RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 8720

Received 16th December 2013
Accepted 17th January 2014

DOI: 10.1039/c3ra47660j

www.rsc.org/advances

Oxone-mediated oxidative carbon-heteroatom bond cleavage: synthesis of benzoxazinones from benzoxazoles with α-oxocarboxylic acids†

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A metal-free oxidative cleavage of benzoxazoles using Oxone as an oxidant has been developed. The *in situ* formed *o*-aminophenol has been proved to react successfully with α-oxocarboxylic acids affording the benzoxazinones in moderate to good yields.

Benzoxazoles are important heterocycles and versatile intermediates in the preparation of a wide variety of biologically and industrially valuable organic compounds.[1] In particular, the catalytic direct C–H bond cleavage of benzoxazoles followed by the C–C and C-heteroatom bond formation with various electrophiles or nucleophiles have received significant attention in recent years.[2] Furthermore, the carbon-heteroatom bond cleavage of benzoxazoles is also an important fundamental transformation in organic chemistry. For example, Lown has reported an efficient cleavage of benzoxazoles to *o*-hydroxy-*N*-substituted anilines in the presence of sodium borohydride/acetic acid.[3a] Other methods were also available for the break of C-heteroatom bond of benzoxazoles under acidic conditions.[3b,c] More recently, the Pt-catalyzed oxidative cleavage of benzoxazoles to the corresponding aminophenols has also been reported.[4] However, there have been no reports concerning a tandem oxidative cleavage of benzoxazoles for the formation of more valuable heterocycles to date.

Oxone is usually environmentally benign and easily handled oxidant that has been used extensively in organic synthesis.[5] For example, the ability of Oxone has been demonstrated in the oxidative cleavage of alkenes or alkynes to the corresponding carboxylic acids and ketones.[6] Oxone is also well known for its oxidative cleavage of dicarbonyls and α-hydroxyketones to carboxylic acids or α-keto esters.[7] Compared to the carbon–carbon bond cleavage, Oxone is less commonly employed in carbon-heteroatom bond cleavage reactions.[5] In continuation of our interest in developing oxidative tandem processes for the construction of heterocycles[8] and the oxidative coupling reactions of α-oxocarboxylic acids.[9] We envisioned that the use of Oxone as an oxidant for the oxidative cleavage of benzoxazoles followed by coupling with α-oxocarboxylic acids might be a useful method for the synthesis of more valuable heterocycles.[10] Herein, we report a facile protocol for the tandem oxidative cleavage/coupling of benzoxazoles with α-oxocarboxylic acids in the presence of Oxone providing the benzoxazinones which are important structural motifs in biological medicinal chemistry and material chemistry.[11]

Our investigation started with the coupling of 5-methylbenzoxazole **1a** with phenylglyoxylic acid **2a** using 1.0 equiv. Oxone as sole oxidant (Table 1). After screening a variety of solvents, it was found that the 5% DMSO/diglyme was the best solvent giving the 6-methyl-3-phenylbenzoxazinone **3a** in 80% isolated yield (entries 1–6). To our delight, simply changing the ratio of **1a** and **2a** from 1 : 1 to 1 : 1.5, the yield of **3a** could be further improved to 90% (entry 7). It should be noted that the reaction did not occur in the absence of Oxone (entry 8). A series of oxidants showed less effective or ineffective (entries 9–12).

Under the optimized reaction conditions, a variety of benzoxazoles **1** were examined for this tandem oxidative coupling reaction (Table 2). Benzoxazoles with 5-substituted electron-rich and -withdrawing groups are all effectively engaged in this reaction (**3a–e**). It is noteworthy that bromo-substituted benzoxazole **1d** was tolerated well and provided the corresponding product **3d** in moderate yield, which could be used for further transformation. The reaction of 6-methylbenzoxazole with **2a** also worked well to give the product **3f** in 76% yield. It should be noted that the reaction could also be scaled up to 2 mmol, the corresponding products **3a** and **3d**, were obtained in good yields.

Various substituted α-oxocarboxylic acids were then tested for this oxidative cleavage/coupling reaction under the optimized conditions. The results are summarized in Table 3. As

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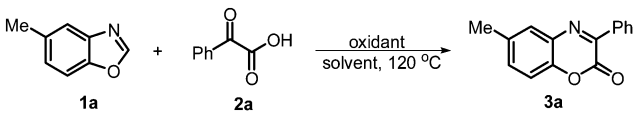
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra47660j

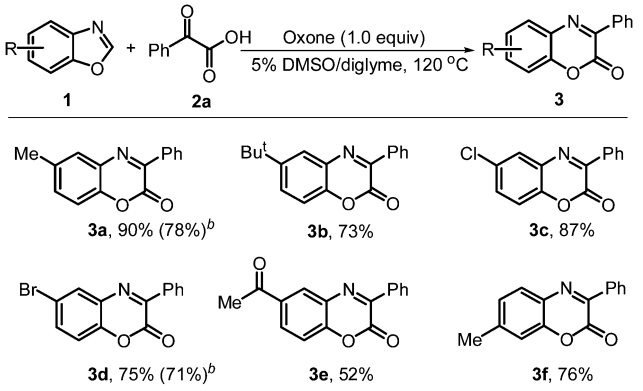
Table 1 Optimization of the oxidative cleavage/coupling of benzoxazoles **1a** with phenylglyoxylic acid **2a**[a]



Entry	Oxidant (equiv.)	Solvent	Yield[b] (%)
1	Oxone (1.0)	DMF	Trace
2	Oxone (1.0)	DCE	N.r.[c]
3	Oxone (1.0)	DME	N.r.[c]
4	Oxone (1.0)	CH_3CN	N.r.[c]
5	Oxone (1.0)	Diglyme	78
6	Oxone (1.0)	5% DMSO/Diglyme	80
7	Oxone (1.0)	5% DMSO/Diglyme	90[d]
8	—	5% DMSO/Diglyme	N.r.[c]
9	$(NH_4)_2S_2O_8$ (1.0)	5% DMSO/Diglyme	26
10	$K_2S_2O_8$ (1.0)	5% DMSO/Diglyme	23
11	BQ (1.0)	5% DMSO/Diglyme	N.r.[c]
12	$PhI(OAc)_2$ (1.0)	5% DMSO/Diglyme	Trace

[a] *Reaction conditions*: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.2 mmol, 1.0 equiv.), oxidant (1.0 equiv.), solvent (2.0 mL), 120 °C, 12 h. [b] Yield of isolated product. [c] N.r. = No reaction. [d] **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.3 mmol, 1.5 equiv.).

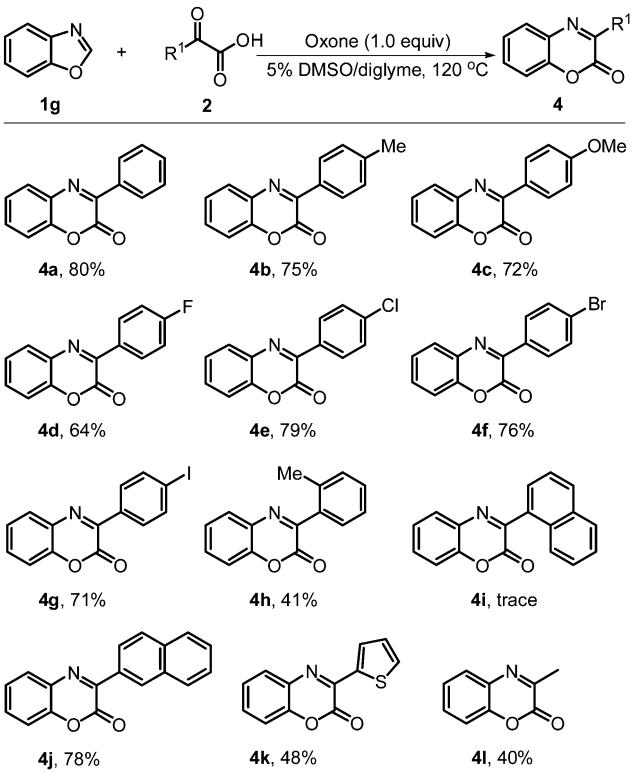
Table 2 Scope of benzoxazoles[a]



[a] All reactions were performed with **1** (0.2 mmol) and phenylglyoxylic acids **2a** (1.5 equiv.), under standard conditions (Table 1, entry 7) at 120 °C. Yields are of the isolated products. [b] Yield on a 2 mmol scale is given in parentheses.

shown in Table 3, this reaction proceeded well with a wide range of *p*-substituted phenylglyoxylic acids and gave the corresponding benzoxazinones in moderate to good yields (**4b**–**g**). Notably, when bromo or iodo group was included in phenylglyoxylic acid, the corresponding products **4f** and **4g** were also obtained in 76% and 71% yields, respectively. The results were significant because the halo groups retained in the benzoxazinones provide opportunities for further transformation under transition metal catalytic systems. On the other hand, substrates bearing an *ortho*-substituent such as *o*-methyl phenylglyoxylic acid **2h** furnished lower yield, probably due to the steric hindrance. Besides the desired product **4h** (41%), the

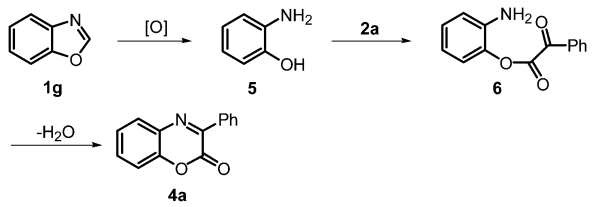
Table 3 Scope of α-oxocarboxylic acids[a]



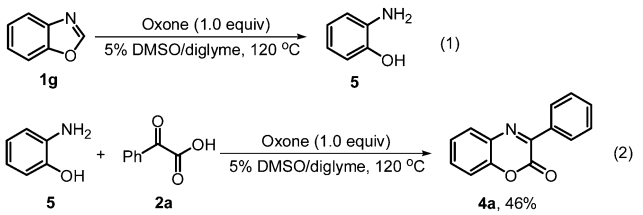
[a] All reactions were performed with **1g** (0.2 mmol) and α-oxocarboxylic acids **2** (1.5 equiv.), under standard conditions (Table 1, entry 7) at 120 °C. Yields are of the isolated products.

byproduct *o*-methylbenzaldehyde was also isolated in 28% yield in this reaction. When α-naphthyloxoacetic acid was employed, only a trace amount of the desired product **4i** was detected and the major product was determined as the α-naphthaldehyde.[12] While, for β-naphthyloxoacetic acid, the corresponding product **4j** was obtained in good yield. These results indicated that the tandem oxidative reaction was hampered by steric hindrance. Hetero- and aliphatic α-oxocarboxylic acids, such as 2-thienylglyoxylic acid and pyruvic acid, resulted in the desired products in somewhat lower yields (**4k** and **4l**).

To gain better insight into the mechanism, some control experiments were conducted under the standard reaction conditions. When benzoxazole **1g** was subjected to the optimized reaction conditions (eqn 1), *o*-aminophenol **5** was detected, which indicated that benzoxazole could undergo the carbon-heteroatom bond cleavage in the presence of Oxone.[4,5] On the other hand, the reaction of *o*-aminophenol **5** with phenylglyoxylic acid **2a** gave the benzoxazinone **4a** in 46% isolated yield (eqn 2), suggesting that aminophenol should be an intermediate in this reaction. On the basis of the above observations, a tentative mechanism is proposed in Scheme 1. *o*-Aminophenol **5** is formed *via* oxidative carbon-heteroatom bond cleavage of benzoxazole under Oxone. A subsequent standard esterification reaction followed by condensation provided the benzoxazinone product.



Scheme 1 Proposed mechanism.



In summary, we have demonstrated an interesting tandem oxidative cleavage/coupling process of benzoxazoles with α-oxocarboxylic acids to the benzoxazinones using Oxone as a sole oxidant under metal-free conditions. The method is compatible with a wide range of easily available reactants and reagents.

Acknowledgements

Financial support from National Natural Science Foundation of China (no. 21102110) and the Fundamental Research Funds of the Central Universities (no. 2011jdhz28) are greatly appreciated.

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