthesized according to a modified literature procedure.[25a] In a screw cap reaction tube (diameter: ca. 2 cm) the corresponding azidosulfides (2 mmol, 1.0 equiv.), ammonium carbamate (4.0 mmol, 312 mg, 2.0 equiv.) and (diacetoxyiodo)benzene (PIDA, 5.0 mmol, 1660 mg, 2.5 equiv.) were suspended in MeOH (4.0 mL). The tube was closed tight immediately, and the reaction mixture was stirred overnight at room temperature. DCM and silica were added, and the volatiles were removed under reduced pressure. Purification of the product by column chromatography (column diameter: ca. 2.5 cm, column length: ca. 25 cm) using *n*-pentane: EtOAc as gradient solution (1:0→1:1→0:1) afforded the corresponding 2-azido sulfoximine **1**.

Experimental procedure for the synthesis of sulfoximidoyl containing triazoles 3: In a screw cap reaction tube (diameter: ca. 2 cm) with a stir bar (10 mm×6 mm), CuI (98% purity, 0.12 mmol, 23.3 mg, 30 mol%) and copper powder (0.08 mmol, 5.1 mg, 20 mol%) were suspended in dry and degassed DCM (0.5 mL). NEt_3 (0.8 mmol, 0.11 mL, 2.0 equiv.) was added, and the resulting suspension was stirred at approx. 400 rpm at room temperature for 20 min. Sequentially, the corresponding iodoalkyne (**2**, 0.4 mmol, 1.0 equiv.) and 2-azido sulfoximine (**1**, 0.4 mmol, 1.0 equiv.) were added. The reaction tube was placed in a preheated aluminum block and the reaction solution was stirred for 12 h at 50 °C and 400 rpm. DCM and SiO_2 were added, and the volatiles were removed under reduced pressure. Column chromatography (column diameter: ca. 2.5 cm, column length: ca. 35 cm) of the crude product on silica using *n*-pentane: EtOAc as gradient solution (1:1→1:2) afforded the desired triazole **3**.

Acknowledgements

R.H. gratefully acknowledges support by the Fonds der Chemischen Industrie e.V. (Kekulé scholarship) and by the Friedrich-Ebert-Stiftung (Promotionsförderung). M.M.A. thanks the Leibniz-Gemeinschaft for financial support (project PHARM-SA K136/2018), and we acknowledge the Alexander von Humboldt Foundation for support of K.R. (AvH research award). The authors thank Mrs. Susanne Pohlmann for her support in synthetic work, Christian Schumacher for his help in the preparation of X-ray samples and fruitful discussion, Victoria Pfennig for critical proofreading, and Dr. Christoph Räuber (all

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RWTH Aachen University) for mechanistic NMR studies. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

All experimental data (experimental procedures, X-ray crystallographic studies, characterization data, and NMR spectra for new compounds) to support the findings of this work can be found within the manuscript or the Supporting Information. Deposition numbers 2169527–2169532 and 2169543 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Keywords: CLICK · copper catalysis · cycloaddition · domino reactions · sulfoximines · sulfur heterocycles

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[27] In an experiment with the 4-azido analog of **1a** (compound **1l** in the Supporting Information) and **2a**, no cycloaddition product was detected under those conditions.
[28] Control reactions showed a pronounced reactivation of the catalytic active species in THF, while in DCM as solvent, this effect is less prominent (see Supporting Information for more details).
[29] We assume that the high catalyst loading is required because of its bonding to **1** and **3**.
[30] By reducing the solvent amount, the product isolation commonly only involved a single column chromatographic purification. Generally, we applied a stirring speed of 400 rpm to ensure efficient mixing of the inhomogeneous probes.
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[42] It its unknown whether the same copper complex is involved in the CuAAC and oxidative coupling reaction or if an additional cooper complex is involved.
[43] At this stage, a reaction mechanism involving a copper(I) triazolide intermediate cannot be fully ruled out.

Manuscript received: November 29, 2022
Accepted manuscript online: December 1, 2022
Version of record online: January 23, 2023

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