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Simple and efficient syntheses of 2-hydroxy-3*H*-phenoxazin-3-ones by aerobic oxidative cross-cyclocondensation in water†

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A novel, simple and versatile synthetic approach that utilized natural renewable low-toxic gallic acid as an organocatalyst was developed for efficient aerobic oxidative cross-cyclocondensations of equimolar 2-aminophenols and 2-hydroxylphenols to afford various 2-hydroxy-phenoxazin-3-ones with moderate to high isolated yields at room temperature in water.

3*H*-Phenoxazin-3-one (PXO), a widespread natural chromophore,[1] was used as a dye and pigment in ancient times, and later developed as a probe for bio-imaging in modern days.[2] PXO derivatives are reported to demonstrate bioactivities to be used for the treatment of malarial, cancer, inflammatory, bacterial infection, neurodegenerative and other diseases.[3] Actinomycin D is one of the most extensively studied PXO derivatives, which embodies a 2-amino-PXO scaffold and displays both antibiotic and anticancer bioactivity.[4] Xanthommatin, a natural 2-amino-PXO biochrome, is abundant in insects, arachnids, and cephalopods.[5] It is of great interest to develop synthetic methodology to prepare new PXO derivatives. The previous synthetic efforts have focused on 2-amino-PXOs.[6] Yoo and Rill discovered that hydroxyl-actinomycin D, which had 2-hydroxy-3*H*-phenoxazin-3-one (HPXO) as the central chromophore structure instead of original 2-amino-PXO, showed unusually high selectivity to DNA binding.[7] An efficient synthetic method for HPXOs is expected to be highly valuable. Nevertheless, there are few reports on the synthesis of HPXO.[8] For instance, laccase-mediated homodimerization of 3-amino-2-hydroxybenzenesulfonic acid in methanol/H_2O gave HPXO-1,6-disulfonic acid with a poor yield of 4%.[9] Small quantities of HPXO were found as byproducts in the reaction of *o*-aminophenol and *p*-benzoquinone in acetic acid,[10] and $K_3[Fe(CN)_6]$ oxidation of 3-hydroxyanthranilic acid in ethanol.[11] Moreover, the common method for HPXO syntheses with hydroxy substitution of 2-amino-PXO requires strong acidic media (Fig. 1A).[7,8,12] Therefore, to develop new environment-friendly methods for the synthesis of HPXO with a high yield is highly desirable.

For sustainable development, green synthesis is highly desirable focusing on environment-friendly manufacturing, and safe and low cost production. Over the past few decades, aerobic oxidations in aqueous solution continue to receive considerable attention from industry and academia due to the use of the most environment-friendly solvent and oxidant with the lowest cost.[13] Undoubtedly, aerobic oxidation in water is desirable since it would avoid the use of flammable organic solvents and the risk of explosion. Recently, we successfully developed a novel and highly efficient methodology to prepare disulfanes in water that used naturally renewable, inexpensive and low-toxic gallic acid (**GA**) as an organocatalyst, inexpensive $MnCO_3$ as a co-catalyst, and dioxygen as the terminal oxidant.[14] Remarkably, this simple metal–organic cooperative catalytic protocol follows a single-electron-transfer route. Herein we expand this **GA**/Mn system to catalyze the cross-

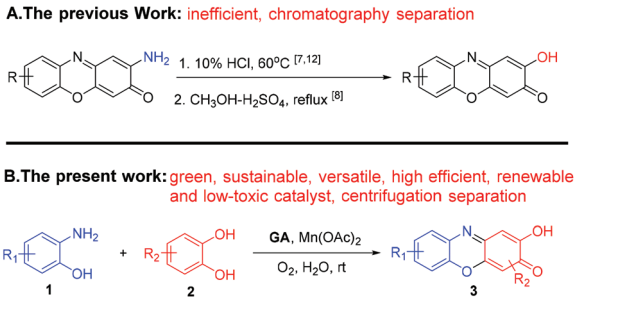

Fig. 1 The previous and present methods to synthesize HPXO derivatives.

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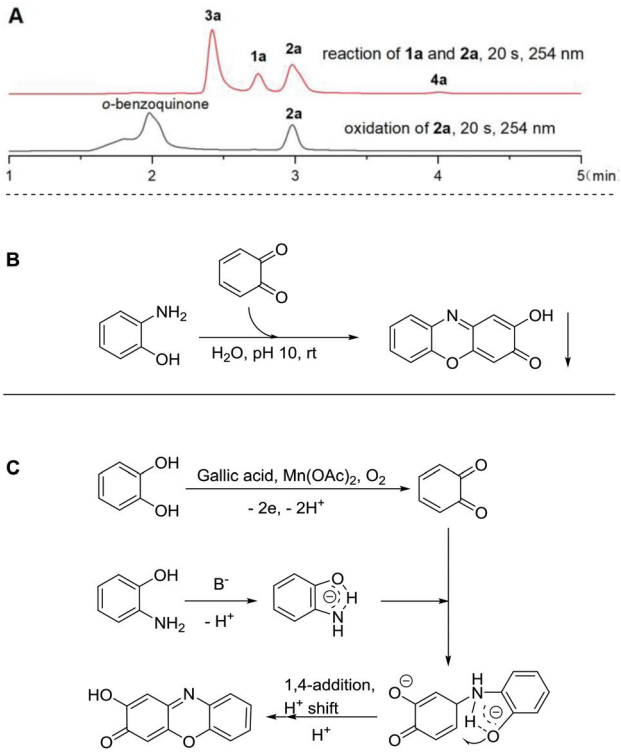
cyclocondensations of 2-aminophenols (**1**) and 2-hydroxylphenols (**2**) to prepare HPXOs (**3**), a synthetic transformation that has not been reported previously (Fig. 1B).

Based on the optimal conditions of our previous research,[14] the initial experiment was carried out using equimolar 2-aminophenol (**1a**) and 2-hydroxylphenol (**2a**) as the test substrates with 0.25 mol% **GA** and $Mn(OAc)_2$ (0.25 mol%) under 0.3 MPa of dioxygen at pH 9 and for 3 h at room temperature. For the convenience of operation, the experiment used $Mn(OAc)_2$ rather than $MnCO_3$ since both of them have similar catalytic activity and $Mn(OAc)_2$ has a higher solubility in water. HPLC detection showed that the initial reaction afforded a mixture of products, including *ca.* 48% HPXO (**3a**), 43% 2-amino-PXO (**4a**), and 9% other products. The result indicated that cross-cyclocondensation of **2a** to **3a** and homodimerization of **1a** to **4a** occurred together. Solubility tests revealed that, in basic water, **2a** dissolved much more quickly and had a higher solubility than **1a**. In the earlier stage of the reaction, a considerable amount of **1a** was not dissolved, which might partially account for the yield of multiple products. Subsequently, the reaction was pretreated with ultrasonication, and different pH values were screened with a lower reactant concentration (Fig. 2). As pH changed from 7.0 to 11.0, the yield of the cross-cyclocondensation product also varied. Remarkably, at pH = 10.0, **3a** could be obtained with a 96.4% HPLC yield. However, at pH = 11, the yield of **3a** dropped. The possible reason is that **3a** degraded under the strong basic conditions.

To gain some insights into reaction route of cross-cyclocondensation, control experiments were carried out (Scheme 1). HPLC traces (Scheme 1A) showed that, in the control experiment of oxidation of **2a** alone at pH 10, about half of **2a** was converted to *o*-benzoquinone in 20 seconds. Under the same conditions, the cross-cyclocondensation of **1a** and **2a** gave a high yield of **3a** as the major product and **4a** as the byproduct.



Scheme 1 The control experiments and proposed mechanism.

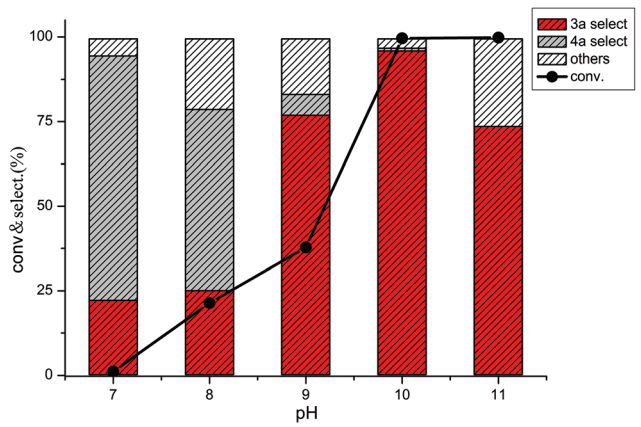
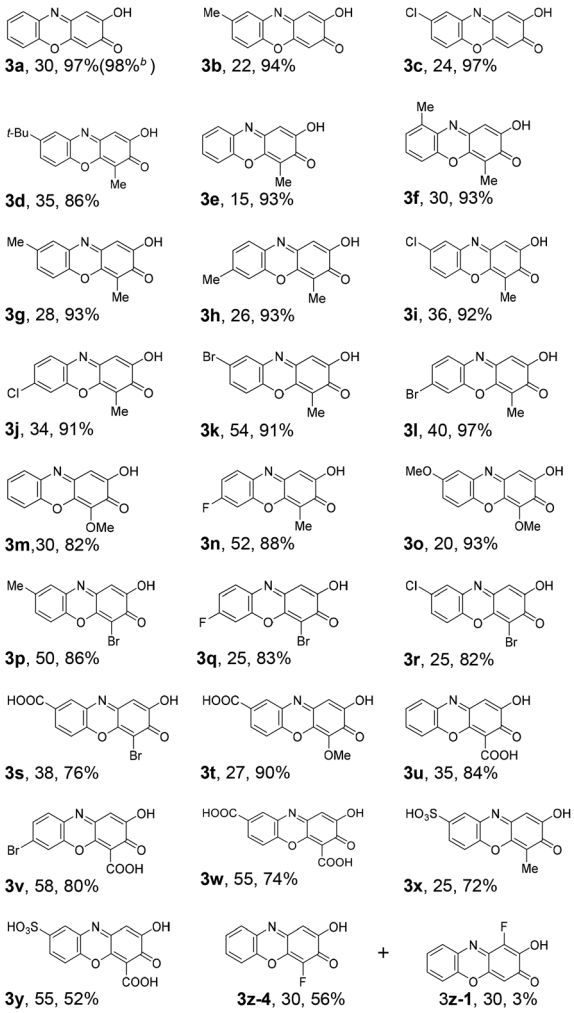


Fig. 2 The pH effect on cross-cyclocondensation between **1a** and **2a**. Reaction conditions: **1a** (1.0 mM), **2a** (1.0 mM), H_2O (50 mL), ultrasonication, **GA** (0.25 mol%), $Mn(OAc)_2$ (0.25 mol%), O_2 (0.3 MPa), 1 h, 150 mL autoclave. HPLC detection. The pH values were adjusted with NaOH.

When fresh *o*-benzoquinone, which was prepared according to the reported method,[15] was added into the aqueous solution of 2-aminophenol, the orange **3a** precipitated immediately, and *o*-benzoquinone almost disappeared (Scheme 1B). As described before, the redox cycle of **GA**/Mn^{2+} could catalyze the single-electron aerobic oxidation.[14] Moreover, electron paramagnetic resonance study of the oxidation of **GA** indicated that **GA** forms its radicals as a function of pH and radical concentration was 1000 times higher at pH 13 than that at pH 9.[16] Thus, we proposed that in the cross-cyclocondensation the more radical species that were formed from **GA** at the higher pH would significantly accelerate the areobic oxidation, and **2a** converted rapidly to the corresponding *o*-benzoquinone, which was beneficial for its subsequent 1,4-additions with the nucleophilic N atom of **1a** (Scheme 1C). Consequently, the cross-cyclocondensation completed within 0.5 h and selectively afforded **3a**. Notably, the gram-scale test gave a 98% isolated yield of **3a** by a simple work-up of acidification, centrifugation and recrystallization, well illustrating its practical application.

Finally, the above reaction conditions were applied to expand the substrate scope. Table 1 provides the results of the corresponding cross-cyclocondensations between equimolar **1** and **2**. The corresponding HPXO products **3a–z** were obtained with moderate to high isolated yields by simple work-up of acidification, centrifugation and recrystallization. Whether substituents belong to electron-donating groups, such as methyl and methoxyl, or electron-withdrawing groups, such as fluoro, chloro, bromo, carboxyl, and sulfonic, all reactions

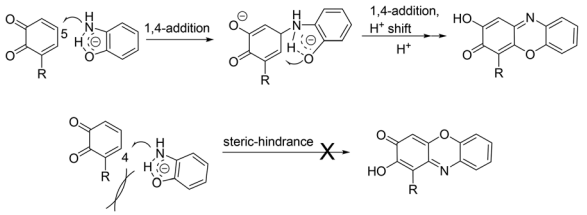
Table 1 The syntheses of HPXZs **3a–z** by the cross-cyclocondensations [product number, reaction time (min), isolated yield][a]



[a] Reaction conditions: **1**s (1.0 mM), **2**s (1.0 mM), **GA** (0.25 mol%), $Mn(OAc)_2$ (0.25 mol%), H_2O (50 mL), pH 10, ultrasonication, 25 °C, 150 mL autoclave. [b] **1** (10.0 mM), **2** (10.0 mM).

were completed within less than 1 h, whereas the electronic properties of the substituents for both substrates did not impose a significant effect. For potential applications of the HPXO derivatives as drugs and fluorescent probes, the introduction of water-soluble groups should be indispensable. Fortunately, compounds **3s–y** that bear one or two carboxyl or sulfonic group(s) could be produced successfully. However, probably owing to their high water solubility, their isolated yields were not as high as their HPLC yields.

It was interesting to find the excellent substituent-oriented regioselectivity for products in the cross-cyclocondensation of 3-substituted **2**. No matter whether the substituents were electron-donating or electron-withdrawing groups, the reactions gave 4-substituted hydroxyphenoxazinones as the sole product (see single crystal diffraction patterns in ESI†) without the positional isomer 1-substituted products in almost all cases.



Scheme 2 The probable reaction route of regioselective cross-cyclocondensation between **1** and 3-substituted **2**.

A possible reaction route is shown in Scheme 2. During the cross-cyclocondensation, by basic deprotonation, **1a** converted to its anion with an intermolecular H bond between N and O atoms. Moreover, the intermediate *o*-benzoquinone contained two Michael addition electrophiles. Then two consecutive Michael additions took place; the first is an intermolecular aza-Michael addition at the 5C site of *o*-benzoquinone and the second one is an intramolecular oxa-Michael addition at the 4C site. When 3-substituted 2-hydroxylphenol was used, aza-Michael additions at the 5C site generated 4-substituted hydroxyphenoxazinone, while at the 4C site gave a 1-substituted product. However, since the steric hindrance of substituent at the 3C site of **2** could completely suppress aza-Michael additions at the 4C site, the cross-cyclocondensations afforded 4-substituted-2-hydroxyl-phenoxazinones **3d–y** with excellent regioselectivity. In contrast, smaller F could not restrain the occurrence of aza-Michael additions at the 4C site, and so the reaction of 3-F-2-hydroxylphenol and **1a** gave the mixed products of **3z–4** and its positional isomer **3z–1** in the ratio of 83 : 17 (^{1}H NMR ratio). Moreover, our tests found that the reaction of **1a** with 2,3-dihydroxybenzoic acid or its ester could not afford the desired HPXO but **4a** as a main product, maybe because the cross-cyclocondensations were prevented by the steric hindrance of much bigger carboxyl groups. Nevertheless, these further demonstrated the substituent-oriented regioselectivity of the cross-cyclocondensation. However, **3u–w** and **3y** could be obtained by the reactions between 2-aminophenols and 3-cyano-2-hydroxylphenol, where the cyano group was completely oxidatively hydrolysed to the carboxyl group.

Conclusions

In summary, we have developed a novel, highly efficient and versatile methodology for the preparation of 2-hydroxy-phenoxazinones using natural renewable gallic acid as an organocatalyst. $Mn(OAc)_2$ is used as a cocatalyst, dioxygen as terminal oxidant and water as solvent. Under very mild conditions, the methodology allows the syntheses of various 2-hydroxy-phenoxazinones in moderate to high yields through the aerobic oxidative cross-cyclocondensation of equimolar 2-aminophenols and 2-hydroxyphenols. The reactions proceeded in a tandem sequence of aerobic oxidation and double Michael 1,4-additions in a simple one-pot procedure. And the excellent substituent-oriented regioselectivity existed in the cross-cyclo-

condensation of 3-substituted 2-hydroxylphenols. Notably, the gram scale test maintained high reaction efficiency. Thus, the methodology with a low catalyst loading and simple isolation paves the way to future development of sustainable reactions for the synthesis of industrially and biomedically important HPXO derivatives.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) F.-X. Yang, G.-X. Hou, J. Luo, J. Yang, Y. Yan and S.-X. Huang, *J. Antibiot.*, 2018, **71**, 1040; (*b*) S. Ahn, J. A. Yoon and Y. T. Han, *Bull. Korean Chem. Soc.*, 2019, **40**, 740; (*c*) H. Lackner, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 375.

2 (*a*) J. Polak, A. Jarosz-Wilkolazka, K. Szalapata, M. Graz and M. Osinska-Jaroszuk, *New Biotechnol.*, 2016, **33**, 255; (*b*) F. Bruyneel, L. D'Auria, O. Payen, P. J. Courtoy and J. Marchand-Brynaert, *ChemBioChem*, 2010, **11**, 1451; (*c*) P. Ravichandiran, A. Boguszewska-Czubara, M. Maslyk, A. P. Bella, P. M. Johnson, S. A. Subramaniyan, K. S. Shim and D. J. Yoo, *Dyes Pigm.*, 2020, **172**, 107828; (*d*) C. Batchelor-McAuley, C. A. Little, S. V. Sokolov, E. Katelhon, G. Zampardi and R. G. Compton, *Anal. Chem.*, 2016, **88**, 11213; (*e*) A. B. Descalzo, M. D. Marcos, C. Monte, R. Martinez-Manez and K. Rurack, *J. Mater. Chem.*, 2007, **17**, 4716; (*f*) X. Wu, J. M. An, J. Shang, E. Huh, S. Qi, E. Lee, H. Li, G. Kim, H. Ma, M. S. Oh, D. Kim and J. Yoon, *Chem. Sci.*, 2020, **11**, 11285.

3 (*a*) A. Bolognese, G. Correale, M. Manfra, A. Lavecchia, O. Mazzoni, E. Novellino, V. Barone, A. Pani, E. Tramontano, P. La Colla, C. Murgioni, I. Serra, G. Setzu and R. Loddo, *J. Med. Chem.*, 2002, **45**, 5205; (*b*) M. Miyake, S. Yamamoto, O. Sano, M. Fujii, K. Kohno, S. Ushio, K. Iwaki and S. Fukuda, *Biosci., Biotechnol., Biochem.*, 2010, **74**, 753.

4 Y. Peng, Y. Wang and X. Wang, *J. Phys. Chem. B*, 2020, **124**, 10007.

5 T. L. Williams, S. A. Lopez and L. F. Deravi, *ACS Sustainable Chem. Eng.*, 2019, **7**, 8979.

6 E. A. Onoabedje, J. I. Ayogu and A. S. Odoh, *ChemistrySelect*, 2020, **5**, 8540.

7 H. Yoo and R. L. Rill, *J. Biochem. Mol. Biol.*, 2003, **36**, 305.

8 A. Bolognese, C. Piscitelli and G. Scherillo, *J. Org. Chem.*, 1983, **48**, 3649.

9 F. Bruyneel, O. Payen, A. Rescigno, B. Tinant and J. Marchand-Brynaert, *Chem. – Eur. J.*, 2009, **15**, 8283.

10 A. Bolognese, G. Scherillo and W. Schäfer, *J. Heterocycl. Chem.*, 1986, **23**, 1003.

11 L. A. Hick, M. K. Manthey and R. J. W. Truscott, *J. Heterocycl. Chem.*, 1991, **28**, 1157.

12 S. Moore, M. Kondo, M. Copeland, J. Meienhofer and R. K. Johnson, *J. Med. Chem.*, 1975, **18**, 1098.

13 (*a*) D. K. Romney, F. H. Arnold, B. H. Lipshutz and C.-J. Li, *J. Org. Chem.*, 2018, **83**, 7319; (*b*) B. H. Lipshutz and S. Ghorai, *Green Chem.*, 2014, **16**, 3660; (*c*) T. Kitanosono, K. Masuda, P. Xu and S. Kobayashi, *Chem. Rev.*, 2018, **118**, 679; (*d*) S. Kobayashi, *Science of Synthesis: Water in Organic Synthesis*, Thieme Chemistry, 2012; (*e*) Z. Huang, F. Li, B. Chen and G. Yuan, *Green Chem.*, 2015, **17**, 2325; (*f*) L. Zhang, W. Wang, A. Wang, Y. Cui, X. Yang, Y. Huang, X. Liu, W. Liu, J.-Y. Son, H. Oji and T. Zhang, *Green Chem.*, 2013, **15**, 2680.

14 L. Song, W. Li, W. Duan, J. An, S. Tang, L. Li and G. Yang, *Green Chem.*, 2019, **21**, 1432.

15 J. Mancebo-Aracil, C. Casagualda, M. Angel Moreno-Villaecija, F. Nador, J. Garcia-Pardo, A. Franconetti-Garcia, F. Busque, R. Alibes, M. Jose Esplandiu, D. Ruiz-Molina and J. Sedo-Vegara, *Chem. – Eur. J.*, 2019, **25**, 12367.

16 A. C. Eslami, W. Pasanphan, B. A. Wagner and G. R. Buettner, *Chem. Cent. J.*, 2010, **4**, 15.