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# Iodine-catalyzed convergent aerobic dehydro-aromatization toward benzazoles and benzazines†

 Xiaolong Tuo, Shanping Chen,\* Pingyu Jiang, Penghui Ni, Xiaodong Wang and Guo-Jun Deng<sup>†</sup>

An iodine-catalyzed aerobic dehydro-aromatization has been developed, providing straightforward and efficient access to various benzoazoles and benzoazines. The present transition-metal-free protocol enables the dehydro-aromatization of tetrahydrobenzazoles and tetrahydroquinolines with molecular oxygen as the green oxidant, along with some other N-heterocycles. Hence, a broad range of heteroaromatic compounds are generated in moderate to good yields under facile reaction conditions.

## Introduction

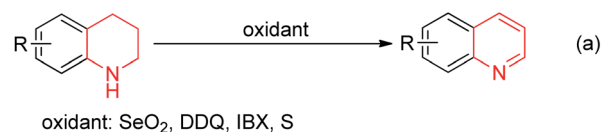
Benzazoles and benzazines have unique pharmacological and biological activities and thus have many applications in natural products and pharmaceutical drugs.<sup>1–3</sup> As a result, chemical researchers have been actively seeking new methodologies to synthesize these compounds. In recent years, dehydrogenative aromatization has emerged as a direct and efficient approach to access heteroaromatic compounds, especially N-heterocycles. This strategy produces a series of benzazines with high value<sup>4</sup> and continues to be an attractive and significant research object in organic synthesis.

The direct dehydro-aromatization methods were generally achieved by using stoichiometric oxidants, such as SeO<sub>2</sub>, DDQ, *o*-iodoxybenzoic acid (IBX) and sulfur (Scheme 1a).<sup>5,6</sup> Recently, transition metal catalysts combined with oxygen as the sole sacrificial reagent were used to enable oxidative dehydrogenative aromatization, such as Au, Pt, Pd, Ru, Fe, and Co.<sup>7–9</sup> On the other hand, in view of the atom-economy requirement and potential application for hydrogen storage, Ir, Ru, Fe and Co catalyst were used for the acceptorless dehydrogenation reactions of N-heterocycles.<sup>10–12</sup> However, due to the involvement of transition metals and other specialized catalysts or amounts of oxidants, these dehydrogenation protocols are often expensive or not environmentally friendly. In recent years, Lewis acids,<sup>13</sup> photoredox catalysis,<sup>14</sup> electrocatalysis<sup>15</sup> and graphene oxide (GO)<sup>16</sup> were used for the same goal (Scheme 1b). In addition, potassium *tert*-butoxide<sup>17</sup> and elemental sulfur<sup>18</sup> also could promote the dehydrogenation process. However, most of these methods are mainly suitable for dehydro-aromatization of N-heterocycles. Hence, developing a convergent catalytic system

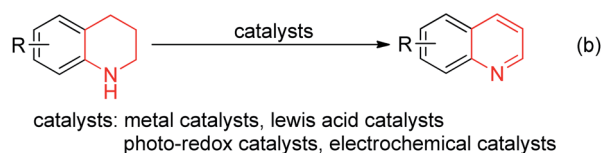
which can be employed for dehydro-aromatization of both carbocycles and N-heterocycles to afford a diversity of heteroaromatic compounds is highly desirable.

Our group has been focusing on synthesizing aromatic heterocyclic compounds, using cyclohexanones as the aryl source *via* a dehydrogenative aromatization sequence.<sup>19,20</sup> In our recent research, cyclohexanones coupled with amines to form tetrahydrobenzimidazoles, which could not be dehydrogenated to produce heteroaromatic compounds under these conditions.<sup>21</sup> As a follow up study, herein, we describe an iodine

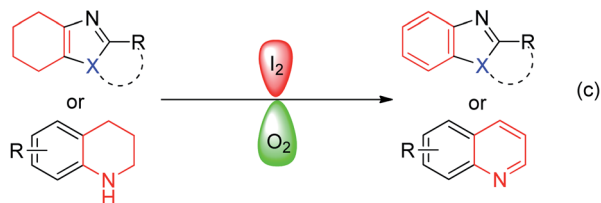
Stoichiometric dehydrogenation:



Catalytic dehydrogenation:



This work:



- metal-free ● green oxidant
- simple conditions ● broad substrate scopes

Scheme 1 Kinds of dehydrogenative aromatization reactions.

Key Laboratory of Environmentally Friendly Chemistry and Application of Ministry of Education, College of Chemistry, Xiangtan University, Xiangtan 411105, China.  
 E-mail: spchen@xtu.edu.cn; gjdeng@xtu.edu.cn

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catalyzed dehydro-aromatization reaction using molecular oxygen as the green oxidant toward various benzazoles and benzazines (Scheme 1c).

## Results and discussion

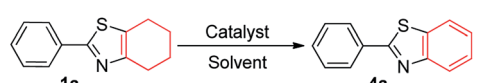
We commenced our studies by choosing 2-phenyl-4,5,6,7-tetrahydrobenzo[*d*]thiazole (**1a**) as the model substrate. The desired product **4a** was afforded in 36% in the presence of KI and oxygen (Table 1, entry 1). Then, a series of iodide-containing reagents such as NaI, NIS, elemental iodine, ICl and NaIO<sub>4</sub> were screened (entries 2–6).<sup>22</sup> The best reaction yield was achieved when elemental iodine was added as the catalyst (entry 4). A control experiment showed that trace of desired product was obtained in the absence of iodine reagent (entry 7). Subsequently, several solvents were tested. All of them did not give a higher yield (entries 8–13). The yield was up to 79% when *o*-dichlorobenzene (*o*-DCB) and toluene were used as the mixed solvent (entry 14). When the reaction atmosphere was changed to air, the reaction yield dramatically decreased (entry 15). A lower yield was obtained when the reaction was performed at 140 °C (entry 16).

With the optimized conditions in hand, we explored the scope of this dehydrogenative aromatization reaction. The model reaction afforded the target product **4a** in 75% isolated yield, and 68% isolated yield could be achieved in a gram-scale reaction. The corresponding products were obtained in moderate to good yields, when 2-phenyl-4,5,6,7-tetrahydrobenzo[*d*]thiazole substrates bearing with various substituents, such as alkyl, aryl,

methoxy and halogen (**4b–4i**). Bulky 1-(naphthalen-1-yl)-4,5,6,7-tetrahydrobenzo[*d*]thiazole and 2-(naphthalen-1-yl)-4,5,6,7-tetrahydrobenzo[*d*]thiazole could also react well to afford the target products in good yields (**4j**, **4k**). The steric effect of groups was not obvious on the reaction and the corresponding products were obtained in 62–74% yields when the carbocycle with an substituent (**4l–4n**). The desired product **4o** could be obtained in 56% yield when 1-benzyl-2-phenyl-4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazole was used as the substrate. Regrettably, 2-phenyl-4,5,6,7-tetrahydrobenzo[*d*]oxazole could not be dehydrogenated under the standard condition (**4p**). Subsequently, we investigated the dehydrogenation of tetracycle-fused system. Benzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole **5a** could be smoothly generated in 71% yield under the standard conditions when 7,8,9,10-tetrahydrobenzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole was used as the substrate. The substrates bearing a substituent such as methyl and halogen on the benzene ring afforded the corresponding product in 63–70% yields (**5b–5d**). The dehydrogenative products were given in 64–71% yields when carbocycle was decorated by an alkyl or aryl substituent (**5e**, **5f**) (Tables 2 and 3).

To further extend the scope of the substrates, we tested a variety of *N*-heterocycles under the standard reaction condition. Fortunately, most of them could give the desired products in moderate to good yields. Quinoline **6a** was generated in 67% yield when 1,2,3,4-tetrahydroquinoline was used as the substrate. Tetrahydroquinolines with a methyl located at 2-, 3-, 4-, or 8-position could afford the corresponding dehydrogenation products in good yields (**6b–6e**). Strong electron-

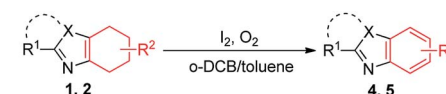
Table 1 Optimization reaction conditions<sup>a</sup>



Entry	Catalyst	Solvent	Yield <sup>b</sup> (%)
1	KI	<i>o</i> -DCB	36%
2	NaI	<i>o</i> -DCB	39%
3	NIS	<i>o</i> -DCB	52%
4	I <sub>2</sub>	<i>o</i> -DCB	71%
5	NaIO <sub>4</sub>	<i>o</i> -DCB	68%
6	ICl	<i>o</i> -DCB	67%
7	—	<i>o</i> -DCB	Trace
8	I <sub>2</sub>	Chlorobenzene	51%
9	I <sub>2</sub>	Toluene	55%
10	I <sub>2</sub>	1,4-Dioxane	23%
11	I <sub>2</sub>	DMSO	Trace
12	I <sub>2</sub>	NMP	ND
13	I <sub>2</sub>	DMA	ND
14 <sup>c</sup>	I <sub>2</sub>	<i>o</i> -DCB/toluene	79% (75%) <sup>f</sup>
15 <sup>c,d</sup>	I <sub>2</sub>	<i>o</i> -DCB/toluene	48%
16 <sup>c,e</sup>	I <sub>2</sub>	<i>o</i> -DCB/toluene	53%

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), catalyst (20 mol%), solvent (0.8 mL), 160 °C, under O<sub>2</sub> (sealed tube), 30 h. <sup>b</sup> GC yield. <sup>c</sup> *o*-DCB/toluene (0.8 mL/0.2 mL). <sup>d</sup> Under air. <sup>e</sup> At 140 °C. <sup>f</sup> Isolated yield. *o*-DCB: *o*-dichlorobenzene, ND: not detected.

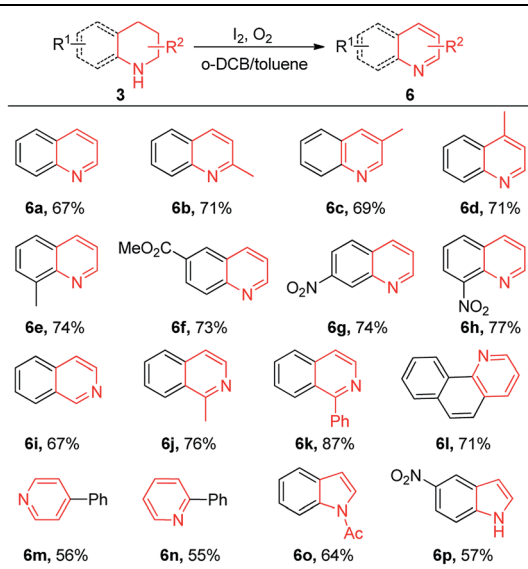
Table 2 Dehydro-aromatization of tetrahydrobenzazoles<sup>a</sup>



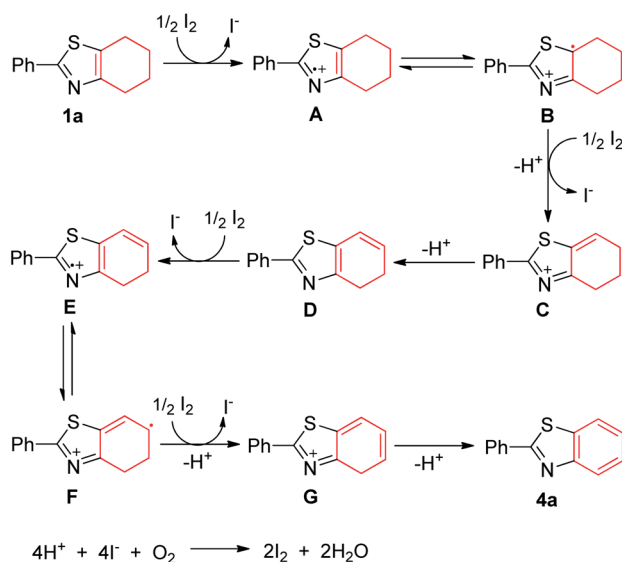
<b>4a</b> , R = H, 75%, 68% <sup>b</sup>	<b>4b</b> , R = CH <sub>3</sub> , 74%	<b>4c</b> , R = <i>t</i> -Bu, 71%	<b>4d</b> , R = Ph, 64%	<b>4e</b> , R = OCH <sub>3</sub> , 61%	<b>4f</b> , R = F, 59%	<b>4g</b> , R = Br, 58%	<b>4h</b> , R = OCH <sub>3</sub> , 59%	<b>4i</b> , R = Cl, 56%
<b>4j</b> , R = 1-naphthyl, 71%	<b>4k</b> , R = 2-naphthyl, 68%	<b>4l</b> , R = Et, 62%	<b>4m</b> , R = <i>t</i> -Bu, 67%	<b>4n</b> , R = Ph, 74%	<b>4o</b> , 56%	<b>4p</b> , 0%		
<b>5a</b> , 71%	<b>5b</b> , 63%	<b>5c</b> , 70%	<b>5d</b> , 68%	<b>5e</b> , 64%	<b>5f</b> , 71%			

<sup>a</sup> Conditions: **1** or **2** (0.2 mmol), I<sub>2</sub> (20 mol%), *o*-DCB/toluene (0.8 mL/0.2 mL), 160 °C, 30 h, under O<sub>2</sub> (sealed tube), isolated yield. <sup>b</sup> 6 mmol scale.



Table 3 Dehydro-aromatization of N-heterocycles<sup>a</sup>

<sup>a</sup> Conditions: **3** (0.2 mmol), I<sub>2</sub> (20 mol%), *o*-DCB/toluene (0.8 mL/0.2 mL), 160 °C, 30 h, under O<sub>2</sub>, isolated yield.



Scheme 2 Possible reaction mechanism.

withdrawing groups, such as ester and nitro groups, attached at tetrahydroquinoline substrates were well tolerated to give the target products (**6f–6h**). The dehydrogenation reactions of 1,2,3,4-tetrahydroisoquinoline smoothly proceeded to give the corresponding isoquinoline products in 67–87% yields (**6i–6k**). Benzo[*h*]quinoline **6l** was produced in 71% yield. In addition, 4-phenylpiperidine and 2-phenylpiperidine could be oxidized to form pyridine products in moderate yields under standard conditions (**6m**, **6n**). Furthermore, indole products could be obtained in good yields when 1-(indolin-1-yl)ethanone and 5-nitroindoline were used (**6o**, **6p**).

On the basis of relevant literatures,<sup>23</sup> a possible reaction mechanism is illustrated in Scheme 2. Initially, nitrogen-centered radical **A** is formed *via* single-electron oxidation process from **1a** in the presence of elemental iodide, and elemental iodide converts into iodine ion. Tautomerization of **A** produces intermediate **B**. Subsequent single-electron oxidation and deprotonation of **B** generates intermediate **C**, which can be further transformed into intermediate **D** *via* a deprotonation. Meanwhile, the second single-electron oxidative dehydrogenation of **D** affords the intermediate **G**, followed by a deprotonation to provide the desired product **4a**. The iodide anion is oxidized to form iodine in the presence of oxygen.

## Conclusions

In conclusion, we have developed a direct dehydro-aromatization of tetrahydrobenzazoles and N-heterocycles, providing a straightforward and efficient approach to a variety of benzazoles and benzazines. The present protocol is achieved by use of elemental iodine as the catalyst and molecular oxygen as the green oxidant, which could produce a broad range of products in moderate to good yields under facile transition-metal-free conditions.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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