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A combination of heterogeneous catalysis and photocatalysis for the olefination of quinoxalin-2(1*H*)-ones with ketones in water: a green and efficient route to (*Z*)-enaminones†

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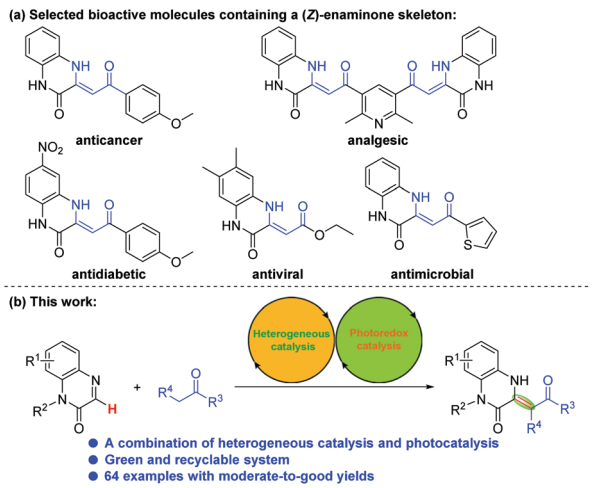
Herein, a novel aqueous reaction for the olefination of quinoxalin-2(1*H*)-ones with ketones through a combinational strategy is described. This reaction features very mild conditions using a simple and cheap catalyst for the synthesis of (*Z*)-enaminones with moderate-to-good yields. Such a methodology successfully combines the heterogeneous Mannich reaction with photocatalysis, and provides a green and practical approach for the synthesis of potentially bioactive (*Z*)-enaminones with a 3,4-dihydroquinoxalin-2(1*H*)-one skeleton.

Introduction

(*Z*)-Enaminones are an important class of organic compounds, which play a central role in organic synthesis and medicinal chemistry.[1] For example, antibacterial drugs such as pefloxacin, ofloxacin and norfloxacin all contain the (*Z*)-enaminone framework. In particular, (*Z*)-enaminones with a 3,4-dihydroquinoxalin-2(1*H*)-one skeleton are discovered to display anticancer, antimicrobial, antidiabetic, and antiviral activities (Scheme 1a).[2] In addition, (*Z*)-enaminones are also commonly used as building blocks for the synthesis of various valuable classes of *N*-heterocycles.[3] However, conventional synthesis methods of these compounds are the cyclization reactions of *o*-phenylenediamines with acylpyruvic acids, furan-2,3-diones or acetylenedicarboxylates, which generally suffer from harsh reaction conditions and a limited substrate scope.[4] Thus, the development of sustainable and efficient approaches for the synthesis of these compounds is of great importance.

Owing to the increasing awareness of the importance of green and sustainable development of chemicals, environment-friendly synthesis methods to minimise chemical waste and meet the 12 principles of Green Chemistry have been attracting interest over the past few decades.[5] However, organic reactions are generally conducted in volatile and toxic organic solvents, which not only consume plenty of non-renewable fossil fuels but also cause environmental pollution. Therefore, considerable efforts are being made to develop green reaction media[6] (water,[6a–f] ionic liquids[6g–j] and so on[6k–m]) so as to meet 'Principle 1, Waste Prevention' and 'Principle 5, Safer Solvents and Auxiliaries' of Green Chemistry.[7]

Photocatalysis has become a powerful methodology for organic synthesis because it features low energy consumption and environmental protection to some degree.[8] Although elegant, this strategy usually needs an additional photocatalyst



Scheme 1 Application and synthesis of (*Z*)-enaminones with a heterocycle skeleton.

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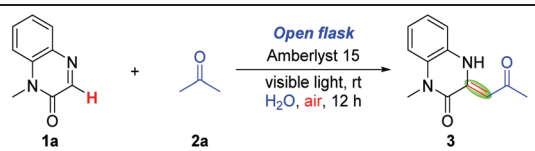
or oxidant, which will not only increase the manufacturing costs but also cause environmental pollution. From the perspective of green chemistry, organic synthesis through the irradiation of visible light without an additional photocatalyst or oxidant has attracted extensive attention in recent years.[9] In the meantime, heterogeneous catalysis has become a sustainable and practical strategy for the construction of valuable compounds.[10] Specifically, ion-exchange resin catalysts have received considerable attention due to their low cost, metal-free composition, easy product purification, catalyst recoverability and reusability.[11] We are interested in developing green catalytic systems[12] for the direct modification of *N*-containing heterocycles,[13] herein, we report a reusable sulfonic ion-exchange resin promoted, photocatalysis method for the direct olefination of quinoxalin-2(1*H*)-ones with ketones in water (Scheme 1b). The recyclable aqueous phase reaction was performed under very mild conditions, providing a green and practical route to various (*Z*)-enaminones bearing 3,4-dihydroquinoxalin-2(1*H*)-one in moderate-to-good yields. Recently, there has been significant progress in the direct C3–H functionalization of quinoxalin-2(1*H*)-ones since they are a valuable class of heterocycles,[14–20] and to the best of our knowledge, however, direct C3–H olefination has never been reported yet.

Results and discussion

The reaction conditions of the olefination of quinoxalin-2(1*H*)-one (**1a**) with acetone (**2a**) were optimised by changing the type and dose of the supported sulfonic acid catalyst, the dose of the starting-material and the reaction time. As outlined in Table 1, (*Z*)-enaminones (**3**) were isolated in 83% yield by performing the reaction of **1a** (0.2 mmol), **2a** (0.6 mmol), and Amberlyst 15 (50 mg) in H_2O (3 mL) under visible light for 12 h (Table 1, entry 1). Other supported sulfonic acid catalysts such as Amberlyst®15, Amberlyst®16 and Dowex 50WX2 gave lower yields (Table 1, entries 2–4). No corresponding product was generated without a catalyst (Table 1, entry 5). The product yield could not be enhanced obviously when the starting-material or catalyst dose was increased or when the reaction time was extended (Table 1, entries 6–8). Instead, the yield was dramatically decreased by reducing the dose of the starting-material or catalyst (Table 1, entries 9 and 10). We also performed the reaction in organic solvents, such as acetone and acetonitrile, and 88% and 85% yields were obtained, respectively (see the ESI†). To meet the demand of green synthesis, we finally chose water as the solvent for the reaction.

With the optimized reaction conditions in hand, we next explored the substrate scope of quinoxalin-2(1*H*)-ones with acetone (Table 2). Initially, a wide range of *N*-substituted quinoxalin-2(1*H*)-ones were studied. Various *N*-substituted groups such as methyl, ethyl, ^{n}butyl, ^{i}butyl, cyclopropylmethyl, cyclohexylmethyl, ester and keto were well tolerated under standard conditions, providing the corresponding (*Z*)-enaminones (**3–12**) in 73–85% yields. It is worth mentioning that quinoxalin-2(1*H*)-one with a sensitive allyl group, which could be further functionalized, gave product (**13**) in 70% yield. *N*-Phenylquinoxalin-2(1*H*)-one also could undergo the reaction smoothly, giving target product (**14**) in 59% yield. A number of quinoxalin-2(1*H*)-ones with different benzyl groups, bearing both electron-donating and electron-withdrawing substituents at the *ortho*-, *meta*-, or *para*-position, gave the corresponding products (**15–28**) in 48–77% yields. The transformations of acetone (**2a**) with quinoxalin-2(1*H*)-one containing a methyl, methoxy ^{t}butyl, halogen or ester group at the C5-, C6-, or C7-position yielded target (*Z*)-enaminones (**29–35**) in 69–78%

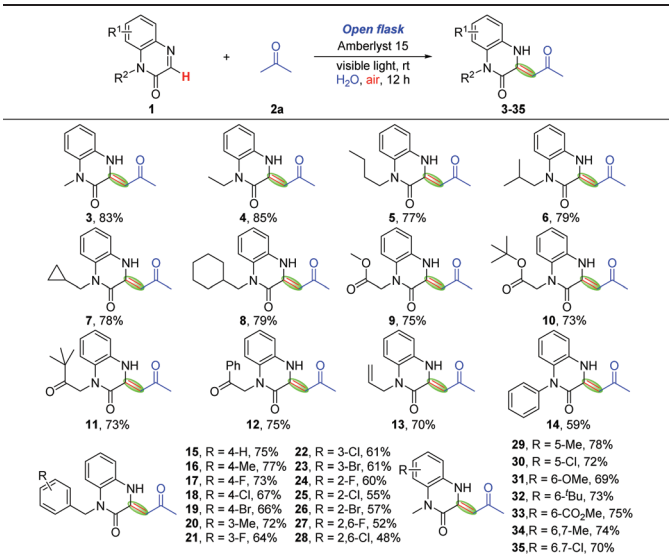
Table 1 Screening of reaction conditions[a]



Entry	Variation from the given conditions	Yield[b] [%]
1	None	83
2	Amberlyst®15 instead of Amberlyst 15	72
3	Amberlyst®16 instead of Amberlyst 15	50
4	Dowex 50WX2 instead of Amberlyst 15	36
5	without Amberlyst 15	0
6	100 mg of Amberlyst 15 was used	85
7	6.0 equivalents of acetone was used	83
8	extended reaction time (24 h)	86
9	25 mg of Amberlyst 15 was used	52
10	1.5 equivalents of acetone was used	62

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), Amberlyst 15 (50 mg), H_2O (3 mL), visible light (LEDs, 420 nm, 5 W), open flask, rt, air, 12 h. [b] Isolated yields.

Table 2 Substrate scope of quinoxalin-2(1*H*)-ones[a,b]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.6 equiv.), Amberlyst 15 (50 mg), H_2O (3 mL), visible light (LEDs, 420 nm, 5 W), open flask, rt, air, 12 h. [b] Isolated yields.

yields. The molecular structure of (*Z*)-enaminone **20** was confirmed by X-ray crystallographic analysis (CCDC 2042085†). According to the crystal structure, we thought that the effect of the hydrogen bond interaction between the amine and carbonyl groups makes the molecules more stable in the (*Z*)-configuration.

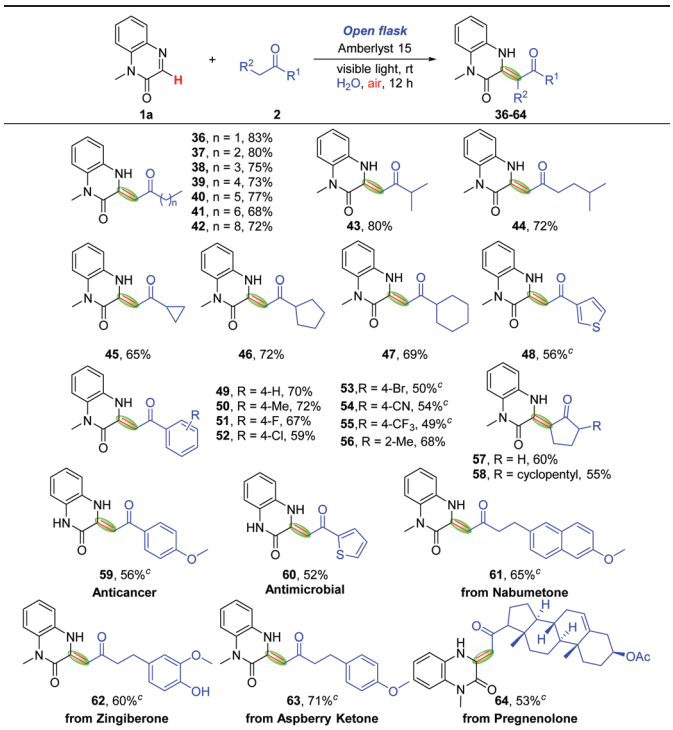
Subsequently, the substrate scope of ketones for the reaction was studied under the standard reaction conditions (Table 3). Both long-chain and cycloalkyl methyl ketones could undergo the reaction smoothly, affording the corresponding (*Z*)-enaminones (**36–47**) in 65–83% yields. Then, some methyl aryl ketones were explored. 1-(Thiophen-3-yl)ethan-1-one could be converted into target product (**48**) with a slightly lower yield, probably because of its relatively poor solubility. A wide range of acetophenones, which bear substituents at the *ortho*- or *para*-position with both electron-donating and electron-withdrawing characteristics, gave the corresponding products (**49–56**) in 49–78% yields. We were pleased to find that the cyclopentanone skeleton could also react with quinoxalin-2(1*H*)-one smoothly to deliver target products (**57** and **58**) in moderate yields. Interestingly, the anticancer molecule (**59**) and antimicrobial molecule (**60**) could also be synthesized in moderate yields using the straightforward strategy. Since (*Z*)-enaminones bearing a 3,4-dihydroquinoxalin-2(1*H*)-one framework are a promising class of biologically active compounds, several bioactive molecules such as nabumetone, zingiberone, raspberry ketone and pregnenolone were selected to react with quinoxalin-2(1*H*)-one directly, giving new (*Z*)-enaminone molecules (**61–64**) in 53–71% yields. The successful transformations demonstrate that the present strategy has a good application value for the synthesis of potentially bioactive quinoxalin-2(1*H*)-one containing (*Z*)-enaminones.

To demonstrate the practicality and efficiency of the reaction, a gram-scale synthesis experiment was performed. As shown in Scheme 2a, a scaled-up model transformation was performed effectively to give target product **3** in 75% yield (1.3 g). Furthermore, the obtained (*Z*)-enaminone could be further converted into various quinoxaline derivatives (**65–68**) using different reaction conditions, which clearly revealed the synthetic utility of this protocol (Scheme 2b).

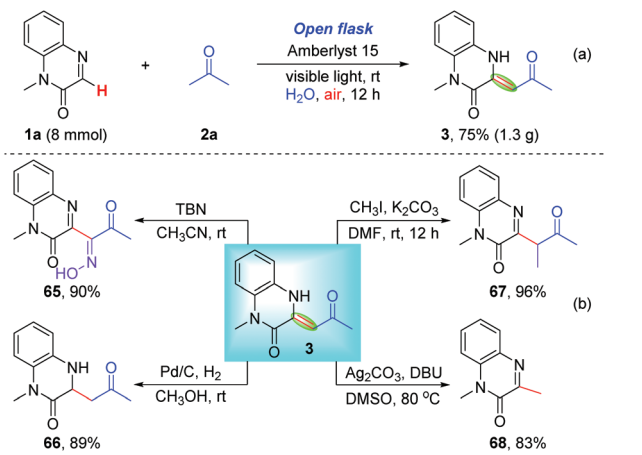
The recyclable experiment was further studied in order to test the recyclability of the present catalytic system (Fig. 1). After completion, the reaction mixture was extracted with ethyl acetate, and the organic layer containing the product was purified. Then, the aqueous phase was reutilized to catalyse the transformation by directly adding starting materials. A slight loss of catalytic activity in the second run and an obvious loss of catalytic activity in the third and fourth runs were observed. The deactivation of the catalyst is probably caused by active site loss and channel plugging of the heterogeneous catalyst.[11d] Retreatment of the catalyst that used for three or four times could regenerate the catalyst with relatively good catalytic activity.

A range of control experiments were then carried out to study the reaction mechanism. Initially, the Mannich-type product **66** was generated instead of target product **3** in 53% yield if the reaction was performed under a nitrogen atmosphere (Scheme 3a). This result indicates that oxygen in air may play a central role in the subsequent dehydrogenation process, which can be verified by the following control experiments using compound **66** as the starting material. First, target product **3** was formed in 0%, 50% and 59% yields when the reaction was performed under a nitrogen, air and oxygen atmosphere, respectively, showing that oxygen acts as the

Table 3 Substrate scope of ketones[a,b]



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.6 equiv.), Amberlyst 15 (50 mg), H_2O (3 mL), visible light (LEDs, 420 nm, 5 W), open flask, rt, air, 12 h. [b] Isolated yields. [c] The reaction was performed for 24 h.



Scheme 2 Gram-scale synthesis and further transformation.

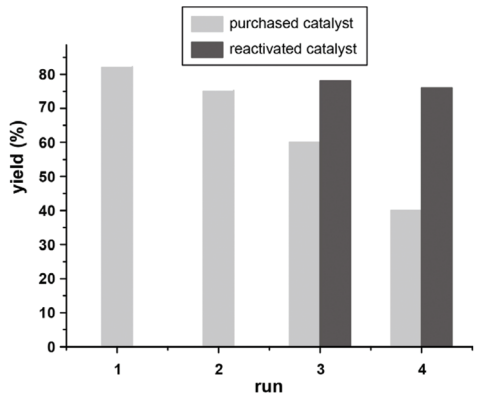
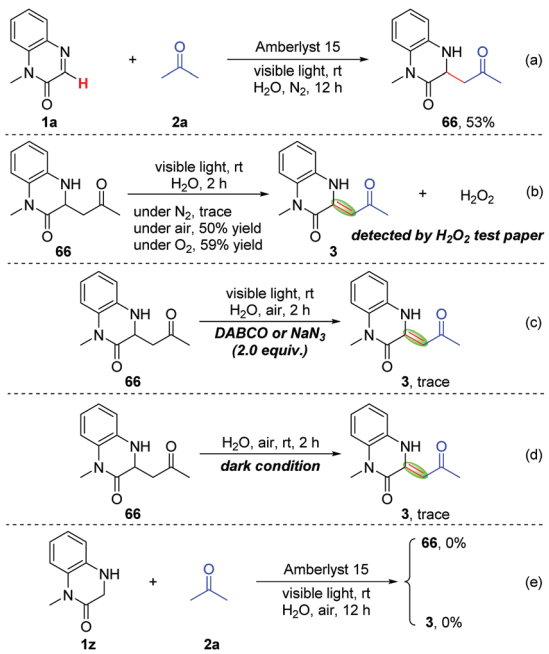


Fig. 1 Recyclability test.



Scheme 3 Control experiments.

oxidant in the dehydrogenation reaction (Scheme 3b). Second, the reactions that involve a singlet oxygen inhibitor (DABCO, 1,4-diazabicyclooctane triethylenediamine or NaN_3) or no visible light did not give target product **3**, demonstrating that singlet oxygen $^1O_2$, which was generated from triplet oxygen $^3O_2$ through photocatalysis, serves as the real oxidant (Scheme 3c and d). To further confirm the assumption, density functional theory (DFT) calculations using the M06-2X functional[21] (see the ESI† for computational details) were performed. We calculated the triplet energy (E_T) and singlet–triplet energy gap (ΔE_{ST}) of **1a**, **3**, and **66**. The results demonstrate that the triplet energies of all three compounds are higher than the excitation energy required for the generation of singlet oxygen (95 kJ mol^{-1}), indicating that all three compounds could act as photosensitizers for the generation of singlet dioxygen (see the ESI, Table S1†). The subsequent electron spin resonance (ESR) experiments further confirmed this conclusion (see the ESI, Scheme S1–3†).

1-Methyl-3,4-dihydroquinoxalin-2(1*H*)-one (**1z**) was also tested under standard conditions, but both Mannich-type product **66** and target product **3** were not obtained (Scheme 3e). A further ESR experiment confirmed the generation of $O_2^{\bullet-}$ (see the ESI, Scheme S4†). Some important intermediates have been determined theoretically by DFT calculations. In addition, ADCH atomic charge analyses showed that the charge on the O_2 fragment changes from 0.041 to −0.430.[22] These results indicate that a single electron transfer (SET) process is involved. Subsequently, an HOO$^\bullet$ radical (part of complex Int2) is formed by a proton transfer process. The electron spin density of Int2 (Fig. 2) confirms the formation of HOO$^\bullet$. Similarly, an HOO$^{\bullet-}$ radical anion is formed through another SET process, and finally H_2O_2 is formed through a proton transfer process.

According to the mechanistic studies and a previous report,[23] a plausible mechanism for the reaction is suggested (Scheme 4). In this transformation, Amberlyst 15 acts as the protonic acid to catalyse the Mannich-type reaction. Initially, acetone **2a** is converted to the enol form (**A**), which is subsequently attacked by protonated imine **B** to give intermediate **C**. Then, Mannich-type product **66** is generated through deprotonation of intermediate **C**. Meanwhile, substrate **1** is excited by visible light to generate the excited-species **1***, which acts as a photocatalyst and undergoes an energy transfer (ET) process with triplet oxygen to give singlet oxygen, along with the regeneration of ground-state substrate **1**.[9g] Finally, the reaction undergoes two SET processes with singlet oxygen $^1O_2$ to produce the target product with the generation of H_2O_2

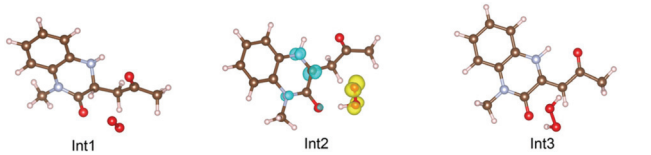
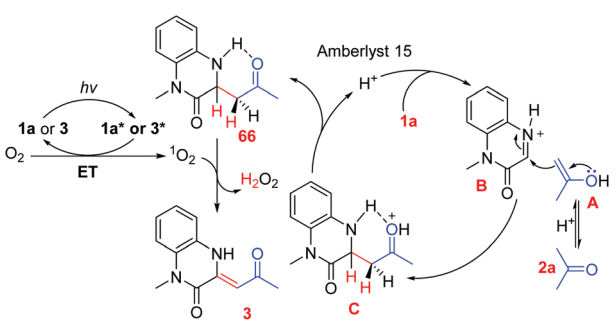


Fig. 2 Optimized geometries of three intermediates. The isosurface of the electron spin density of Int2 is also shown.



Scheme 4 Plausible mechanism.

(detected by hydrogen peroxide test paper). The obtained intermediate **66** and product **3** also can act as photocatalysts to promote the photocatalytic cycle.

Conclusions

This study describes a novel aqueous reaction for the synthesis of potentially bioactive (*Z*)-enaminones with a 3,4-dihydroquinoxalin-2(1*H*)-one skeleton through a combination of heterogeneous catalysis and photocatalysis. As demonstrated using model systems, various (*Z*)-enaminones were obtained in moderate-to-good yields when different substrates were used. Control experiments revealed that the Mannich type mechanism and subsequent SET process were responsible for the reaction.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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