EurJOC
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Chemistry Europe
European Chemical Societies Publishing

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202000716

Link to VoR: https://doi.org/10.1002/ejoc.202000716

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Iridium-Catalyzed Carbenoid Insertion of Sulfoxonium Ylides for Synthesis of Quinoxalines and β-keto thioethers in Water

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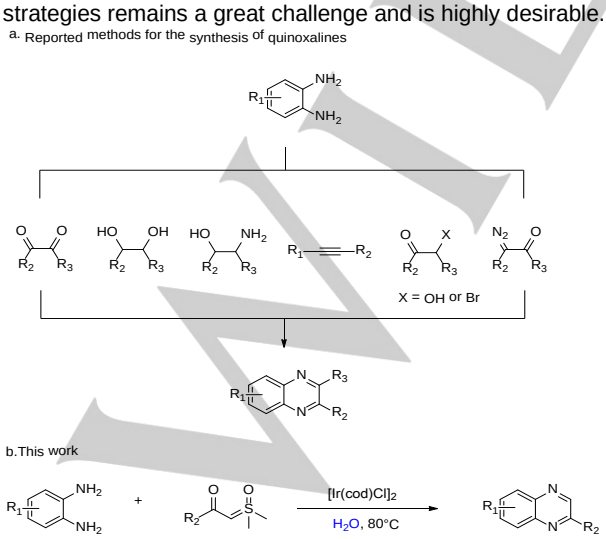
Abstract: Sulfoxonium ylides as safe carbene precursors are described for iridium-catalyzed carbene insertions and annulation, providing a facile and green approach to access a variety of quinoxaline derivatives in water. This water-mediated method also allows the preparation of β-keto thioethers under mild condition.

Quinoxalines and their related derivatives are ubiquitous scaffolds found in numerous biologically active molecules[1], which exhibit a wide range of activities such as antiviral[2], antibacterial[3], anti-inflammatory[4], anticonvulsant[5], anticancer[6], anti HIV[7] and antidepressant[8]. Besides, they are widely used as major building blocks in the dye, organic functional materials and commercial drugs[9]. Due to their strong biological activity and wide utilities, diverse well-established methods have been developed to construct these structural motifs involving the condensation of 1,2-aryldiamines with 1,2-dicarbonyl compounds[10], and oxidative cyclization of 1,2-diamines with vicinal diols[11], amino alcohols[12], terminal or internal alkynes[13], α-hydroxy ketones[14] or α-bromo ketones[15] (**Scheme 1**). However, these approaches suffer from poor availability of starting materials, tedious procedures, harsh reaction conditions and the generation of chemical waste. Organosulfur compounds play an important role in biology and organic synthesis, and the construction of C-S bond has received considerable attention[16]. So developing more efficient and sustainable synthetic strategies remains a great challenge and is highly desirable.



Scheme 1. The synthesis of quinoxalines.

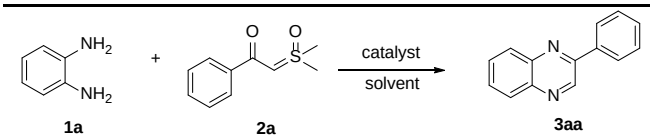
In recent years, carbenoid-based X-H (where X is any heteroatom) insertion reactions have arisen as a powerful and efficient tool to construct diverse carbon-heteroatom bonds[17]. Among these copious transformations, diazo compounds are the most often employed metal carbene precursors which can undergo the generation of metal–carbenoids in situ and then insertion into X-H bond to deliver the products[18]. Due to their unique reactivity, some methods using diazo compounds as coupling partners for synthesis of quinoxalines were developed[19]. Nevertheless, diazo compounds suffer from synthetic inconvenience, potential danger of rapid exothermic reaction and instability. In order to address the potential issues and overcome the disadvantages, it is urgent to develop new and alternative pathway to these carbene sources.

Recently, sulfoxonium ylides emerge as new surrogates of carbene precursors with higher security and stability, and have been successfully applied in a series of carbenoid-based reactions[20]. It was noted that Vaitla and co-workers reported only one example of synthesizing quinoxaline scaffold from o-phenylenediamine and a sulfoxonium ylide under microwave, which needs high temperature and toxic toluene as the solvent. Despite the progress, more efficient and green methods are still needed. Furthermore, our previous work has demonstrated the first example of water-mediated C-H functionalization using sulfoxonium ylides as coupling partners[21]. To the best of our knowledge, synthesis of quinoxalines via water-mediated N-H insertions derived from sulfoxonium ylides has not been reported yet, which prompted us to expand these safe carbene reagents into more environmentally benign and efficient protocol for synthesizing quinoxalines. With this regard, we report a novel, facile and green approach to access a variety of quinoxaline derivatives from 1,2-aryldiamines and sulfoxonium ylides utilizing water as a green solvent.

The investigation of our work was started by optimizing the reaction conditions with the model substrates of *o*-phenylenediamine **1a** and dimethyloxosulfonium benzoylmethylide **2a** to furnish the corresponding product **3aa** (**Table 1**). The activity of diverse catalysts was first examined, of which $[Rh(cod)Cl]_2$, $[Cp^*IrCl_2]_2$ and $[Ir(cod)Cl]_2$ all offered the compatible yields of 2-phenylquinoxaline when the reactions were carried out in DCE at 80 °C (entry 2,4 and 5). Given the goals of sustainable chemistry, our group has been keen to the study of non-organic solvent system. In this regard, we attempted to run this reaction in aqueous media. When utilizing water as the solvent, $[Ir(cod)Cl]_2$ was found to be the most

effective (entry 12), and $[Cp^*IrCl_2]_2$ showed comparable performance with a yield of 84%. While other catalysts in water did not provide the product. Next the effect of temperature was evaluated and we found that lower temperature resulted in incomplete conversion of starting material **1a** (entry 14) while higher temperature led to side reactions of ylide **2a** (entry 15).

Table 1. Optimization of reaction conditions[a].



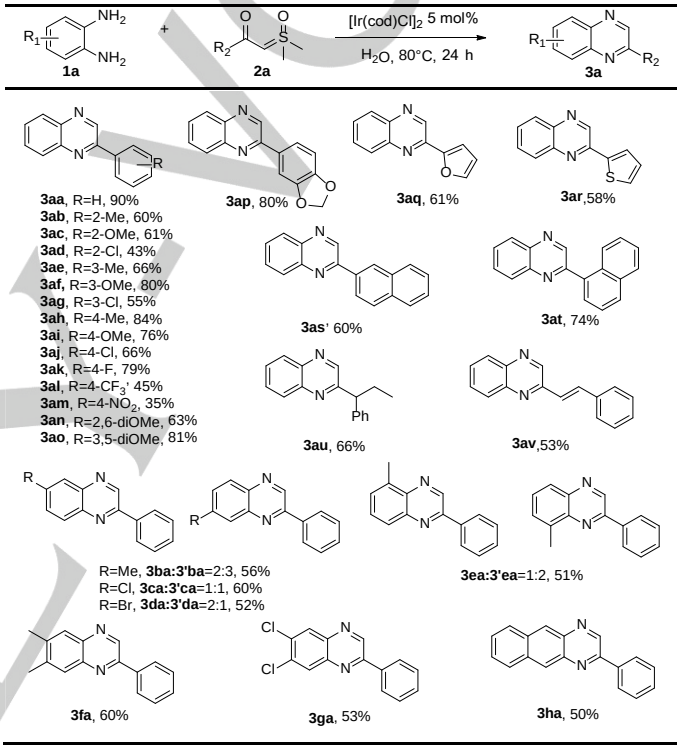
1a **2a** **3aa**

Entry	Catalyst	Solvent	Temp. (℃)	Yield[b]
1	$[Cp^*RhCl_2]_2$	DCE	80	N.R.
2	$[Rh(cod)Cl]_2$	DCE	80	80%
3	$Rh_2(OAC)_4$	DCE	80	Trace
4	$[Cp^*IrCl_2]_2$	DCE	80	83%
5	$[Ir(cod)Cl]_2$	DCE	80	81%
6	$Cp^*Co(CO)I_2$	DCE	80	50%
7	$Mn(CO)_5Br$	DCE	80	40%
8	$[Ru(p\text{-cymene})Cl_2]_2$	DCE	80	55%
9	PPhAuCl	DCE	80	40%
10	$[Rh(cod)Cl]_2$	H_2O	80	N.R.
11	$[Cp^*IrCl_2]_2$	H_2O	80	84%
12	$[Ir(cod)Cl]_2$	H_2O	80	90%
13	-	H_2O	80	Trace
14	$[Ir(cod)Cl]_2$	H_2O	60	75%
15	$[Ir(cod)Cl]_2$	H_2O	100	68%

[a] Reaction conditions : **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (5 mol%), solvent (1.5 mL), under air. [b] Isolated yields.

With the optimized conditions in hand, this protocol was applied to a wide range of sulfoxonium ylides (**Table 2**). The reaction of *o*-phenylenediamine **1a** with dimethyloxosulfonium benzoylmethylide **2a** provided the corresponding product **3aa** in 90% yield. Introduction of electron-donating and -withdrawing as well as halogen groups into different positions of the benzene ring was fully tolerated to furnish the corresponding products in moderate to good yields (**3ab-3ao**). Most ylides bearing electron-donating groups performed better than those bearing electron-withdrawing groups under this condition. When the phenyl moiety was replaced by other aromatic rings such as pepper ring, thiophene, furan ring and naphthalene, the desired products were still obtained in moderate to good yields (**3ap-3at**). Besides, aliphatic and alkenyl sulfoxonium ylides also exhibited good reactivity (**3au** and **3av**). To further demonstrate the scope of this reaction, diverse substituted *o*-phenylenediamines were investigated. The reaction of 3-methyl-*o*-phenylenediamine with ylide **2a** formed the desired quinoxaline **3ba** and **3'ba** as a mixture of two inseparable isomers in a ratio of 2:3 observed via ^1H NMR spectra while 2-methyl- *o*-phenylenediamine and diamines bearing chloride or bromine at meta-position provided products as two types of regioisomers in moderate yields (**3ca-3ea**), which were individually isolated by column chromatography. Symmetrical disubstituted *o*-phenylenediamines bearing methyl or chloride group on the aromatic ring were also well tolerated. And benzoquinoxalines was synthetized using naphthalene-2,3-diamine as the starting materials.

Table 2. Synthesis of diverse quinoxalines from *o*-phenylenediamines and various sulfoxonium ylides.

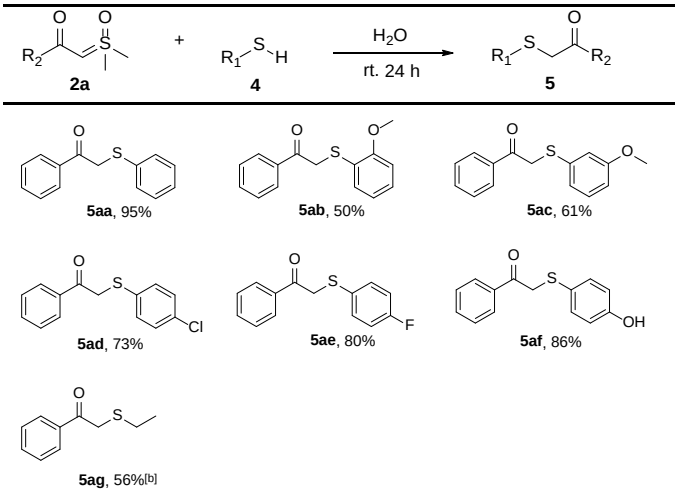


Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[Ir(cod)Cl]_2$ (5 mol%), H_2O (1.5 mL), under air. Desired product **3** was isolated by column chromatography on silica gel (eluent: PE/EA = 100/1).

Since this tandem annulation reaction was based on carbene insertion and carried out in water, we wish to further explore the generality and applications of this environmentally benign method and expand the scope to a greater extent. Recently, metal-catalyzed or even catalyst-free insertions of sulfoxonium ylides into the S-H bond have been reported respectively for accessing an array of important functionalized structural motifs[22]. However, previous strategies have not detached from the organic solvent system yet. Obviously, to run these transformations in water is of great value and highly desired for establishing the green carbene chemistry. Herein, we hope to achieve the water-mediated synthesis of β‐keto thioethers via S-H bond insertion of carbenoids generated from sulfoxonium ylides (**Table 3**). To our delight, the reaction of sulfoxonium ylides with aryl thiols proceeded smoothly in water at room temperature without any external catalyst. Alkyl thiols such as ethyl mercaptan could undergo the same transformation as well affording the product **5ag** when 1M HCl was added. And

this simple and direct method can be applied to diverse substrates to furnish structurally different β-keto thioethers (**5aa-5ag**).

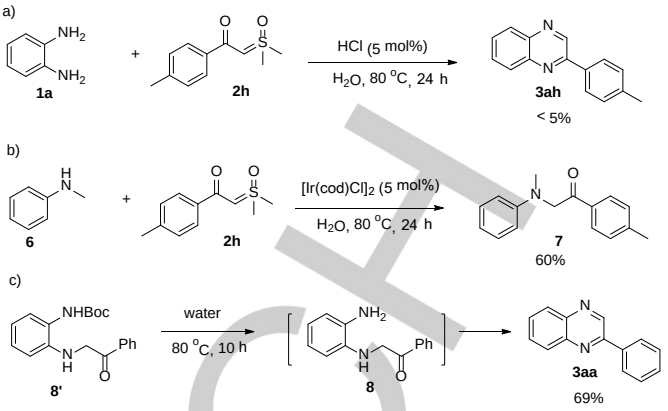
Table 3. Synthesis of β-keto thioethers[a].



[a] Reaction conditions: **2a** (0.2 mmol), **4** (0.4 mmol), H_2O (1.5 mL), Desired product **5** was isolated by column chromatography on silica gel (eluent: PE/EA = 100/1).

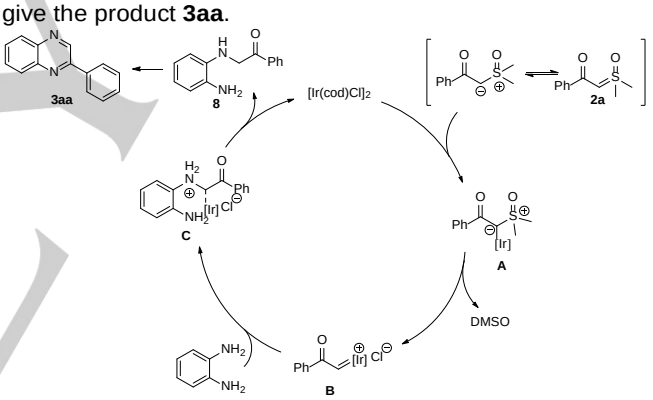
[b] 1M HCl (10 μL) was used.

We conducted a series of control reactions to explore the reaction mechanism. Considering the iridium complex may liberate catalytic amount of acid which may catalyze the reaction, we tried to run the reaction under acidic condition. When HCl (5 mol%) was used as the catalyst, only little amount of the product was observed indicating that this transformation might not be catalyzed by HCl (**Scheme 2**, a). Reaction of N-methylaniline (**6**) with sulfoxonium ylide **2h** under the standard condition afforded the N-H insertion product **7** in 60% yield (**Scheme 2**, b), which indicated that the reaction may proceed via key N-H insertion followed by condensation. In addition, to confirm that the step of condensation was promoted by water, We attempted to synthesize and isolate intermediate **8** (**Scheme 2**, c), however intermediate **8** could not be isolated directly, which all led to the formation of the final product **3aa** indicating that this intermediate **8** might be too unstable and reactive to stay in this form under aqueous media. Still, we provided an alternative way to verify this process. We prepared **8'** [pro-**8**] which would generate **8** *in situ* through N-Boc deprotection in water. The treatment of **8'** in water under heating (80 °C for 10 h) afforded **3aa** in 69% yield, which indicated that the cyclocondensation and oxidative aromatization of the *in situ* formed **8** could afford the product **3aa**.



Scheme 2. Mechanistic studies.

Based on the observed experiments and reported literatures[19b, 22b, 23], a plausible reaction mechanism is proposed (**Scheme 3**). Initially, sulfoxonium ylide **2a** is activated by Ir species to give the Ir complex **A**, which undergoes the elimination of DMSO to form the iridium carbene complex **B**. This carbene can be inserted into the N-H bond of anilines to afford the complex **C**. Followed by the regeneration of the catalyst and the formation of the intermediate **8**, cyclocondensation step proceeds rapidly to give the product **3aa**.



Scheme 3. Proposed mechanism for the formation of **3aa**.

In conclusion, we have demonstrated a novel and green synthetic strategy for the preparation of quinoxalines (through a cascade involving carbene generation, N-H insertion and cyclocondensation) utilizing sulfoxonium ylides as safe carbene sources. And this method was applied to more general X-H insertions (X=S and N) for synthesis of β-keto thioethers and β-keto anilines under mild and economical conditions. We believe this environmentally benign work will exhibit great potential and inspiration for the development of green carbene chemistry.

Acknowledgements

We are grateful for the support from the National Natural Science Foundation of China (Grant No: 81373259; 81573286).

Keywords: Quinoxalines • Carbene insertion • Green synthesis • *o*-Phenylenediamine • Iridium-catalyzed

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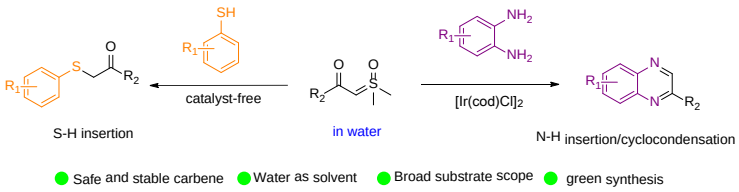
10.1002/ejoc.202000716

Entry for the Table of Contents

Key topic：carbene insertion



This work demonstrated an effective and green synthetic strategy for the preparation of quinoxalines utilizing sulfoxonium ylides as safe carbene sources via a key N-H insertion. And this method was applied to S-H insertions for synthesis of β-keto thioethers as well under mild and economical conditions. This strategy avoids the safety issues of diazo compounds and the use of organic solvents, which meets the goals and growing needs for sustainable chemistry.