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Amidation

Rhodium-Catalyzed *ortho*-Amidations in the Preparation of Thiadiazine 1-Oxides

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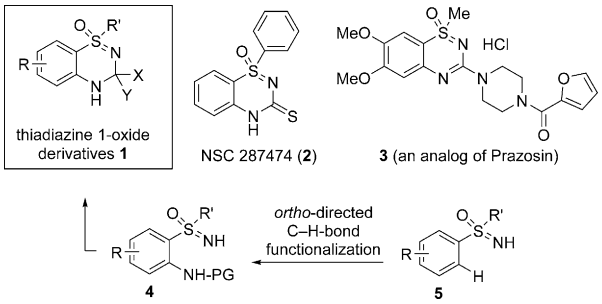
Abstract: Rhodium-catalyzed *ortho*-amidations of sulfoximines lead to key intermediates for the preparation of thiadiazine 1-oxides. Following a straightforward protocol, a variety of synthetically valuable compounds can be obtained, thus circumventing common multistep approaches towards potentially bioactive products.

The first derivatives of thiadiazine 1-oxides were reported by Wagner and Reinöhl as early as 1964.[1] A few years later, Williams and Cram,[2] as well as industrial colleagues at Beiersdorf[3] and Gödecke,[4] developed new synthetic strategies towards such compounds. Those preparative investigations were the basis for numerous bioactivity studies that revealed interesting properties of thiadiazine 1-oxide derivatives **1** useful for medical applications.[5,6] For example, NSC 287474 (**2**) was found to be a potential reverse transcriptase inhibitor for the protection of lymphocytes against HIV,[7] and in animal tests thiadiazine 1-oxide **3** revealed equipotent blood-pressure-lowering activity as the commercial antihypertensive drug Prazosin (Scheme 1).[8]

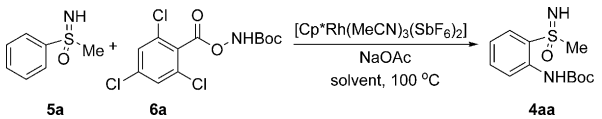
Commonly, thiadiazine-1-oxides **1** are prepared by multiple-step syntheses starting from N-protected 2-thio-substituted anilines or *ortho*-nitroaryl thioethers.[1–4,9] With the goal of easing access to such interesting compounds and being inspired by our previous work in this area,[10] we wondered about an alternative strategy starting from readily available, commercial sulfoximines **5**. Selective introduction of an amino group in the *ortho* position of the sulfoximidoyl substituent by metal-catalyzed directed C–H bond functionalization[11] would lead to key intermediates **4**, which could further be modified to provide straightforward access to range of target products **1**.[12] The success of this approach is described here.



Scheme 1. General structure of thiadiazine 1-oxides **1** and two bioactive derivatives **2** and **3**; envisaged syntheses of **1** via **4** starting from sulfoximines **5**.

On the basis of the work by Chang,[13] Glorius,[14] and others[15] we decided to focus on directed C–H bond amidations under rhodium catalysis.[16] *S*-Methyl-*S*-phenyl-sulfoximine (**5a**) and *tert*-butyl(2,4,6-trichlorobenzoyl)oxycarbamate (**6a**) were chosen as representative substrates. The catalytic system of $[Cp^*Rh(MeCN)_3(SbF_6)_2]$ and NaOAc in 1,2-DCE at 100 °C for 12 h provided the desired product **4aa** in 55% yield (Table 1, entry 1). Using *tert*-amylOH or acetonitrile as solvent gave **4aa** in lower yields (Table 1, entries 2 and 3). Also increasing the amount of **6a** decreased the yield of **4aa** (36%; Table 1, entry 4). Assuming that the latter result was due to partial substrate decomposition, the sulfoximine-to-oxycarbamate was varied. Supporting our hypothesis, the yield of **4aa** raised to 64% and 71% when 1.2 equiv and 2.0 equiv, respectively, of **5a** was applied (Table 1, entries 5 and 6). Finally, the best result was achieved with 3.0 equiv of **5a** providing **4aa** in 81% yield (Table 1, entry 7).

Table 1. Optimization of the amidation conditions.[a]



Entry	**5a**/**6a** ratio	Solvent	Yield of **4aa** [%]
1	1:1.2	1,2-DCE	55
2	1:1.2	*tert*-AmylOH	36
3	1:1.2	MeCN	30
4	1:2	1,2-DCE	36
5	1.2:1	1,2-DCE	64
6	2:1	1,2-DCE	71
7	3:1	1,2-DCE	81

[a] Reaction conditions: Stirring of sulfoximine **5a**, oxycarbamate **6a**, $[Cp^*Rh(MeCN)_3](SbF_6)_2]$ (5 mol%), NaOAc (1.2 equiv) in the given solvent at 100 °C under argon for 12 h. DCE = 1,2-dichloroethane.

A screening of other *N*H-Boc oxycarbamates (Boc = *tert*-butoxycarbonyl) with different aryl substituents (see Supporting

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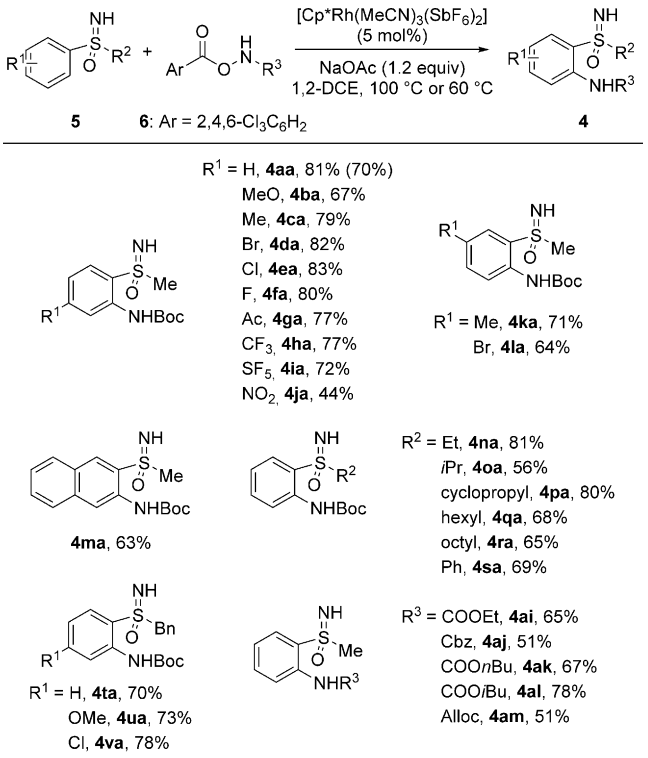
Information, Table S1) showed that **6a** was the amidating agent of choice, leading to the highest yields of **4aa**.

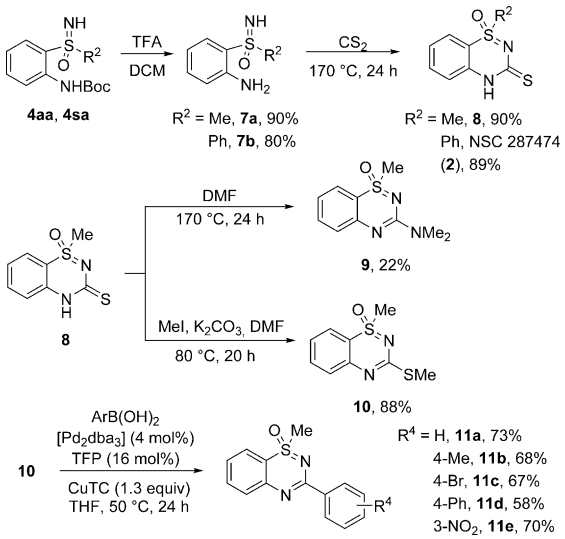
With the optimal conditions in hand, the substrate scope was evaluated (Scheme 2).[17] *S*-Aryl-*S*-methyl sulfoximines with various substituents on the aromatic ring reacted smoothly in the rhodium-catalyzed amidation reaction with *tert*-butyl(2,4,6-trichlorobenzoyl)oxycarbamate (**6a**) affording the corresponding *ortho*-amidation products (**4aa**–**4ma**) in good to moderate yields (44–83%).



Scheme 2. Rhodium-catalyzed *ortho*-amidation [performed at 100 °C, except for catalyzes leading to **4ai**–**4am** (60 °C)]; common scale: 0.6 mmol with respect to sulfoximines **5**. The result of a 1.5 mmol scale experiment for **4aa** is shown in parentheses.

para-Halo-substituted products **4da** and **4ea** showed the best results (82 and 83% yield, respectively). The lowest yield (44%) was observed in the formation of **4ja** having a *para*-nitro-substituent. It was noted that *meta*-substituted (**5k** and **5l**) and 2-naphthyl sulfoximines (**5m**) showed an exclusive site selectivity, providing single regioisomeric products (**4ka**–**4ma**) in good yields (63–71%). Also, the reactions of *S*-phenyl sulfoximines with other *S*-alkyl substituents (other than methyl) proceeded well, giving **4na**–**4ra** in yields ranging from 56 to 81%. With diphenyl sulfoximine **5s**, only mono-amidation to give **4sa** (in 69% yield) was observed. Furthermore, *S*-aryl-*S*-benzyl sulfoximines **4ta**–**4va** were formed in good yields (70–78%). Finally, other oxycarbamates varying in the amido substituent were used in the reaction with **5a**. As those reagents (**6i**–**6m**) degraded at 100 °C, the catalyses were performed at 60 °C. As a result, products **4ai**–**4am** were obtained in yields ranging from 51 to 78%.[17]

The subsequent investigations focused on converting the catalytically prepared *ortho*-*N*HBoc aryl sulfoximines **4** into thiadiazine 1-oxide derivatives **1** (Scheme 3). Cleavage of the Boc group of sulfoximines **4aa** and **4sa** provided *ortho*-amino-substituted sulfoximines **7a** and **7b** in yields of 90 and 80%,

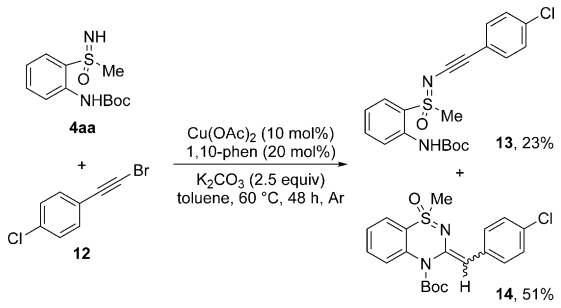


Scheme 3. Syntheses of thiadiazine 1-oxide derivatives.

respectively (Scheme 3). Subsequent reactions of those products with carbon disulfide at 170 °C for 24 h led to cyclizations forming thiadiazine 1-oxide **8** in 90% yield and NSC 287474 (**2**) in 89% yield. Thiadiazine 1-oxides **9** (22%) and **10** (88%) were then obtained by treatment of **7a** with DMF at 170 °C for 24 h and the reaction of **7a** with methyl iodide under basic conditions at 80 °C for 20 h.[18]

Heteroaromatic thioether **10** was recognized as a valuable intermediate for Liebeskind–Srogl-type cross-coupling reactions[19] with boronic acids to allow further extension of the molecular diversity of the thiadiazine 1-oxide derivatives (Scheme 3). Using a catalyst system consisting of tris(dibenzylideneacetone)dipalladium(0) [Pd_2dba_3], TFP [tri(2-furyl)phosphine], and CuTC (TC = thiophene-2-carboxylate) in THF at 50 °C for 24 h gave cross-coupling products **11a**–**e** in yields ranging from 58 to 73%. It was also noted that reactive functional groups such as bromo and nitro substituents at the aryl boronic acids were tolerated, allowing for potential additional structural modifications at later synthetic stages.

Finally, we demonstrated a selective derivatization of the sulfur-bound *N*H group of *N*HBoc-containing sulfoximine **4aa** (Scheme 4). Treatment of **4aa** in toluene with 1-(bromoethynyl)-4-chlorobenzene (**12**) in the presence of $Cu(OAc)_2$, 1,10-phenanthroline and K_2CO_3 for 48 h at 60 °C[20] led to two products, which were identified as N-alkynylated sulfoximine **13** (23%) and thiadiazine 1-oxide **14** (51%). Based on the demonstrated reactivity pattern of the former product type,[21] it is reasonable to assume that the formation of heterocycle **14** proceeded via **13** by a regioselective intramolecular nucleophilic attack of the triple bond by the *N*HBoc moiety of **13**.



Scheme 4. Copper-catalyzed N-alkynylation of **4aa**.

In summary, we developed a new access towards thiadiazine 1-oxides with rhodium(III)-catalyzed *ortho*-amidations of *N*H-sulfoximines as the key transformation. As the starting materials are readily available commercially, a variety of products can now be obtained in a straightforward manner, leading to core scaffolds for potentially bioactive molecules.

Experimental Section

General procedure for the rhodium-catalyzed amidation

A Schlenk tube (25 mL) was charged with sulfoximine **5** (0.60 mmol), aroyloxycarbamat **6** (0.20 mmol), $[Cp^*Rh(MeCN)_3(SbF_6)_2]$ (8.3 mg, 0.010 mmol), and NaOAc (19.7 mg, 0.24 mmol). Under an argon atmosphere, dry 1,2-dichloroethane (1.0 mL) was added to the mixture by syringe, and stirring was continued at 100 °C for 12 h. Then, the mixture was cooled to room temperature, diluted with dichloromethane (10 mL), and filtered through a Celite pad. After washing with dichloromethane (3×20 mL), the filtrate was concentrated, and the product was purified by flash column chromatography on silica gel with a mixture of *n*-pentane and acetone as the eluent affording **4** as a pure product. For additional experimental details, see the Supporting Information.

General procedure for the palladium-catalyzed cross-coupling

A Schlenk tube (25 mL) was charged with 1-methyl-3-(methylthio)-benzo[*e*][1,2,4]thiadiazine 1-oxide (**10**, 45.2 mg, 0.20 mmol), the boronic acid (0.22 mmol), $[Pd_2dba_3]$ (7.3 mg, 0.0080 mmol), tri(2-furyl)phosphine (7.4 mg, 0.032 mmol), and CuTC (49.7 mg, 0.26 mmol). Under an argon atmosphere, dry THF (2.0 mL) was added to the mixture by syringe. After stirring at 50 °C for 24 h, the mixture was cooled to room temperature, was washed with saturated $NaHCO_3$ solution, and extracted with EtOAc (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash column chromatography on silica gel with *n*-pentane/acetone (20:1) as eluent, affording **11** as a pure product. For additional experimental details, see the Supporting Information.

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Keywords: heterocycles · *ortho*-amidation · rhodium catalysis · sulfoximines · thiadiazine 1-oxides

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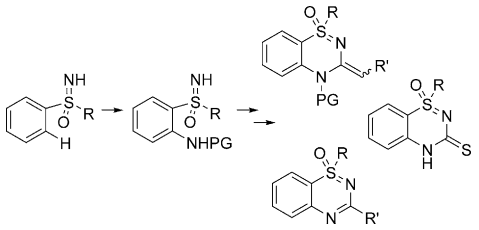

A channel to thiadiazine 1-oxides: Rhodium-catalyzed *ortho*-amidations of sulfoximines with aroyloxycarbamates show a high functional group tolerance and provide key intermediates for biologically interesting thiadiazine 1-oxides.

Amidation

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Rhodium-Catalyzed *ortho*-Amidations in the Preparation of Thiadiazine 1-Oxides