

Cyclic Sulfoximine and Sulfonimidamide Derivatives by Copper-Catalyzed Cross-Coupling Reactions with Elemental Sulfur

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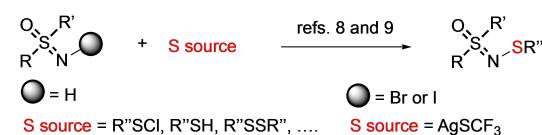
Abstract: Copper-catalyzed cross-coupling reactions of α -bromoaryl *NH*-sulfoximines with elemental sulfur lead to benzo[*d*][1,3,2]dithiazole-1-oxides, which represent a new class of three-dimensional heterocycles. The reactions proceed under mild conditions showing good functional group and heterocycle tolerance. By imination/oxidation, the initial cross-coupling products can be converted to unprecedented cyclic sulfonimidamides derivatives. Furthermore, a seven-membered heterocycle was obtained by a ruthenium-catalyzed ring-expansion with ethyl propiolate.

Keywords: copper catalysis; elemental sulfur; sulfoximines; sulfonimidamides; cross-coupling reactions

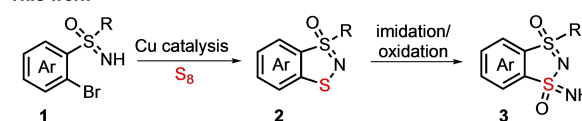
Sulfoximines have attracted considerable attention over the past several decades. As typical high oxidation state sulfur compounds, their molecular architectures offer attractive properties for drug and crop protection chemistry including metabolic stability, hydrogen-bond donor/acceptor capabilities, and structural diversity.^[1] As response to the needs of organic synthesis and industrial applications, *N*-functionalizations of *NH*-sulfoximines have been greatly advanced.^[2] In this context, the synthesis of three-dimensional heterocycles has become an important research area.^[3] A high degree of saturation and the presence of stereogenic centers are important factors in the drug discovery process.^[4] Synthesizing three-

dimensional heterocycles with sulfur cores has been an ongoing research interest of our group, and we devised various protocols for accessing compounds such as benzothiazines and derivatives thereof,^[5] benzo[*c*]isothiazole 2-oxides,^[6] and other related compounds.^[7] In this series, however, cyclic structures resulting from formal *N*-sulfenylations and ring closures are still lacking. This is surprising in light of the large number of recent straightforward methods for the generation of new N–S bonds from *NH*-sulfoximines with reagents such as RSCl, RSH, RSSR, and R'R''NSR.^[8,9] In order to close this synthetic gap, we decided to focus on heterocycles **2** as molecular targets (Scheme 1). Considering substrate accessibility, 2-bromoaryl sulfoximines **1** were identified as attractive starting materials.^[10] In addition, we envisaged avoiding the aforementioned toxic and odorous sulfur reagents and applying easy-to-use elemental sulfur (S₈) instead.^[11] As the result of a long-lasting endeavor, we can now report a copper-catalyzed cross-coupling

Previous work



This work



Scheme 1. *N*-Thiolations of sulfoximines.

reactions of *S*-2-bromophenyl NH-sulfoximines **1** with elemental sulfur under very mild reaction conditions leading to benzo[*d*][1,3,2]dithiazole-1-oxides **2**, which can then be further converted into novel cyclic sulfonimidamides **3** by imination/oxidation protocols (Scheme 1).^[12]

Preliminary studies had indicated that a combination of diaryl NH-sulfoximine **1a** and 2.0 equiv. of elemental sulfur led to heterocycle **2a** in 53% yield (as determined by NMR spectroscopy with CH₂Br₂ as internal standard) when a reagent mixture of 1.3 equiv. of K₂CO₃, 20 mol% of CuI, and 20 mol% of 2,2'-bipyridine (L¹) was applied in DMF at room temperature for 12 h (Table 1, entry 1). An inert atmosphere was not required. Encouraged by this result, a screening of the reaction conditions was initiated. The results are shown in Table 1. Changing the copper source from CuI to CuOAc or copper(I) thiophen-2-carboxylate (CuTc) proved unsuitable leading to **2a** in only trace quantities (Table 1, entries 2 and 3). While the

solvents THF and DCE were inferior to DMF, the use of DMSO raised the yield of **2a** to 65% (Table 1, entries 1 and 4–6). With K₃PO₄, Cs₂CO₃, or Na₂CO₃ as the base in DMSO, the yield of **2a** dropped as compared to K₂CO₃ (Table 1, entries 7–9). Using substituted bipyridines L² (4,4'-dimethyl-2,2'-bipyridine) and L³ (4,4'-di-*tert*-butyl-2,2'-bipyridine) instead of L¹ as ligand affected the yield of **2a** to a minor degree (Table 1, entries 10 and 11). Finally, the application of 1,10-phenanthroline (1,10-phen, L⁴) proved beneficial leading to **2a** in 86% yield. Isolation by column chromatography gave **2a** in 81% yield (Table 1, entry 12). Without a ligand or reducing the amount of CuI from 20 mol% to 10 mol% afforded **2a** in yields of only 5% and 53%, respectively (Table 1, entries 13 and 14). Without a metal salt, no reaction occurred (Table 1, entry 15).

With the optimized reaction conditions in hand, the substrate scope was investigated. The results are shown in Scheme 2. In general, reactions with *S,S*-diaryl sulfoximines showed a broad functional group tolerance, and substrates with various substituents on the two arenes including methyl, methoxy, halo, trifluoromethyl, and nitro groups reacted well, providing the corresponding products **2a–v** in yields ranging from 41–86%. Neither electronic factors of the

Table 1. Optimization of reaction conditions.^[a]

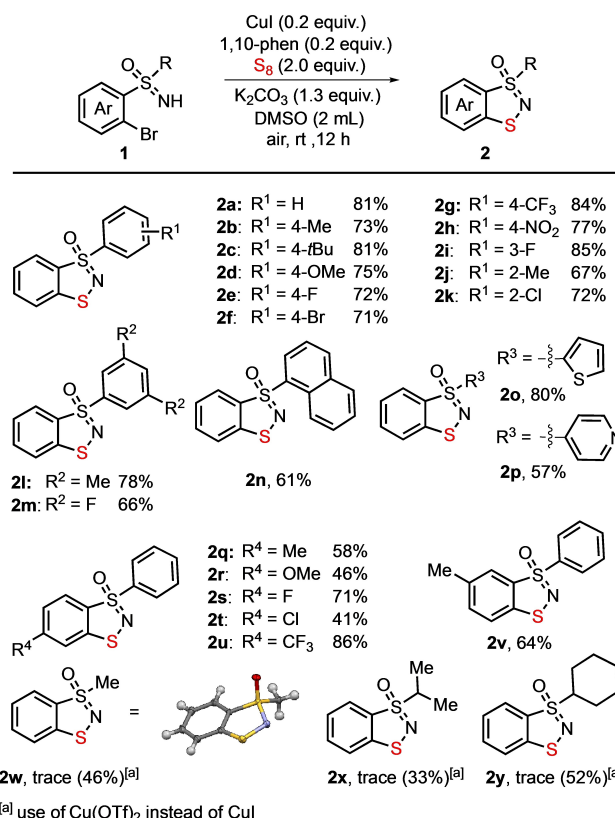
entry	Cu salt	ligand	base	solvent	yield ^[b]
1	CuI	L ¹	K ₂ CO ₃	DMF	53%
2	CuOAc	L ¹	K ₂ CO ₃	DMF	Trace
3	CuTc	L ¹	K ₂ CO ₃	DMF	Trace
4	CuI	L ¹	K ₂ CO ₃	THF	20%
5	CuI	L ¹	K ₂ CO ₃	DCE	Trace
6	CuI	L ¹	K ₂ CO ₃	DMSO	65%
7	CuI	L ¹	K ₃ PO ₄	DMSO	Trace
8	CuI	L ¹	Cs ₂ CO ₃	DMSO	Trace
9	CuI	L ¹	Na ₂ CO ₃	DMSO	46%
10	CuI	L ²	K ₂ CO ₃	DMSO	68%
11	CuI	L ³	K ₂ CO ₃	DMSO	63%
12	CuI	L ⁴	K ₂ CO ₃	DMSO	86% (81%) ^[c]
13	CuI	—	K ₂ CO ₃	DMSO	5%
14 ^[d]	CuI	L ⁴	K ₂ CO ₃	DMSO	53%
15	—	L ⁴	K ₂ CO ₃	DMSO	0%

^[a] Reaction conditions: **1a** (0.20 mmol), S₈ (12.8 mg, 0.40 mmol), base (0.26 mmol), Cu salt (0.04 mmol), and ligand (0.04 mmol) in the solvent (2.0 mL) at rt in air for 12 h.

^[b] Determined by ¹H NMR analysis of the crude reaction mixture using CH₂Br₂ as the internal standard.

^[c] In parentheses, yield of **2a** after isolation by column chromatography.

^[d] Use of 10 mol% of CuI.



Scheme 2. Substrate scope (0.2 mmol scale) and X-ray crystal structure of **2w**.^[14]

substituents nor their position on the arene had a clear effect. To highlight three particular aspects: First, also substrates with heteroarenes could be applied, as illustrated by the conversions of sulfoximines **1o** and **1p** with *S*-2-thienyl and *S*-4-pyridinyl substituents, respectively, which afforded **2o** and **2p** in 80% and 57% yield, respectively. Second, in the reaction of *S*-2-bromophenyl-*S*-2-chlorophenyl-sulfoximine (**1k**) a high halo selectivity was observed providing **2k** in 72% yield. Apparently, the bromo arene side reacted faster in the heterocycle formation leaving the C–Cl bond of the other arene intact. Third, as revealed in conversions of **1q–v** the reaction tolerated a wide range of substituents at the bromo-substituted arene, but the yields of the corresponding products (**2q–v**) varied significantly.

For example, while **1r** and **1t** bearing a methoxy and a chloro group at the *para* position gave **2r** and **2t** in only moderate yields (46% and 41%, respectively), analogously substituted **1s** and **1u** with a *para*-fluoro and a *para*-trifluoromethyl group led to **2s** and **2u** in higher yields of 71% and 86%, respectively. Noteworthy is also that in the reaction of dibromo derivative **1f** only cyclized **2f** and no other sulfide was observed (by LCMS analysis) revealing a high regioselectivity in the halo activation.

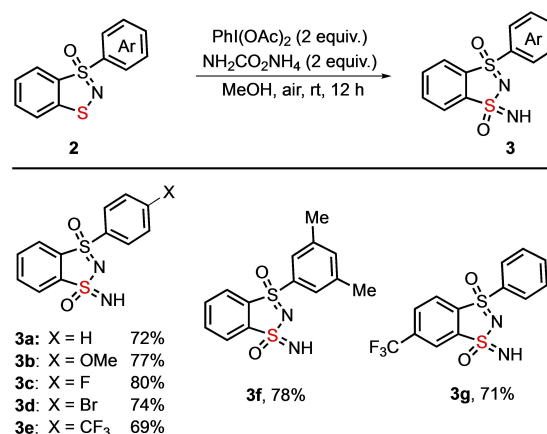
Reactions of *S*-alkyl-*S*-aryl sulfoximines proved more challenging due to a rapid decomposition of the starting materials under standard conditions. In this case, a change of the copper source offered a solution. Thus, applying Cu(OTf)₂ instead of CuI

gave 2-alkyl-substituted products **2w–y** in yields of 46% (**2w**), 33% (**2x**), and 52% (**2y**). The molecular structure of **2w** (Scheme 2) was confirmed by single-crystal X-ray analysis.^[14] Performing the reactions of **1a** and **1f** on a 4 mmol scale led to 0.73 g of **2a** and 1.04 g of **2f** corresponding to yields of 74% and 80%, respectively.

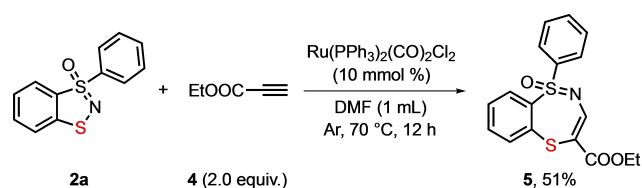
Imidation with or without subsequent oxidation of lower oxidation-state sulfur compounds in combination with a hypervalent iodine reagent and ammonium carbamate is a powerful strategy for the synthesis of sulfoximines and sulfonimidamides.^[15]

Applying this approach here on compounds **2** led to cyclic sulfonimidamides **3** with structures reminiscent to saccharin and analogous aza bioisosteres (Scheme 3).^[13,16] Thus, in a single step, products **3a–g** were obtained from the corresponding heterocycles **2** in yields ranging from 69% to 80% with d.r. values between 1:1 and 1:2. Significant substitution effects were not observed.

The synthetic potential of products **2** was further demonstrated by a ruthenium-catalyzed ring expansion reaction of **2a** with ethyl propiolate (**4**), which gave the seven-membered heterocycle **5** in 51% yield (Scheme 4).^[17,18]



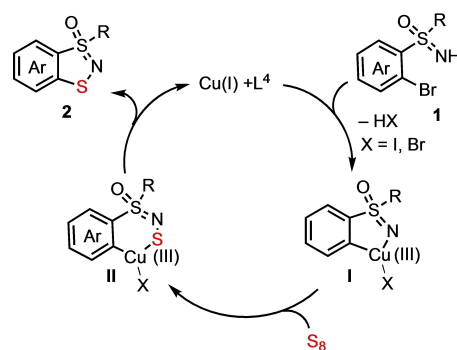
Scheme 3. Imination/oxidation reactions of **2** (0.2 mmol scale).



Scheme 4. Ring expansion of **2a** (0.1 mmol scale).

Based on the aforementioned experimental results and literature reports,^[19] we propose a mechanistic pathway for the formation of heterocycles **2** as depicted in Scheme 5.^[20] Starting from Cu(I), oxidative addition into the C–Br bond leads to a Cu(III) intermediate, which upon loss of HX provides copper-based heterocycle **I**. Sulfur insertion gives **II**. Finally, reductive elimination of **II** results in the formation of product **2** and regenerates the Cu(I) catalyst, which re-enters the catalytic cycle. Alternatively, a C–S bond could be formed first, which upon S–N coupling provides the product.^[19]

In summary, we developed a copper-catalyzed cross-coupling reactions of α -bromoaryl NH-sulfoximines with elemental sulfur leading to



Scheme 5. Proposed mechanism.

benzo[*d*][1,3,2]dithiazole-1-oxides. The transformations occur under mild reaction conditions (at room temperature in air), show good functional group tolerance, and lead to structurally interesting three-dimensional heterocycles. Through a combined imination/oxidation process the initial products can be converted into new heterocyclic sulfoximide derivatives. Alternatively, seven-membered heterocycles can be prepared by alkyne insertion into the S–N bond under ruthenium catalysis.

Experimental Section

General procedure for the preparation of cyclic sulfoximines derivatives. A mixture of sulfoximine **1** (0.20 mmol), S₈ (12.8 mg, 0.40 mmol, 2 equiv.), CuI (7.6 mg, 20 mol%), 1,10-phen (1,10-phenanthroline) (7.2 mg, 20 mol%), K₂CO₃ (35.9 mg, 0.26 mmol, 1.3 equiv.), and DMSO (2 mL) in a 10 mL sealed vial was stirred at room temperature for 12 h. Upon completion, ethyl acetate (10 mL) was added to dilute the mixture, which was then washed with an aqueous solution of ammonia (4 mL) and brine (10 mL). The organic layer was separated, dried over Mg₂SO₄ and evaporated under reduced pressure. The product was purified by flash column chromatography to give product **2**.

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