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Oxidation of 2-arylindoles for synthesis of 2-arylbenzoxazinones with oxone as the sole oxidant†

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A novel and efficient method for the oxidation of 2-arylindoles to synthesize 2-arylbenzoxazinones utilizing oxone as the sole oxidant has been developed. The reaction tolerates a wide range of functional groups and allows quick and atom-economical assembly of a variety of valuable 2-arylbenzoxazinones in high yields.

Benzoxazinones are some of the most important fused heterocycles in many biological compounds and pharmaceutical drugs (Fig. 1).[1] They are also versatile building blocks in organic synthesis and medicinal chemistry.[2] For example, 2-aryl-benzoxazinones are valuable synthetic intermediates for the synthesis of bioactive quinazolin-4(3*H*)-one derivatives (Fig. 1).[3] Therefore, the methods for the synthesis of benzoxazinones have received intensive attention over the past decade.[4] In addition to cyclization of anthranilic acid or *N*-acetylanthranilic acid,[5] palladium catalyzed carbonylation reactions have emerged for the synthesis of benzoxazinones. Alper and co-workers[6] and Wu and Beller[7] have independently developed palladium catalyzed carbonylation of *ortho*-haloanilines to synthesize benzoxazinones. Palladium-catalyzed direct carbonylation of benzanilides or aryl urea derivatives for the synthesis of benzoxazinones has been developed by the Yu group[8] and the Lloyd-Jones and Booker-Milburn group,[9] respectively. Recently, Liu and co-workers have developed an interesting palladium catalyzed C≡C triple bond cleavage of 2-azidoalkynylbenzenes for the synthesis of benzoxazinones.[10] Despite these advances, novel and efficient methods for the synthesis of benzoxazinones that are compatible with various functional groups and proceed under mild conditions remain highly desirable.

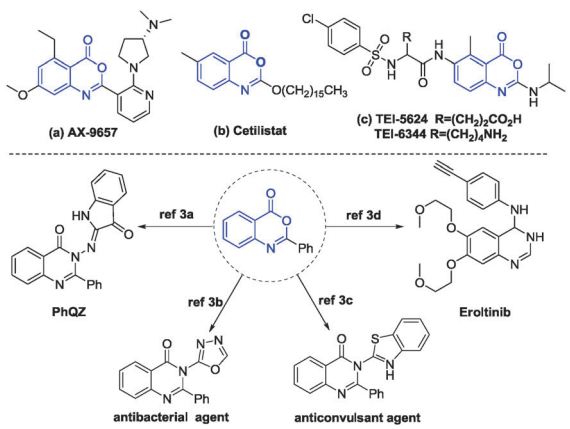

Fig. 1 Some bioactive benzoxazinones and their applications in the synthesis of bioactive quinazolin-4(3*H*)-ones.

The selective oxidation is one of the most useful reactions for organic transformations.[11] Particularly, oxidation reactions that utilize environmentally benign peroxides or O_2 as the oxidants are preferable according to the principles of green chemistry.[12] Oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$), which is a stable, nontoxic and inexpensive oxidant, shows great efficiency in many oxidative transformations,[13] for example oxidation of aldehydes to carboxylic acids,[14] epoxidation of alkenes,[15] and oxidative cleavage of alkenes or alkynes to carboxylic acids.[16] In this communication, we report the direct oxidation of 2-arylindoles for the synthesis of 2-arylbenzoxazinones using oxone as the sole oxidant under transition-metal-free conditions.

Initially, 2-phenylindole **1a** was chosen as a test substrate to optimize the reaction conditions (Table 1). A variety of oxidants such as $K_2S_2O_8$, $(NH_4)_2S_2O_8$, TBHP, *m*-CPBA and *t*BuOO*t*Bu were screened (Table 1, entries 1–5). 2-Phenylbenzoxazinone product **2a** was observed when $(NH_4)_2S_2O_8$ was used as the oxidant, albeit in only 20% yield. H_2O_2 which is a good oxidant in Baeyer–Villiger oxidation was also screened.[17] However, only a trace of **2a** was obtained (Table 1, entry 6). Further screening of oxidants revealed that oxone showed great efficiency for this transformation. The yield of 2-phenylbenzoxazinone **2a** improved dramatically to 91% in the presence of oxone (Table 1, entry 7). Optimization of different solvents revealed that DCE and CH_3CN were inferior to CH_3NO_2 in the reaction (Table 1, entries 8 and 9). It should be noted that a slightly low yield of 2-phenylbenzoxazinone **2a** was

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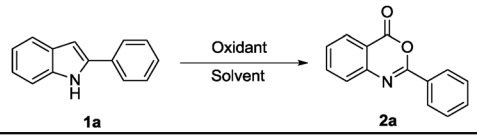
† Electronic supplementary information (ESI) available: Experimental procedure, characterization data, CIF of compound **2a**, ^1H and ^{13}C NMR spectra of compounds **2**. CCDC 942843. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc44215b

Table 1 Optimization reaction conditions for direct oxidation of 2-phenylindoles[a]



1a 2a

Entry	Oxidant	Solvent	T (°C)	Yield[b] (%)
1	$K_2S_2O_8$	CH_3NO_2	80	nr
2	$(NH_4)_2S_2O_8$	CH_3NO_2	80	20
3	TBHP	CH_3NO_2	80	16
4	*t*BuOO*t*Bu	CH_3NO_2	80	nr
5	*m*-CPBA	CH_3NO_2	80	7
6	H_2O_2	CH_3NO_2	80	5
7	Oxone	CH_3NO_2	80	91
8	Oxone	DCE	80	45
9	Oxone	CH_3CN	80	70
10	Oxone	CH_3NO_2	80	78[c]
11	Oxone	CH_3NO_2	60	10
12	Oxone	CH_3NO_2	100	93
13	Oxone	CH_3NO_2	120	90

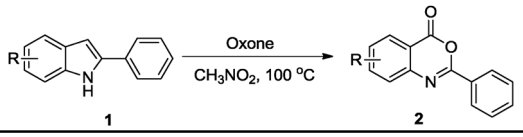
[a] Reaction conditions: **1a** (0.2 mmol), oxidant (3.0 equiv.) in solvent (2 mL), under air. [b] Isolated yield. [c] K_2CO_3 (2.0 equiv.) was added.

obtained when the reaction was conducted under basic conditions (Table 1, entry 10). The reaction temperature was also varied, and 100 °C gave the best result (Table 1, entries 11–13).

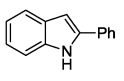
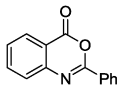
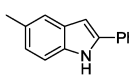
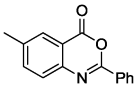
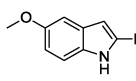
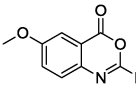
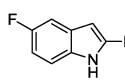
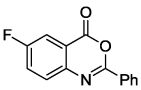
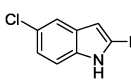
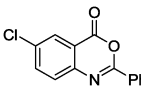
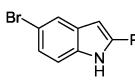
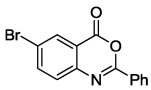
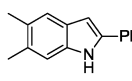
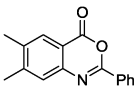
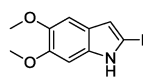
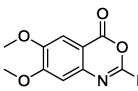
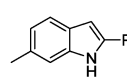
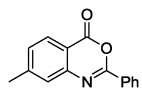
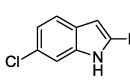
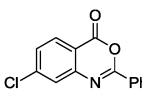
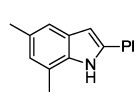
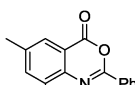
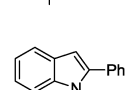
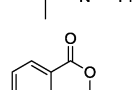
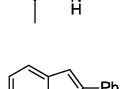
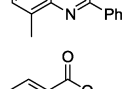
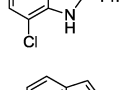
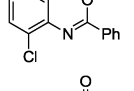
With the optimized reaction conditions established, the scope and generality of the reaction were investigated (Table 2). The reaction showed high functional group tolerance and proved to be a quite general methodology for the preparation of 2-phenylbenzoxazinones. It is noteworthy that the reaction was insensitive to the electronic effects of the substrates. 5-Methyl, fluoro, chloro or bromo substituted indoles **1b**–**1f** reacted smoothly to give the corresponding products **2b**–**2f** in high yields (Table 2, entries 2–6). Methoxyl substituted 2-phenylindoles gave moderate yields of benzoxazinones due to the partial decomposition of the products (Table 2, entries 3 and 8). Both 6- and 7-substituted indoles showed similar reactivity to that of 5-substituted indoles in the transformations. Satisfactorily, a wide range of valuable 6- or 7-substituted 2-phenylbenzoxazinones **2g**–**2m** were synthesized in high yields (Table 2, entries 7–13). In addition, 2-phenyl-4*H*-naphtho[1,2-*d*][1,3]oxazin-4-one **2n** was also obtained in 60% yield when 2-phenyl-1*H*-benzo[*g*]indole **1n** was used as the substrate (Table 2, entry 14).

Next, the effects of the substituents on the aryl ring of 2-arylindoles were examined (Table 3). Similarly, the reaction was insensitive to the electronic effects of the substituents. As shown in Table 3, 2-arylindoles with methyl, methoxyl, fluoro, chloro and bromo groups on the aryl rings all gave the corresponding benzoxazinones **2o**–**2u** in good to excellent yields. Moreover, 2-(5,6,7,8-tetrahydronaphthalen-1-yl)-1*H*-indole **1v** reacted smoothly to give the desired benzoxazinone **2v** in 75% yield implying that this transformation was insensitive to steric hindrance. However, simple indole was inert in the reaction. Indol-2-yl pivalate **1w** was transformed into indolin-2-one **3** in 86% yield under the standard conditions. And isatoic anhydride **4** was obtained in 78% yield when 2-imidazole substituted indole **1x** was used as the substrate (Scheme 1). It should be noted that the obtained 2-arylbenzoxazinones can be further transformed into a variety of pharmaceuticals, which are anti-bacterial, anti-fungal and anti-tumor agents, through simple operations.[18] Therefore, our oxidation reaction could provide a useful route for drug discovery.

Table 2 Oxidation of 2-phenylindoles for the synthesis of 2-phenylbenzoxazinones with oxone[a]



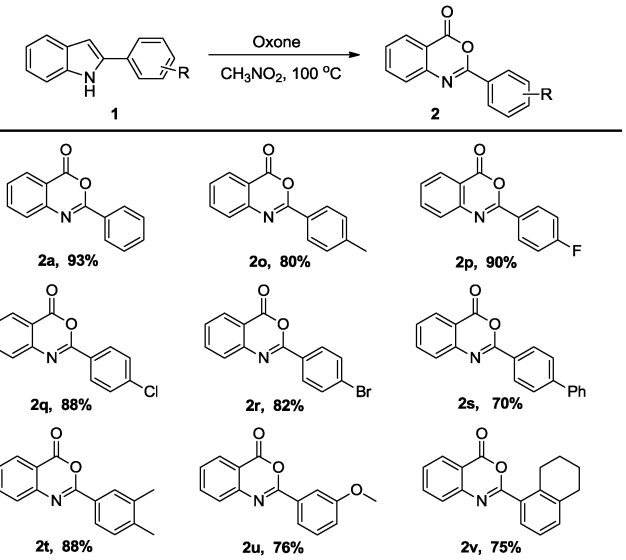
1 2

Entry	Substrate **1**	Product **2**	Yield[b] (%)
1	 **1a**	 **2a**	93
2	 **1b**	 **2b**	90
3	 **1c**	 **2c**	52
4	 **1d**	 **2d**	76
5	 **1e**	 **2e**	84
6	 **1f**	 **2f**	83
7	 **1g**	 **2g**	80
8	 **1h**	 **2h**	50
9	 **1i**	 **2i**	85
10	 **1g**	 **2g**	88
11	 **1k**	 **2k**	92
12	 **1l**	 **2l**	80
13	 **1m**	 **2m**	70
14	 **1n**	 **2n**	60

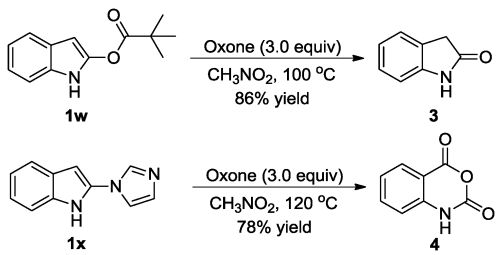
[a] Reaction conditions: **1a** (0.2 mmol), oxone (3.0 equiv.) in CH_3NO_2 (2 mL) at 100 °C for 8–10 h. [b] Isolated yield.

To gain more insight into the mechanism of the reaction, oxidation of 2-phenyl-3*H*-indol-3-one **A** was performed under the standard conditions. The 2-phenylbenzoxazinone **2a** was

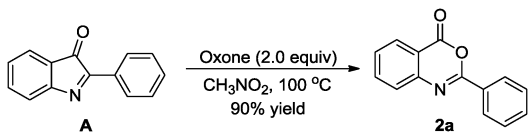
Table 3 Oxidation of 2-arylindoles for the synthesis of 2-arylbenzoxazinones with oxone[a,b]



[a] Reaction conditions: **1a** (0.2 mmol), oxone (3.0 equiv.) in CH_3NO_2 (2 mL) at 100 °C for 8–10 h. [b] Isolated yield.



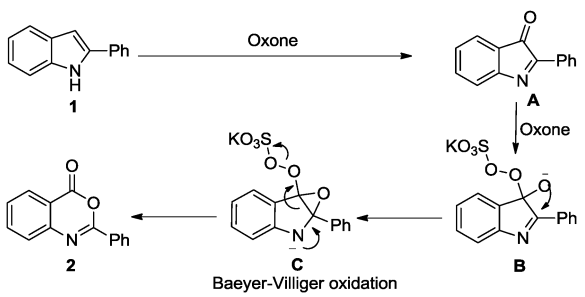
Scheme 1 Oxidation of 2-heteroatom substituted indoles.



Scheme 2 Oxidation of 2-phenyl-3*H*-indol-3-one **A**.

obtained in 90% yield (Scheme 2). This result indicated that the 2-phenyl-3*H*-indol-3-one **A** was probably an intermediate for the oxidation of 2-phenylindole **1** by oxone.

On the basis of the above results and literature reports,[10,13] a tentative mechanism is shown in Scheme 3. Firstly, oxidation of 2-phenylindole **1** by oxone gives 2-phenyl-3*H*-intermediate **A**.[13,19] Then, Baeyer–Villiger oxidation of the intermediate **A** generates the product **2**.[20]



Scheme 3 Proposed mechanism for the oxidation reaction.

In summary, we have developed a simple, efficient and practical method for the oxidation of 2-arylindoles to synthesize 2-arylbenzoxazinones. Environmentally benign, inexpensive, and safe oxone was found to be a particularly effective terminal oxidant in the reaction. The reaction tolerates a wide range of functional groups and is a reliable method for the rapid assembly of a variety of valuable 2-arylbenzoxazinones in high yields under mild conditions.

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