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Halocyclizations of Unsaturated Sulfoximines

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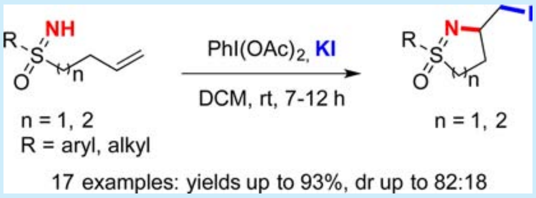
Supporting Information

ABSTRACT: A method for halocyclizations of *S*-alkenylsulfoximines is reported. When unsaturated *NH*-sulfoximines are treated with a combination of iodobenzene diacetate and potassium iodide, a transformation to the corresponding five- and six-membered cyclic products occurs providing *S*-oxides of dihydro isothiazoles and tetrahydro-1,2-thiazines, respectively, in moderate to high yields with good diastereoselectivities and excellent regioselectivities.

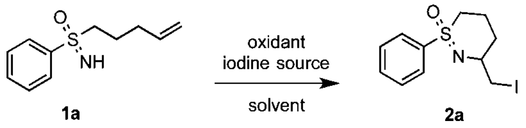


Because of their unique structure and bioactivity, sulfoximines have found broad application in organic synthesis, medicinal chemistry, and agrochemistry.[1] In the past decades, the development of new methods for the construction of sulfoximidoyl moieties and their incorporation into organic molecules under mild conditions received continuous attention.[2] In particular, catalytic transformations of sulfoximines have led to numerous potentially biologically active target molecules.[3] Among those, cyclic compounds with sulfoximidoyl-type core structures proved attractive. Although various methods for their preparation have already been developed, new approaches allowing the introduction of a broader variety of functional groups are of interest. A few known strategies are noteworthy. For example, Harmata and co-workers reported the synthesis of benzothiazine *S*-oxides through palladium-catalyzed coupling reactions,[4] and we prepared related compounds by rhodium-catalyzed *ortho* C−H functionalization of *S*-arylsulfoximines.[5] Applying RCM and RCEYM to sulfoximines with two adjacent unsaturated side chains resulted in the formation of partially hydrogenated cyclic derivatives.[6] Recently, a metal-free synthesis of 1,2-thiazines starting from sulfoximines was introduced.[7]

In the past decades, various approaches for haloaminations of C−C double bonds have been reported.[8] Most of them were copper-catalyzed radical cyclizations[9] and Lewis acid promoted[10] or palladium-catalyzed ring closures.[11] Alternatively, hypervalent iodine reagents have been applied allowing metal-free aminoacetoxylations,[12] intramolecular amidohydroxylations,[13] and haloaminations.[14] Inspired by these findings, we envisaged that combining such synthetically attractive olefin difunctionalizations, in particular the previously mentioned iodine-based metal-free ones, with sulfoximine chemistry would be useful in the preparation of cyclic compounds with sulfoximidoyl core structures such as tetrahydro-1,2-thiazine 1-oxides (**2**) and dihydroisothiazole oxides (**4**). The success of this approach is illustrated here.

For the initial phase of the project, *S*-(pent-4-en-1-yl)-*S*-phenylsulfoximine (**1a**) was selected as the model compound. The conceived intramolecular iodoamination was first attempted with 2 equiv of potassium iodide and 1.2 equiv of 2-iodoxybenzoic acid (IBX) in chloroform. To our delight, the desired cyclic product, 3-iodomethyl-substituted 3,4,5,6-tetrahydro-1-phenyl-1λ^4-1,2-thiazine 1-oxide (**2a**), was obtained in 55% yield (Table 1, entry 1). With the aim of increasing the yield of **2a**, two other oxidants were applied next (Table 1, entries 2 and 3). Compared to the initial experiment with IBX, the use of DMP (Dess−Martin periodinane) led to a slightly diminished yield of 49% for **2a** (Table 1, entry 2). However,

Table 1. Optimization of the Reaction Conditions[a]



entry	oxidant (equiv)	iodide (equiv)	solvent	yield (%)	dr[b]
1	IBX (1.2)	KI (2.0)	$CHCl_3$	55	70:30
2	DMP (1.2)	KI (2.0)	$CHCl_3$	49	65:35
3	PIDA (1.2)	KI (2.0)	$CHCl_3$	71	66:34
4	PIDA (1.2)	KI (2.0)	THF	59	59:41
5	PIDA (1.2)	KI (2.0)	acetone	67	70:30
6	PIDA (1.2)	KI (2.0)	DMF	n.r.[d]	
7	PIDA (1.2)	KI (2.0)	DCM	76	63:37
8	PIDA (1.2)	n-Bu_4NI (2.0)	DCM	n.r.[d]	
9	PIDA (1.2)	CuI (2.0)	DCM	19	52:48
10	PIDA (1.2)	I_2 (2.0)	DCM	68	67:32
11	PIDA (1.2)	KI (1.5)	DCM	75	62:38
12	PIDA (1.2)	KI (5.0)	DCM	73	67:33
13	PIDA (1.5)	KI (2.0)	DCM	82	75:25
14	PIDA (2.0)	KI (2.0)	DCM	67	78:22
15[c]	PIDA (1.5)	KI (2.0)	DCM	92	77:23
16[c]	PIDA (1.5)	KI (1.5)	DCM	85	69:31
17[c]	PIDA (1.5)	KI (1.2)	DCM	77	75:25

[a] Reaction conditions: sulfoximine **1a** (0.2 mmol), oxidant (see entries), iodine source (see entries) and solvent (2 mL) at room temperature for 30 h, sealed tube. [b] Determined by ^1H NMR analysis. [c] Reaction time of 12 h. [d] n.r. = no reaction.

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with iodobenzene diacetate (PIDA) as oxidant, the halocyclization of **1a** proceeded better, and product **2a** was isolated in 71% yield (Table 1, entry 3). Thus, PIDA was utilized in all subsequent reactions.

Testing the influence of the solvent (Table 1, entries 4–7) revealed that nonhalogenated solvents such as THF and acetone resulted in somewhat lower yields. In DMF, **2a** was not formed at all. The highest yield (76%) was achieved when the cyclization was performed in DCM, and hence, this solvent was used for the following optimization attempts.

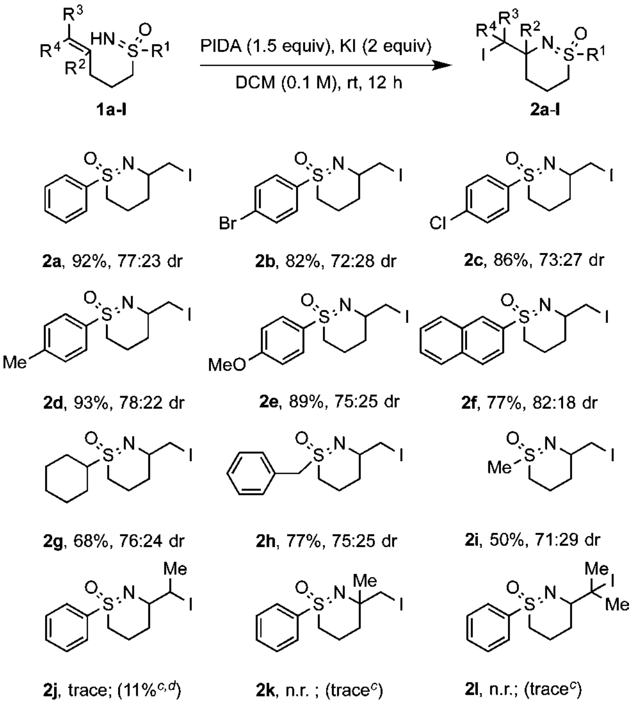
Next, the role of the iodide source was examined (Table 1, entries 8–10). Tetrabutylammonium iodide did not afford product **2a**. With CuI, the yield of **2a** was only 19%. Employing elemental iodine led to a slightly lower yield of **2a** (68%) compared to the reaction with KI. Subsequently, the quantities of KI and the oxidant PIDA were altered (Table 1, entries 11–14). Decreasing the amount of KI from 2.0 to 1.5 equiv or raising it to 5.0 equiv showed no beneficial effect. An increase in the amount of PIDA to 1.5 equiv resulted in an improved yield of **2a** (82%). However, raising it further to 2.0 equiv lowered the yield (Table 1, entry 14), most likely due to the instability of the product toward the excess of oxidant in the reaction medium. Monitoring the progress of the reaction by TLC and ^{1}H NMR revealed an optimal time of 12 h, resulting in a yield of 92% for **2a** (Table 1, entry 15). Two additional experiments showed that with less than 2.0 equiv (1.5 or 1.2 equiv) of KI the yield of **2a** dropped to 85% and 77%, respectively (Table 1, entries 16 and 17).

Under all conditions (Table 1), the diastereomeric ratio (dr) of **2a** remained essentially unaffected, averaging about 70:30 (with variations between 52:48 to 78:22). In each case, **2a** (the *exo* product) was the sole product, probably due to its kinetically favored formation.[12] The corresponding *endo* product was never observed.

With the optimized conditions in hand, the substrate scope was investigated (Scheme 1).[15] When *S*-(pent-4-en-1-yl)-*S*-arylsulfoximines **1a–f** were cyclized, the corresponding products **2a–f** were obtained in good to high yields (77% to 93%) and dr (72:28 to 82:18). The presence of both electron-donating and -withdrawing substituents on the *S*-aryl was equally tolerated. The highest dr of 82:18 was observed in the reaction with *S*-(2-naphthyl) derivative **1f**, which gave **2f** in 77% yield. Application of *S*-alkenyl-*S*-alkylsulfoximines **1g–i** afforded the respective products in moderate to good yields (50–77%) and dr (up to 76:24). Attempts to cyclize substrates **1j–l** with trisubstituted double bonds remained unsuccessful under the standard reaction conditions, which was most likely due to steric effects induced by the additional methyl substituents. Increasing the reaction temperature to 50 °C raised the yield of **2j** to 11%.

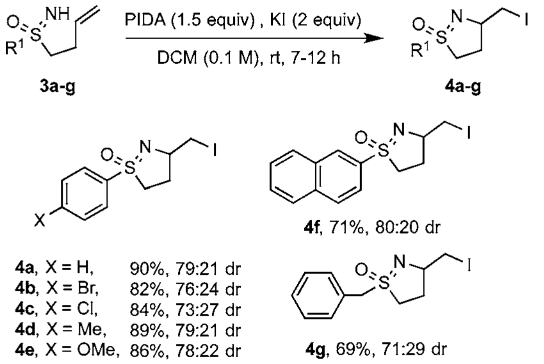
Next, we wondered about the potential of the halocyclization method for the synthesis of the analogous five-membered heterocycles **4**. Such 3-substituted 3*H*-1λ^4-4,5-dihydroisothiazole 1-oxides required *S*-(but-3-en-1-yl)sulfoximines as starting materials,[15] and accordingly, **3a–g** were prepared and subjected to the reaction conditions developed before (Scheme 2). To our delight, products **4a–g** were obtained in high yields (69–90%) and good dr (71:29–80:20). In general, the results in terms of yield and stereoselectivity were similar to those of the preparation of the six-membered analogues **2**. Electronic effects induced by substituents at the *S*-arenes played only a minor role (e.g., see compounds **4a–e**). In addition, *S*-naphthyl- and *S*-benzyl-substituted products **4f** and **4g** were obtained in good yields with dr values at almost the same selectivity level.

Scheme 1. Synthesis of Tetrahydro-1,2-thiazine 1-Oxides[a,b]



[a]All reactions performed with sulfoximines **1** on a 0.30 mmol scale in sealed tubes. [b]The dr was determined by ^{1}H NMR analysis. [c]Performed at 50 °C for 7 h. [d]Only a single diastereomer was detected.

Scheme 2. Synthesis of Dihydrooisothiazole Oxides[a,b]

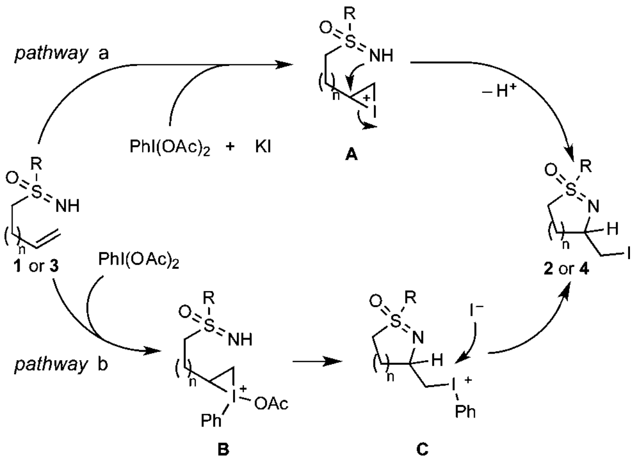


[a]All reactions performed with sulfoximines **3** on a scale of 0.30 mmol scale in sealed tubes. [b]The dr was determined by ^{1}H NMR analysis.

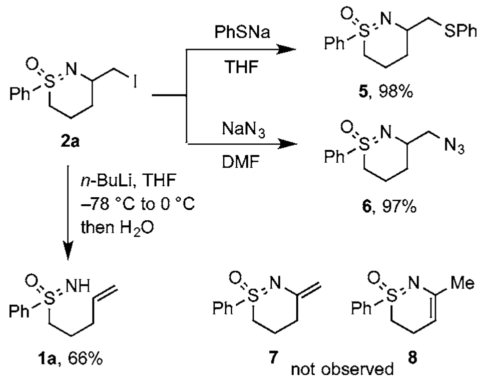
On the basis of previous reports,[12,16] two plausible pathways are possible (Scheme 3). In pathway a, the substrate forms an iodonium species **A** by electrophilic addition of I$^+$, which is generated by oxidation of KI with PIDA. Subsequently, **A** cyclizes by intramolecular nucleophilic attack of the sulfoximidoyl nitrogen leading to the desired product (**2** or **4**). Alternatively (pathway b), the olefinic part of the substrate interacts with the hypervalent iodine reagent generating iodonium ion **B**. Then, **B** is intramolecularly attacked by the sulfoximidoyl nitrogen to form species **C**, which upon reaction with I$^-$ leads to the final product (**2** or **4**).

To demonstrate the synthetic utility of the products, a few derivatizations were attempted (Scheme 4). First, **2a** was treated with sodium thiophenolate to afford thioether **5** in 98%

Scheme 3. Plausible Mechanistic Pathways



Scheme 4. Transformations of 2a



yield. Changing the nucleophile to sodium azide gave **6** in 97% yield. To our surprise, **2a** underwent a ring-cleavage reaction when subjected to *n*-BuLi in THF at low temperature. After hydrolytic workup, **1a** was obtained in 66% yield. None of the expected olefinic products **7** and **8** were observed. Apparently, **2a** had not reacted by the hypothesized deprotonation followed by loss of iodide. Instead, an iodine/lithium exchange had occurred forming a new primary lithium reagent, which stabilized itself by ring opening through *β*-elimination. The resulting anion (formally a *N*Li-sulfoximine) was then hydrolyzed upon workup to give the observed product **1a**.

In summary, we found a new protocol for the generation of *S*-oxides of dihydroisothiazoles and tetrahydro-1,2-thiazines through halocyclization. When treated with a combination of iodobenzene diacetate and potassium iodide, easily accessible *NH*-*S*-alkenylsulfoximines undergo a smooth ring-closure reaction to afford the corresponding five- and six-membered heterocycles in high yields. The reactions proceed with excellent regioselectivity providing the *exo* products with good diastereoselectivity. Nucleophilic substitutions allow straightforward product modifications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00958.

General experimental procedure and characterization details (PDF)

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Notes

The authors declare no competing financial interest.

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