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Synthesis of Isothiazoles and Isoselenazoles through Rhodium-Catalyzed Oxidative Annulation with Elemental Sulfur and Selenium

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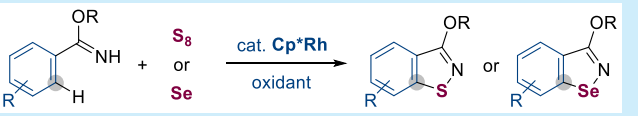
ABSTRACT: A rhodium-catalyzed oxidative annulation of benzimidates with elemental sulfur for the direct construction of isothiazole rings is reported. The proposed reaction mechanism involving Rh(I)/Rh(III) redox is supported by a stoichiometric reaction of metallacycle species as well as DFT calculations. This method is also applicable to selenium cyclization to produce isoselenazole derivatives. The alkoxy substituent at C3 can be used for further functionalization of the azole core.



Heteroaromatic compounds containing sulfur or selenium atoms constitute the core structures of many functional organic materials and biologically active compounds.[1] In particular, benzisothiazole derivatives have been of vital use in a series of antipsychotic medicines such as tiospirone, ziprasidone, perospirone, and lurasidone.[2] Additionally, oxidized and alkylated analogues of benzisothiazoles occupy an important position for pharmaceutical and agrochemical applications (Figure 1). Ebselen (2-phenyl-1,2-benzoselenazol-3-one) is a well-known oxidized selenium variant with multiple medical uses.[3] It is notable that this molecule exhibits promising inhibitory activity against COVID-19 protease.[4]

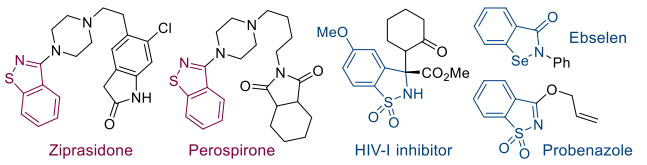
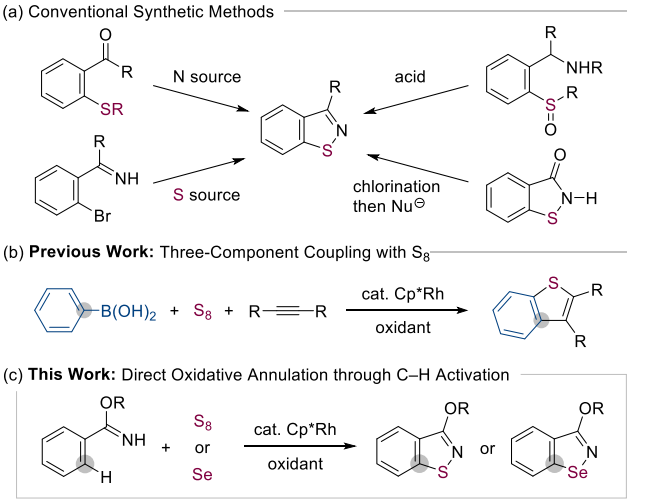


Figure 1. Representative examples of benzisothiazole (benzisoselenazole) derivatives in bioactive compounds.

Conventional synthetic methods for benzisothiazoles involve the cyclization of *ortho*-disubstituted benzene derivatives,[1,5] which would be prepared via cumbersome multistep processes (Scheme 1a). The structural diversity in the cyclized products is thus considerably limited by the availability of these precursors, and a similar issue should be addressed for the synthesis of selenium analogues. Moreover, the handling difficulty of organosulfur and organoselenium compounds is usually problematic in practical use. Elemental sulfur (also known as S_8) is one of the most important raw materials for modern chemical production because of its low cost and user-friendly nature (stable, nonvolatile, nonhygroscopic, nontoxic, and nonodorous). A number of C−S bond-forming reactions have been established exploiting this as the sulfur source.[6,7]

Scheme 1. Representative Synthetic Methods for Isothiazoles



In contrast, the utility of S_8 in direct C−H functionalization[8] has rarely been explored despite the fact that atom transfer of S, Se, and Te from elemental chalcogenides into the metal−carbon bond of Ni(II) metallacycle species has been known for more than 20 years.[9] In 2014, Shi reported a Cu-mediated benzoisothiazolone synthesis using the (pyridin-2-yl)-isopropylamine (PIP-amine) bidentate directing group.[10] Recently, Gong and Song developed a catalytic variant of this using Ni with the aid of the 2-amino alkylbenzimidazole

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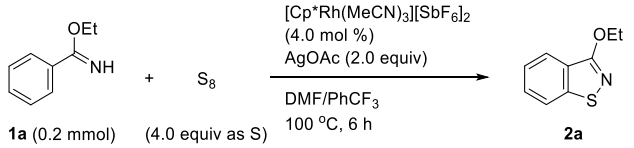
directing group.[11] As a related example of the selenium annulation, Nishihara achieved a Ni-catalyzed synthesis of benzoisoselenazolones adopting an 8-quinolyl auxiliary.[12] We previously achieved the synthesis of benzo[*b*]thiophenes through a Rh-catalyzed three-component coupling reaction of arylboronic acids, alkynes, and S_8 (Scheme 1b).[13,14] To the best of our knowledge, only these four reports successfully utilized elemental chalcogenides with the C−H activation strategy. As part of our continuous research interest in this field, we envisioned utilizing this sulfur annulation protocol for the concise assembly of isothiazole derivatives, and herein we report a direct oxidative annulation of imidates with elemental sulfur and selenium (Scheme 1c).

Our initial study was conducted to optimize the reaction conditions using ethyl benzimidate (**1a**) as a representative substrate (Table 1). To our delight, the desired product **2a** was

Table 1. Optimization Study[a]



1a (0.2 mmol) (4.0 equiv as S) **2a**

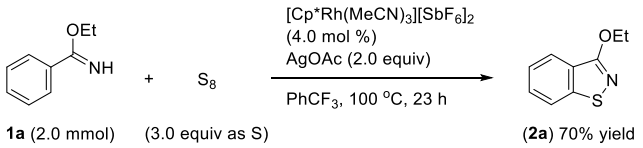
entry	deviation from the standard conditions	yield[b]
1	–	81%
2	without catalyst	n.d.
3	$[Cp^*RhCl_2]_2$ (2.0 mol %) as the catalyst	51%
4	$Cp^*Co(CO)I_2$ (4.0 mol %) as the catalyst with $AgSbF_6$ (10 mol %)	n.d.
5	$[Ru(p\text{-cymene})Cl_2]_2$ (8.0 mol %) as the catalyst	trace
6	$Cu(OAc)_2$ (1.0 equiv) instead of AgOAc	7%
7	S (2.0 equiv), average of three runs	81%
8	$PhCF_3$ as the solvent, S (2.0 equiv)	94% (94%)
9	DMF as the solvent, S (2.0 equiv)	trace

[a]Standard conditions: **1a** (0.2 mmol), S_8 (0.8 mmol as S), AgOAc (0.4 mmol), and $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4.0 mol %) in solvent (DMF 0.1 mL + $PhCF_3$ 0.2 mL). [b]Determined by NMR analysis. Isolated yield is in parentheses. n.d. = not detected.

obtained in 81% yield under the standard conditions using sulfur powder (4.0 equiv as S), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ as the catalyst (Cp^* = pentamethylcyclopentadienyl), and AgOAc as the oxidant in DMF/$PhCF_3$ as the solvent (entry 1). No competing polysulfide formation was observed. The reaction did not proceed without the catalyst (entry 2). A chloride complex $[Cp^*RhCl_2]_2$ was moderately productive (entry 3), whereas an analogous cobalt complex was totally inactive even in the presence of $AgSbF_6$ as an anion source (entry 4). The ruthenium complex $[Ru(p\text{-cymene})Cl_2]_2$ was also not an active catalyst (entry 5). The product yield significantly dropped when $Cu(OAc)_2$ was used as the oxidant instead of AgOAc (entry 6). The amount of sulfur could be reduced to 2.0 equiv (entry 7), but the yield varied somewhat (66−97%). Thus, 3.0 equiv of sulfur was preferred to be used for the sake of better reproducibility (see Schemes 2 and 3). After further optimization, the target product was obtained in 94% isolated yield employing $PhCF_3$ as the solvent (entry 8), whereas DMF was not a suitable solvent (entry 9). This reaction could be conducted on a 2.0 mmol scale to give **2a** in 70% isolated yield (Scheme 2).

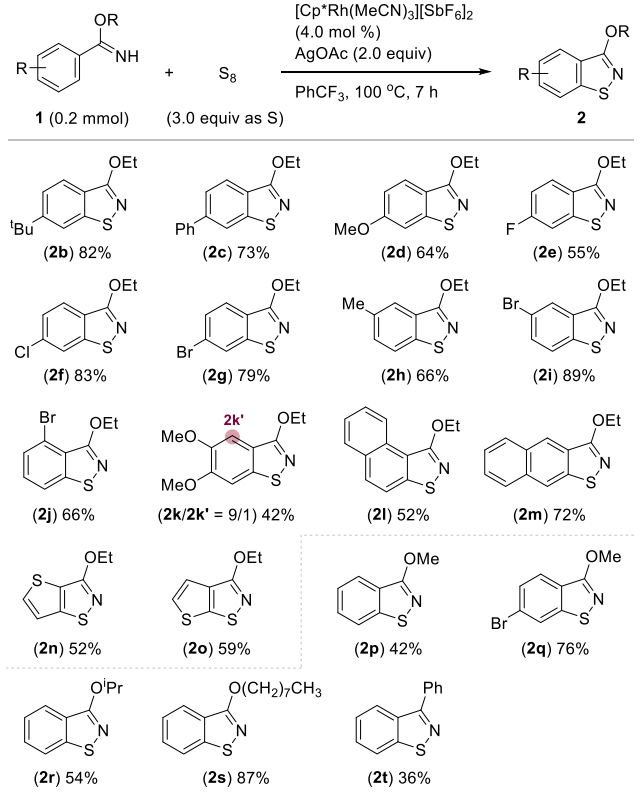
Under the optimized reaction conditions, the scope of imidate derivatives was then evaluated (Scheme 3). This

Scheme 2. Scaled-Up Reaction



1a (2.0 mmol) (3.0 equiv as S) (**2a**) 70% yield

Scheme 3. Substrate Scope[a]



[a]Reaction conditions: **1** (0.2 mmol), S_8 (0.6 mmol as S), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (4.0 mol %), and Ag_2O (0.4 mmol) in $PhCF_3$ (0.3 mL).

protocol was applicable to a series of benzimidates bearing a substituent at the *para* (**1b**−**1g**), *meta* (**1h**, **1i**), or *ortho* (**1j**) position, producing the corresponding benzisothiazoles in moderate to high yields. For the reaction of *meta*-substituted substrates, the C−H bond at a sterically more accessible site was preferentially activated to give C5-functionalized products. It is notable that the bromo group (**1g**, **1i**, **1j**), which is hardly tolerated in conventional synthetic methods, remained intact under the present conditions. This is highly beneficial for postfunctionalization of the benzisothiazole scaffold. 3,4-Dimethoxyimidate **1k** afforded a mixture of two isomers (**2k** + **2k′**), whereas naphthyl imidates **1l** and **1m** gave **2l** and **2m**, respectively, as single isomers. The present method was suitable for the reaction of thienyl imidates **1n** and **1o** to give the corresponding products in moderate yields. Additionally, we examined the effect of substituents at the imine carbon. Benzimidates with methyl (**1p**, **1q**), isopropyl (**1r**), and *n*-octyl (**1s**) groups at the oxygen atom were also applicable to the reaction, whereas benzophenone imine (**1t**) was less productive because of the competing hydrolysis. Unfortunately, benzamidine derivatives were not applicable to the present reaction system (not shown).

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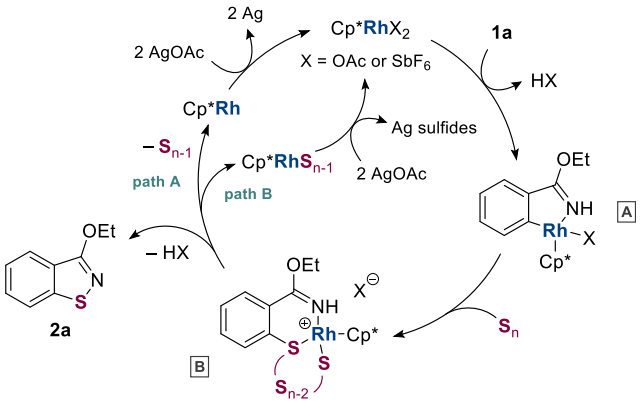
A proposed mechanism of the oxidative annulation is shown in Scheme 4. A catalytically active Rh(III) species, assumed to

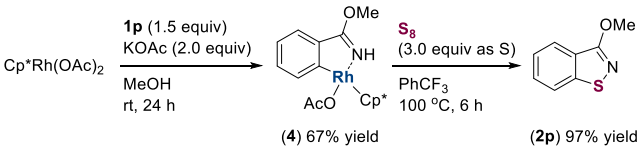
Scheme 4. Proposed Reaction Mechanism



be Cp*Rh(OAc)(SbF_6), undergoes coordination-assisted C–H activation to afford five-membered metallacycle **A**. This step would not be rate-limiting because no obvious KIE was detected (see the Supporting Information). Insertion of a sulfur atom into the Rh–C bond of the intermediate is effected to form cationic six-membered complex **B**. The coupling product would be liberated through N–S reductive elimination and deprotonation, giving a Cp*Rh(I) complex (path A) or a Cp*Rh(III) sulfide species (path B). The active Rh(III) species is then regenerated through oxidation (path A) or anion exchange (path B) with AgOAc, closing the catalytic cycle.

Although the mechanistic details for the sulfur atom migration into the metallacycle species has not been established, this process would be experimentally supported by a stoichiometric reaction (Scheme 5). We used a literature

Scheme 5. Preparation and Stoichiometric Reaction of Rhodacycle Complex 4 with Elemental Sulfur



procedure[15] to prepare Rh complex **4**, which is structurally relevant to the proposed reaction intermediate, and treated it with elemental sulfur in $PhCF_3$ as the solvent. As expected, **2p** was obtained in 97% yield. This result suggested that the silver salt did not participate in the sulfur insertion and reductive elimination steps, ruling out the occurrence of higher-valent Rh(IV) or Rh(V) species within the reaction mechanism.[15,16]

To gain further insight into the mechanism, we conducted a computational study adopting **1p** as a model compound.[17] Here the composition of elemental sulfur was assumed to be a cyclic S_8 molecule,[18] and dichloromethane (DCM) was employed as the solvent because its electric permittivity is similar to that of $PhCF_3$. Figure 2 displays an energy profile relative to a cationic $[Cp^*Rh(OAc)(MeCN)]^+$ complex (**intA**). After the coordination of **1p**, the C–H activation step was calculated as a concerted metalation–deprotonation (CMD) process to output an activation free energy (enthalpy) barrier of 19.6 (18.3) kcal/mol (**intB** → **intC**). The AcOH

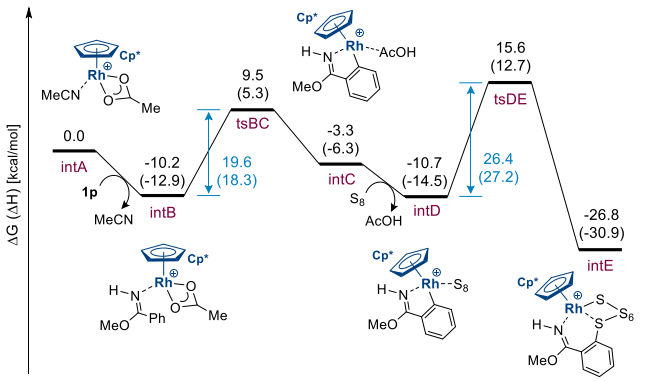


Figure 2. Partial Gibbs free energy profile of the reaction. Values in parentheses are relative enthalpies calculated at the ωB97X-D/6-311+G(d,p)&SDD/PCM(CH_2Cl_2)//ωB97X-D/6-31G+(d,p)&LANL2DZ level.

ligand is then replaced by an S_8 molecule to give **intD**. Subsequently, a sulfur atom directly bound to the metal inserts into the Rh–C linkage with a free energy (enthalpy) barrier of 26.4 (27.2) kcal/mol (**intD** → **intE**). It is noteworthy that the coordinated sulfur atom within **intD** carries a positive APT charge of +0.427, thereby facilitating the nucleophilic attack of the arylrhodium species onto it.[19] A negative charge of −1.096 at the "leaving" sulfur atom within **tsDE** also indicates that this process can be seen as an S_N2-type reaction (Figure 3).

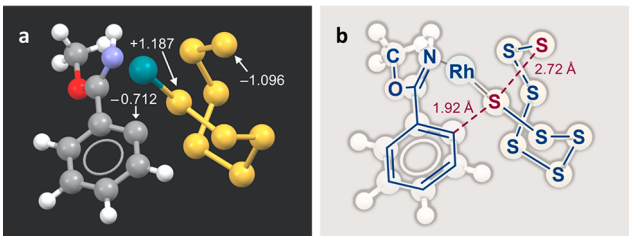


Figure 3. (a) Optimized molecular geometry of the transition state **tsDE** with APT charges. Atom colors: carbon (gray), hydrogen (white), oxygen (red), nitrogen (bulue), sulfur (yellow), and rhodium (green). (b) Atom labeling with selected bond lengths. The Cp* ligand has been omitted for the sake of clarity.

Unfortunately, all attempts to optimize the transition state structure for the N–S reductive elimination were unsuccessful because of the flexible conformational change of the sulfur chain.

To our delight, the present method was applicable to the synthesis of isoselenazoles using elemental selenium (Scheme 6). Upon treatment with 3.0 equiv of selenium powder under the standard conditions, imidate **1a** was successfully converted to the desired product **3a** in 75% yield. *Para*-substituted imidates (**1c**, **1g**) also reacted smoothly. The selenium cyclization exhibited lower regioselectivity, as the *meta*-Br imidate **1i** afforded a mixture of two isomers (**3i** + **3i′**). Imidates bearing an *ortho* substituent (**1j**), a naphthyl ring (**1m**), or a thiophene ring (**1n**, **1o**) were applicable as well, producing the corresponding isoselenazoles in high yields. Analogous methoxyimidates **1p** and **1u** were also productive, and the reaction of **1u** could be conducted on a 1.0 mmol scale.

Finally, we examined derivatization of the coupling products to highlight the synthetic utility of the developed method

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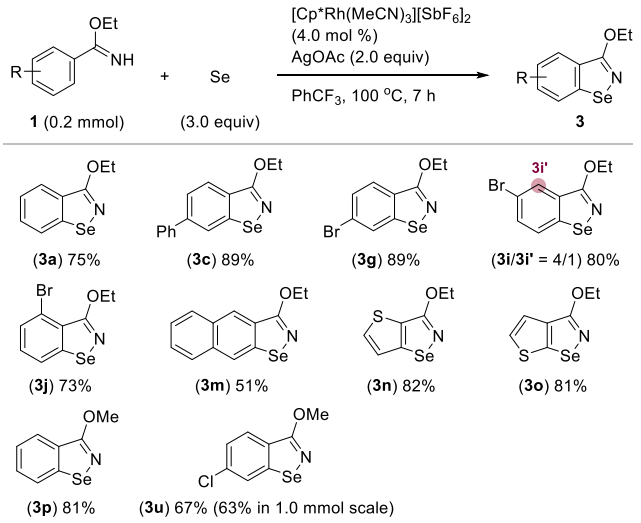
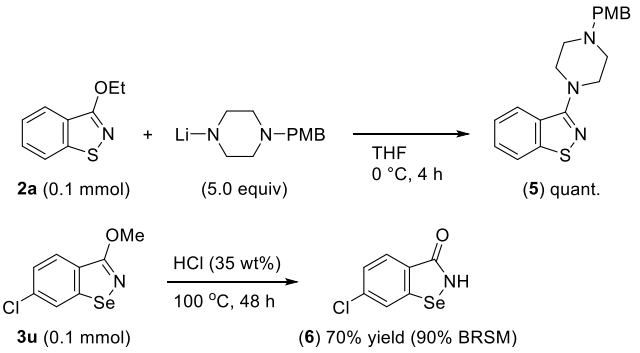
Scheme 6. Direct Annulation with Elemental Selenium[a]



[a]Reaction conditions: **1** (0.2 mmol), Se (0.6 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (4.0 mol %), and AgOAc (0.4 mmol) in $PhCF_3$ (0.3 mL).

(Scheme 7). The alkoxy group at C3 of **2a** was a suitable leaving group for the direct substitution with a lithium amide

Scheme 7. Derivatization of the Coupling Products



reagent, and the corresponding 3-aminoisothiazole **5** was obtained quantitatively. In addition, hydrolysis of **3u** under acidic conditions afforded isoselenazolone **6** in 70% yield. This compound would be a useful synthetic intermediate for a series of C3-substituted isoselenazoles as well as ebselen derivatives.[20]

In conclusion, we have developed a Cp*Rh-catalyzed oxidative annulation using elemental sulfur/selenium for the direct construction of isothiazole/isoselenazole rings. In view of the easy availability of imidate derivatives, this method is particularly useful for the synthesis of these heterocycles bearing functionalities on the benzene fragment. The proposed catalytic mechanism involving a Rh(I)/Rh(III) redox system was supported by a stoichiometric reaction of metallacycle species as well as DFT calculations. Further synthetic application of S_8 under Rh catalysis is currently being studied in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03674.

- Experimental procedures, computational method, product identification data, and copies of NMR spectra (PDF)
- Atomic coordinates of all calculated molecules (XYZ)

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Notes

The authors declare no competing financial interest.

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