1,2,6-Thiadiazine 1-Oxides: Unsaturated Three-Dimensional S,N-Heterocycles from Sulfonimidamides

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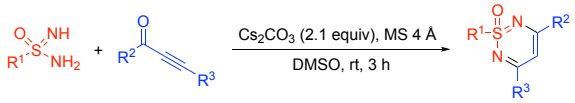
Supporting Information Placeholder



ABSTRACT: Unprecedented three-dimensional 1,2,6-thiadiazine 1-oxides have been prepared by an aza-*Michael*-addition/cyclization/condensation reaction sequence starting from sulfonimidamides and propargyl ketones. The products have been further functionalized by standard cross-coupling reactions, selective bromination of the heterocyclic ring and conversion into a *β*-hydroxy substituted derivative. A representative product was characterized by single crystal X-ray structure analysis.

Among sulfur-containing biologically active compounds, sulfonamides have hold a pole position for decades being present in a plethora of medicinal and agricultural relevant molecules.[1,2] In contrast, only marginal attention has been paid to their mono-aza analogues sulfonimidamides. Just recently a rising interest for using sulfonimidamides as bioisosters of sulfonamides in the design of bioactive compounds has been noted, both in academic research and industry.[3,4] One reason for this growing interest is rooted in their attractive and tunable physico- and biochemical properties, such as high metabolic and chemical stability and adjustable donor-acceptor attributes.[5] Moreover, introduction of the second nitrogen substituent offers the opportunity of potential chirality and possible modifications in defined three-dimensional directions. In this context, cyclic sulfonimidamides are particularly interesting, serving as building blocks for feasible three-dimensional heterocycles with two *endo*-cyclic nitrogens included in the heterocycle, or with one *endo*- and one *exo*-cyclic nitrogen substituent. Moreover, the construction of annulated ring systems is possible (Figure 1, top). Surprisingly, so far only a few cyclic sulfonimidamides have been reported.[6] For example, researcher at Hoffmann-La Roche investigated six- and seven-membered cyclic or bicyclic sulfonimidamides as BACE1 inhibitors for potential treatment of Alzheimer´s disease (Figure 1, A).[6g-j] BASF Agrochemicals developed cyclic sulfonimidamide derivatives of the marketed insecticide sulfoxaflor with the aim to improve physicochemical properties and reduce toxicity in a series of pesticides (Figure 1, B).[6k,l] Further cyclic sulfonimidamides have been reported as bioisosters of carboxylic acids[6c] or sultams[6d]

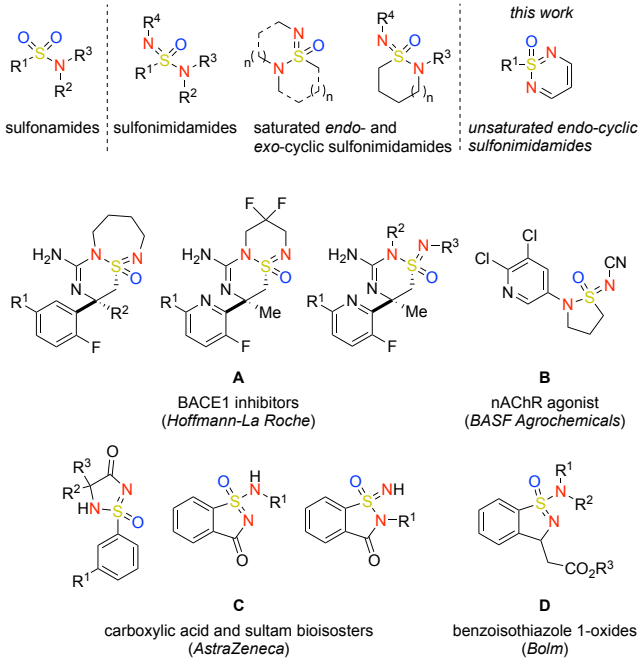
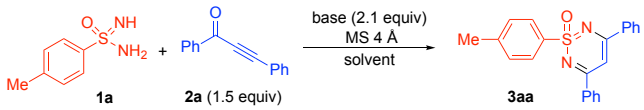


Figure 1. Structure of sulfonamides, sulfonimidamides, and sulfonimidamide-based heterocycles with relevance in medicinal chemistry and unprecedented unsaturated cyclic sulfonimidamides as approach of this work.

(Figure 1, C). Recently, our group reported benzoisothiazole derivatives as three-dimensional cyclic sulfonimidamides with an *exo*-cyclic nitrogen substituent (Figure 1, D).[6e] Surprisingly, to the best of our knowledge, no unsaturated cyclic sulfonimidamides have been reported to date. Thus, we felt challenged to contribute in this field by developing a synthetic method for these compounds. In particular, the syntheses of 1,2,6-thiadiazine 1-oxides was envisaged (Figure 1, top right corner).

Inspired by previously reported protocols from Williams and Cram[7] and an improved protocol by our group[8] for an aza-*Michael* addition/cyclisation/condensation reaction sequence between sulfoximines or sulfondiimides and propargyl ketones, we hypothesized that a complementary methodology could access the desired heterocycles.[9]

Table 1. Optimization of Reaction Conditions[a]



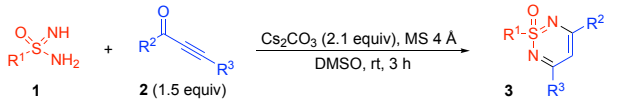
entry	base	solvent	temp (°C)	time (h)	yield (%)[b]
1	-	DMSO	rt	24	0
2	-	DMSO	80	24	0
3	NaH	DMSO	rt	24	47
4	NaH	DMSO	80	24	46
5	KOH	DMSO	rt	3	47
6	NEt_3	DMSO	rt	3	0
7	KO*t*-Bu	DMSO	rt	3	31
8	Na_2CO_3	DMSO	rt	24	0
9	K_2CO_3	DMSO	rt	3	62
10	Cs_2CO_3	DMSO	80	3	82
11	Cs_2CO_3	DMSO	rt	3	88
12[c]	Cs_2CO_3	DMSO	rt	3	45
13[d]	Cs_2CO_3	DMSO	rt	3	57
14[e]	Cs_2CO_3	DMSO	rt	3	75
15[f]	Cs_2CO_3	DMSO	rt	3	76
16	Cs_2CO_3	DMF	rt	3	76
17	Cs_2CO_3	DMA	rt	3	13
18	Cs_2CO_3	1,4-dioxane	rt	24	0
19	Cs_2CO_3	MeOH	rt	3	0

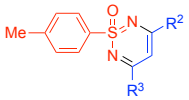
[a]Reaction conditions: **1a** (0.12 mmol), **2a** (1.5 equiv), base (2.1 equiv), solvent, c = 0.06 M, MS 4 Å (5 mg), under argon. [b]After purification by flash column chromatography. [c]Performed in air and without MS 4 Å. [d]Use of 1.0 equiv of Cs_2CO_3. [e]Use of 4.0 equiv of Cs_2CO_3. [f]Use of 3.0 equiv of **2a**.

For the optimization studies, 4-methylbenzenesulfonimidamide (**1a**) and 1,3-diphenylprop-2-yn-1-one (**2a**) were chosen as representative test substrates. The first reactions were performed in DMSO at room temperature and at 80 °C for 24 h without adding base. Under these conditions, no product formation was observed (Table 1, entries 1 and 2). Following reported conditions from Williams and Cram for the syntheses of unsaturated cyclic sulfoximines,[7] we tested sodium hydride as base, which furnished the product **3aa** in 47% yield (Table 1, entry 3). An increase of the temperature had no influence on the yield (Table 1, entry 4). After testing of different bases (Table 1, entries 5-9), we finally applied our previously reported conditions for the syntheses of unsaturated cyclic sulfoximines and sulfondiimides,[8] with Cs_2CO_3 as base at 80 °C. Now, product **3aa** was isolated in 82% yield (Table 1, entry 10). Pleasingly, elevated temperatures were not necessary for this transformation, and at ambient temperature **3aa** was obtained in a yield of 88% (Table 1, entry 11). At this stage, we also tested the reaction in air and with a reduced amount of Cs_2CO_3, but in both cases the yield dropped dramatically (Table 1, entries 12 and 13). Diminished yields were also obtained when the amount of propargyl ketone **2a** or the amount of the base were increased (Table 1, entries 14 and 15). After having identified Cs_2CO_3 as the most promising base, different solvents were screened (Table 1, entries 16-19). Taking into account the solubility of Cs_2CO_3, we primarily focused on employing polar solvents,[10] but none of the tested solvents gave superior yields compared with DMSO. In conclusion, Cs_2CO_3 (2.1 equiv) as base in DMSO as solvent at room temperature were identified as optimal reaction condition for this transformation (Table 1, entry 11).

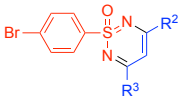
With these reaction conditions in hand, the scope with various sulfonimidamides **1** and propargyl ketones **2** was investigated (Scheme 1). First, the substituents on the propargyl ketone **2** were varied, while 4-methylbenzenesulfonimidamide (**1a**) was kept as reaction partner (Scheme 1, left). Diaryl-substituted propargyl ketones **2b-l** proved to be efficient reaction partners in this transformation, and all heterocyclic products **3ab-al**, with exception of the 4-nitrophenyl substituted example **3ak**, could be isolated in high to excellent yields. In general, less sterically hindered substrates gave higher yields, as exemplified by *ortho*-, *meta*- and *para*-methylphenyl substituted heterocycles **3ab-ad**. With bulky 2,4,6-trimethyl-substituted propargyl ketone **2t** as reaction partner the yield of **3at** was only 26%. Electronic effects had only a minor influence on the

Scheme 1. Substrate Scope with Respect to Sulfonimidamides 1 and Propargyl Ketones 2





3aa: $R^2 = R^3$ = Ph 88%
3ab: R^2 = *p*-Me-C_6H_4, R^3 = Ph 95%
3ac: R^2 = *m*-Me-C_6H_4, R^3 = Ph 80%
3ad: R^2 = *o*-Me-C_6H_4, R^3 = Ph 65%
3ae: R^2 = *p*-MeO-C_6H_4, R^3 = Ph 90%
3af: R^2 = *p*-Br-C_6H_4, R^3 = Ph 89%
3ag: R^2 = *p*-Cl-C_6H_4, R^3 = Ph 77%
3ah: R^2 = *o*-Cl-C_6H_4, R^3 = Ph 84%
3ai: R^2 = *p*-F-C_6H_4, R^3 = Ph 88%
3aj: R^2 = *p*-F_3C-C_6H_4, R^3 = Ph 90%
3ak: R^2 = *p*-O_2N-C_6H_4, R^3 = Ph 15%
3al: R^2 = 2-naphthyl, R^3 = Ph 95%
3am: R^2 = 2-thienyl, R^3 = Ph 86%
3an: R^2 = 2-furyl, R^3 = Ph 43%
3ao: R^2 = *t*-butyl, R^3 = Ph 65%
3ap: R^2 = Ph, R^3 = cyclopropyl 78%
3aq: R^2 = Ph, R^3 = H 13%
3ar: $R^2 = R^3$ = *p*-Br-C_6H_4 85%
3as: R^2 = Me, R^3 = Et 26%
3at: R^2 = *p*-MeO-C_6H_4, R^3 = 2,4,6-trimethylphenyl 26%
3au: R^2 = H, R^3 = Ph 0%



3ba: $R^2 = R^3$ = Ph 71%
3bg: R^2 = *p*-Cl-C_6H_4, R^3 = Ph 86%
3bp: R^2 = Ph, R^3 = cyclopropyl 90%

3ca: $R^2 = R^3$ = Ph 96%
3cg: R^2 = *p*-Cl-C_6H_4, R^3 = Ph 90%
3ch: R^2 = *o*-Cl-C_6H_4, R^3 = Ph 84%
3cp: R^2 = Ph, R^3 = cyclopropyl 74%

yields. Both substrates with electron-donating groups, such as *para*-methylphenyl-substituted propargyl ketone **2b**, and propargyl ketones with electron-withdrawing groups, such as *para*-fluorophenyl-substituted **2i** and *para*-trifluoromethylphenyl-substituted **2j** gave the corresponding heterocycles **3ab**, **3ai**, and **3aj** in high to excellent yields. Heteroaryl-substituted propargyl ketones **2am** and **2an** could also be engaged in this reaction, furnishing products **3am** and **3an** in 86% and 43%, respectively. Exemplified by the *para*-chlorophenyl substituted product **3ag**, a successful analytical separation of the enantiomers was carried out on chiral-phase HPLC (see Supporting Information). The reaction protocol was also compatible with aryl-alkyl substituted propargyl ketones. For example, heterocycles **3ao** and **3ap** were isolated in 65% and 78% yield, respectively. The same effects were observed for the heterocycles **3bp** and **3cp**, varying additionally on the sulfur-substituent. A representative example for a dialkyl-substituted heterocycle is **3as**. Terminal alkyne **2q** gave 5-unsubstituted heterocycle **3aq** in only 13% yield, and no product was observed with phenylpropargyl aldehyde (**2u**) as substrate. With the intention to further expand the reaction scope, R^1 on the sulfonimidamide **1** was varied next. In this sense 4-bromobenzenesulfonimidamide (**1b**) and methanesulfonimidamide (**1c**) were chosen as further reaction partners with differently substituted propargyl ketones **2**. To our delight, all of the tested substrates proved to be efficient reaction partners producing the corresponding heterocycles in high to excellent yields (Scheme 1, right). Finally, the reaction was performed on a 1 mmol scale for substrates **1a** and **2a**. Here, the heterocycle **3aa** was isolated in 78% yield.

Single-crystals of **3ao** suitable for X-ray diffraction measurement were obtained by slow evaporation of an ethylacetate solution at room temperature. The molecular structure of the *tert*-butyl substituted heterocycle **3ao** revealed a noncoplanar heterocyclic ring with an out-of-plane tilt of the sulfur atom by 0.54 Å (Figure, and Figure S2). According to the work of Lovering and others,[11] who stated that the three-dimensionality is one of the key success factors in drug design, these new heterocyclic sufonimidamide scaffolds could be also interesting from the medicinal and crop protection chemists' point of view.

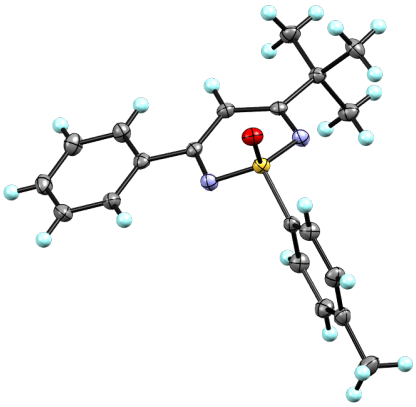


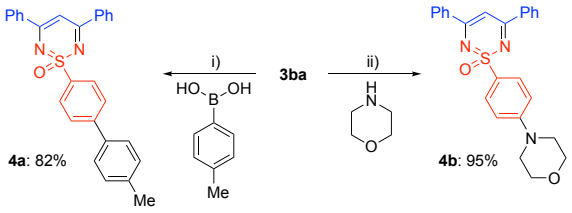
Figure 2. The ORTEP plot of the molecular structure of 3ao with the thermal displacement parameters at 50 % probability level.

To further illustrate the synthetic value of the prepared heterocycles, *para*-bromophenyl-substituted products **3ba** and **3af** have been subjected to two standard cross-coupling reactions (Scheme 2, a and b).[12] For the heterocycle with the *para*-bromophenyl moiety on the sulfur substituent, Suzuki–Miyaura cross-coupling with 4-tolylboronic acid, 2 mol% of $Pd(PPh_3)_4$ as catalyst and K_2CO_3 as base in refluxing aqueous acetonitrile furnished **4a** in 82% yield. Applying a Buchwald–Hartwig-type amination on the same heterocycle with morpholine as coupling partner gave product **4b** in a yield of 95% (Scheme 2, a). Employing the same conditions for Suzuki–Miyaura and Buchwald–Hartwig-type reactions to heterocycle **3af** resulted in two further cross-coupled products **5a** and **5b** in 95% and 77%, respectively (Scheme 2, b).

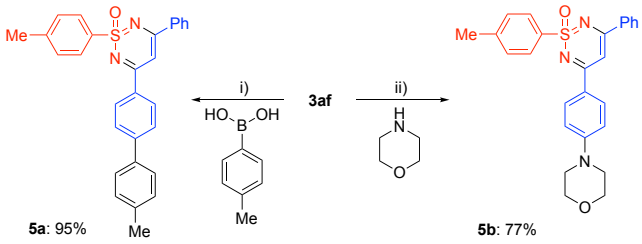
A possible derivatization by modifying the substituent on the sulfur atom was demonstrated by deprotonation of the *S*-methyl group with *n*-BuLi and subsequent nucleophilic addition to benzophenone, resulting in *β*-hydroxy-substituted derivative **6** in 80% yield (Scheme 2, c).[13]

Scheme 2. Functionalization of Selected Products

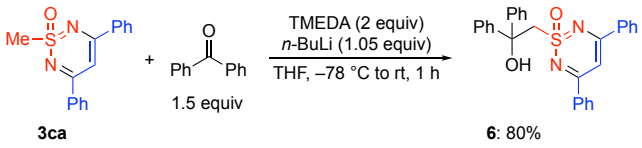
a) Cross-coupling reactions of **3ba**[a]



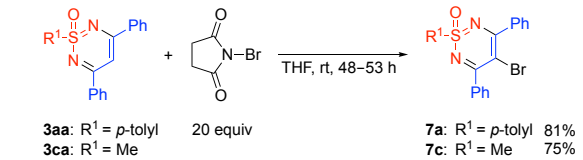
b) Cross-coupling reactions of **3af**[a]



c) Functionalization of the *S*-methyl group



d) Bromination of the heterocyclic ring



[a]Reaction conditions: i) 4-tolylboronic acid (1.2 equiv), $Pd(PPh_3)_4$ (0.02 equiv), K_2CO_3 (1.4 equiv), MeCN:H_2O 3:1, 12 h, reflux, under argon. ii) morpholine (1.2 equiv), $Pd(OAc)_2$ (0.02 equiv), *rac*-BINAP (0.03 equiv), Cs_2CO_3 (1.4 equiv), toluene, reflux, 12 h, under argon.

At this stage, only position 4 in the newly prepared 3,5-disubstituted 1,2,6-thiadiazine 1-oxides remained untouched for possible substituents. With the intention to further functionalize this position, the introduction of a bromine substituent was envisaged, providing a good basis for possible subsequent modifications. Heterocycles **3aa** and **3ca** were therefore treated with an excess of *N*-bromosuccinimide in THF for 48 h and 53 h at room temperature. Hence, C4-brominated heterocycles **7a** and **7c** could be isolated in yields of 81% and 75%, respectively (Scheme 2, d).

In summary, unprecedented three-dimensional unsaturated cyclic sulfonimidamides have been prepared in good to excellent yields. The molecular structure of a representative product was confirmed by single-crystal X-ray diffraction. Product functionalizations were demonstrated by standard cross-coupling reactions, bromination of the heterocyclic ring in addition to functionalization of the *endo*-cyclic sulfur substituent.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, characterization data, NMR spectra for new compounds X-ray crystallography data and CIF files (PDF)

Accession Codes

CCDC 1985011 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.

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Notes

The authors declare no competing financial interest.

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