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Synthesis of benzothiazonine by rhodium-catalyzed denitrogenative transannulation of 1-sulfonyl-1,2,3-triazole and thiochromone†

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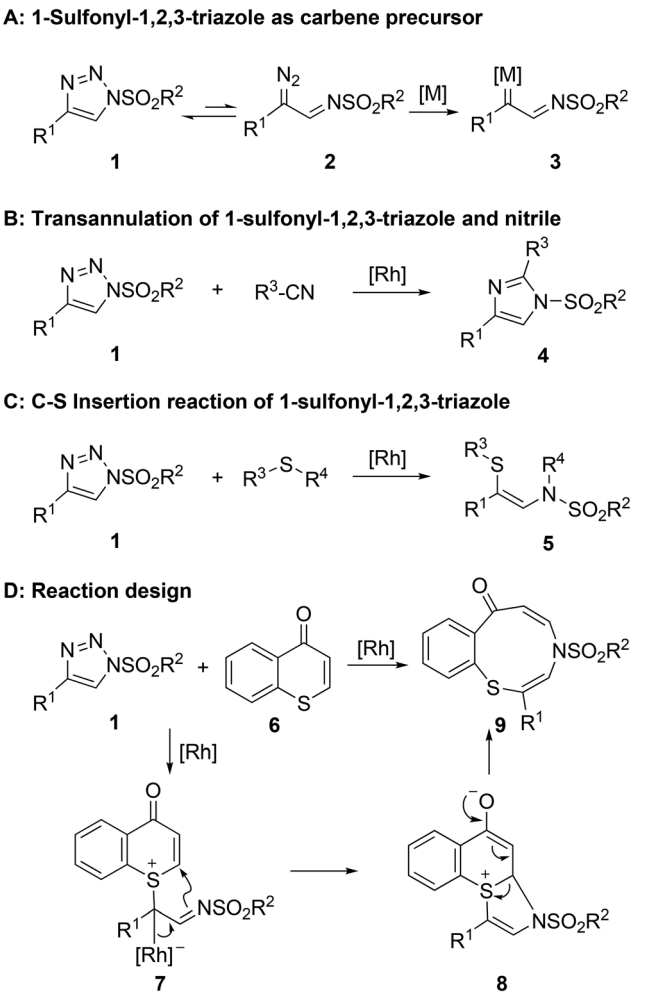
A facile synthesis of multi-functionalized benzothiazonine was achieved by the rhodium-catalyzed denitrogenative annulation of 1-sulfonyl-1,2,3-triazole and thiochromone. In view of the excellent atom economy, broad substrate scope and easy availability of starting materials, the protocol provided an efficient strategy for the construction of medium *N,S*-heterocycles.

1,2,3-Triazole, which can be synthesized *via* click reaction, is a very important heteroarene acting as a widespread motif in bioactive molecules and drugs, as a linker in materials science, in biological studies and so on.[1] Furthermore, a Dimroth equilibrium could be established between triazole **1** and α-diazo imine **2** (Scheme 1A) when an electron-withdrawing group was attached at the 1-position of 1,2,3-triazole. Consequently, Gevorgyan, Fokin and co-workers reported in 2008 that with a rhodium catalyst, 1-sulfonyl-1,2,3-triazole could act as a precursor of α-imino rhodium carbene **3** to react with nitrile producing imidazole (Scheme 1B).[2] α-Imino rhodium carbene **3** is electrophilic at carbene carbon and nucleophilic at imine nitrogen, making it a useful 1,3-dipole synthon in organic synthesis. Following the landmark work, various groups investigated the transformations of 1-sulfonyl-1,2,3-triazole, and α-imino rhodium carbene **3** has become one of the most important intermediates in the synthesis of nitrogen-containing compounds, especially in the construction of 5- and 6-membered (hetero)cycles.[3,4] However, a rare case of medium ring synthesis employing **3** was reported.

The *N,S*-heterocycle is a prevalent skeleton in many drugs (Fig. 1). For instance, there is a 5-membered *N,S*-heterocycle in famotidine and oxacillin; cephalexin, trifluoperazine and chlormezanone contain a 6-membered *N,S*-heterocycle. 7-Membered *N,S*-heterocycles can be found in diltiazem and quetiapine.[5] To the best of our knowledge, medium *N,S*-heterocycles are still unknown as drugs; however, benefitting from the ring strain, medium-sized *N,S*-heterocycles usually bear a unique conformation, which is important in drug dis-



Scheme 1 Background and reaction design.

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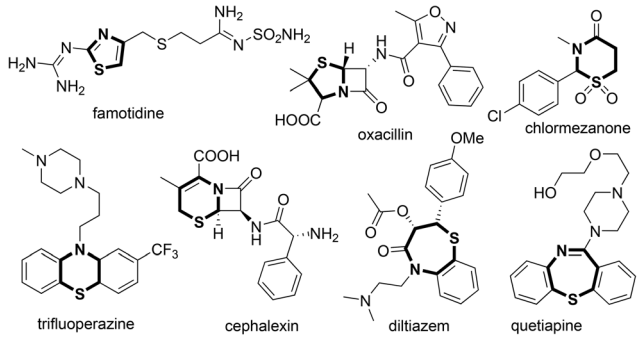


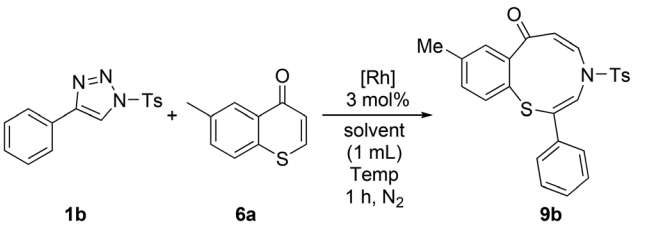
Fig. 1 Representative *N,S*-heterocycle-containing drugs.

covery. Thus, efficient synthetic methodology for medium *N,S*-heterocycles is highly desirable. The conformational strain and entropic factor in the transition state make it difficult to construct medium rings,[6] and only a few protocols have been developed to afford 8- or 9-membered *N,S*-heterocycles, including intramolecular F–C reaction, metathesis, nucleophilic cyclization and so on.[7] Accordingly, new and efficient synthetic methods for medium-sized *N,S*-heterocycles are still needed.

As mentioned, transannulation of 1-sulfonyl-1,2,3-triazole was an effective strategy to produce *N*-heterocycles. In the previous reports, sulfur could attack the carbene carbon in α-imino rhodium carbene **3** and the following cleavage of the C–S bond would finally yield the C–S insertion product (Scheme 1C).[8] Accordingly, a synthetic protocol for 9-membered *N,S*-heterocycle thiazonine was designed (Scheme 1D). The nucleophilic addition of sulfur in thiochromone **6** to carbene carbon would give sulfur ylide **7** and intramolecular Michael addition of **7** would produce **8**. The following departure of sulfur furnishes the desired 9-membered thiazonine **9**. Herein, we report our successful establishment of the protocol for medium-sized *N,S*-heterocyclic benzothiazonine synthesis.

With triazole **1b** and thiochromone **6a** as model substrates, the reaction was first tried in DCE with 3 mol% $Rh_2(OAc)_4$ as the catalyst, and benzothiazonine **9b** was isolated in 65% yield as depicted in entry 1, Table 1. Based on the initial result, the screening of reaction conditions was performed by evaluating various rhodium catalysts. Common rhodium(II) salts, such as $Rh_2(OAc)_4$, $Rh_2(esp)_2$, $Rh_2(adc)_4$, $Rh_2(piv)_4$ and $Rh_2(oct)_4$, could catalyse the reaction, and the desired benzothiazonine **9b** was obtained in good yields (entries 1–5) except for $Rh_2(tfa)_4$ and $Rh_2(dpf)_4$, in which cases, no reaction occurred and triazole **1b** decomposed gradually (entries 6, 7). Although $Rh_2(oct)_4$ performed best (entry 5), $Rh_2(OAc)_4$ was selected for further screening because an improved yield of **9b** can be achieved when reducing the dosage of triazole **1b** to 1.4 equivalents (84%, entry 8). Further screening of solvents (entries 9–12) revealed that toluene was the most suitable solvent in which **9b** was generated in 87% yield; no reaction took place in reflux DCM. When the dosage of $Rh_2(OAc)_4$ was increased to 5 mol%, **9b** was obtained in 93% yield (entry 13) and when the temperature was elevated to 90 °C, **9b** could be obtained almost quantitatively (entry 14), and these were selected as the optimal conditions.

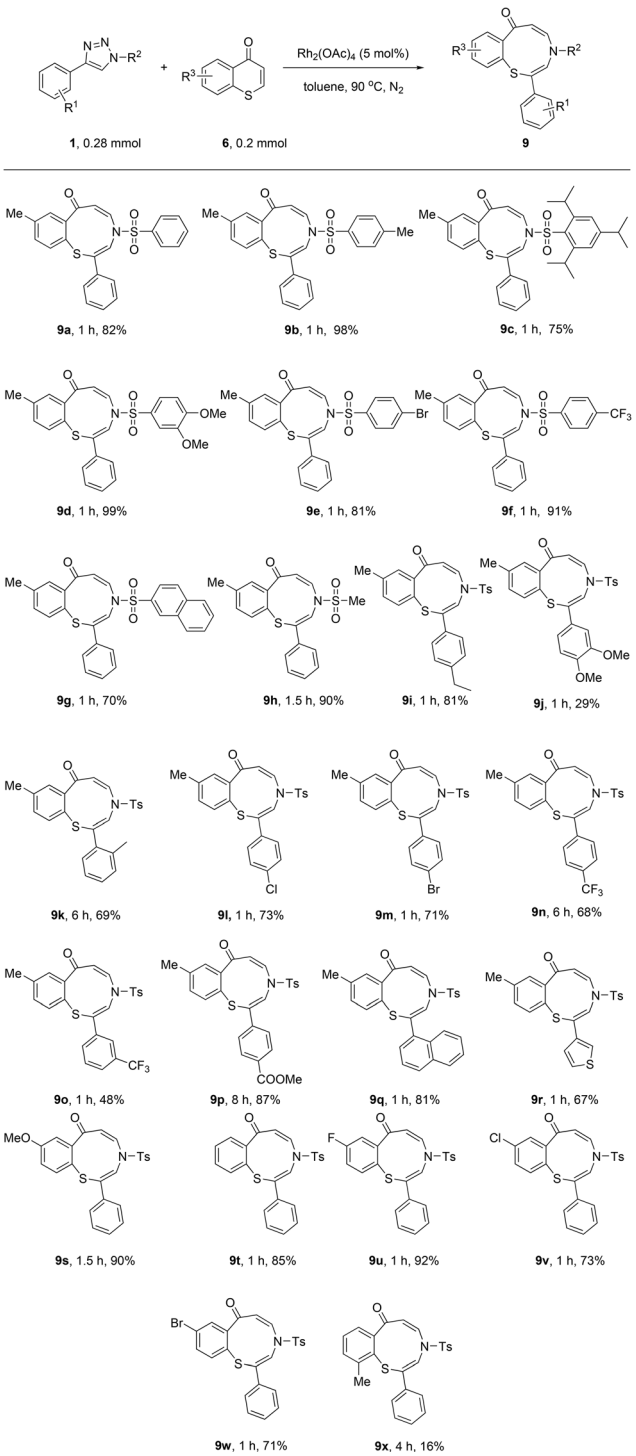
Table 1 Optimization of reaction conditions[a]



Entry	**1b : 6a**	[Rh]	Solvent	Temp. (°C)	Yield[b] (%)
1	2 : 1	$Rh_2(OAc)_4$	DCE	Reflux	65
2	2 : 1	$Rh_2(esp)_2$	DCE	Reflux	78
3	2 : 1	$Rh_2(esp)_2$	DCE	Reflux	73
4	2 : 1	$Rh_2(piv)_4$	DCE	Reflux	74
5	2 : 1	$Rh_2(oct)_4$	DCE	Reflux	80
6	2 : 1	$Rh_2(tfa)_4$	DCE	Reflux	—
7	2 : 1	$Rh_2(dpf)_4$	DCE	Reflux	—
8	1.4 : 1	$Rh_2(OAc)_4$	DCE	Reflux	84
9	1.4 : 1	$Rh_2(OAc)_4$	Toluene	80	87
10	1.4 : 1	$Rh_2(OAc)_4$	TCE	80	79
11	1.4 : 1	$Rh_2(OAc)_4$	$CHCl_3$	Reflux	74
12	1.4 : 1	$Rh_2(OAc)_4$	DCM	Reflux	—
13[c]	1.4 : 1	$Rh_2(OAc)_4$	Toluene	80	93
14[c]	1.4 : 1	$Rh_2(OAc)_4$	Toluene	90	98

[a] General conditions: **1b**, **6a** (0.2 mmol), [Rh] (3 mol%), and solvent (1 mL) at reflux. [b] Isolated yield. [c] [Rh] (5 mol%) was used. Ts = tosyl, OAc = acetate, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate, adc = 1-adamantanecarboxylate, piv = pivalate, oct = octanoate, tfa = trifluoroacetate, dpf = *N,N′*-diphenylformamidinate, DCE = 1,2-dichloroethane, TCE = 1,1,2-trichloroethane, and DCM = dichloromethane.

The investigation of the transannulation reaction scope (Scheme 2) under the optimal conditions began with testing various sulfonyls. Generally, sulfonyl groups influence the reaction to some extent: electron-abundant arylsulfonyl substituted benzothiazonines **9a–d** could be generated in 75%–99% yields, and electron-deficient arylsulfonyl substituted benzothiazonines **9e** and **9f** could be formed in 81% and 91% yields, respectively. The steric effect of the sulfonyl would depress the reaction and as a result, the yields of **9c** and **9g** were reduced to 75% and 70%, respectively; the mesyl substituted product **9h** was obtained in 90% yield. The substituents on 4-aryl of the triazole affected the reaction remarkably: alkyl substituted benzothiazonine **9i** was delivered in 81% yield but a strong electron-donating group destabilized the triazole and the corresponding product **9j** was obtained in only 29% yield. When methyl was located at the *ortho*-position, **9k** was produced in 69% yield. Normally, the electron-withdrawing groups retarded the reaction and **9l–o** were isolated in moderate to good yields (48%–73%); however, **9p** was obtained in 87% yield, which means that the ester group was well compatible. 1-Naphthyl substituted **9q** was generated in 81% yield, and considering the lower yield of **9k**, it is difficult to ascertain the impact of the steric effect on the reaction. Gratifyingly, the heteroaryl group could be tolerated and **9r** could be afforded in an acceptable yield (67%). The substituents on the thiochromone were also evaluated; methoxy and fluoro substituted products were formed in excellent yields (**9s**: 90% and **9u**: 92%),

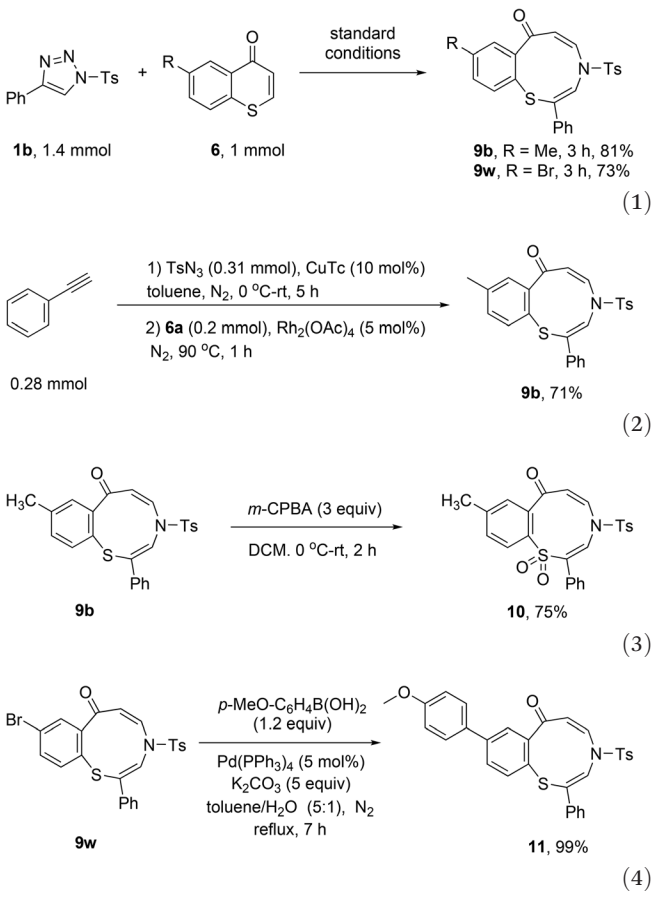


Scheme 2 Reaction scope.

whereas chloro and bromo substituted **9v** and **9w** were obtained in lower yields (73% and 71%). Thiochromone without any substituents led to the formation of **9t** in 85% yield. When methyl was present at the *ortho*-position to sulfur, the reaction was hampered seriously and only a 16% yield of **9x** was achieved, illustrating the vital influence of the steric effect around the sulfur atom on the reaction. The strong electron withdrawing group (benzoyl) on the aryl group of thiochromone was not compatible and only a complicated mixture was obtained.

It is worth mentioning that a sulfur atom was essential to the reaction, and when it was replaced with oxygen (chromone) or nitrogen (quinolin-4(1*H*)-one), no desired similar heterocycle was generated and triazole **1b** was decomposed gradually. When benzothiopyran-4-one was employed, only an unrecognizable mixture was obtained, indicating the necessity of the double bond.

Several experiments were conducted to illustrate the potential of the protocol in organic synthesis. The reaction could be extended to a 1 mmol scale and the yields of the desired benzothiazonines **9b** and **9w** were still satisfactory (81% and 73% respectively, eqn (1)). A one-pot procedure starting from an alkyne was also established, in which triazole was formed *via* click reaction between the alkyne and sulfonyl azide under the catalysis of CuTc; **6a** and $Rh_2(OAc)_4$ were added and allowed to react at 90 °C for 1 h, and finally, **9b** was isolated in 71% yield (eqn (2)). The sulfur could be oxidized to sulfone **10** by *m*-CPBA (eqn (3)). Moreover, Suzuki coupling of **9w** with boronic acid gave the biphenyl product **11** in quantitative yield (eqn (4)).



In summary, we have established a practical synthetic protocol for medium-sized *N,S*-heterocycles, and functionalized benzothiazonine was afforded in a quantitative yield with a broad scope. Synthetic applications were also conducted illus-

trating the potential of the method. Based on the excellent atom economy and easy availability of the starting materials, the protocol provided an efficient strategy for the construction of medium heterocycles and could find more applications in organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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