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Metal-Free C3 Hydroxylation of Quinoxalin-2(1*H*)-ones in Water

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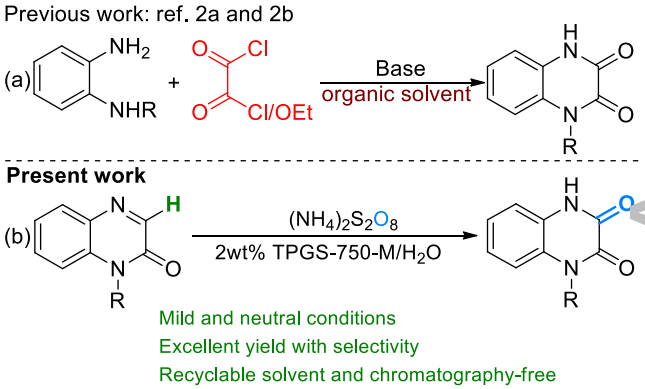
Abstract. A practical protocol for the preparation of quinoxaline-2,3(1*H*,4*H*)-diones through direct C(sp2)-H hydroxylation of quinoxalin-2(1*H*)-ones in recyclable DL-α-Tocopherol methoxypolyethylene glycol succinate solution (2 wt% in water) (TPGS-750-M/H_2O) was developed. The target products were exclusively generated and could be collected through extraction and recrystallization.

Keywords: hydroxylation; quinoxalin-2(1*H*)-one; in water; TPGS-750-M; green chemistry

Introduction

The direct hydroxylation of C(sp^2)-H bond in heterocycles is a powerful tool for the construction of C-OH bonds, for which the establishment of efficient and practical protocols is still a field of interest owing to the widespread presence of hydroxylated heterocyclic compounds in natural products, synthetic pharmaceuticals, agrochemicals and functional materials. In addition, the hydroxylated heterocycles also serve as useful and versatile building blocks and synthetic intermediates in organic synthesis. Over the past decades, plenty of efforts and remarkable progress have been made in the development of novel hydroxylation reaction.[1] However, for a majority of hydroxylation reactions, transition-metal catalysts and harmful organic solvent are demanded to promote the chemical process, which not only greatly restricts their application in pharmaceutical industry but also cause environmental problem.

Quinoxaline-2,3-dione and their derivatives play an important role in organic synthesis, pharmaceutical chemistry and materials science.[2] Traditionally, N-functionalized quinoxaline-2,3-diones are prepared through base-promoted condensation reaction between mono N-substituted 1,2-diaminobenzenes and oxalyl chloride (or ethyl chloroglyoxalate) (Scheme 1a).[2a, 2b] However, from a practical and eco-friendly point of view, those procedures still suffer from some drawbacks, such as the difficulties of preparation and isolation of mono N-substituted substrates, the usage of toxic oxalyl chloride and volatile organic solvent, and harsh reaction conditions. Given the readily available quinoxalin-2(1*H*)-ones, significant progress has been achieved on the C-H bond functionalization of quinoxalin-2(1*H*)-ones, including the regioselective alkylation,[3] alkoxylation,[4] arylation,[5] acylation,[6] amination,[7] trifluoromethylation[8] and phosphonation reaction[9]. During the past decade, water has received much attention as the expected reaction medium for organic reactions due to safety, cost and environmental concerns.[10] However, to the best of our knowledge, the aqueous construction of C-3 hydroxylated quinoxalin-2(1*H*)-ones through hydroxylation of quinoxalin-2(1*H*)-ones has not been reported.



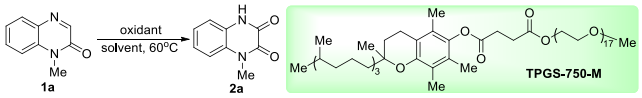
Scheme 1. Synthesis of *N*-substituted quinoxaline-2,3(1*H*,4*H*)-diones

As a part of our ongoing interest in functionalization of quinoxalin-2(1*H*)-ones,[11] herein we reported a sustainable method for the clean preparation of various mono *N*-functionalized

quinoxaline-2,3(1*H*,4*H*)-diones through direct hydroxylation of *N*-functionalized quinoxalin-2(1*H*)-ones in water (Scheme 1b). In the present reaction, the desired product can be obtained through simple extraction and recrystallization without tedious column chromatography.

Results and Discussion

Table 1. Optimization of reaction conditions[a]

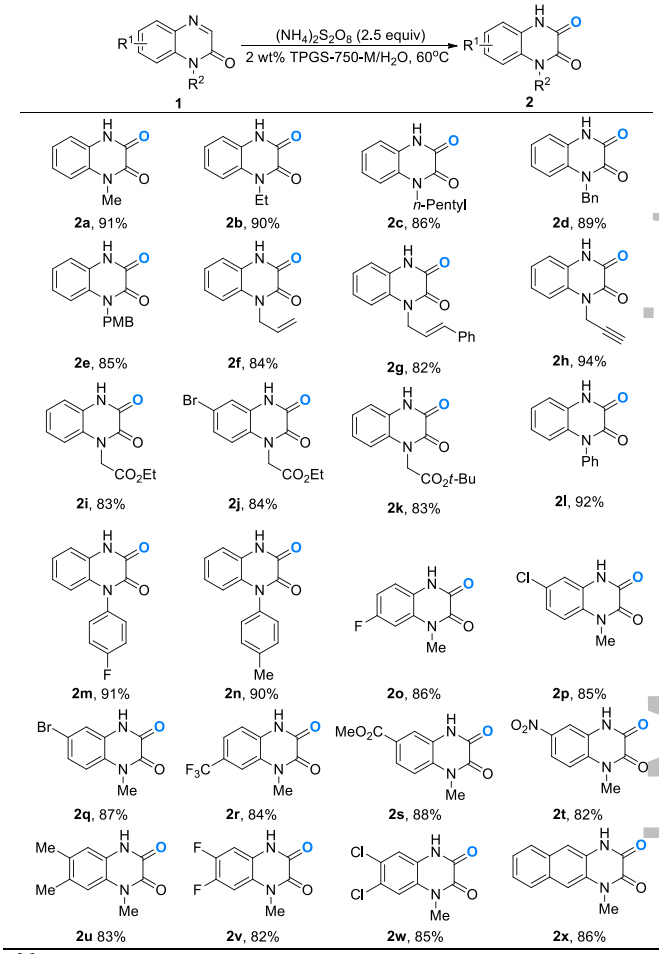


Entry	Oxidant(equiv.)	Solvent	Yield[b]
1	$(NH_4)_2S_2O_8$ (2.5)	H_2O	38%
2	$(NH_4)_2S_2O_8$ (2.5)	2 wt% SDS/H_2O	61%
3	$(NH_4)_2S_2O_8$ (2.5)	2 wt% TEBAC/H_2O	52%
4	$(NH_4)_2S_2O_8$ (2.5)	2 wt% NP-40/H_2O	81%
5	$(NH_4)_2S_2O_8$ (2.5)	2 wt% Span-60/H_2O	83%
6	$(NH_4)_2S_2O_8$ (2.5)	2 wt% Triton-X100/H_2O	78%
7	$(NH_4)_2S_2O_8$ (2.5)	2 wt% TPGS-750-M/H_2O	94%
8	$K_2S_2O_8$ (2.5)	2 wt% TPGS-750-M/H_2O	13%
9	$Na_2S_2O_8$ (2.5)	2 wt% TPGS-750-M/H_2O	18%
10	TBHP (2.5)	2 wt% TPGS-750-M/H_2O	N.R.
11	H_2O_2 (2.5)	2 wt% TPGS-750-M/H_2O	N.R.
12	$(NH_4)_2S_2O_8$ (3)	2 wt% TPGS-750-M/H_2O	94%
13	$(NH_4)_2S_2O_8$ (2)	2 wt% TPGS-750-M/H_2O	86%
14[c]	$(NH_4)_2S_2O_8$ (2.5)	2 wt% TPGS-750-M/H_2O	63%
15[d]	$(NH_4)_2S_2O_8$ (2.5)	2 wt% TPGS-750-M/H_2O	92%
16	--	2 wt% TPGS-750-M/H_2O	N.R.

[a] Conditions: **1a** (0.1 mmol), oxidant, H_2O (0.4 mL), surfactant, 12 h.
[b] Estimated by ^1H NMR using diethyl phthalate as internal reference.
[c] at 40 ℃.
[d] at 80 ℃. TEBAC: benzyltriethylammonium chloride; NP-40: substitute octylphenoxypolyethoxyethanol.

Our preliminary study began with *N*-methylquinoxalin-2(1*H*)-one (**1a**) as a model substrate to optimize the reaction conditions (Table 1). Treatment of **1a** with $(NH_4)_2S_2O_8$ (2.5 equiv.) at 60 °C in water for 12 hours resulted in 38% yield of the desired product *N*-methylquinoxaline-2,3(1*H*,4*H*)-dione (**2a**) and 40% conversion of **1a** (Table 1, entry 1). The low yield of the transformation was probably due to the poor solubility of **1a** in water. To address this issue, we introduced the 2 wt% sodium dodecylsulfate (SDS) as a surfactant[1k, 12] to improve the solubility of **1a**. To our delight, the yield of **2a** was improved to 61% (entry 2). Next, a series of surfactants[13] (entries 3 - 7) were surveyed and DL-α-Tocopherol methoxypolyethylene glycol succinate solution (2 wt% in water) (TPGS-750-M) was found to be the most efficient surfactant for this hydroxylation reaction (entry 7). Various oxidants were also investigated, revealing that $(NH_4)_2S_2O_8$ is more suitable for the transformation (entries 8 - 11). Increasing the loading of $(NH_4)_2S_2O_8$ to 3 equiv. did not provide an improved yield of **2a** (entry 12), however, decreasing to 2 equiv. led to a lower yield of **2a** (entry 13). Further efforts in varying the reaction temperature did not give improved yield of the target product (entries 14 - 15). No hydroxylation reaction was observed in the absence of $(NH_4)_2S_2O_8$, and the raw material **1a** was wholly recovered (entry 16).

Table 2. Reaction Scope[a]



[a] Reaction conditions: **1** (0.5 mmol), $(NH_4)_2S_2O_8$ (1.25 mmol), 2 wt% TPGS750M/H_2O (2 mL), 60 ℃, 12 h.

With the optimal reaction conditions in hand (Table 1, entry 7), we then explored the scope of this aqueous hydroxylation reaction. As shown in Table 2, a series of N-substituted quinoxalin-2(1*H*)-ones were allowed, and all the yields of desired products were ≥ 82%. The N-1 position of quinoxalin-2(1*H*)-ones with varying length chains, and various isomeric structures of alkyl and functionalized phenyl substituents underwent the present reaction smoothly to deliver the expected products in good to excellent yields (**2a** - **2w**). The developed reaction was tolerant of a series of important functional-groups, including alkenyl (**2f** and **2g**), alkynyl (**2h**), and ester (**2i** - **2k**) groups, which could allow an opportunity for further functionalization. When N-free quinoxalin-2(1*H*)-one was used as substrate, only a trace amount of the desired product was detected. Quinoxalin-2(1*H*)-ones bearing electron-withdrawing, -neutral, and -donating substituents at phenyl ring could stereo-selectively

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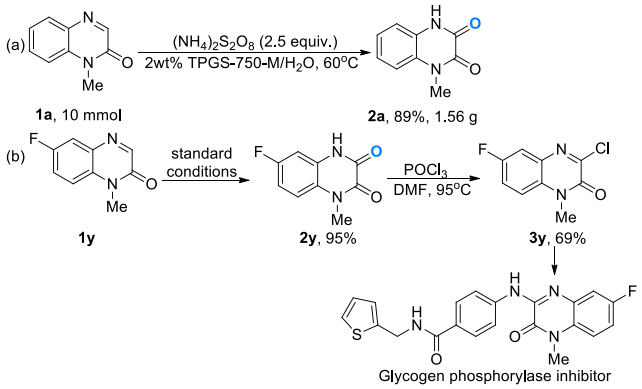
furnish the expected products (**2o** - **2t**) in excellent yields. A wide range of functional-groups are well tolerated including fluoro (**2o**), chloro (**2p**), bromo (**2j** and **2q**), trifluoromethyl (**2r**), ester (**2s**) and nitro (**2t**) at the different positions of substrates. Di-substituted quinoxalin-2(1*H*)-ones (**1u** - **1w**) and 3,4-dihydrobenzo[g]quinoxalin-2(1*H*)-one (**1x**) provided the desired products (**2u** - **2x**) in excellent yields. Remarkably, all the targeted products were easily collected through simple extraction and recrystallization without using tedious silica gel column chromatograph purification.[14] No hydroxylation reaction occurred when quinolin-2(1*H*)-one was used as reaction substrate.



Scheme 2. Gram-scale reaction and synthetic application

Next, a large-scale synthesis of *N*-methylquinoxaline-2,3(1*H*,4*H*)-dione **2a** was carried out under the optimized conditions (Scheme 2a). To our delight, the hydroxylation reaction provided the target product **2a** in 89% yield (1.56 g), showing a high potential application for industry scale-up. The absence of organic side-products when employing $(NH_4)_2S_2O_8$ offered a great opportunity to us for investigations on sequential synthesis. Performing the reaction in 1 wt% TPGS-750-M/H_2O leading to the target product **2a** in 75% yield. Increasing the concentration of **1a** to 0.5 mmol/mL resulted in a drop in the yield of **2a** (81%). Coupled with a subsequent chlorination reaction upon simple workup, this reaction led to **3y**, which is a key precursor for the synthesis of commercial available drug, namely Glycogen phosphorylase inhibitor (Scheme 2b).[2b]

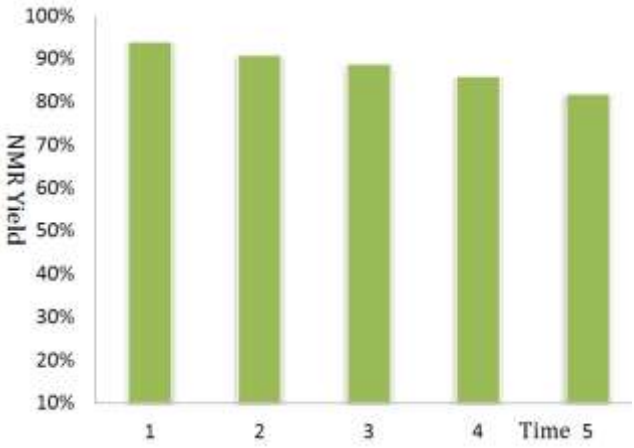
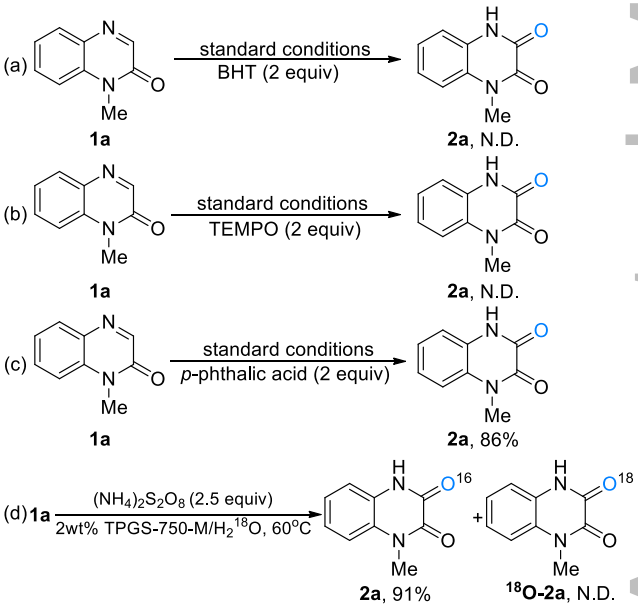


Figure 1 Recyclability of TPGS-750-M/H_2O
Conditions: **1a** (0.3 mmol), $(NH_4)_2S_2O_8$ (0.75 mmol), 2 wt% TPGS-750-M/H_2O (1.2 mL), to the recycled water, only 0.3 mmol of **1a**, 0.75 mmol of $(NH_4)_2S_2O_8$ were added, and the next cycle was carried out under the same conditions, ^{1}H NMR yields were reported

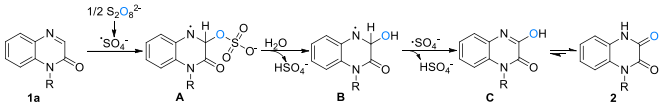
The sustainability of the reaction media was also examined in the template reaction. After completion of the hydroxylation reaction, the target product **2a** was extracted with ethyl acetate and only fresh reagents (**1a** and $(NH_4)_2S_2O_8$) was added to the TPGS-750-M/H_2O solution for the next hydroxylation reaction cycle. As illustrated in Figure 1, the chemical process could be repeated 5 times without an obvious loss in reaction efficiency.



Scheme 3. Control Experiments

To understand the reaction mechanism, a series of control experiments were carried out as shown in Scheme 3. The hydroxylation reaction of **1a** under the standard conditions in the presence of 2 equiv. of radical scavenger (BTH or TEMPO) gave no desired product, suggesting that the present reaction might proceed through a free-radical pathway (Scheme 3a-b). When *p*-phthalic acid, a well-known hydroxyl radical inhibitor, was added to the reaction mixture

under the standard conditions, an 86% NMR yield of product **2a** was detected (Scheme 3c), indicating that hydroxyl free-radical might not be involved in the transformation. When the reaction of **1a** was conducted in 2 wt% TPGS-750-M/$H_2{}^{18}O$ under nitrogen atmosphere, no ^{18}O-labeled product **2a** was detected by GC-MS analysis. Taken together, the incorporated oxygen atom of **2a** originated from $(NH_4)_2S_2O_8$.



Scheme 4. Proposed Reaction Mechanism

Based on these above-mentioned experiment results and previous literature reports,[1k, 15] a plausible mechanism is depicted in Scheme 4. At first, the substrate **1** reacts with the *in situ* generated sulfate radical anion to form a nitrogen-centred radical **A**. Then, the radical **A** is attacked by water to generate free-radical **B**, which coupled with sulfate radical anion to afford 3-hydroxy-1-methylquinoxalin-2(1*H*)-one (**C**) with the release of bisulfate anion. Finally, compound **C** rapidly tautomerized to form the more stable product **2**.

Conclusions

In summary, we have developed a simple and efficient method for the clean preparation of various *N*-functionalized quinoxaline-2,3(1*H*,4*H*)-diones (25 examples, 82 - 94%) through direct C(sp^2)-H hydroxylation of quinoxalin-2(1*H*)-ones in recyclable 2 wt% TPGS-750-M/H_2O. The $(NH_4)_2S_2O_8$ has a dual function (acts as oxidant and oxygen source) in this transformation, thus simplifying the reaction conditions and operation. The TPGS-750-M/H_2O solution can be easily recycled up to 5 times by simple extraction without the significant loss of its reaction efficiency. Importantly, the target products were exclusively produced and could be easily collected through extraction and recrystallization. In comparison with the traditional synthetic protocols, the developed methodology has the following advantages such as operational simplicity and high scalability, mild condition, readily availability of starting material, eco-friendly and sustainable reaction medium, chemical waste minimization which make this present protocol highly attractive in organic synthesis and pharmaceutical chemistry.

Experimental Section

General Procedure for the Synthesis of Quinoxaline-2,3(1*H*,4*H*)-diones 2

To a solution of quinoxalin-2(1*H*)-ones (0.5 mmol) in water (2 mL, containing 2 wt% TPGS-750-M) was added $(NH_4)_2S_2O_8$ (1.25 mmol). The reaction mixture was stirred at 60 °C for about 12 h. After completion of the reaction, the resulting mixture was extracted with EtOAc (3 X 6 mL) and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to about 3 mL under vacuum, then 5 mL of petroleum ether was added. After 30 min, filtered to obtain the desired quinoxaline-2,3(1*H*,4*H*)-diones **2**.

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UPDATES

Metal-Free C3 Hydroxylation of Quinoxalin-2(1*H*)-ones in Water

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A clean protocol for the preparation of *N*-functionalized quinoxaline-2,3(1*H*,4*H*)-diones through hydroxylation reaction in recyclable TPGS-750-M/H_2O was established.