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A niobium-catalyzed coupling reaction of α-keto acids with *ortho*-phenylenediamines: synthesis of 3-arylquinoxalin-2(1*H*)-ones†

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A general methodology to access valuable 3-arylquinoxalin-2(1*H*)-ones was developed, by the reaction of α-keto acids with *ortho*-phenylenediamines in the presence of ammonium niobium oxalate (ANO) as a catalyst. The reactions were conducted in only 10 min under ultrasonic irradiation as an alternative energy source, affording water as the only co-product. A total of twenty-three different 3-arylquinoxalin-2(1*H*)-ones were selectively obtained in good to excellent yields by this atom-efficient protocol. Additionally, $^{1}H-^{15}N$ HMBC experiments were used to reveal the regioisomerism of the obtained products.

Introduction

Nitrogen heterocycles are one of the most important classes of naturally occurring and synthetic compounds, with a number of biological activities, being present in countless marketable drugs, high-performance materials and dyes.[1] Among these compounds, 3-substituted quinoxalin-2(1*H*)-ones are privileged chemical skeletons in drug discovery, which have been extensively studied, presenting an impressive spectrum of important biological properties.[2] For instance, the 3-phenol-quinoxalin-2(1*H*)-one derivative **A** has demonstrated effective aldol reductase (ALR2) activity,[3] the pyridyl derivative **B** has proved to be a potent VEGFR-2 kinase inhibitor, blocking the angiogenesis process and showing anticancer activity,[4] while the pyrrolidinyl derivative **C** is a prolyl oligopeptidase inhibitor, exhibiting antidepressant activity.[5] Another important compound is caroverine (**D**), a spasmolytic marketed drug (Tinnex®), which is indicated for the treatment of tinnitus in humans (Fig. 1).[6]

In view of the wide spectrum of pharmacological applications of 3-substituted quinoxalin-2(1*H*)-ones, the development of efficient, general and selective synthetic methods to access these compounds is of great interest. In this context, several methodologies based on the C–H activation strategies of pre-formed quinoxalin-2(1*H*)-ones, including arylation,[7] amidation,[8] acylation,[9] alkynylation[10] and phosphonation reactions,[11] have emerged as robust alternatives to install valuable functional groups at the C3 position of the quinoxalin-2(1*H*)-one core. However, the need for prior preparation of the starting quinoxalinones, together with the use of volatile solvents, large excess of oxidants or strong bases are some limitations of this strategy. One alternative approach to access 3-substituted quinoxalinones is the reaction of *ortho*-phenylenediamine (1,2-diaminobenzene) with functionalized ketone derivatives.[12]

Since 1991, when Fontana and co-workers[13] disclosed the use of α-keto acid derivatives in the decarboxylative acylation of N-heterocycles, they have emerged as green acyl transfer agents in a number of organic transformations.[14] Furthermore, α-keto acids have also been widely applied as carbonyl partners in condensation/cyclization reactions, in the presence of several nucleophiles, to access different hetero-

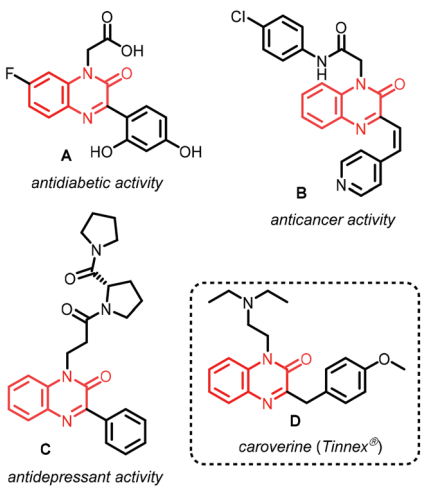

Fig. 1 Bioactive 3-substituted quinoxalin-2(1*H*)-ones.

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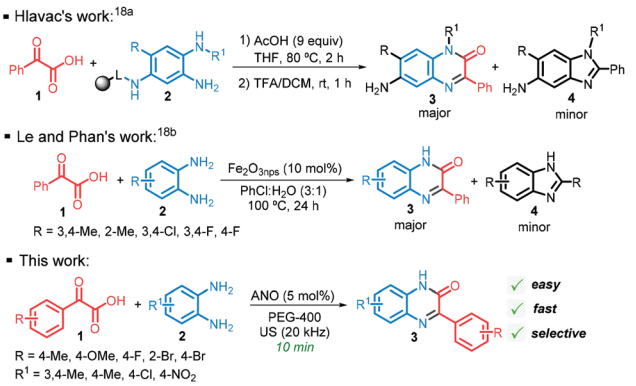


Scheme 1 Previous and present work to prepare quinoxalin-2(1*H*)-ones **3** from α-keto acids **1**.

cyclic compounds.[15] In this sense, α-keto acids have been used as 2-carbon suppliers in reactions with *o*-phenylenediamines to prepare 3-arylquinoxalin-2(1*H*)-ones.[12] This protocol was originally used for analytical purposes, in the characterization of α-keto acids as the respective quinoxalinols[16] and in the synthesis of few bioactive derivatives.[17] A second product that can be obtained in this reaction, however, is the respective benzimidazole, and the ratio between the 6- and 5-membered products depends on several factors, such as the nature of the solvent, the use or not of catalyst/additives, the temperature, the structure of the reagents, *etc*.[15a,18] These two products can be separated by column chromatography; however, chromatography has been identified as a major contributor for solvent waste within the medicinal chemistry discipline, mainly when considering large scale production.[19] In addition, the use of acid additives, flammable VOCs and organochlorine solvents under heating for a long period (up to 24 h) is the significant drawback of the current protocols (Scheme 1).[18]

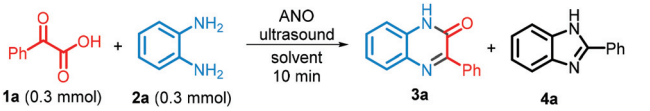
Recently, we have described the reaction of α-keto acids with *ortho*-functionalized anilines (*o*-SH and *o*-OH) using ammonium niobium oxalate (ANO) as a cheap, bench stable and easy to handle catalyst, and PEG-400 as a solvent. Despite the excellent yields obtained of the respective 2-arylbenzothiazoles and 3-aryl-2*H*-benzo[*b*][1,4]benzoxazin-2-ones under conventional heating (100 °C, 2 h), it was observed that ultrasonic irradiation could be successfully employed as a green, alternative energy source, in order to enhance the reaction efficiency while reducing the reaction time.[20]

Accordingly, as a continuation of our efforts in the development of green protocols to access valuable bioactive scaffolds, we report herein the regioselective ultrasound-assisted niobium-catalyzed reaction between aryl α-keto acids **1** and *o*-phenylenediamines **2** to obtain 3-arylquinoxalin-2(1*H*)-ones **3** (Scheme 1).

Results and discussion

The reaction conditions were investigated as outlined in Table 1, employing phenylglyoxylic acid (PGA) **1a** and *o*-phenylenediamine **2a** as starting materials. Firstly, we examined the effect of the solvent using 5 mol% of ANO as a catalyst and ultrasound (US) as a non-conventional energy source.

Table 1 Optimization of the reaction conditions to prepare 3-phenylquinoxalin-2(1*H*)-one **3a**[a]



Entry	ANO (mol%)	Solvent	**3a** Yield[b] (%)	**4a** Yield[b] (%)
1	5	EtOH	36	21
2	5	H_2O	70	20
3	5	MeCN	41	21
4	5	DMSO	57	20
5	5	Glycerol	65	—
6	**5**	**PEG-400**	**96**	—
7	10	PEG-400	92	—
8	3	PEG-400	89	—
9	1	PEG-400	85	—
10	—	PEG-400	70	—
11[c]	5	PEG-400	89	—

[a] A mixture of **1a** (0.3 mmol), **2a** (0.3 mmol) and ANO in 0.5 mL of solvent was sonicated (20% of amplitude) in an open flask for 10 min. [b] Isolated yield. [c] The reaction was performed using conventional heating (oil bath) at 70 °C, for 1 h.

As mentioned before, the formation of 2-phenylbenzimidazole **4a** is a competitive reaction which contributes to decrease the yield of the desired 3-phenylquinoxalin-2(1*H*)-one **3a**. Both the reaction yield and the selectivity to **3a** were directly affected by the solvent, as it can be seen in Table 1, entries 1–6. When EtOH was used as the solvent, a mixture of **3a** and **4a** was obtained in 57% overall yield with a **3a** : **4a** ratio of 63 : 37 (Table 1, entry 1). A remarkable increase in the reaction yield to 90% was observed using H_2O as the solvent; however the co-product **4a** was still formed in a considerable amount (**3a** : **4a** ratio of 78 : 22; Table 1, entry 2). The reaction yields decreased when H_2O was replaced for the polar aprotic solvents MeCN and DMSO, and a mixture of **3a** and **4a** was obtained in 62% and 77% yields (Table 1, entries 3 and 4). The expected 3-phenylquinoxalin-2(1*H*)-one **3a** was the only product (isolated in 65% yield) when glycerol was used as the solvent (Table 1, entry 5). This result has motivated us to explore the use of the equally non-volatile PEG-400 as the solvent and to our delight, the product **3a** was formed solely in 96% yield after 10 min of sonication (Table 1, entry 6). Once the solvent with the best performance was found, the effect of the catalyst amount was evaluated (1, 3 and 10 mol%) and a slight decrease in the yields was observed in all cases, although the selectivity to **3a** remained unaffected (Table 1, entries 7–9 *vs*. entry 6). However, in the absence of ANO as the catalyst, a notable decrease in the reaction efficiency was observed, and the product **3a** was obtained in only 70% yield (Table 1, entry 10). Finally, carrying out the reaction under conventional heating (70 °C) led to an increase in the reaction time to 1 h, affording the desired product **3a** in 89% yield (Table 1, entry 11). This outcome confirms that US irradiation

plays a crucial role in the reaction, accelerating the process remarkably. Considering the data from Table 1, the conditions of entry 6, *i.e.*, the sonication of equivalent amounts of **1a** and **2a** in the presence of ANO (5 mol%) as the catalyst and PEG-400 as the solvent, were chosen for subsequent studies.

With the best conditions in hand, a study was carried out in order to establish the scope and limitations of the protocol (Table 2). The respective 3-arylquinoxalin-2(1*H*)-one **3** was the only product obtained in all the tested examples, except in the reaction of 4-chlorobenzene-1,2-diamine **2d** (R^1 = 4-Cl) with PGA **1a** (R = H), which afforded an about 1 : 1 mixture of quinoxalin-2(1*H*)-one **3n** and 6-chloro-2-phenyl-1*H*-benzo[*d*]imidazole **4n** in 75% overall yield (Table 2). Similar to unsubstituted *o*-phenylenediamine **2a** (R^1 = H), the electron-rich *o*-phenylenediamine **2b** [R^1 = 4,5-$(Me)_2$] was a suitable substrate in the reaction with PGA **1a**, affording the respective quinoxalin-2(1*H*)-one derivative **3g** in 85% yield. The unsymmetrical electron-rich *o*-phenylenediamine **2c** [R^1 = 4-Me] was a good substrate in the reaction with PGA **1a** (R = H), affording the expected 3-arylquinoxalin-2(1*H*)-ones **3k** and **3k*** as an inseparable mixture of isomers (**3k : 3k*** ratio = 1.3 : 1) in 85% yield. The electron-poor *o*-phenylenediamines **2d** (R^1 = 4-Cl) and **2e** (R^1 = 4-NO_2) however were less reactive substrates and the respective products **3n** and **3r*** were isolated in 40% (together with 35% of **4n**) and 37% yields.

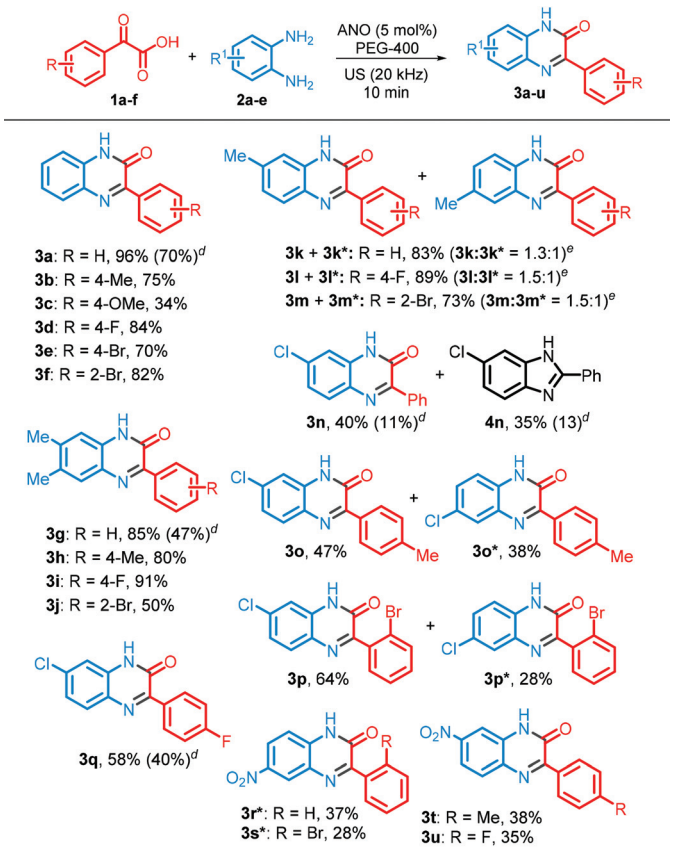
Following, we investigated the reactivity of differently substituted α-keto acids **1** with *o*-phenylenediamine **2a**. As can be seen in Table 2, any remarkable influence was observed when weak electron-donor (**1b**, R = 4-Me) and electron-withdrawing (**1d**, R = 4-F and **1e**, 4-Br) groups were attached in the *para*-position, and the respective products **3b**, **3d** and **3e** were obtained in 75%, 84% and 70% yields. 2-Bromophenylglyoxylic acid **1f** (R = 2-Br) was also a good substrate for the reaction, affording the expected product **3f** in 82% yield, indicating that the steric effect did not influence the reaction performance. The presence of the strong electron-donor methoxy group in **1c** (R = 4-MeO) however negatively influenced the reaction, and the respective quinoxalin-2(1*H*)-one **3c** was obtained in only 34% yield. A similar reactivity was observed in the reactions of *p*-substituted arylglyoxylic acids **1b** and **1d** with 4,5-dimethylbenzene-1,2-diamine **2b**, with the respective products **3h** and **3i** being isolated in 80% and 91% yields, respectively. In this case, 2-bromophenylglyoxylic acid **1f** was less reactive, and the expected product **3j** was obtained in 50% yield.

Regarding unsymmetrical electron-rich *o*-phenylenediamine **2c** [R^1 = 4-Me], a notable loss of selectivity was observed by employing phenylglyoxylic acid derivatives **1d** (R = 4-F) and **1f** (R = 2-Br) as substrates, giving an inseparable mixture of the products **3l : 3l*** (**3l : 3l*** ratio = 1.5 : 1) and **3m : 3m*** (**3m : 3m*** ratio = 1.5 : 1) in 89% and 73% yields, respectively (Table 2).

As mentioned before, for reactions with PGA **1a**, the presence of a chlorine atom in the starting 4-chlorobenzene-1,2-diamine **2d** (R^1 = 4-Cl) has changed the reactivity of the substrate, causing the loss of selectivity for the phenylquinoxalin-2(1*H*)-one **3n**. In the reaction of *p*-tolylglyoxylic acid **1b** with 4-chlorobenzene-1,2-diamine **2d**, the expected quinoxalin-2(1*H*)-one was obtained in 85% overall yield, as a mixture of 7-chloro-**3o** (47%) and 6-chloro-3-(*p*-tolyl)quinoxalin-2(1*H*)-one **3o*** (38%). A mixture of isomers was also obtained in the reaction between **2d** and 2-bromophenylglyoxylic acid **1f**, which afforded **3p** and **3p*** in 64% and 28% yields, respectively. Interestingly, **2d** reacted with the electron-poor 4-fluorophenylglyoxylic acid **1d** (R = 4-F) to give exclusively 7-chloro-3-(4-fluorophenyl)quinoxalin-2(1*H*)-one **3q** (58% yield) under the optimal conditions. As anticipated for the reactions with PGA **1a**, a notable decrease in reactivity was observed when 4-nitrobenzene-1,2-diamine **2e** (R^1 = 4-NO_2) was used as a substrate. For instance, products **3t** (R = Me) and **3u** (R = F) were obtained in only 38% and 35% yields by the reaction of **2e** with **1b** and **1d**, respectively. The yield decreases even more when 2-bromophenylglyoxylic acid **1f** was used, and a mixture of isomers **3s** and **3s*** was obtained in 28% overall yield (Table 2).

As demonstrated in the optimization studies, the reaction of **1a** with **2a** proceeded to some extent in the absence of ANO,

Table 2 Substrate scope for the synthesis of 3-arylquinoxalin-2(1*H*)-ones **3**[a,b,c]



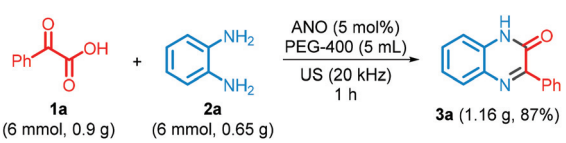
[a] A mixture of **1** (0.3 mmol), **2** (0.3 mmol) and ANO (5 mol%) in PEG-400 (0.5 mL) was sonicated (20% of amplitude) in an open flask for 10 min. [b] Asterisk represents the presence of a regioisomer (substituted at C6). [c] Isolated yield. [d] Reaction performed in the absence of ANO. [e] Regioisomers ratio determined by ^{1}H NMR (ref. 23).

affording 3-phenylquinoxalin-2(1*H*)-one **3a** in 70% yield after sonication for 10 min (Table 1, entry 10). Aiming to speculate on the effectiveness of this catalyst-free approach, it was extended to other substrates. Thus, phenylglyoxylic acid **1a** reacted with 4,5-dimethylbenzene-1,2-diamine **2b** and 4-chlorobenzene-1,2-diamine **2d** to afford the expected products **3g** and **3n** in 47% and 11% yields, respectively (Table 2). In the case of **2d**, 6-chloro-2-phenyl-1*H*-benzo[*d*]imidazole **4n** was also isolated in 13% yield. The reaction of 4-fluorophenylglyoxylic acid **1d** with **2d** afforded, under the catalyst-free conditions, **3q** in 40% yield. Taken together, these results confirm the importance of ANO as a catalyst in the developed reaction, mainly regarding the reaction scope.

In order to show the synthetic usefulness of this protocol to access the pharmaceutically interesting quinoxalin-2(1*H*)-one core, a gram-scale synthesis (5 mmol) was performed. Satisfactorily, the desired 3-phenylquinoxalin-2(1*H*)-one **3a** was obtained in 87% yield after 1 h under the optimal conditions, demonstrating the robustness of our methodology (Scheme 2).

Considering that this important reaction, which gives access to biologically valuable compounds, can be driven towards the formation of two regioisomers when 4-substituted-benzene-1,2-diamines **2** are used, an accurate method for the easy determination of the regioisomeric ratio is required. There are no additional data in the literature which can be explored to identify quinoxalin-2(1*H*)-one regioisomers such as **3** and **3***. Chromatography and ^{1}H NMR techniques are normally used to access the regioisomeric ratio,[17,18,21] while X-ray analysis has also been employed to determine the ratio values, which is not a trivial and fast routine confirmation.[22] On the other hand, some reports do not present any information about regioisomerism,[18,23] neither improvement in the selectivity towards one of the two possible regioisomers.[24] Aiming to offer such a simple protocol to determine the regioisomeric ratios of some of the 3-arylquinoxalin-2(1*H*)-ones **3** prepared in this work, we developed a 2D NMR-based experiment, by using ^{1}H–^{15}N HMBC.

Initially, we set out COSY, HSQC, and HMBC 2D NMR experiments to try undoubtedly identifying all hydrogen and carbon atoms in the quinoxalin-2(1*H*)-one **3** and benzimidazole **4** which were prepared in this work (Fig. 2). However, for most of the analyzed compounds, the 2D NMR experiments were not enough to identify each hydrogen at the phenyl ring from the benzenediamine partner, due to the consolidated multiplicity standard. Then, to confirm the regioisomerism, ^{1}H–^{15}N HMBC NMR experiments were carried out to easily obtain the characterization data. The evidence is based on the huge ^{15}N NMR chemical shift difference between sp^2 and sp^3 hybridized nitrogen atoms.



Scheme 2 Gram-scale synthesis of **3a**.

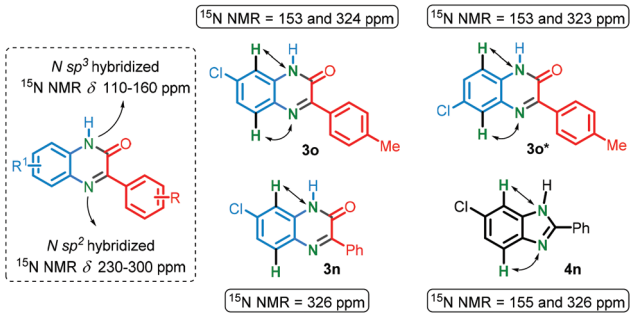


Fig. 2 Chemical shifts of sp^2 and sp^3 hybridized nitrogen atoms.

As can be seen in Fig. 2, quinoxalin-2(1*H*)-one **3o** has two types of nitrogen atoms: one sp^3 hybridized nitrogen, associated with a secondary amide group (^{15}N NMR chemical shifts ranging from 110 to 160 ppm), and one sp^2 hybridized nitrogen, related to a six-membered aromatic heterocycle (^{15}N NMR chemical shifts ranging from 230 to 330 ppm). Thus, the correlation between the hydrogen atoms from the phenyl ring of the benzenediamine partner with these two types of nitrogen atoms provides the unambiguous characterization of each regioisomer. The same profile is observed in the ^{15}N NMR chemical shifts of the benzimidazole **4n** (Fig. 2). In the ^{1}H–^{15}N HMBC NMR spectra of the products **3r***, **3s***, **3t** and **3u**, bearing a nitro group (R^1 = NO$_2$), another nitrogen atom was observed in the 2D spectra with a downfield chemical shift (^{15}N NMR chemical shifts ranging from 355 to 395 ppm). It is worth mentioning that ^{1}H–^{15}N HSQC NMR experiments failed in providing the ^{1}H–^{15}N correlation, probably due to a possible keto–enol tautomerism of the products **3**. Finally, the ^{1}H–^{15}N HMBC NMR experiment can be used for a routine analysis (2–5 hours) to access the regioisomers of the quinoxalin-2(1*H*)-one **3** core, without additional parameter optimization, employing samples of around 20 mg of the compound in 600 μL of DMSO-d$_6$ solvent. In terms of parameter selection, the ^{1}H–^{15}N HMBC NMR experiment is a consolidated technique,[25] and the delay optimization for $^{1}J_{NH}$ was not necessary (95 Hz). For the long-range ^{1}H–^{15}N correlation, a coupling constant of 5 Hz provided satisfactory correlations. Even if only one correlation is obtained in the ^{1}H–^{15}N HMBC experiment, equally we can determine the structural assignment of the regioisomer (Fig. 2, product **3n**). For the ^{1}H–^{15}N HMBC NMR experiments of products **3r***, **3s***, **3t** and **3u**, containing the nitro group, a wider spectral window should be used to avoid the folding process (see the ESI† for the pictures of the spectra).

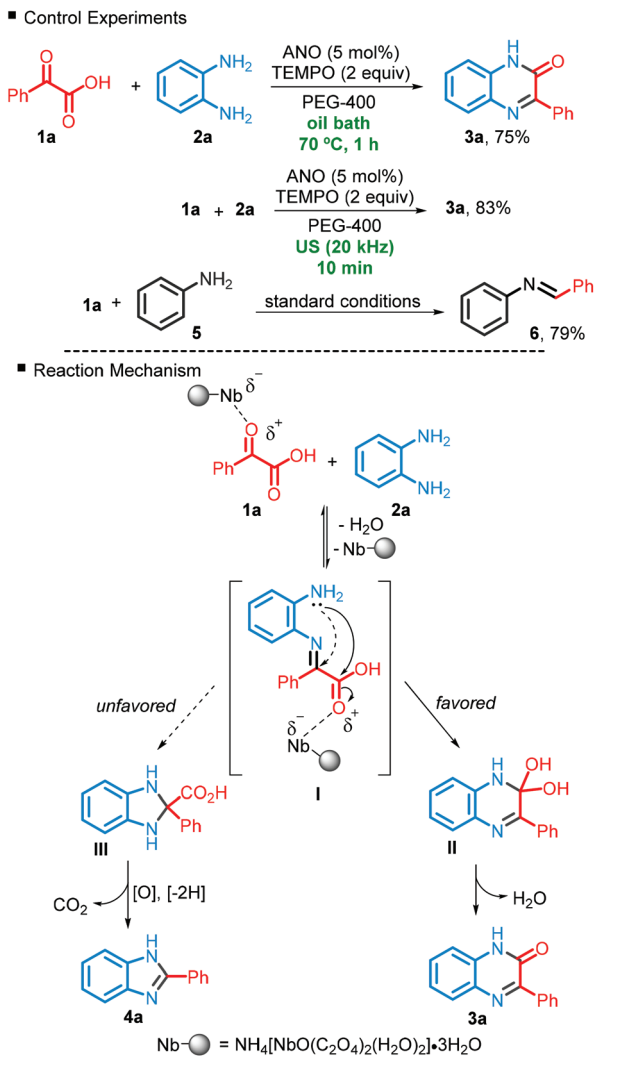
Some additional experiments were performed aiming to suppress or minimize the formation of the co-product **4n** in the reaction of 4-chlorobenzene-1,2-diamine **2d** with PGA **1a** (Table S1†). For this purpose, the energy source, the US intensity and the catalyst parameters were evaluated. When the intensity of US was increased to 60% of amplitude, the selectivity was moved to benzimidazoles **4n** and the overall yield was inferior to that of the optimal conditions. For the reactions employing conventional heating (70 °C, oil bath) or US

without a catalyst, the overall yields were unsatisfactory, and the low selectivity was maintained. A similar study was performed for the reaction of 4-nitrobenzene-1,2-diamine **2e** with **1a**, aiming to improve the yield of **3r**. Again, no improvement in the reaction performance was observed, with the degradation of the reagents being observed. Conclusively, these results indicate the propensity for a decarboxylative coupling of the α-keto acid **1a** with *o*-phenylenediamine **2d** and the consequent formation of 2-substituted benzimidazoles **4n** under strong US irradiation (see Scheme 3 for a plausible mechanism).[15a]

Finally, control experiments were designed in order to give substantial support to elucidate a possible reaction mechanism. Considering the usual reactivity of α-keto acid **1** through a radical mechanism,[14] we have investigated the behavior of the reaction between PGA **1a** and *o*-phenylenediamine **2a** in the presence of 2 equiv. of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) as a radical scavenger using both conventional heating and US conditions (Scheme 3, control experiments). In both cases, no change in the reaction efficiency was observed, and the expected product **3a** was obtained in 75% and 83% yields, discarding the hypothesis of a radical pathway in the reaction mechanism.

Based on this and considering a possible anionic mechanism, we have investigated what would be the rate-determining reaction step, since two main possibilities are allowed: (1) NH_2-free group of **2a** attacking the keto site of **1a**, giving an imine intermediate, or (2) NH_2-free group attacking the carboxylic acid site, giving an amide intermediate. Thus, by carrying out an experiment using aniline **5** as a NH_2-free source, under the standard reaction conditions, the respective decarboxylated imine derivative **6** was formed in 79% yield, without any amide derivative (Scheme 3, control experiments).[18b] Additionally, the double bond isomerism of the product **6** was confirmed by the 2D NOESY NMR experiment (see the ESI†).

Based on these control experiments and in the literature,[14] a plausible mechanism was proposed. Initially, an ANO-catalyzed reaction between the keto portion and an NH_2-free unit affords the Schiff-base intermediate **I**, which can follow two main reaction pathways: (1) addition to the imine sp^2 carbon (dashed arrow) and/or (2) the amide formation by an addition/elimination to the acid portion (solid arrow). In our case, the attack on the acid carbonyl site is favored, forming the fused six-membered heterocycle intermediate **II**, which is dehydrated to give the quinoxalin-2(1*H*)-one **3a**. This selectivity to **II** over the five-membered intermediate **III** (and so **4a**) could be attributed to a complexation of the catalyst (ANO) to the carbonyl in **I**, favoring the nucleophilic attack by the remaining NH_2 group (Scheme 3, reaction mechanism).



Scheme 3 Control experiments and plausible reaction mechanism.

Conclusions

Herein we described an easy, mild and efficient protocol to access 3-arylquinoxalin-2(1*H*)-ones. Ammonium niobium oxalate proved to be an efficient catalyst for the reaction, promoting the annulation between *o*-phenylenediamines and α-keto acids in only 10 min. The reactions are highly selective, producing water as the sole by-product. Ultrasound irradiation was used as an alternative energy source and PEG-400 as a green and cheap solvent. ^{1}H–^{15}N HMBC NMR experiments proved to be a robust and reliable technique to access quinoxalin-2(1*H*)-one and benzimidazole regioisomers.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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