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Synthesis of 1,2-Benzothiazines by a Rhodium-Catalyzed Domino C−H Activation/Cyclization/Elimination Process from *S*-Aryl Sulfoximines and Pyridotriazoles

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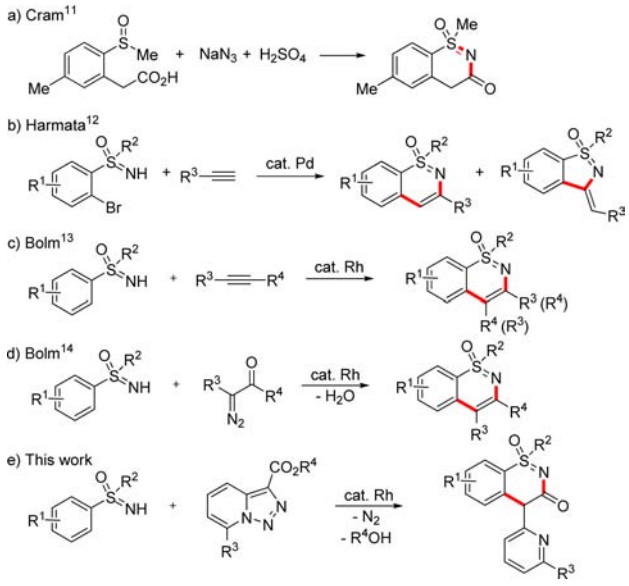
Supporting Information

ABSTRACT: A method for the synthesis of a large number of 1,2-benzothiazines bearing pyridyl as well as carbonyl groups is developed from rhodium-catalyzed carbene insertions into aromatic C−H bonds of *S*-aryl sulfoximines using pyridotriazoles by denitrogenative cyclization followed by the elimination of alcohols. The present method involves the N−H/C−H activation of simple alkyl aryl sulfoximines and has the advantages of a broad substrate scope, high functional group tolerance, and good regioselectivity.

Sulfoximines are novel privileged scaffolds that have been applied as pharmaceuticals and bioactive compounds as well as ligands and chiral auxiliaries in asymmetric syntheses.[1] As a consequence, the development of efficient methods for the synthesis of sulfoximines and their functionalizations is greatly needed. In general, the functionalizations of sulfoximines are classified into the following two groups: N−H and C−H functionalizations. Among these methods, N−H functionalization is more interesting due to the intrinsically nucleophilic nitrogen atom. In this regard, many chemists, including Bolm and Harmata, have demonstrated a large number of N−H functionalizations such as *N*-silylation,[2] *N*-halogenation,[3] *N*-alkylation,[4] *N*-vinylation,[5] *N*-arylation,[6] *N*-acylation,[4e,7] and *N*-imidoylation[8] of N−H sulfoximines along with N−S[9] and N−P[10] bond formation. However, despite the significant advances made in the functionalization of sulfoximines, only a few examples of 1,2-benzothiazines, which are more attractive pharmacophores as a type of cyclic sulfoximine, have been reported. For the first time, Williams and Cram reported synthetic approaches toward 1,2-benzothiazines bearing a carbonyl group by a sulfoxide imidation/ring-closure reaction sequence (Scheme 1a).[11] Harmata and co-workers demonstrated a synthetic method of 1,2-benzothiazines bearing an *endo*-double bond by a Sonogashira type cross-coupling of an *ortho*-bromo sulfoximine and subsequent intramolecular alkyne amidation (Scheme 1b).[12] Recently, Bolm and co-workers reported rhodium-catalyzed oxidative annulation of sulfoximines and alkynes[13] as well as rhodium-catalyzed directed carbene insertions into aromatic C−H bonds of *S*-aryl sulfoximines by dehydration as a regioselective approach to 1,2-benzothiazines having symmetric and nonsymmetric substitution patterns at the *endo*-double bond (Scheme 1c,d).[14]

However, to our knowledge, there are no synthetic methods for carbonyl group-embedded 1,2-benzothiazines having a wide range of substituents on the thiazinyl ring. In continuation of our studies directed toward the development of efficient synthetic methods using sulfoximine, diazo, and triazole compounds,[6m,8,15] herein we report unprecedented 1,2-benzothiazines bearing specific substitution patterns (pyridyl as well as carbonyl groups) by a rhodium-catalyzed domino C−H activation/cyclization/elimination process from *S*-aryl sulfoximines and pyridotriazoles (Scheme 1e).

Scheme 1. Methods to Synthesize 1,2-Benzothiazines



First, we investigated a Rh-catalyzed cyclization reaction of sulfoximine (**1a**) with ethyl 7-chloro-[1,2,3]triazolo[1,5-*a*]-

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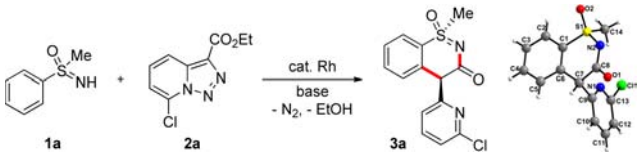
pyridine-3-carboxylate (**2a**)[16] to obtain 1,2-benzothiazine (**3a**) (Table 1). Reaction of **1a** with **2a** in the presence of

Table 1. Reaction Optimization[a]



1a 2a 3a

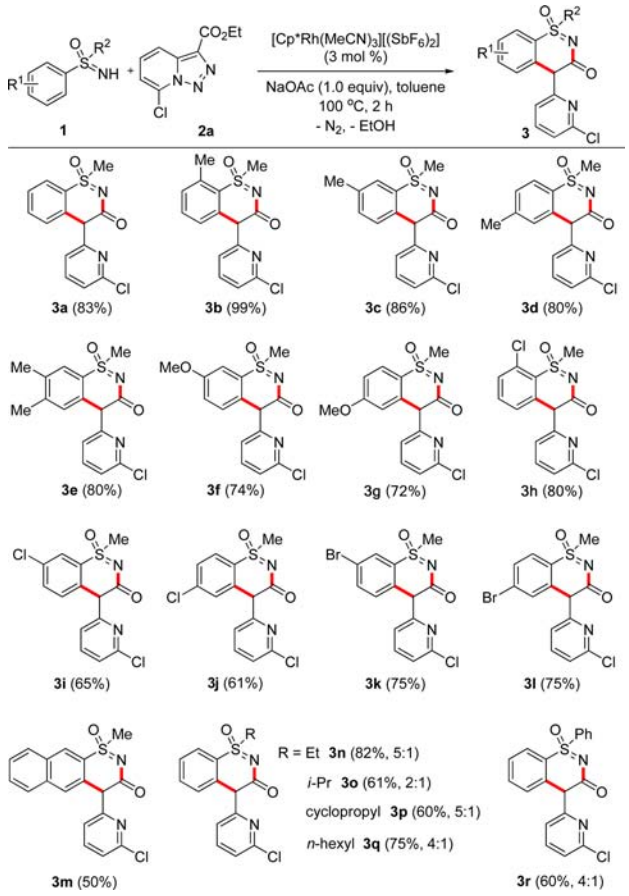
entry	base	solvent	temp (°C)	time (h)	yield (%)[b]
1[c]	NaOAc	DCE	100	12	0
2[d]	NaOAc	DCE	100	12	0
3	NaOAc	DCE	100	12	60
4	NaOAc	toluene	100	12	72
5	NaOAc	toluene	100	12	80
6	LiOAc	toluene	100	12	70
7	KOAc	toluene	100	12	0
8	NaOAc	toluene	100	12	85
9	NaOAc	toluene	100	2	86 (83)[e]
10	NaOAc	toluene	60	2	0
11	NaOAc	toluene	80	2	80
12	NaOAc	toluene	120	2	40
13[f]	NaOAc	toluene	100	2	0

[a]Reactions conditions: **1a** (0.1 mmol, 1 equiv) and **2a** (1.1 equiv) were used (entries 1−4); **1a** (1.2 equiv) and **2a** (0.1 mmol, 1 equiv) were used (entries 5−13). $[Cp^*Rh(MeCN)_3][(SbF_6)_2]$ (2 mol %, entries 1−7; 3 mol %, entries 8−12) and base (1.0 equiv) in solvent (1.0 mL) were used under N_2. [b]NMR yields using dibromomethane as an internal standard. [c]$[Cp^*RhCl_2]_2$ (4 mol %) was used as the catalyst. [d]$[Cp^*RhCl_2]_2$ (4 mol %) and $AgSbF_6$ (20 mol %) were used. [e]Isolated yield. [f]Rh catalyst was not used.

$[Cp^*RhCl_2]_2$ (4 mol %) or $[Cp^*RhCl_2]_2$ (4 mol %) and $AgSbF_6$ (20 mol %) in dichloroethane (DCE) was not effective (entries 1 and 2). To our delight, when **1a** (0.1 mmol, 1 equiv) was reacted with **2a** (1.1 equiv) in the presence of $[Cp^*Rh(MeCN)_3][(SbF_6)_2]$ (2 mol %) as a catalyst and NaOAc (1 equiv) as a base in DCE (100 °C, 12 h), the desired **3a** was obtained in 60% yield (entry 3). The replacement of DCE with toluene increased the product yield to 72% (entry 4). When **2a** was used as the limiting reagent (**1a**:**2a** = 1.2:1), **3a** was produced in 80% yield (entry 5). Although KOAc was totally ineffective (entry 7), LiOAc produced 1,2-benzothiazine in 70% yield (entry 6). The efficiency (yield as well as reaction rate) of the present method is dependent on the reaction temperature (entries 8−12). The optimized conditions were accomplished from the reaction of **1a** (1.2 equiv) with **2a** (0.1 mmol, 1 equiv) using $[Cp^*Rh(MeCN)_3][(SbF_6)_2]$ (3 mol %) and NaOAc (1 equiv) in toluene (1.0 mL) at 100 °C for 2 h, affording **3a** in 83% isolated yield (entry 9). The structure of **3a** was confirmed by X-ray crystallography (see the Supporting Information).

With the optimized conditions, we then examined the scope and limitations of the present method by investigating a wide range of substituents on the aryl group of the sulfoximines **1** in the reaction with **2a** (Scheme 2). Electronic variation of substituents on the aryl ring of **1** had little effect on the reaction efficiency. The sulfoximines bearing both electron-donating groups (Me and MeO) and electron-withdrawing groups (Cl and Br) on the aryl ring were satisfactorily tolerated under the reaction conditions and afforded the corresponding 1,2-benzothiazines **3** in good to excellent yields. The tolerance of

Scheme 2. Substrate Scope of Sulfoximines[a]



[a]Reaction conditions: **1** (1.2 equiv) was reacted with **2a** (0.2 mmol, 1 equiv) in the presence of $[Cp^*Rh(MeCN)_3][(SbF_6)_2]$ (3 mol %) and NaOAc (1.0 equiv) in toluene (2.0 mL) under N_2 at 100 °C for 2 h. Ratios in parentheses indicate diastereomeric ratios by ^1H NMR.

the chloro and bromo groups is especially useful, as the following catalytic cross-coupling reactions are promising. *S*-2-naphthalenyl sulfoximine **1m** was selectively cyclized to the product **3m** in 50% yield. Isomeric 1,2-benzothiazine derived from the 1-position of the 2-naphthalenyl group was not detected at all due to steric congestion. Modification of the *S*-alkyl substituents in *S*-phenyl-*S*-alkyl sulfoximines resulted in the formation of 1,2-benzothiazines.

S-Phenyl sulfoximine **1n** bearing a *S*-ethyl group underwent the cyclization to produce the corresponding 1,2-benzothiazine **3n** in 82% (*dr* = 5:1) yield. *S*-Isopropyl- and cyclopropyl-substituted *S*-phenyl sulfoximines (**1o** and **1p**) turned out to be compatible with the optimized conditions. *S*-*n*-Hexyl-*S*-phenyl sulfoximine **1q** was subjected to the Rh-catalyzed cyclization reaction, providing **3q** in 75% yield. Gratifyingly, the Rh-catalyzed cyclization using *S*-diphenyl sulfoximine **1r** took place to afford **3r** in 60% yield. However, methyl [1,2,3]triazolo[1,5-*a*]pyridine-3-carboxylate did not react with sulfoximine.

On the basis of the above cyclization, we next examined the substrate scope of pyridotriazoles bearing substituents on the pyridyl rings (Scheme 3). When pyridotriazole (**2b**) having an electron-withdrawing bromo group on the pyridyl ring was subjected to *S*-phenyl sulfoximine **1a** under the optimized conditions, the cyclization took place smoothly, providing the corresponding 1,2-benzothiazine **4a** in 75% yield. We were pleased to obtain 1,2-benzothiazine **3b** in 99% yield from the

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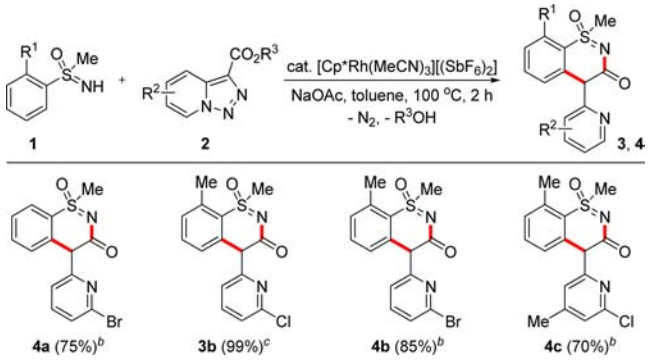
Scheme 3. Substrate Scope of Pyridotriazol[a]

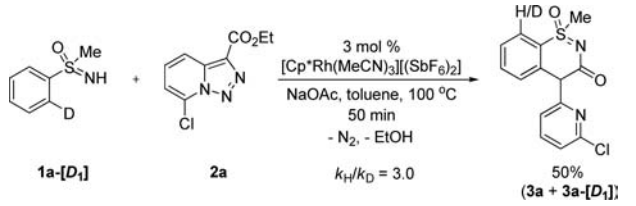


[a]Reaction conditions: **1** (1.2 equiv) was reacted with **2a** (0.2 mmol, 1 equiv) in the presence of $[Cp^*Rh(MeCN)_3][(SbF_6)_2]$ (3 mol %) and NaOAc (1.0 equiv) in toluene (2.0 mL) under N_2 at 100 °C for 2 h. [b]R^3 = Et. [c]R^3 = Me.

treatment of *S*-2-methylphenyl sulfoximine **1b** with methyl 7-chloro-[1,2,3]triazolo[1,5-*a*]pyridine-3-carboxylate (**2c**). Additionally, the reaction of **1b** with **2b** led to the formation of **4b** in an 85% yield. Methyl- and chloro-substituted pyridotriazole (**2d**) are applicable to the present cyclization, affording the corresponding 1,2-benzothiazine **4c** in 70% yield.

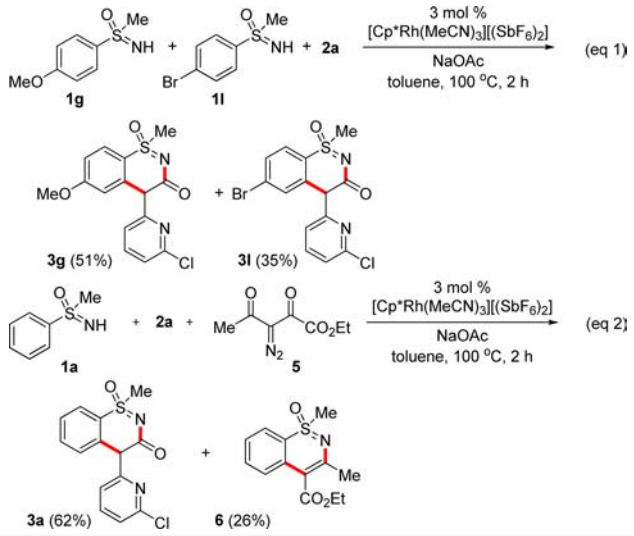
Next, we performed kinetic isotope effect (KIE) studies to obtain insight into the cyclization reaction mechanism (Scheme 4). A KIE was observed (k_H/k_D = 3.0), implying that C−H bond cleavage at the 2-position of *S*-phenyl sulfoximine is most likely involved in the rate-determining step.

Scheme 4. Intramolecular Kinetic Isotope Effect

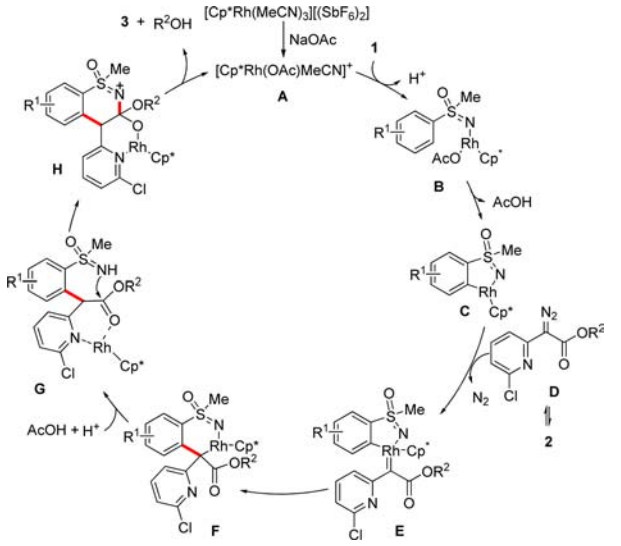


To acquire knowledge in the catalytic cycle, we conducted competition experiments between electron-rich 4-methoxy and electron-deficient 4-bromo substituted *S*-aryl sulfoximines (**1g** and **1l**) in the reaction with pyridotriazole (**2a**), furnishing mainly 1,2-benzothiazine **3g** derived from the electron-rich sulfoximine (eq 1). This result discloses that the electron-rich sulfoximine is preferentially transformed into the desired 1,2-benzothiazine. Next, reactivity between pyridotriazole and diazo compounds was compared. Treatment of **2a** and ethyl 3-diazo-2,4-dioxopentanoate (**5**) with *S*-phenyl sulfoximine (**1a**) provided 1,2-benzothiazines **3a** and **6** in 62% and 26% yields, respectively (eq 2). This result indicates that pyridotriazole (**2a**) is more reactive than the diazo compound (**5**).

Although the exact mechanism of the present transformation remains unclear, a plausible reaction mechanism is proposed in Scheme 5. When $[Cp^*Rh(MeCN)_3][(SbF_6)]_2$ is treated with NaOAc, replacement of acetonitrile by acetate via decoordination allows facile access to the acetate-ligated cationic rhodium(III) complex **A**. Subjecting **A** to the sulfoximine **1** results in the formation of the intermediate **B** by deprotonation. After the five-membered rhodacyclic intermediate **C** is formed via electrophilic C−H bond cleavage,[13] the diazoimine **D**



Scheme 5. Proposed Mechanism



generated *in situ* from the pyridotriazole **2** via liberation of nitrogen gas is coordinated with **C** to afford the rhodium-carbene **E**. Migratory insertion of the carbene **E** into the rhodium−carbon bond provides the rhodacyclic intermediate **F**. After protoderhodation to **G**, nucleophilic addition to the activated pyridyl ester followed by elimination of alcohol produces 1,2-benzothiazines **3** with the aid of $[Cp^*Rh^{III}]$ as a Lewis acid with regeneration of the catalyst.[14] On the other hand, the process can take into account an intramolecular 1,2-aryl shift of an intermediate generated by association of the rhodacycle **C** and diazoimine **D**. It is noteworthy that the pyridyl group assists this conversion instead of poisoning the catalyst. Most likely, chelation of rhodium between the pyridyl and ester groups in **G** activates the carbonyl group for the intramolecular nucleophilic cyclization.

In summary, we have developed an efficient synthetic method for a wide range of 1,2-benzothiazines bearing pyridyl as well as carbonyl groups by a rhodium-catalyzed domino C−H activation/cyclization/elimination of alcohol process starting from *S*-aryl sulfoximine and pyridotriazole compounds.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01750.

Experimental procedures, characterization data, X-ray crystallography data (**3a**), and copies of NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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