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Author(s): Schöbel, Jan-Hendrik; Elbers, Philipp; Truong, Khai-Nghi; Rissanen, Kari; Bolm, Carsten

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1,2-Benzothiazine Derivatives from Sulfonimidamides by Metal-Catalyzed Annulation Reactions in Solution and under Solvent-Free Mechanochemical Conditions

Jan-Hendrik Schöbel,[a] Philipp Elbers,[a] Khai-Nghi Truong,[b] Kari Rissanen,[b] and Carsten Bolm[a,*]

[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, D-52074 Aachen, Germany
Phone: (+49)-241-8094675;
E-mail: carsten.bolm@oc.rwth-aachen.de

[b] Department of Chemistry, University of Jyvaskyla, P.O. Box 35, Survontie 9B, FI-40014 Jyväskylä, Finland

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Abstract: Three-dimensional aza-analogues of 1,2-benzothiazine 1,1-dioxides have been prepared from sulfonimidamides. Two different protocols are presented. The first is a rhodium-catalyzed annulation reaction with α-sulfonyloxyketones leading to 4-unsubstituted benzothiazine derivatives. By selective bromination with NBS the heterocyclic ring can further be functionalized. In the second approach, an iridium catalyst is applied under solvent-free mechanochemical conditions providing products with 3,4-disubstituted thiazine rings from diazoketo esters and diazoketo sulfones.

Keywords: 1,2-benzothiazine; C–H activation; iridium catalysis; mechanochemistry; rhodium catalysis; sulfonimidamide

1,2-Benzothiazines are well-recognized compounds in medicinal chemistry, and many derivatives have been explored as target structures in drug development.[1] Among them, 1,2-benzothiazine 1,1-dioxides or so-called sultams (Scheme 1, **A**) hold an exceptional position due to their excellent pharmacological profile. For example, Piroxicam (Scheme 1, **A1**)[2] has been the first example of the oxicam family functioning as a nonsteroidal anti-inflammatory drug (NSAID).[3] Structural modifications of this cyclic sulfonamide are under constant development and have deepened the interest in this compound class. For example, pyrazole-fused derivatives **A2** (Scheme 1) have shown promising antibacterial, antiviral, and antioxidant properties.[4] In addition, 1,2-benzothiazine 1,1-dioxides with antimicrobial activities have been reported (Scheme 1, **A3**).[5]

Following the idea of bioisosteric replacement as a key concept in medicinal chemistry,[6] analogues benzo-fused sulfoximines **B** (Scheme 1) have caught the attention of the community[7,8] leading to the development of a range of protocols for their synthesis.[9] Among them, the most common and straightforward approaches involve metal-catalyzed C–H bond activation/cyclization sequences. More recently, benzo-fused sulfondiimines **C** have been described (Scheme 1).[10] With the vision and intention to extend the chemistry of such hexavalent sulfur compounds, we now wondered about cyclic sulfonimidamides (Scheme 1, bottom), which, to the best of our knowledge, have yet remained unstudied.[11,12] Considering that such 1-amino-1,2-benzothiazine 1-oxides formally represent bioisosteric monoaza analogues of benzo-fused sulfonamides **A**,[6,7] their absence in our current chemical space is surprising. Here, we report two synthetic strategies towards such molecules involving rhodium- and iridium-catalyzed annulation reactions as key C–C and C–N bond forming processes (Scheme 1, bottom).

The first approach for synthesizing 1-amino-1,2-benzothiazine 1-oxides started from a protocol for a rhodium catalysis leading to sulfoximines introduced by Glorius.[9i] In a subsequent study, we had demon-

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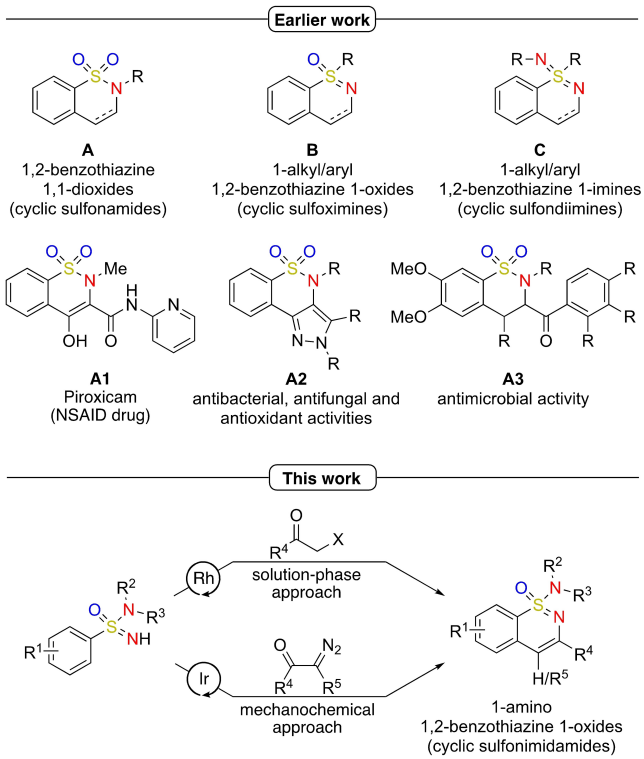

Scheme 1. (Top) various types of 1,2-benzothiazines **A**–**C** and selected examples of bioactive benzo-fused sultams **A1**–**A3**; (bottom) synthetic strategy towards development of various 1-amino-1,2-benzothiazine 1-oxides described here.

strated its applicability in accessing 4-unsubstituted 1,2-benzothiazines.[10] Considering observations leading to these previous achievements, we selected 1-(*S*-phenylsulfonimidoyl)piperidine (**1a**) and α-substituted (pseudo)halo ketones **2a**–**5a** as starting materials for optimizing the reaction conditions for the envisaged 1-amino-1,2-benzothiazine 1-oxide syntheses. The results are summarized in Table 1.

To our delight, already the first experiments led to success. Reacting sulfonimidamide **1a** with α-tosyl substituted acetophenone **2a** in the presence of $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5 mol%), NaOAc (1.4 equiv.), and $Cu(OAc)_2$ (10 mol%) in MeOH at 40 °C for 12 h gave 1,2-benzothiazine **6aa** in 68% yield (Table 1, entry 1). Applying mesyl-substituted **3a** instead of **2a** in the reaction with **1a** improved the yield of **6aa** to 91% (Table 1, entry 2). Using less reactive α-chloro and α-bromo acetophenones **4a** and **5a**, respectively, proved inefficient (Table 1, entries 3 and 4). Increasing the reaction temperature from 40 °C to 60 °C reduced the yield of **6aa** to 65% (Table 1, entry 5). A screening of solvents (Table 1, entries 6–10) revealed that no product was formed in DCM, 1,2-DCE, and toluene. Methanol could only be substituted by ethanol, which gave **6aa** in 44% yield. As these results in solution were not satisfactory, we wondered if the reaction could also be performed under mechanochemical solvent-free conditions.[13,14] Hence, all components required for the catalysis were mixed in a ball mill reactor for 6 h at 25 Hz, and starting from sulfonimidamide **1a** and α-sulfonyloxyketone **3a** as substrates, **6aa** was obtained in 22% yield (Table 1, entry 11). Besides the targeted product, phenacyl-acetate was isolated in 56% yield. Thus, in general such solvent-free catalyses were possible, but further optimization appeared necessary for improving the reaction outcome. Under standard conditions, $[Cp^*Rh(MeCN)_3][SbF_6]_2$ proved catalytically superior over other metal complexes as shown by competing experiments with $[Rh(OAc)_2]_2$, $[Cp^*IrCl_2]_2$, $[Cp^*Co(CO)I_2]$, $[Cp^*RhCl_2]_2$ and $[Cp^*Rh(OAc)_2]_2$ (Table 1, entries 12–16). While the first three complexes were inactive leading to no product at all, the latter two afforded **6aa** in 76% and 73% yield, respectively, which had to be compared to a yield of 91% with the original catalyst. The need of the metal catalysis was proven by a test reaction in its absence, which did not provide any product (Table 1, entry 17).

Using the optimized conditions (Table 1, entry 2), the substrate scope was explored (Scheme 2). First, sulfonimidamides **1** with various aryl moieties were applied, keeping α-mesyl-substituted acetophenone **3a** as constant reaction partner. From these experiments, 1,2-benzothiazines **6aa**–**fa** were obtained in yields ranging from 55% to 91%. At the upper end, a yield of 89% was achieved in the formation of *para*-tolyl-substituted 1,2-benzothiazine **6ba**, which compared well to the previously observed 91% yield for **6aa**. A lower yield of 55% was obtained for **6ca**, bearing a *tert*-butyl group on the phenyl ring. Almost the same result (56% yield) was found for nitro-containing **6da**, which indicated a minor importance of electronic factors.

The yield was not significantly affected by *meta*- or *ortho*-substitution on the aryl moiety as revealed by the fact that the two chloro-substituted products **6ea** and **6fa** were obtained in very similar yields (77% for **6ea** and 72% for **6fa**). Noteworthy, only a single regioisomer was observed in the generation of **6ea** corresponding to the heterocycle formation at the less hindered site. Analogous results were obtained when sulfonimidamides **1a**, **1g**, and **1h** were reacted with *para*-bromo substituted acetophenone derivative **3b** which led to **6ab**, **6gb**, and **6hb** in yields of 90%, 85%, and 67% respectively. Applying sulfonimidamide **1i** bearing a dimethylamino substituent instead of the piperidinyl group as in **1a** in the reaction with **3a** afforded product **6ia** in 72% yield. Unsuitable were sulfonimidamides with free or mono-silylated amino groups as represented by **1j** and **1k**, respectively, with which the targeted products **6ja** and **6ka** could not be obtained.

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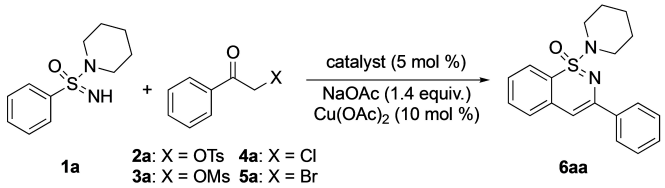
Table 1. Optimization of the reaction conditions for the synthesis of 1-amino-1,2-benzothiazine 1-oxide **6 aa**.[a]



entry	solvent	catalyst	ketone **2**	T (°C)	t (h)	yield (%)
1	MeOH	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	**2 a**	40	12	68
2	MeOH	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	**3 a**	40	12	91[b]
3	MeOH	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	**4 a**	40	12	0
4	MeOH	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	**5 a**	40	12	7
5	MeOH	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	**3 a**	60	12	65[b]
6	MeCN	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	**3 a**	40	12	0
7	DCM	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	**3 a**	40	12	0
8	1,2-DCE	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	**3 a**	40	12	0
9	toluene	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	**3 a**	40	12	0
10	EtOH	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	**3 a**	40	12	44
11[c]	–	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	**3 a**	–	6	22[b,d]
12	MeOH	$[Cp^*RhCl_2]_2$	**3 a**	40	12	76
13	MeOH	$[Rh(OAc)_2]_2$	**3 a**	40	24	0
14	MeOH	$[Cp^*Rh(OAc)_2]_2$	**3 a**	40	12	73
15	MeOH	$[Cp^*IrCl_2]_2$	**3 a**	40	24	0
16	MeOH	$[Cp^*Co(CO)I_2]$	**3 a**	40	24	0
17	MeOH	–	**3 a**	40	24	0

[a] Reaction conditions: **1 a** (0.15 mmol), **2 a**, **3 a**, **4 a**, or **5 a** (0.21 mmol), NaOAc (1.4 equiv.), solvent (3 mL), under argon. Yields determined by ^{1}H NMR spectroscopy (internal standard: anisole), except noted otherwise.
[b] After purification by flash column chromatography.
[c] Reaction performed in a ball mill reactor (25 Hz).
[d] Isolation of 56% of phenacylacetate as by-product.

Single crystal X-ray diffraction analysis confirmed the molecular structures of 1,2-benzothiazine **6 da** and **6 fa**.[15] A closer look to the binding geometry revealed the presence of non-coplanar annulated ring systems in both molecules thereby representing three-dimensional heterocycles with potential relevance of medicinal chemistry (Scheme 2 and Figures S2–S5).[16]

All products presented in Scheme 2 were unsubstituted at position 4 of the thiazine ring. With the goal to expand the substrate scope by preparing 3,4-disubstituted 1,2-benzothiazine derivatives, the reaction between sulfonimidamide **1 a** and α,α-disubstituted sulfonyloxyketones **7 a** was tested. To our disappointment, no reaction occurred (Scheme 3, top). Thus, an alternative strategy was required, and a short screening of standard scaffold modifications revealed that **6 aa** underwent a highly efficient site-selective bromination with NBS/AIBN in CCl_4 at elevated temperature to give 4-bromo-3-phenyl disubstituted **9** in 98% yield. Although still subject for being demonstrated in future work, we see in product **9** a valuable and versatile building block for further functionalizations by cross-couplings.[17]

Until now, all products had an aromatic group at position 3 of the heterocycle, and position 4 was either unsubstituted or brominated. In order to expand the structural portfolio, another synthetic approach towards 1,2-benzothiazines with fully substituted thiazine rings was investigated next. In the context of sulfoximine and sulfondiimine chemistry,[9b,10] we had developed rhodium catalyses for C–H bond functionalizations with 2-diazo-3-oxo esters **10** as coupling partners providing heterocyclic products in high yields. In light of these results, analogous reactions of **10** with sulfonimidamides **1** were expected to lead to 1,2-benzothiazines **11** characterized by structural variability at position 3 and carboxyl or sulfonyl groups at position 4 of the heterocycle. Table 2 summarizes the process optimization with sulfonimidamide **1 a** and ethyl 2-diazo-3-oxobutanoate (**10 a**) as reaction partners.

To our disappointment, the previously optimized reaction conditions with a combination of $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5 mol%) and NaOAc (1.2 equiv.) in MeCN at 100 °C proved ineffective here (Table 2, entry 1). Varying the reaction temperature was beneficial but even then, the maximal yield of product **11 aa**

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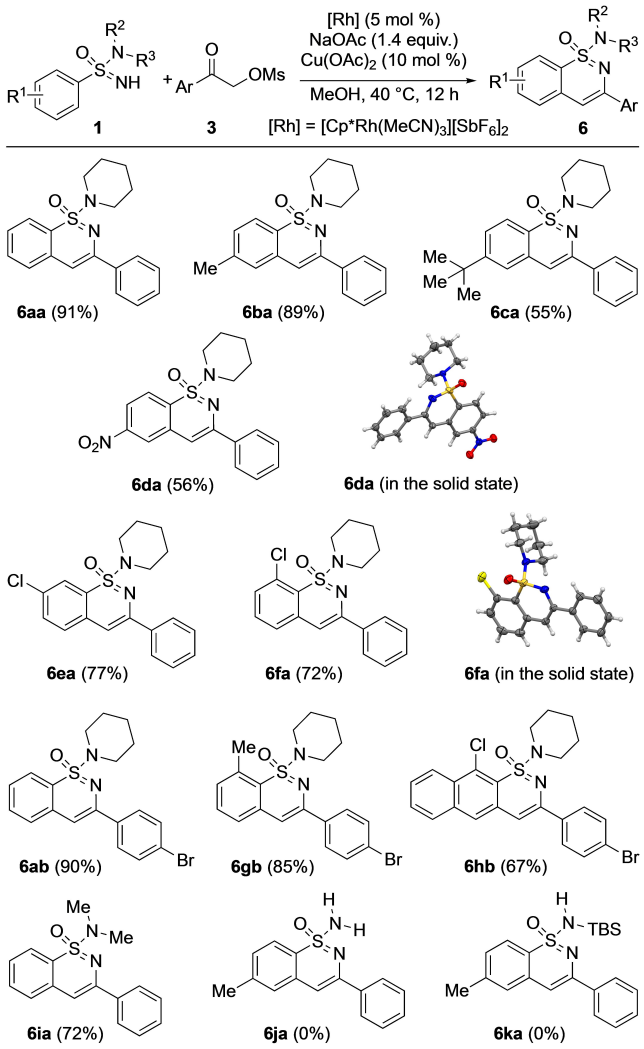
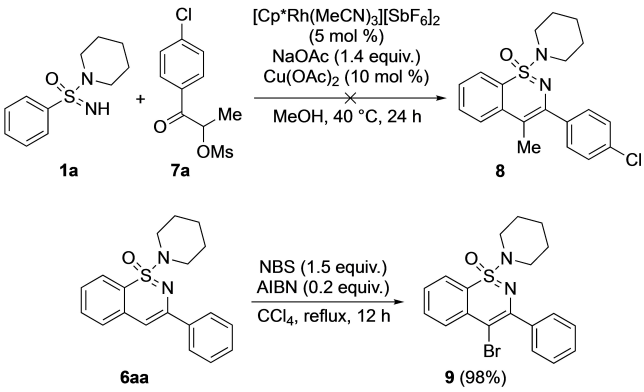


Scheme 2. Substrate scope for the formation of **6** starting from of sulfonimidamides **1** and ketones **3** and molecular structure of **6 da** and **6 fa** in the solid state as revealed by X-ray crystal structure analysis.



Scheme 3. (Top) attempted synthesis of 3,4-disubstituted heterocycle **8**; (bottom) bromination of **6 aa**.

remained low (up to 26%; Table 2, entries 2 and 3). Performing the catalysis in 2,2,2-trifluoroethanol (TFE) instead of MeCN had a positive effect on the yield of **11 aa**, but still the results remained unsatisfying (up to 36%; Table 2, entries 4–6). Without the rhodium complex, no product was formed (Table 2, entry 7).[18]

Assuming that elevated temperatures were problematic due to substrate decomposition, an alternative protocol was searched for. In this context, the findings by Pawar, who was able to couple sulfoximines with diazoketones under iridium catalysis at room temperature, caught our attention.[9a] Transferring these conditions with $[Cp^*IrCl_2]_2$ (2.5 mol %) as catalyst and PivOH (2.0 equiv.) as additive in TFE to the reaction of sulfonimidamide **1 a** and diazoketone **10 a** provided product **11 aa** in 34% yield (Table 2, entry 8). Using hexafluoro-2-propanol (HFIP) instead of TFE as solvent, improved the yield of **11 aa** to 52% (Table 2, entry 10).[19] A subsequent screening of other solvents confirmed the pronounced influence of the reaction media. To our great surprise, we had to note that in none of the tested systems (1,2-DCE, DCM, MeOH, EtOH, MeCN, and toluene), product **11 aa** was formed (Table 2, entries 11–16). A control experiment ensured that also in HFIP the presence of the metal complex was essential for the product formation (Table 2, entry 17).

As a consequence of these disappointing results in solution, the strategy was changed and we studied the aforementioned iridium catalysis with **1 a** and **10 a** as substrates under solvent-free conditions in a ball mill reactor.[20,21] Already the first attempt was successful. Milling **1 a** and **10 a** in the presence of 2.5 mol % of $[Cp^*IrCl_2]_2$ and 2 equiv. of PivOH for 1 h at a frequency of 25 Hz gave **11 aa** in 35% yield (Table 2, entry 18). With sand as additive, the product yield increased to 63% yield (Table 2, entry 19), and finally, **11 aa** was formed in 99% when silica was used as additive (Table 2, entry 20). Isolation by column chromatography gave **11 aa** in 97% yield. To answer the question whether silica itself was involved in the reaction or acted as grinding auxiliary, a control experiment was performed. For this, silica was added to the reaction mixture with HFIP as solvent (Table 2, entry 21). Based on the fact that this change had only minor effect on the yield of **11 aa** (47% with silica versus 52% without silica, see Table 2, entry 10) we conclude that silica did not participate in the reaction and rather took the role of a grinding auxiliary.

With the optimized reaction conditions in hand, the substrate scope of this mechanochemical iridium catalysis was explored (Scheme 4).

First, sulfonimidamides **1 b** and **1 d** were tested in combination with ethyl 2-diazo-3-oxobutanoate (**10 a**). While *para*-tolyl-substituted derivative **1 b** reacted with **10 a** to give 1,2-benzothiazine **11 ba** in 90% yield,

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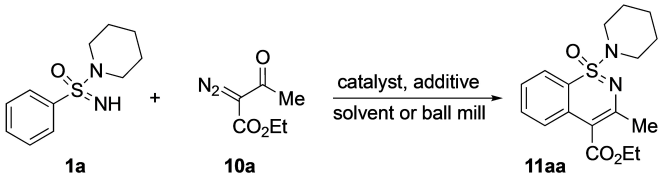
Table 2. Optimization of the reaction conditions for the synthesis of 1-amino-1,2-benzothiazine 1-oxide **11 aa**.[a]



entry	solvent	catalyst (mol %)	additive (equiv.)	T (°C)	t (h)	yield (%)
1	MeCN	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.0)	NaOAc (1.2)	100	3	0
2	MeCN	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.0)	NaOAc (1.2)	50	3	26
3	MeCN	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.0)	NaOAc (1.2)	rt	12	12
4	TFE	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.0)	NaOAc (1.2)	100	3	20
5	TFE	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.0)	NaOAc (1.2)	50	3	36
6	TFE	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.0)	NaOAc (1.2)	rt	12	16
7	TFE	–	NaOAc (1.2)	50	12	0
8	TFE	$[Cp^*IrCl_2]_2$ (2.5)	PivOH (2.0)	rt	2	41, 34[b]
9	TFE	$[Cp^*IrCl_2]_2$ (2.5)	PivOH (2.0)	40	12	0
10	HFIP	$[Cp^*IrCl_2]_2$ (2.5)	PivOH (2.0)	rt	2	52
11	1,2-DCE	$[Cp^*IrCl_2]_2$ (2.5)	PivOH (2.0)	rt	2	0
12	DCM	$[Cp^*IrCl_2]_2$ (2.5)	PivOH (2.0)	rt	2	0
13	MeOH	$[Cp^*IrCl_2]_2$ (2.5)	PivOH (2.0)	rt	2	0
14	EtOH	$[Cp^*IrCl_2]_2$ (2.5)	PivOH (2.0)	rt	2	0
15	MeCN	$[Cp^*IrCl_2]_2$ (2.5)	PivOH (2.0)	rt	2	0
16	toluene	$[Cp^*IrCl_2]_2$ (2.5)	PivOH (2.0)	rt	2	0
17	HFIP	–	PivOH (2.0)	rt	12	0
18[c]	–	$[Cp^*IrCl_2]_2$ (2.5)	PivOH (2.0)	–	1	35
19[c]	–	$[Cp^*IrCl_2]_2$ (2.5)	PivOH (2.0) + sand	–	1	63
20[c]	–	$[Cp^*IrCl_2]_2$ (2.5)	PivOH (2.0) + silica	–	1	99, 97[b]
21	HFIP	$[Cp^*IrCl_2]_2$ (2.5)	PivOH (2.0) + silica	rt	2	47

[a] Reaction conditions: **1 a** (0.10 mmol), **10 a** (0.15 mmol), solvent (1 mL), under argon. Yields determined by ^{1}H NMR spectroscopy (internal standard: anisole), except noted otherwise.
[b] After purification by flash column chromatography.
[c] Reaction performed in a ball mill reactor (25 Hz); grinding auxiliaries were added in a quantity equal to the total weight of all reagents.

1 c bearing a *para*-nitro group reacted sluggishly providing **11 ca** in only 17% yield. In the next three experiments, sulfonimidamide **1 a** was reacted with (hetero)aryl-containing diazoketones **10 b–d**. In each case, the corresponding product was formed, but the yields for **11 ab**, **11 ac**, and **11 ad** varied from 52% for thienyl-substituted **11 ad** to 94% for *para*-tolyl-containing **11 ac**. The latter very positive result was confirmed by the 92% yield for **11 bc** resulting from a reaction between **1 b** and **10 c**. Applying diazoketo ester **10 d** with a thienyl group in couplings with sulfonimidamides **1 g** and **1 h** led to **11 gd** and **11 hd** in yields of 70% and 66%, respectively, which showed the applicability of *ortho*-substituted sulfonimidamides on one hand and on the other indicated the difficulty in obtaining high yields with thienyl-based diazoketo ester **10 d**. The formation of sulfonyl-containing **11 ae** – albeit only in 41% yield – revealed that also diazoketo sulfones such as **10 e** could be applied in these couplings. As observed in the aforementioned rhodium catalysis (Scheme 2), sulfonimidamides with free or mono-silylated amino groups were unsuitable here too. Thus, starting from **1 a** and either **1 j** or **1 k**, **11 ja** and **11 ka**, respectively, remained inaccessible.

In summary, we developed two protocols for the preparation of 1-amino-1,2-benzothiazine 1-oxides. One of them is a rhodium-catalyzed annulation reaction starting from sulfonimidamides and α-substituted mesyl ketones. It proceeds in solution and leads to 4-unsubstituted 1,2-benzothiazine derivatives. 3,4-Disubstituted products can then be accessed by selective bromination of the heterocycle at ring position 4. The second protocol, which directly provides 3,4-disubstituted 1,2-benzothiazine derivatives, utilizes iridium catalysts. Attempts to perform the coupling in solution met with limited success. However, under solvent-free mechanochemical conditions in a ball mill reactor the product yields were very high. In this case, combinations of sulfonimidamides and diazoketo esters or diazoketo sulfones were the starting materials. The molecular structures of two representative heterocycles were determined by single

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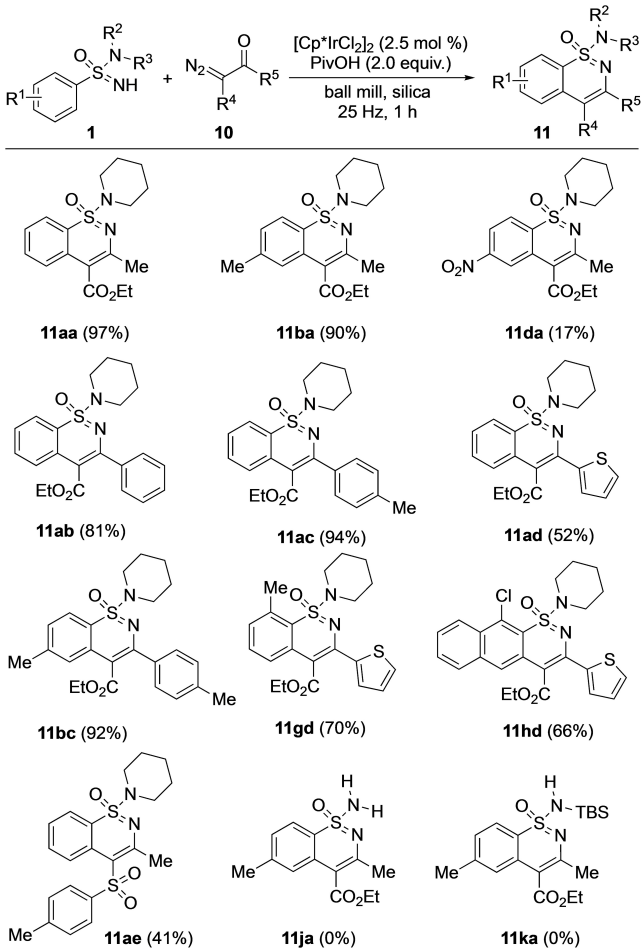

Scheme 4. Substrate scope for the formation of **11** starting from sulfonimidamides **1** and diazoketones **10**.

crystal X-ray diffraction analysis, which revealed interesting three-dimensional geometries of the annulated heterocycle.

Experimental Section

General procedure for preparation of 1,2-benzothiazines 3 exemplified by the synthesis of compound 6 aa. An oven-dried Schlenk tube equipped with a magnetic stirring bar and a septum was charged with 1-(*S*-phenylsulfonimidoyl) piperidine (**1 a**, 33.6 mg, 0.150 mmol 1.0 equiv.), 2-oxo-2-phenylethyl methanesulfonate (**3 a**, 45.0 mg, 0.210 mmol, 1.4 equiv.), sodium acetate (17.2 mg, 0.210 mmol, 1.4 equiv.), copper(II) acetate (2.7 mg, 0.015 mmol, 0.1 equiv.) and tris(acetonitrile) pentamethyl-cyclopentadienyl rhodium(III) hexafluoroantimonate (6.2 mg, 0.0073 mmol, 0.05 equiv.). Anhydrous methanol (3 mL) was added by using a syringe, and the resulting mixture was stirred for 12 h under an atmosphere of argon at 40 °C. After completion of the reaction, the mixture was filtered through a pad of Celite and washed with DCM (50 mL). The mixture was concentrated under reduced pressure, and silica gel flash column chromatography (gradient elution: *n*-pentane/ethyl acetate, 99/1 to 9/1) afforded 44.7 mg (91%) of product **6 aa**.

Procedure for the synthesis of brominated 1,2-benzothiazine 9. An oven-dried Schlenk tube equipped with magnetic stirring bar and septum was charged with 1,2-benzothiazine **6 aa** (35.0 mg, 0.108 mmol, 1.0 equiv.), *N*-bromosuccinimide (28.8 mg, 0.162 mmol, 1.5 equiv.), and azobisisobutyronitrile (3.5 mg, 0.022 mmol, 0.2 equiv.). Carbon tetrachloride (2 mL) was added by using a syringe, and the resulting mixture was refluxed for 12 h under an atmosphere of argon. After completion of the reaction, water was added and the crude mixture was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and the solvents removed under reduced pressure. Purification by flash column chromatography with *n*-pentane/ethyl acetate (9/1) as gradient elution afforded 42.5 mg (98%) of 1,2-benzothiazine **9**.

General procedure for the solvent-free mechanochemical synthesis of 1,2-benzothiazines 11 exemplified by the synthesis of compound 11 aa. A stainless steel milling vessel (5 mL volumetric capacity) equipped with two stainless steel balls (7 mm in diameter), was charged with 1-(*S*-phenylsulfonimidoyl)piperidine (**1 a**, 22.4 mg, 0.100 mmol, 1.0 equiv.), ethyl 2-diazo-3-oxobutanoate (**10 a**, 23.4 mg, 0.150 mmol, 1.5 equiv.), PivOH (20.4 mg, 0.200 mmol, 2.0 equiv.), silica (70 mg), and pentamethylcyclopentadienyl iridium dichloride dimer (2.0 mg, 0.0025 mmol, 0.025 equiv.). To perform the reactions under an inert atmosphere, a cannula connected to a slight argon stream was held into the milling vessel before the cap was tightly closed. The mechanochemical reaction was conducted for 1 h at a milling frequency of 25 Hz. After completion of the reaction, the powdery reaction mixture was directly transferred from the milling vessel to the column. Residues inside the milling vessel were extracted with a small amount of chloroform and also added to the column. Finally, 1,2-benzothiazine **11 aa** was isolated after purification by silica gel flash column chromatography (gradient elution: *n*-pentane/ethyl acetate, 99/1 to 9/1) to give 32.4 mg (97%).

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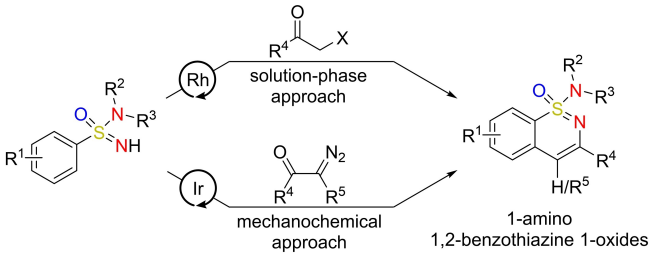
1,2-Benzothiazine Derivatives from Sulfonimidamides by Metal-Catalyzed Annulation Reactions in Solution and under Solvent-Free Mechanochemical Conditions

Adv. Synth. Catal. **2021**, *363*, 1–9

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