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Synthesis of 2,3-Diarylquinoxaline Carboxylic Acids in High-Temperature Water

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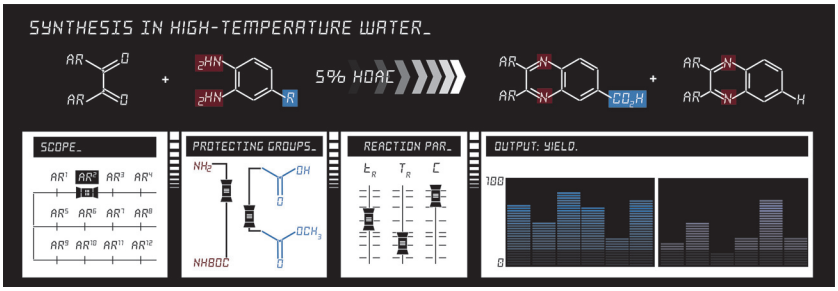

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Abstract Aromatic carboxylic acids are prone to decarboxylate in high-temperature water (HTW). While the decarboxylation kinetics of several aromatic carboxylic acids have been explored, studies on their compatibility with organic syntheses in HTW are scarce. Herein, we report the hydrothermal synthesis (HTS) of 2,3-diarylquinoxaline carboxylic acids from 1,2-diarylketones and 3,4-diaminobenzoic acid. A detailed study of the reaction parameters was performed to identify reaction conditions towards minimal decarboxylation. Thirteen 2,3-diarylquinoxaline-6-carboxylic acids are obtained at temperatures between 150–230 °C within 5–30 minutes. The reported conditions feature comparable performance to those of classic syntheses, avoiding volatile organic solvents, strong acids and toxic catalysts. Decarboxylated quinoxalines arise as side products in variable amounts via direct decarboxylation of the 3,4-diaminobenzoic acid. To completely inhibit the decarboxylation, we show that suitable structural analogues of 3,4-diaminobenzoic acid can act as starting compounds. Thus, ester hydrolysis of methyl 3,4-diaminobenzoate and deprotection of di-Boc-protected 3,4-diminobenzoic can be coupled with the HTS of quinoxaline towards quinoxaline carboxylic acids, while fully avoiding decarboxylated side products.

Key words quinoxalines, high-temperature water, green chemistry, decarboxylation, hydrothermal synthesis

The chemical industry has actively contributed to humankind's technological development. Advances in medicine, transport, and communication would be inconceivable without the supply of different compounds, from bulk to fine chemicals. The growing demand for these chemicals has simultaneously created a serious problem: The chemical industry is also a significant contributor to environmental pollution.[1] Counteracting such harmfulness is a prime current goal. Measures towards preventing waste generation in chemical synthesis include, but are not limited to, using renewable over non-renewable resources and developing green chemical syntheses. The greenness of a chemical synthesis relies on a combination of factors, including the toxicity of all the employed compounds, the energy input, and the amount of waste generated.

Among these factors, reaction solvents are in fact a key component. They are typically used in the highest quantity for both synthesis and purification procedures.[2] The majority of solvents in the synthetic toolbox of organic chemists are volatile organic compounds (VOCs), e.g., aromatics, alkyl halides, ethers, alcohols, nitriles, or amides. Among other features, such as low molecular weights and high vapor pressures, the dielectric constants of VOC solvents provide reaction media of suitable polarity for solubilizing a plethora of starting materials. Nevertheless, this advantage is overshadowed by the inherent risks and harmfulness of many VOC solvents, e.g., toxicity, flammability, and the formation of ground-level smog.[3] Clearly, green reaction media are needed as alternative to classical solvents. These should ideally perform comparably or better than VOC solvents (with respect to, e.g., reaction speed, reaction yields, and ease of purification), while featuring ready availability and low cost.

As part of our interest in synthesizing heteroaromatic compounds and high-performance materials in a greener fashion, we have focused on water as a solvent. Water is non-toxic and does not exhibit the drawbacks of VOC solvents. Using water as a solvent and organic synthesis, espe-

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Miriam M. Unterlass studied chemistry, process engineering and materials science in Würzburg (Germany), Southampton (UK), and Lyon (France). She pursued her PhD at the Max Planck Institute of Colloids and Interfaces (Germany), and performed her postdoc at the Ecole Supérieure de Physique et Chimie Industrielles (ESPCI) in Paris (France). In 2013 she joined the Technische Universität Wien (Austria) as independent group leader, received her habilitation in materials chemistry in 2018, and became tenured assistant professor in 2019. Since 2018, Miriam is an Adjunct Principal Investigator at the Centre for Molecular Medicine of the Austrian Academy of Sciences. In June 2021, Miriam joined the University of Konstanz (Germany) as full professor of solid state chemistry. Her research interests revolve around compounds rich in aromatic and heterocyclic functions for either materials or biological applications, or both. A particular focus in the Unterlass Lab are non-classical sustainable synthetic approaches, especially involving hydrothermal synthesis and automation.

cially of (hetero)aromatics, seem incompatible with each other. The low polarity of many starting compounds in water might hinder their reaction in such a polar protic solvent. Nonetheless, the pool of organic reactions performed under aqueous conditions has grown over decades.[4] Many carbon-rich starting materials can be reacted in water by using additives, e.g., surfactants or cyclodextrins.[5] These essentially provide hydrophobic cavities in water, inside which the desired reaction takes place. Alternatively, water can be heated up to high temperatures. Implementing a high-temperature-water-based approach is significantly simpler than others as the starting materials and hot water are typically the only components involved.

The *hydrothermal* (HT) regime, referring to liquid water at 150 < T < 250 °C, 4 < p < 20 bar, is found at significantly lower temperatures and pressures than the subcritical and supercritical regime. Compared to water at room temperature, the physicochemical properties of liquid water are significantly different throughout the different high-temperature water (HTW) regimes. More interestingly, the HT regime already provides suitable polarity and acid–base properties for performing organic synthesis (Figure 1a).[6] The static dielectric constant (ε) of liquid water decreases as a function of the temperature. Therefore, organic starting compounds with negligible solubility in water at 25 °C typically exhibit higher solubility in HTW. The acid–base properties of liquid water also change as a function of the temperature. The ionic product (K_w) in the HT regime is three orders of magnitude higher than at room temperature, up to a maximum at 250 °C. This increase in K_w provides a suitable reaction medium to perform acid–base-catalyzed reactions. On top of these synthetic advantages, purification procedures are significantly simplified in reactions performed in HTW. After cooling to room temperature, low-polarity products phase-separate, avoiding long purification sequences in favor of filtration or decantation steps. All these features provide conditions for, as we believe, expanding the synthetic toolbox of organic chemists towards more reactions in HTW. In particular, established syntheses towards heteroaromatics commonly employ VOC solvents, harsh conditions (e.g., strong acid or basic compounds, me-

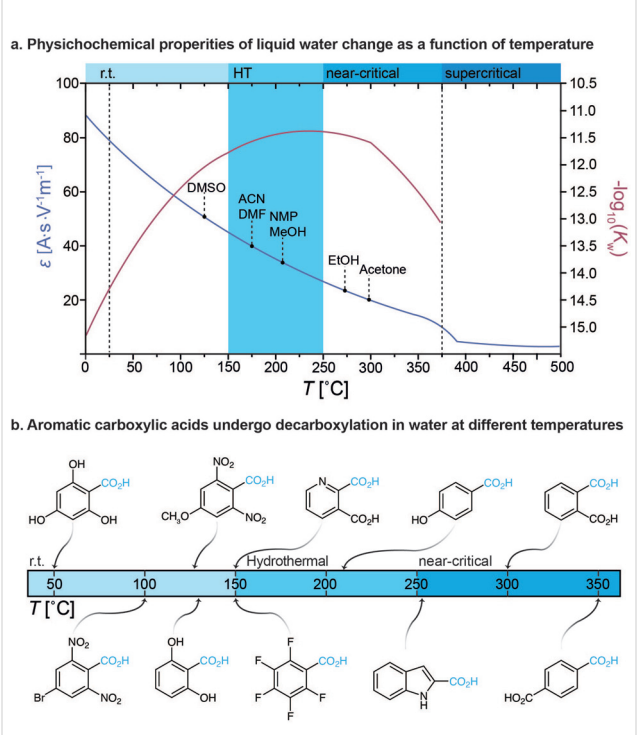


Figure 1 (a) Physicochemical properties of liquid water at different temperatures: static dielectric constant (ε) and ionic product (K_w depicted as $pK_w = -\log_{10}K_w$). The arrows compare the approximate ε value of different organic solvents at r.t. with that of water at the temperature indicated on the x-axis. DMSO: dimethyl sulfoxide, ACN: acetonitrile, DMF: dimethylformamide, NMP: *N*-methyl-2-pyrrolidone. (b) Decarboxylation temperatures of aromatic carboxylic acids in H_2O. The figure shows selected examples of decarboxylation throughout the different HTW regimes. A comprehensive overview is provided in the Supporting Information.

tallic catalysts) and long purification sequences. Greener alternatives are heavily sought-after for synthesizing heteroaromatic compounds. Here, the HT regime is expected to assume roles of both classical solvents and acid–base catalysts for synthesizing heteroaromatics, and thereby facilitating their purification.

Within the subcritical and supercritical regimes, reactions towards forming heteroaromatics are in fact scarce, and the majority of studies deal with aquathermolysis of heteroaromatics, i.e., ring-opening of heteroaromatics.[7] Below the temperatures comprehended by the subcritical and supercritical regimes, several contributions have reported the synthesis of heteroaromatics. At moderate temperatures, i.e., between room temperature and 150 °C, these syntheses commonly employ relatively highly polar starting materials in combination with catalysts.[8] However, the ε value of liquid H_2O is still high at moderate temperatures and it is expected that low-polarity starting compounds are not sufficiently solubilized. This is typically the case of syntheses towards highly conjugated heteroaromatics. To promote the formation of heteroaromatics in water, the required conditions go beyond moderate temperatures and the HT regime already provides an ideal interplay between polarity and acid–base properties. Interestingly, at temperatures higher than 150 °C, the reports of heteroaromatics synthesized in water are significantly more limited. To the best of our knowledge, these reports include benzimidazoles,[9] perylene and naphthalene bisimides,[10] perinones,[11] and more recently quinoxalines.[12]

The heteroaromatic quinoxaline scaffold is prevalent within compounds with applications in either materials science or medicinal chemistry.[13] Classically, their synthesis is performed via the reaction between 1,2-diketones and *o*-phenylendiamine (*o*-PDA) analogues, i.e., the Hinsberg cyclization, in alcohols as solvents and with strong acids as catalysts.[14] In water, quinoxalines via the Hinsberg cyclization have been achieved as follows: (*i*) at low or moderate temperatures in the presence of a catalyst (either synthetic or commercially available);[15] (*ii*) at room temperature without any catalyst towards dialkylquinoxalines, while diarylquinoxalines are obtained in low yields (<20%);[16] (*iii*) via the HT approach towards 2,3-diarylquinoxalines and biquinoxalines recently reported by our group.[12] The latter HT synthesis proceeds solely in water at 230 °C for 60 minutes, and is shortened to 10 minutes in solutions of 5% acetic acid (HOAc) at the same temperature. Therefore, the HT approach neither requires the preparation of a catalyst nor its laborious removal from the reaction mixture. Hence, further impact on the overall synthetic greenness is avoided. The HTS of quinoxalines is compatible with a broad scope of starting materials bearing diverse functional groups. However, in our recent work,[12] we did not investigate substrates bearing carboxylic acids (CO_2H) as (*i*) they might condense with the amino groups available in *o*-PDA analogues towards forming, e.g., benzimidazoles, or (*ii*) decarboxylation of the CO_2H functions might occur in HTW. In the present work, we address the compatibility of the HTS of quinoxalines with carboxylic acid groups.

Hydrothermal fluids in the Earth's crust play a crucial role in natural petrochemical processes. Many petro- and geochemical studies have shown that aromatic carboxylic acids decarboxylate to various extents in HTW [Figure 1b and Table S1 (see the Supporting Information) for a summary].[17]

All these studies on HTW focus on the decarboxylation kinetics of the CO_2H groups. To the best of our knowledge, the study of pathways to conserve the CO_2H groups in HTW is essentially unexplored. Conserving these groups is essential in multistep syntheses towards, e.g., amide or ester formation. Here, we show that the HTS of quinoxalines can be tuned to conserve the CO_2H group. Lower temperatures within the HT regime offer a certain control over decarboxylation while simultaneously forming quinoxalines with good yields. Moreover, carefully selected starting compounds with sufficient aquathermal stability and versatility can avoid decarboxylation via reactions in tandem with the HTS of quinoxalines.

We selected the reaction between 4,4′-dimethoxybenzil (**1**) and 3,4-diaminobenzoic acid (**2**) as a model system to study the HTS of quinoxalines bearing CO_2H groups (Figure 2a). In a standard experiment, the starting materials are suspended in water and the mixture is heated in a microwave reactor to the target reaction temperature (T_r) for the indicated reaction time (t_r). After cooling to room temperature, the crude reaction mixture was filtered, purified and analyzed by ^{1}H NMR (see the Supporting Information for details). The results of the experiments under all the tested conditions are shown in Figure 2. In a first experiment, we reacted equimolar amounts of 4,4′-dimethoxybenzil (**1**) and 3,4-diaminobenzoic acid (**2**) in 5% HOAc under the previously reported conditions, i.e., T_r = 230 °C, t_r = 10 minutes.[12] As expected, analysis of the crude product by ^{1}H NMR showed that the target quinoxaline **3** was obtained as the major product. However, further signals suggested the presence of a second product in a lower amount than compound **3**. Analysis of the remaining signals in the ^{1}H NMR spectrum pointed to the presence of 2,3-bis(4-methoxyphenyl)quinoxaline (**4**), i.e., the decarboxylated analogue of compound **3**. Purification was conducted to isolate pure compound **3** in 79% yield (Figure 2b), whereas the yield of compound **4** was 18% (Figure 2c, NMR yield). The structures of compounds **3** and **4** were confirmed by their ^{1}H and ^{13}C NMR spectra. The starting material 4,4′-dimethoxybenzil was detected in only 1% in relation to its initial amount (Figure 2d), confirming the efficient quinoxaline formation under the tested conditions. Note that unreacted 3,4-diaminobenzoic acid was in principle washed away after filtering, and self-condensation products of 3,4-diaminobenzoic acid were not detected (NMR).

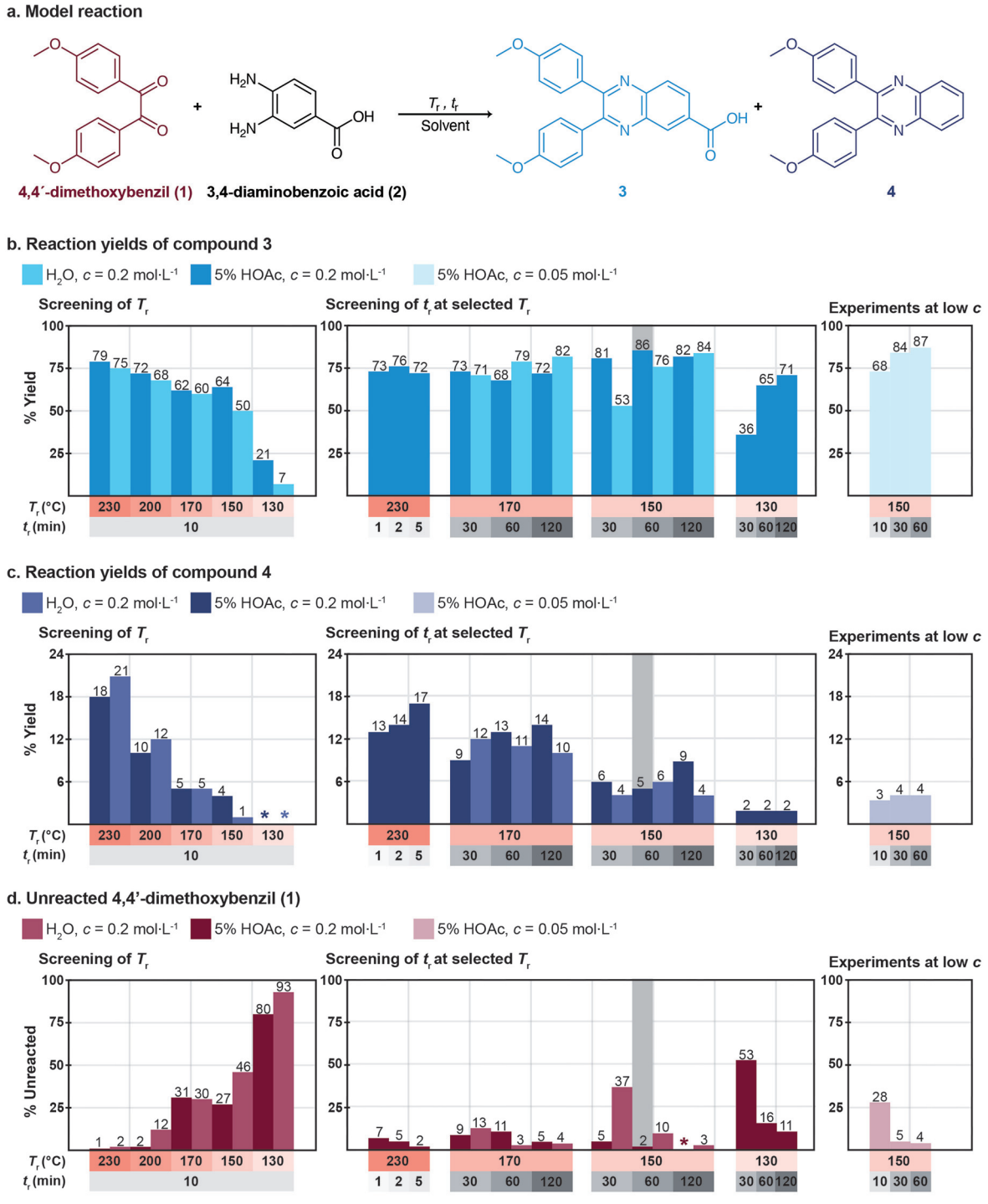


Figure 2 Screening of the reaction conditions for synthesizing quinoxaline **3** under HT conditions. (a) The model reaction was performed under various conditions (T_r, t_r, c and solvent). The histograms depict the reaction yields of (**b**) compound **3**, (**c**) compound **4**, and (**d**) the amount of unreacted 4,4′-dimethoxybenzil with respect to the initial amount. Isolated yields are presented for compound **3**; the yields of compound **4** and the amount of 4,4′-dimethoxybenzil were determined by NMR. * Compounds were not detected. For details, please refer to the Supporting Information.

In our recently reported HTS of quinoxalines, we found that *o*-phenylendiamine dihydrochloride (*o*-PDA·2HCl) reacts with benzil to produce 2,3-diphenylquinoxaline in solely water (i.e., without added HOAc) at T_r = 230 °C.[12] Analogously to *o*-PDA·2HCl, the CO_2H function in the 3,4-diaminobenzoic acid is a source of protons. We hypothesized that the inherent acidity of the 3,4-diaminobenzoic acid might also self-catalyze the reaction and influence the yields of compound **3** and **4**. To test this, we performed a second experiment on the model reaction in nothing but water at T_r = 230 °C for t_r = 10 minutes. The analysis by ^{1}H NMR of the crude reaction product showed that it was indeed mainly composed of a mixture of target compound **3** and the decarboxylation product **4**. Compounds **3** and **4** were obtained in yields of 75% and 21%, respectively. These reaction yields can be considered similar to those of the experiment employing 5% HOAc as the solvent. Similar to the first experiment, 4,4′-dimethoxybenzil was recovered in minor amounts (2%), evincing a satisfactory conversion of the starting compound. The conducted experiments suggested that at 230 °C, (*i*) the acidity provided by the CO_2H group in the 3,4-diaminobenzoic acid was sufficient to catalyze the quinoxaline formation, and (*ii*) the presence of HOAc did not further influence the formation of compound **3** and the decarboxylation.

The so far discussed experiments showed that the formation of compound **3** was complete after heating at 230 °C for 10 minutes. Yet, compound **4** was obtained in yields of up to 21%. Despite the lower yields of compound **4** compared to **3**, further purification was necessary to separate the compounds. Thus, we next focused on decreasing the amount of decarboxylation product in the crude mixture. To achieve this, it was essential that the employed reaction temperature (T_r) and reaction time (t_r) were compatible with both the efficient formation of the quinoxaline and the maximum inhibition of the decarboxylation reaction. We hypothesized that T_r values <230 °C might decrease the decarboxylation rate, hence ideally favoring compound **3** as the main product. Therefore, we performed the model reaction at 130 ≤ T_r ≤ 200 °C for t_r = 10 minutes in both 5% HOAc and in solely water for comparison. We found that the yield of compound **3** varies with T_r. For reactions performed in 5% HOAc, compound **3** was obtained in 72% yield at 200 °C and a further decrease to 62% was observed when the reaction was performed at 170 °C. Interestingly, compound **3** was still obtained in 64% yield at 150 °C, while the yield decreased to 21% at 130 °C. At a T_r value within the HT regime (150–250 °C), compound **3** was obtained in moderate to high yields within only 10 minutes, whereas the yield of **3** indeed drops below the HT regime. The experiments performed solely in water for 10 minutes at different T_r values showed a similar behavior, i.e., the yields of compound **3** decreased as a function of T_r. Interestingly, the yields of compound **3** for the reactions performed solely in water (i.e., in the absence of HOAc) were influenced to a higher extent by lowering T_r. At 200 °C, the yield of compound **3** in solely water was slightly lower than that of the experiment in 5% HOAc. This was also observed in the experiments at 170 °C (yields of compound **3**: 60% in water and 62% in 5% HOAc). However, at 150 °C and 130 °C, compound **3** was obtained in 5% HOAc with higher yields than in solely H_2O. For experiments in nothing but water, we hypothesize that the catalysis is performed by different sources of acid depending on the T_r. At high T_r, we believe that there is a significant contribution from both H_2O itself as a H^+ source and from the CO_2H group of 3,4-diaminobenzoic acid. At low T_r, the acidity provided by the HT conditions is lowered (*cf.* Figure 1a) and 3,4-diaminobenzoic acid plays the main catalytic role. Note that the pK_a value of the 3,4-diaminobenzoic acid (e.g., pK_a = 4.2 for benzoic acid) is expected to be different from that of HOAc (pK_a = 4.8). At T_r ≤ 150 °C in the absence of HOAc, the acidity of 3,4-diaminobenzoic acid is not sufficient to catalyze the quinoxaline formation, hence, lower yields of compound **3** are obtained. These lower yields, as a consequence of slower quinoxaline formation, are also consistent with the amount of unreacted 4,4′-dimethoxybenzil for reactions performed at 150 °C and 130 °C. At these T_r values, the experiments in nothing but water for 10 minutes contain more unreacted 4,4′-dimethoxybenzil than those in 5% HOAc (see Figure 2d). From an alternative perspective, lower yields of compound **3** might arise from a faster decarboxylation rate in water compared to 5% HOAc. Conversely, the yields of compound **4** in fact show that the decarboxylation decreased at lower T_r (Figure 2c). For reactions performed in 5% HOAc for 10 minutes, the yields of compound **4** decreased from 18% (at 230 °C) to 10% when the reaction was performed at 200 °C. Further drops to 5% and 4% were observed for the experiments at 170 °C and 150 °C, respectively. Compound **4** was not isolated in the experiments performed at 130 °C, suggesting that decarboxylation was inhibited at this temperature. These results indicated that T_r indeed offers control over the decarboxylation. The experiments in nothing but water and 5% HOAc for t_r = 10 minutes showed almost identical yields for compound **4** at the tested T_r values. Thus, HOAc does not significantly influence the decarboxylation reaction at any of the tested T_r values for this short reaction time. Summarizing, the screening at different T_r values showed that (*i*) T_r = 150 °C or 170 °C yielded the highest amount of compound **3** (50–64%) simultaneously with low yields for the decarboxylation product **4** (1–5%), and (*ii*) at T_r ≤ 150 °C and a short t_r, reactions performed in 5% HOAc yielded compound **3** in higher amounts than those solely in water.

After observing that T_r indeed offers control over decarboxylation in our model reaction, we aimed at increasing the yields of compound **3** by varying the reaction time (t_r). The selected T_r value is essential to decide whether a t_r shorter or longer than 10 minutes is needed. The low amount of 4,4′-dimethoxybenzil found in the experiments at 230 °C suggests that the formation of compound **3** is al-

most complete after 10 minutes. We hypothesized that prolonged heating at 230 °C might promote higher decarboxylation, hence decreasing the yield of compound **3**. Conversely, a shorter t_r might yield lower amounts of compound **4** without dropping the yields of **3** considerably. To gain insight on this, we conducted the model reaction at 230 °C with t_r values < 10 minutes. The yields of compound **3** stagnated between 72% and 76% after heating for $t_r \leq$ 5minutes, whereas the yields of compound **4** and the amount of unreacted 4,4′-dimethoxybenzil changed as a function of t_r. Interestingly, heating at 230 °C for 1 minute was in fact enough to yield 13% of compound **4**, the amount of which slightly increased with time. Complementarily, the amount of 4,4′-dimethoxybenzil decreased as a function of t_r, which indicates that the formation of compound **3** is driven to completeness very rapidly at 230 °C.

We next investigated the effect of t_r at $T_r \leq$ 170 °C. At these T_r values for t_r = 10 minutes, the amount of unreacted 4,4′-dimethoxybenzil ranged between 31% (at 170 °C) and 93% (at 130 °C). We expected to favor the formation of compound **3** by extending t_r. At 170 °C, prolonged heating for 30 minutes in 5% HOAc increased the yield of compound **3** to 73%. Further extending t_r neither increased nor decreased the yield. In solely water, the yield reached 79% after 60 minutes, whereas heating for 120 minutes only increased the yield to 82%. Extended t_r values indeed increased the yields of compound **3**, albeit with decarboxylation reaching almost identical yields in both 5% HOAc and solely in water (e.g., yields of compound **4** in 5% HOAc with t_r = 10 min: 5%, 30 min: 9%, 60 min: 13%, 120 min: 14%). We next studied the effect of longer t_r values at 150 °C. Here, the yields of compound **3** for the reactions performed in 5% HOAc increased to 81% after 30 minutes. Prolonged heating for 60 and 120 minutes led to similar yields of 86% and 82%. In solely water for t_r = 30 and 60 minutes, the yields of compound **3** were lower than those in 5% HOAc, namely 53% and 76%, respectively. These results were consistent with the experiments run for 10 minutes at 150 °C, i.e., HOAc accelerates the reaction. Interestingly, the yields of compound **3** solely in water reached 84% after 120 minutes of reaction. This is comparable to the experiments performed in 5% HOAc for 60 minutes (86%) and 120 minutes (82%) at the same T_r. The similar yields among these experiments are consistent with a catalytic role for HOAc. A prolonged t_r in solely water compensates for the lack of added acid catalyst. More interestingly, the yield of compound **4** was only 5% after heating for 60 minutes at 150 °C. A further increase to 9% was observed for the yield of compound **4** yield after 120 minutes. Overall, the yields for **4** at 150 °C suggest that decarboxylation at this T_r is less favored than at 170 °C. We also performed experiments over extended reaction times at T_r = 130 °C. Since HOAc was shown to be essential to accelerate the reaction at 130 °C over 10 minutes, we only performed experiments in 5% HOAc at this T_r. The absence of decarboxylation at 130 °C was ideal despite the low reaction yields for compound **3** (up to 21% in 5% HOAc for t_r = 10 min). After 120 minutes at 130 °C, the yield of compound **3** reached 71% and decarboxylation also takes place. Moreover, 4,4′-dimethoxybenzil was still recovered (11%). To summarize, among the tested T_r and t_r values, the experiments at T_r = 150 °C yielded the highest amount of compound **3** without promoting decarboxylation significantly.

The concentration of the starting materials (*c*) showed a significant effect on the reaction yield in our previously reported HTS of quinoxalines. Therefore, we performed experiments at T_r = 150 °C and at different *c* values. Decarboxylation of several aromatic carboxylic acids in HTW has been shown to follow first-order kinetics.[18] We anticipated that experiments at *c* values above 0.2 mol·L^{-1} might show comparable or even higher decarboxylation. To avoid this, we selected *c* = 0.05 mol·L^{-1} for performing experiments at T_r = 150 °C and t_r = 10, 30 and 60 minutes. Interestingly, the yields of compounds **3** and **4** did not change significantly compared to the experiments performed at comparable T_r and t_r values at *c* = 0.2 mol·L^{-1}. This indicated that the tested concentrations did not influence the formation of compounds **3** and **4** significantly. Overall, the experiments performed over extended reaction times and at different concentrations showed that the most suitable conditions to yield compound **3** (86%) with minimum decarboxylation (5% yield for compound **4**) are T_r = 150 °C for 60 minutes in 5% HOAc. Next, we performed experiments to scale up our model reaction. We employed the same experimental setup, i.e., a microwave reactor, increasing the reaction volume, and keeping the conditions established previously (see further details in the Supporting Information). Satisfactorily, without further changes of the reaction parameters, compound **3** (0.6 g, 78% yield) was obtained without a significant drop in the reaction yield.

The presence of compound **4** in the crude products of the model reaction clearly suggests that both quinoxaline formation and a decarboxylation reaction take place at the majority of the T_r values examined. Two pathways towards compound **4** are conceivable: (*i*) the quinoxaline in compound **3** is formed first and then decarboxylates to yield compound **4**, or (*ii*) the starting 3,4-diaminobenzoic acid decarboxylates first to *o*-PDA, which is followed by formation of the quinoxaline. In principle, both pathways could coexist. However, it is plausible that a particular pathway might be predominant due to increased or even exclusive decarboxylation from 3,4-diaminobenzoic acid or compound **3**. Such a difference would not be rare since slight structural differences can significantly influence the decarboxylation of aromatic carboxylic acids (*cf.* Figure 1b and Table S1 in the Supporting Information). In the realm of heteroaromatics bearing CO_2H groups specifically, indole-2-carboxylic acid yields indole quantitatively when subjected to water at 255 °C for 20 minutes,[19] quinolinic acid exhibits total decarboxylation of the CO_2H group at position 2 after 60 minutes at 150 °C,[18] whilst isomeric pyridine carboxylic

acids decarboxylate to give pyridine at 150 °C (2-pyridine-carboxylic acid) and 250 °C (3-pyridine-carboxylic acid and 4-pyridine-carboxylic acid).[20]

To shine light on the origin of the yields of compound **4**, the aquathermal stability of compound **3** and 3,4-diaminobenzoic acid were examined. Solutions of these compounds (c = 0.05 mol·L^{-1}) in 5% HOAc were heated for 30 minutes at 150 °C. Furthermore, experiments at 230 °C were also conducted. We found that the aquathermal stabilities of compound **3** and 3,4-diaminobenzoic acid were significantly different. Compound **3** was recovered after heating at both 150 °C and 230 °C. Neither the degradation of compound **3** nor decarboxylation towards compound **4** was observed. In contrast, 3,4-diaminobenzoic acid exhibited aquathermal lability at the tested T_r values (see Figure S15 in the Supporting Information). For the experiment performed at 150 °C, 3,4-diaminobenzoic acid was recovered and *o*-PDA was also produced. More interestingly, 3,4-diaminobenzoic acid was fully converted into *o*-PDA and 2-methylbenzimidazole after heating at 230 °C. The presence of 2-methylbenzimidazole is in principle explained by the condensation between *o*-PDA and HOAc. This indicates that condensation reactions between *o*-PDA and carboxylic acids with sufficient aquothermal stability might take place under the tested conditions. Since the 3,4-diaminobenzoic acid readily decarboxylates to form *o*-PDA, even at 150 °C, we hypothesize that self-condensation products of 3,4-diaminobenzoic acid were not observed due to the favored decarboxylation.

Overall, the aquathermal stability experiments clarified that compound **4** is in fact generated via pathway (*ii*), i.e., decarboxylation of 3,4-diaminobenzoic acid, exclusively.

Having established the main pathway towards compound **4** in the model reaction, we focused on circumventing the decarboxylation of 3,4-diaminobenzoic acid. Density functional theory calculations have been performed to study the decarboxylation of hydroxybenzoic acids in water at high temperatures.[17c] It has been shown that in aqueous solution the solvation differences between hydroxybenzoic acids and their transition states for decarboxylation seem to influence the decarboxylation. The decarboxylation rates follow trends predicted by the resonance effect of the hydroxy groups, where *ortho*- or *para*-hydroxy-substituted benzoic acids decarboxylate faster. Moreover, it has been proposed that proton transfer from the CO_2H group towards decarboxylation might be mediated by a molecule of water.

Therefore, the decarboxylation kinetics of the 3,4-diaminobenzoic acid are expected to be influenced by the structural features. We hypothesized that decarboxylation would be circumvented by the selection of analogues of 3,4-diaminobenzoic acid with better aquothermal stability. The selection of the analogue is crucial. The analogue should feature low or ideally no decarboxylation, while the reactivity towards quinoxaline formation must be conserved. To this end, we selected methyl 3,4-diaminobenzoate (**2a**) as an analogue of 3,4-diaminobenzoic acid. The selected compound contains the CO_2H group protected as a methyl ester and the amino (NH_2) substituents required to form the quinoxaline. We envisioned a sequence consisting of quinoxaline formation and ester hydrolysis to yield compound **3** in a HT one-pot fashion. Thus, we conducted the reaction between **2a** and 4,4′-dimethoxybenzil at T_r = 230 °C in 5% HOAc over different t_r values (Figure 3). The hydrolysis of methyl benzoate in HTW proceeds with low conversion at 175 °C and 200 °C, whereas temperatures beyond 250 °C facilitate the ester hydrolysis.[21] Therefore, we performed the reaction at the highest possible T_r in our setup to favor both ester hydrolysis and quinoxaline formation. Note that methyl 2,3-bis(4-methoxyphenyl)quinoxaline-6-carboxylate (**5**) was the major expected product of this reaction. After 10 minutes of heating at 230 °C, compounds **5** and **3** were obtained in yields of 85% and 6%, respectively. More interestingly, extended reaction times decreased the yield of compound **5** while simultaneously increasing those of compound **3** (Figure 3b). This suggested that the increase in the yields of compound **3** was propelled by the ester hydrolysis from compound **5**. To our delight, compound **4**, i.e., the decarboxylation product, was not detected (according to NMR) in the crude product mixtures at any of the tested t_r values. After 3 hours, compound **3** was obtained in 77% yield, and further extending the t_r did not increase the yield. These results confirmed that compound **3** can be synthesized in HTW with good yields from methyl 3,4-diaminobenzoate (**2a**), whilst excluding the formation of the decarboxylation product.

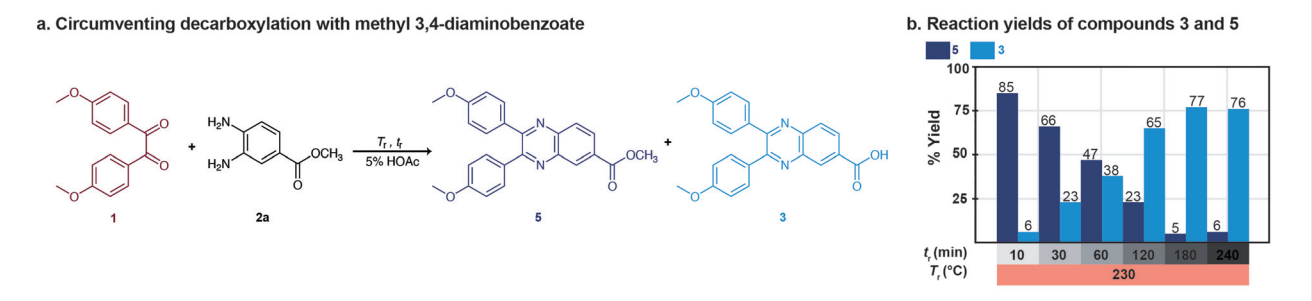


Figure 3 (a) Reaction between 4,4′-dimethoxybenzil and methyl 3,4-diaminobenzoate towards the one-pot synthesis of compound **3**. (b) Reaction yields of compounds **3** and **5** for the experiments at different t_r values at 230 °C.

We additionally explored a second strategy towards circumventing the decarboxylation of 3,4-diaminobenzoic acid. We hypothesized that analogues of 3,4-diaminobenzoic acid with substituted NH_2 groups would also exhibit different decarboxylation kinetics. Modification of the NH_2 substituents seems counterintuitive since they are required to form the quinoxaline ring. Nevertheless, we examined di-Boc-protected 3,4-diaminobenzoic acid **2b** as the starting compound to synthesize compound **3** hydrothermally for the following reasons. Boc-protected amines are synthetically accessible, and in some cases are even commercially available. More importantly, prior reports showed that Boc-protected aromatic amines can be deprotected by heating in water at 150 °C without further additives,[22] and in fact our group showed that di-Boc-protected *o*-phenylendiamine undergoes one-pot deprotection followed by quinoxaline formation in water at 230 °C.[12] We envisioned a similar sequence of deprotection–quinoxaline formation towards compound **3** starting from di-Boc-protected 3,4-diaminobenzoic acid and 4,4′-dimethoxybenzil (Figure 4). To test our hypothesis, the reaction was performed at 150 °C in 5% HOAc over different t_r values. After 30 minutes of reaction, compound **3** was obtained in 54% yield and the yield stagnated between 58–65% over longer reaction times (Figure 4c). Surprisingly, no signals corresponding to compound **4**, i.e., the decarboxylation product, were detected (NMR) in the crude product. Note that the reactions performed from 3,4-diaminobenzoic acid at an identical T_r and c (0.05 mol·L^{-1}) yielded up 4% of compound **4**. A close look into the amount of unreacted starting compounds revealed that the amount of di-Boc-protected 3,4-diaminobenzoic acid stabilizes between 17–25% after 1 hour of reaction (Figure 4b). After this time, the deprotection stagnated and the formation of compound **3** stopped due to a lack of 3,4-diaminobenzoic acid to propel quinoxaline formation. Increasing the T_r drives the deprotection to completeness, albeit compound **4** is obtained in 9% and 11% yields at 170 °C and 200 °C, respectively. These yields for compound **4** are comparable to those of the reactions from 3,4-diaminobenzoic acid (see Figure 2c, e.g., 9% at 170 °C over 30 min, 10% at 200 °C over 10 min).

To sum up, the Boc-protecting groups prevented the decarboxylation at 150 °C but the formation of compound **3** was not complete. However, the protecting effect was lost for reactions performed at 170 °C and 200 °C.

We were gladly surprised by the result at 150 °C. In principle, Boc-protecting groups might disfavor the decarboxylation by, e.g., decreasing the resonance effect of the NH_2 substituents or hindering the formation of the hydrogen-bond bridge mediating decarboxylation. However, after the deprotection reaction, the 3,4-diaminobenzoic acid obtained in situ might still undergo decarboxylation. In fact, this is consistent with the experiments at $T_r \geq 170$ °C. We propose that the rate of deprotection plays a fundamental

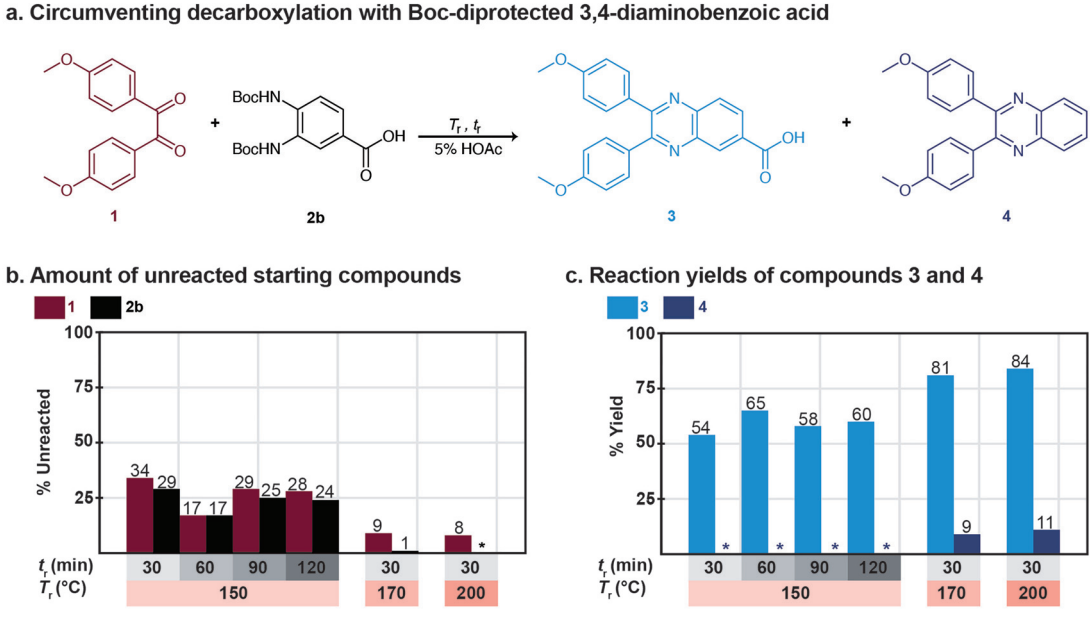


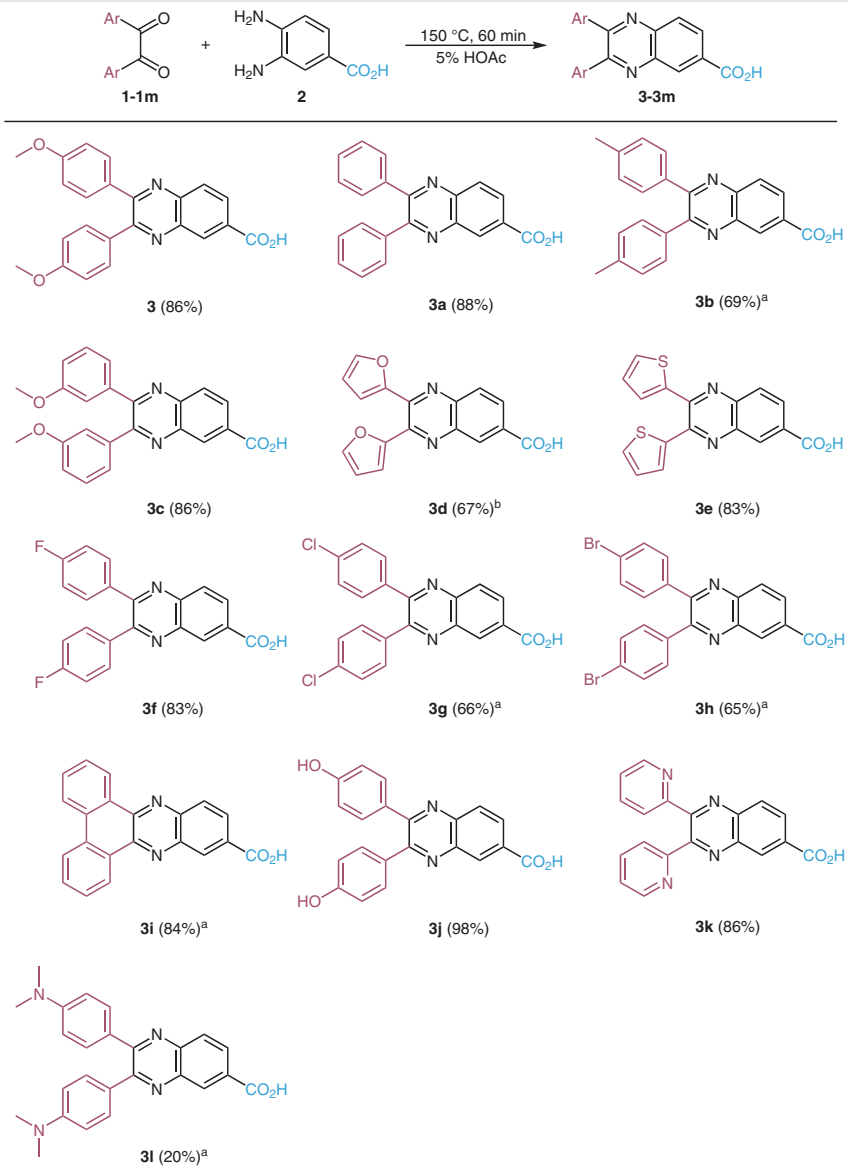
Figure 4 (a) Reaction between 4,4′-dimethoxybenzil and di-Boc-protected 3,4-diaminobenzoic acid towards compound **3** via deprotection and quinoxaline formation. (b) The amount of starting materials detected (NMR) after performing the reaction at different T_r and t_r values. (c) Reaction yields of compounds **3** and **4** (NMR). * Compounds were not detected.

role in inhibiting decarboxylation via control of the concentration of the 3,4-diaminobenzoic acid as a function of t_r. For experiments employing 3,4-diaminobenzoic acid, the concentration of the compound readily reaches the highest value (e.g., 0.2 or 0.05 mol·L^{-1}) after heating in water. In contrast, the 3,4-diaminobenzoic acid is produced by deprotection in experiments with the di-Boc-protected analogue. It is plausible that the rate of deprotection controls the concentration of the 3,4-diaminobenzoic acid. We hypothesize that the concentration of 3,4-diaminobenzoic acid at 150 °C does not reach a maximum but rather oscillates over time. After deprotection, the produced 3,4-diaminobenzoic acid is simultaneously consumed to form compound **3**. Note that this hypothesis assumes that quinoxaline formation is much faster than decarboxylation under the tested conditions. Since high T_r values are expected to increase the deprotection rate, the 3,4-diaminobenzoic acid is released at a higher rate at $T_r \geq 170$ °C. This seems to provide a concentration of 3,4-diaminobenozoic acid sufficient to trigger decarboxylation. Overall, these hypotheses would justify the presence of decarboxylation products in experiments performed at 170 °C and 200 °C.

Summarizing, we have presented three synthetic approaches towards compound **3** under HT conditions. First, the reaction between 3,4-diaminobenzoic acid (**2**) and 4,4′-dimethoxybenzil at 150 °C over 60 minutes in 5% HOAc yields compound **3** (86%) with the lowest amount of decarboxylation side product (Method A). Second, methyl 3,4-diaminobenzoate (**2a**) can be successfully used instead of **2** towards compound **3** in a one-pot quinoxaline formation followed by ester hydrolysis at 230 °C in 3 hours (77% yield, Method B). Finally, di-Boc-protected 3,4-diaminobenzoic acid (**2b**) reacts with 4,4′-dimethoxybenzil at 150 °C over 60 minutes to yield 65% of compound **3** (Method C). To our satisfaction, methods B and C circumvented the formation of the decarboxylation products.

After developing conditions towards compound **3** from 3,4-diaminobenzoic acid and different structural analogues, we aimed at broadening the substrate scope, mainly by pursuing methods A and B. Method C was not considered since the deprotection reaction is not complete and purification procedures would be longer than those involved with methods A and B. For method A, we reacted different 1,2-diarylketones with 3,4-diaminobenzoic acid (**2**) to yield compounds **3a–l**. The corresponding products were obtained in yields ranging from 65% to 98% (Scheme 1). The products were characterized by ^{1}H and ^{13}C NMR spectroscopy. Analogues of benzil substituted with halogens were employed to yield compounds **3f–h**, albeit the yields of compounds **3g** and **3h** were lower than that of 2,3-bis(4-fluorophenyl)quinoxaline-6-carboxylic acid (**3f**). We found that the decreased yields were caused by the low solubility of the starting compounds 4,4′-dichlorobenzil and 4,4′-dibromobenzil in water at 150 °C. For compounds **3g** and **3h**, the reactions performed at 230 °C for 10 minutes yielded the target quinoxalines in yields of 66% and 65%, respectively. Similarly, the synthesis of compound **3i** at 150 °C for 30 minutes resulted in a low yield. We suspected that similar to 4,4′-dichlorobenzil and 4,4′-dibromobenzil, the low solubility of the starting compound 9,10-phenanthrenequinone in water at 150 °C influenced the reaction yield. However, the synthesis of compound **3i** at 230 °C over 10 minutes resulted in a satisfactory 84% yield. Compounds **3j** and **3k**, featuring hydroxy groups and pyridine rings, respectively, were obtained in high yields (98% and 86%) at 150 °C over 30 minutes. Interestingly, the decarboxylation analogues of **3j** and **3k** were not detected by TLC and the NMR spectra of the crude products showed exclusively signals for the target compounds.

In contrast, the synthesis of compound **3l** was challenging. Product **3l** was not obtained after heating at 150 °C for 30 minutes, instead unreacted pure 4,4′-bis(dimethylamino)benzil was recovered. Surprisingly, performing the reaction at 230 °C for 10 minutes yielded compound **3l** in 20% yield, whereas the decarboxylated analogue **4l** was obtained in 61% yield (Scheme 1). We suspected that decarboxylation of compound **3l** could contribute to the generation of **4l**. Since compound **3l** was synthesized at 230 °C, we suspected that this high T_r might trigger the decarboxylation pathway from compound **3l**. To test this, we heated pure compound **3l** at 230 °C for 10 minutes in 5% HOAc. After cooling, compound **3l** was recovered and compound **4l** had not formed. Thus, direct decarboxylation from compound **3l** was not contributing to the presence of compound **4l** under the tested conditions. We previously observed that the HTS of quinoxalines was significantly influenced by other sources of acidity and basicity. In particular, Hünig's base (*N*,*N*-diisopropylethylamine, DIPEA), significantly disfavors quinoxaline formation.[12] This suggested that the basicity of the *N*,*N*-dimethylamine groups might be the feature responsible for increasing the amount of decarboxylation product **4l** (indirectly, through disfavoring quinoxaline formation). Nevertheless, compound **3k** was obtained in high yield despite featuring pyridine rings with basic character. While the pK_b values in water at room temperature for *N*,*N*-dimethylaniline (pK_b = 8.85) and pyridine (pK_b = 8.77) are comparable, substituents impact significantly the acid–base properties.[23] Compound **3l** features *para*-substituted *N*,*N*-dimethylamino moieties, whereas **3k** contains 2-substituted pyridine rings. Thus, we hypothesize that the observed result might be caused by further differences in the basicity due to the substitution pattern. We propose that 4,4′-bis(dimethylamino)benzil decreases the rate of quinoxaline formation from the 3,4-diaminobenzoic acid. Under these conditions, the 3,4-diaminobenzoic acid undergoes decarboxylation to give *o*-PDA followed by reaction towards compound **4l** to a higher extent. Note that further experiments are needed to gain additional insight on this hypothesis.



Scheme 1 Scope of the 2,3-diarylquinoxaline-6-carboxylic acids synthesized in this work via Method A. [a] Synthesized at 230 °C over 10 minutes in 5% HOAc. [b] Synthesized at 150 °C over 5 minutes in 5% HOAc.

The synthesis presented in Method A is a relatively rapid (5–60 min) and efficient Hinsberg cyclization under mild HT conditions that tolerates a CO_2H functional group. Using 5% HOAc as the solvent, which can be equated with vinegar, without any further additives, can be considered benign and straightforward. Thus, as a benign alternative synthesis, its application should match or ideally overcome established approaches. Therefore, we compared the performance of the HTS of quinoxaline carboxylic acids developed herein with state-of-the art syntheses. Specifically, we compared our results with all syntheses towards compounds **3**–**3l** reported to date in the Reaxys database, and found 42 reported methods for the preparation these compounds. The reported syntheses are conducted under reflux for prolonged reaction times in HCl, glacial HOAc, or alcohols such as ethanol and methanol containing variable amounts of HOAc (see Table S2 in the Supporting Information for details on the reported syntheses). The yields for the reported syntheses ranged between 38% (for compound **3g**) and quantitative conversion (e.g., compounds **3b** and **3f**). Note that the reaction yields from these prior reports might be the result of either incomplete reactions of the starting materials or due the presence of side products from decarboxylation reactions or oxidation of the diamines. The reaction yields for Method A do not stand behind those reported in the literature but are comparable (e.g., 88% for

compound **3a** compared to yields of 60–99% for the reported syntheses) or higher (e.g., 98% for compound **3j** compared with the 53% yield reported in the literature; 84% for compound **3i** compared with 32%). Nevertheless, the number of syntheses towards compounds **3**–**3l** is relatively low compared to, e.g., the syntheses of their structural analogues without CO_2H groups (527 syntheses reported for 2,3-diarylquinoxalines prepared from the corresponding 1,2-diketones and *o*-PDA). This low number of reported syntheses is expected as compounds **3**–**3l** represent a specific group of quinoxalines synthesized from a particular *o*-PDA analogue. To complement the literature comparison, we performed experiments in MeOH and EtOH as solvents. We selected these alcohols since they are frequently employed in the presence of variable amounts of HOAc for synthesizing quinoxalines classically. The model reaction towards compound **3** was performed in solutions of 5% HOAc in MeOH and EtOH for 30 minutes at 150 °C. Note that the conditions in MeOH are similar to those reported previously by Zhao et al. [MeOH/HOAc (9/1), T_r = 160 °C, t_r = 5 min].[24] The reaction yield for compound **3** did not change significantly compared to that employing HTW. The reaction performed in 5% HOAc in EtOH yielded 87% of compound **3**, whereas changing to MeOH yielded 89% of **3**. Interestingly, compound **4** was not detected (NMR) in these reactions performed in alcohols as solvents. Hence, decarboxylation is in principle not observed in superheated alcoholic environments. Our experiments showed that decarboxylation of 3,4-diaminobenzoic acid was a non-negligible side-reaction in HTS. Nonetheless, the fact that comparable yields are obtained in both HTS and in MeOH/EtOH containing HOAc points at other issues, which we can only speculate to be related to, e.g., the solubility of the starting compounds and product. Overall, the HTS of 2,3-diarylquinoxaline carboxylic acids reported herein uses a clean solvent, shows comparable or better performance than reported syntheses, and avoids the use of strong acids, complex catalysts, and VOC solvents.

We also aimed at a broader substrate scope for Method B. To this end, we reacted methyl 3,4-diaminobenzoate (**2a**) with selected 1,2-diketones (Figure 5a). Since method B is performed at 230 °C, we dedicated special attention to the products obtained in low yields through Method A due to the low solubility of the 1,2-diketones in water at 150 °C. Compounds **3i**, **3j**, and **3k** were not targeted via Method B since Method A gave satisfactory yields. The desired products were successfully obtained with yields ranging from 67–88%. Overall, the reaction yields were comparable to those obtained via Method A (Figure 5b). We continued to observe the presence of minor amounts of the corresponding methyl ester analogues in the crude products. Nevertheless, these products could be removed by washing with solvent (EtOAc or EtOH/H_2O mixtures) with only a slight decrease in the yield. We aimed at comparing the performance of Method B with reported syntheses in the literature. To the best of our knowledge, the synthesis of compounds **3**–**3l** has not been targeted via the quinoxaline formation–hydrolysis sequence proposed in Method B. In principle, this one-pot sequence would require performing the quinoxaline formation and ester hydrolysis in separate steps. To gain insight into this, we performed the synthesis of compound **3** via Method B by employing 5% HOAc in MeOH and EtOH, instead of water. As we expected, compound **5**, i.e., the methyl ester analogue of **3**, was exclusively obtained in alcoholic solvents, whereas **3** was not detected (Figure 5c and Figure S16 in the Supporting Information). This confirmed that quinoxaline formation was achieved in superheated alcohols, whereas hydrolysis towards compound **3** did not take place in the same system. This clearly shows that water outperforms alcoholic solvents in the one-pot quinoxaline formation–ester hydrolysis presented herein. More importantly, Method B offers a simplified purification procedure. The hydrolysis of esters is typically performed under strong basic conditions followed by neutralization to isolate the target carboxylic acid. In contrast, HTW is a suitable reaction medium for performing both quinoxaline synthesis and ester hydrolysis. The products are purified by filtration and washing to remove the unreacted ester. Compared to the hydrolysis of methyl benzoate in HTW,[21] the methyl ester group is hydrolyzed in this work with good yields, at lower temperatures, and without prolonging the reaction time significantly. We hypothesize that the quinoxaline might be facilitating the hydrolysis and are currently aiming at driving the ester hydrolysis to completeness.

In summary, we have studied the formation of 2,3-diarylquinoxaline carboxylic acids by hydrothermal synthesis. We have shown that CO_2H-bearing quinoxalines can be synthesized with minimum decarboxylation in water at elevated temperatures. Starting from 3,4-diaminobenzoic acid, different reaction conditions (T_r, t_r, c, and the absence and presence of HOAc) were explored towards forming compound **3** and the corresponding syntheses were performed as duplicates. The amounts of compound **3**, compound **4**, i.e., the decarboxylated analogue of **3**, and unreacted starting materials were determined by solution NMR and product isolation. Among the explored conditions, T_r = 150 °C and t_r = 60 minutes in the presence of 5% HOAc was identified as optimal, i.e., the highest product yields and lowest decarboxylated side product yields were obtained. By employing these conditions, a broad scope of 2,3-diarylquinoxaline-6-carboxylic acids could be obtained – most in good to excellent yields. Due to the presence of decarboxylation products, different purification protocols were explored. Furthermore, we have shown that different sources of Brønsted acidity catalyze quinoxaline formation under HT conditions. The CO_2H group in the substrate 3,4-diaminobenzoic acid slightly accelerates quinoxaline formation, whereas the presence of HOAc allows the synthesis of 2,3-diarylquinoxaline carboxylic acids without considerably

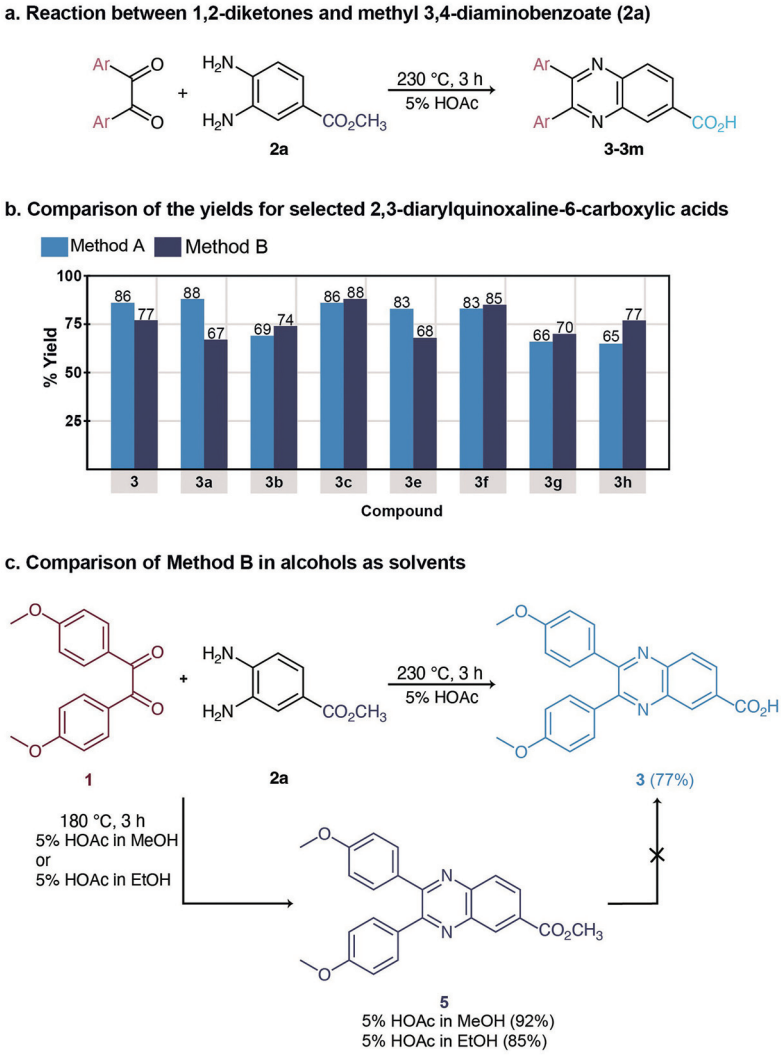


Figure 5 **a**. Synthesis of 2,3-diarylquinoxaline-6-carboxylic acids via Method B. **b**. Comparison between reaction yields of Methods A and B for selected compounds. **c**. Method B in solutions of 5% HOAc in alcohols such as MeOH or EtOH yields compound **5**.

prolonging t_r at a moderate T_r (150 °C) within the HT regime. Conversely, substrates bearing additional basic functions or halogens show lower conversion at 150 °C, which we attribute to their basicity and low solubility at that T_r. Decarboxylation is not detected when methanol or ethanol with 5% HOAc are employed as media, i.e., being well-established conventional reaction conditions. However, the yields of the target quinoxaline carboxylic acids are very similar when generated by HTS and by conventional protocols, as shown by both a literature comparison and reference experiments.

We suggest that HTS can be used as a fully competitive means towards quinoxaline carboxylic acids while, compared to established protocols, avoiding VOC solvents. HTS is not yet part of the standard toolbox of synthetic organic chemists. Hence, there is still much room for exploring the vast chemical space of possible and synthetically interesting transformations. Also, there is a striking necessity for further studying the reaction conditions and side reactions. We have herein shed some light on decarboxylation as a side reaction when CO_2H-bearing substrates and products are involved in HTS. Intriguingly, (*i*) decarboxylation does not occur in acidified alcohols, (*ii*) has not been observed in other cyclocondensations via HTS that also employ CO_2H-bearing compounds (e.g., towards cyclic imides, imidazoles, or perinones),[9–11] (*iii*) HTW is in the synthetic organic chemistry community not conventionally associated with promoting decarboxylation (as is, e.g., treatment with H_2SO_4 at elevated temperatures in β-keto ester hydrolysis and decarboxylation), but (*iv*) is in the petrochemistry/geo-

chemistry community known to occur to varying extents (that strongly depend on substitution patterns and *T*) for aromatic carboxylic acids. The striking need to study various aspects of HTS in depth is significantly impeded by the compounds involved—may it be substrates, intermediates, products, or additives—behaving quite differently in HTW than in 'conventional' environments, and by the high-*T*, high-*p* and corrosive (high K_w) conditions rendering in situ, e.g., spectroscopic studies extremely challenging. Yet, we firmly believe that a deeper understanding of HTS is required in order to harvest the full potential of this technique for sustainable synthesis.

Chemicals were purchased from TCI Chemicals and Sigma-Aldrich, and were used without further purification. di-Boc-protected 3,4-diaminobenzoic acid was synthesized according to a reported procedure.[25] The microwave-assisted reactions were conducted in an Anton Paar 400 Monowave in G10 and G30 glass vials. Deionized water was employed in all the experiments. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL 400 MHz spectrometer. Deuterated chloroform (99.8%) and DMSO-d_6 (99.8%) were employed as solvents. Chemical shifts are reported in parts per million (ppm) using the residual signal of the solvent [$CHCl_3$ (δ_H = 7.26 and δ_C = 77.16) and DMSO (δ_H = 2.50 and δ_C = 39.7)] as a reference.

2,3-Diarylquinoxaline-carboxylic Acids 3–3l; General Procedures

Method A

In a G10 microwave vial, 3,4-diaminobenzoic acid (**2**) (0.6 mmol) and the corresponding 1,2-diketone (0.6 mmol) were suspended in a solution of 5% HOAc (3 mL). The vial was placed in the cavity of the microwave reactor and heated as fast as possible to 150 °C (power = 200 W, stirring at 1000 rpm). Unless otherwise stated, the target temperature was held for 60 min, and afterwards the reaction was then cooled to r.t. Different temperatures and reaction times are indicated when employed. All products precipitated as solids after cooling. The solids were filtered, washed with distilled water and dried overnight at room temperature. Filtration and drying or washing with EtOH, MeOH, or EtOAc yielded pure compounds **3**–**3l**.

Method B

In a G10 microwave vial, methyl 3,4-diaminobenzoate (**2a**) (0.6 mmol) and the corresponding 1,2-diketone (0.6 mmol) were suspended in a solution of 5% HOAc (3 mL). The vial was placed in the cavity of the microwave reactor and heated as fast as possible to 230 °C (power = 400 W, stirring at 1000 rpm). The target temperature was held for 3 h and the reaction was then cooled to r.t. The crude products precipitated as solids after cooling down. The solids were filtered, washed with distilled water and dried overnight at room temperature. Pure compounds **3** were obtained after suspending the crude product in EtOAc, MeOH or EtOH. Please refer to the corresponding experimental for each compound for the precise purification procedure.

2,3-Bis(4-methoxyphenyl)quinoxaline-6-carboxylic Acid (3)

Method A: 4,4′-Dimethoxybenzil (**1**) and 3,4-diaminobenzoic acid (**2**) were reacted according to the general procedure. The crude product was purified by suspending in EtOAc (10 mL) followed by filtration. For scaling up, the reaction was also conducted following the general protocol in a G30 microwave glass vial by suspending equimolar amounts of the starting compounds (2 mmol) in 5% HOAc (10 mL).

Yield: 187 mg (86%); 598 mg (79%) for the experiment in EtOAc (10 mL); yellow solid.

Method B: 4,4′-Dimethoxybenzil (**1**) and methyl 3,4-diaminobenzoate (**2a**) were reacted according to the general procedure. The crude product was purified by suspending in EtOAc (5 mL) followed by filtration.

Yield: 180 mg (77%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.58 (d, *J* = 1.9 Hz, 1 H), 8.24 (dd, *J* = 8.7, 1.9 Hz, 1 H), 8.14 (d, *J* = 8.7 Hz, 1 H), 7.47 (d, *J* = 8.8 Hz, 2 H), 7.47 (d, *J* = 8.9 Hz, 2 H), 6.94 (d, *J* = 8.4 Hz, 4 H), 3.78 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.8, 160.1, 160.0, 154.3, 153.7, 142.3, 139.6, 131.7, 131.3, 131.2, 130.9, 130.9, 130.6, 129.2, 129.1, 113.7, 55.3.

2,3-Diphenylquinoxaline-6-carboxylic Acid (3a)

Method A: Benzil and 3,4-diaminobenzoic acid (**2**) were reacted according to the general procedure. The crude product was suspended in EtOAc (5 mL) and stirred for 5 min. The solid was filtered and dried at r.t.

Yield: 173 mg (88%); beige solid.

Method B: Benzil and methyl 3,4-diaminobenzoate (**2a**) were reacted according to the general procedure. The crude product was suspended in EtOAc (5 mL) and stirred for 5 min. The solid was filtered and dried at r.t.

Yield: 132 mg (67%); beige solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.64 (d, *J* = 1.8 Hz, 1 H), 8.30 (dd, *J* = 8.7, 1.8 Hz, 1 H), 8.21 (d, *J* = 8.7 Hz, 1 H), 7.54–7.45 (m, 4 H), 7.45–7.31 (m, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.6, 154.8, 154.2, 142.4, 139.7, 138.4, 132.1, 130.7, 129.8, 129.7, 129.5, 129.3, 129.2, 129.1, 128.1.

2,3-Bis(4-methylphenyl)quinoxaline-6-carboxylic Acid (3b)

Method A: 4,4′-Dimethylbenzil (0.6 mmol) and 3,4-diaminobenzoic acid (**2**) (0.6 mmol) were heated at 230 °C for 10 min in 5% HOAc (3 mL). After cooling, the crude product was filtered and dried at room temperature overnight. The crude product was suspended in EtOAc (3mL) and filtered to yield the pure compound.

Yield: 146 mg (69%); white solid.

Method B: 4,4′-Dimethylbenzil and methyl 3,4-diaminobenzoate (**2a**) were reacted according to the general procedure. The crude product was suspended in EtOAc (5 mL) and stirred for 5 min. The solid was filtered and dried at r.t.

Yield: 156 mg (74%); white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.61 (d, *J* = 1.9 Hz, 1 H), 8.27 (dd, *J* = 8.7, 1.9 Hz, 1 H), 8.18 (d, *J* = 8.7 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 4 H), 7.18 (d, *J* = 8.0 Hz, 4 H), 2.32 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.6, 154.7, 154.0, 142.3, 139.6, 138.8, 138.7, 135.7, 131.9, 130.7, 129.7, 129.6, 129.3, 129.2, 128.7, 20.9.

2,3-Bis(3-methoxyphenyl)quinoxaline-6-carboxylic Acid (3c)

Method A: 3,3′-Dimethoxybenzil and 3,4-diaminobenzoic acid (**2**) were reacted according to the general procedure. The crude product was suspended in a mixture of EtOH/H_2O (1:1, 5 mL) and heated at boiling for 1 min. The suspension was cooled to r.t. and filtered to yield the pure product.

Yield: 198 mg (86%); beige solid.

Method B: 3,3′-Dimethoxybenzil and methyl 3,4-diaminobenzoate (**2a**) were reacted according to the general procedure. The crude product was suspended in a mixture of EtOH/H_2O (1:1, 5 mL) and stirred at r.t. for 5 min. The solid was filtered and dried at r.t.

Yield: 203 mg (88%); pale yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.65 (d, *J* = 1.8 Hz, 1 H), 8.30 (dd, *J* = 8.7, 1.8 Hz, 1 H), 8.21 (d, *J* = 8.7 Hz, 1 H), 7.28 (t, *J* = 8.0 Hz, 2 H), 7.09–7.03 (m, 4 H), 7.00–6.95 (m, 2 H), 3.66 (s, 3 H), 3.66 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.6, 158.8, 154.6, 153.9, 142.3, 139.7, 132.1, 130.8, 129.6, 129.3, 129.2, 122.0, 122.0, 115.1, 114.9, 114.8, 55.1.

2,3-Di(furan-2-yl)quinoxaline-6-carboxylic Acid (3d)

Method A: 2,2′-Furil (0.6 mmol) and 3,4-diaminobenzoic acid (**2**) (0.6 mmol) were heated at 150 °C for 5 min in 5% HOAc (3 mL). After cooling, the crude product was filtered and dried at room temperature overnight. The crude product was suspended in EtOH (3 mL) and stirred at r.t. for 5 min. The solid was filtered and washed with EtOH (2 mL) to yield the pure product.

Yield: 123 mg (67%); yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.55 (d, *J* = 1.9 Hz, 1 H), 8.26 (dd, *J* = 8.7, 1.9 Hz, 1 H), 8.14 (d, *J* = 8.7 Hz, 1 H), 7.94 (m, 2 H), 6.83 (d, *J* = 3.5 Hz, 1 H), 6.78 (d, *J* = 3.5 Hz, 1 H), 6.73 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.5, 150.08, 150.06, 145.6, 145.2, 143.4, 142.9, 141.9, 139.2, 132.4, 130.5, 130.0, 129.1, 114.1, 113.5, 112.4, 112.3.

2,3-Di(thiophen-2-yl)quinoxaline-6-carboxylic Acid (3e)

Method A: 2,2′-Thenil and 3,4-diaminobenzoic acid (**2**) were reacted according to the general procedure. The crude product was suspended in MeOH (3 mL) and stirred for 5 min. The solid was filtered and washed with MeOH (2 mL) to yield the pure product.

Yield: 173 mg (83%); yellow solid.

Method B: 2,2′-Thenil and methyl 3,4-diaminobenzoate (**2a**) were reacted according to the general procedure. The crude product was suspended in EtOH (5 mL) and stirred at r.t. for 5 min. The solid was filtered and dried at r.t.

Yield: 137 mg (68%); yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.50 (d, *J* = 1.9 Hz, 1 H), 8.23 (dd, *J* = 8.7, 1.9 Hz, 1 H), 8.09 (d, *J* = 8.7 Hz, 1 H), 7.82 (m, 2 H), 7.28 (m, 2 H), 7.12 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.6, 147.9, 147.3, 141.8, 140.7, 140.5, 139.1, 132.3, 130.9, 130.4, 130.3, 130.2, 129.94, 129.88, 128.9, 128.1, 128.0.

2,3-Bis(4-fluorophenyl)quinoxaline-6-carboxylic Acid (3f)

Method A: 4,4′-Difluorobenzil and 3,4-diaminobenzoic acid (**2**) were reacted according to the general procedure. The crude product was suspended in a mixture of EtOH/H_2O (1:1, 5 mL) and heated at boiling for 1 min. The suspension was cooled to r.t. and filtered to yield the pure product.

Yield: 179 mg (83%); beige solid.

Method B: 4,4′-Difluorobenzil and methyl 3,4-diaminobenzoate (**2a**) were reacted according to the general procedure. The crude product was suspended in a mixture EtOH/H_2O (1:1, 5 mL) and stirred at r.t. for 5 min. The solid was filtered and dried at r.t.

Yield: 184 mg (85%); beige solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.63 (m, 1 H), 8.30 (m, 1 H), 8.21 (dd, *J* = 8.7, 2.9 Hz, 1 H), 7.54 (m, 4 H), 7.24 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.6, 163.8, 163.8, 161.4, 161.3, 153.8, 153.2, 142.3, 139.7, 134.8, 134.7, 132.2, 132.1, 132.1, 132.0, 130.7, 129.6, 129.2, 115.3, 115.1.

2,3-Bis-(4-chlorophenyl)quinoxaline-6-carboxylic Acid (3g)

Method A: 4,4′-Dichlorobenzil (0.6 mmol) and 3,4-diaminobenzoic acid (**2**) (0.6 mmol) were heated at 230 °C for 10 min in 5% HOAc (3 mL). After cooling, the crude product was filtered and dried at room temperature overnight. The crude product was suspended in EtOAc (3 mL) and stirred at r.t. The suspension was filtered to yield the pure product.

Yield: 159 mg (66%); white solid.

Method B: 4,4′-Dichlorobenzil and methyl 3,4-diaminobenzoate (**2a**) were reacted according to the general procedure. The crude product was suspended in EtOAc (3 mL) and stirred at r.t. for 5 min. The solid was filtered and dried at r.t.

Yield: 166 mg (70%); beige solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.64 (d, *J* = 1.8 Hz, 1 H), 8.32 (dd, *J* = 8.6, 2.0 Hz, 1 H), 8.23 (d, *J* = 8.7 Hz, 1 H), 7.54–7.47 (m, 8 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.5, 153.6, 153.0, 142.4, 139.8, 137.1, 134.3, 134.2, 132.4, 131.7, 131.6, 130.7, 129.8, 129.3, 128.3.

2,3-Bis-(4-bromophenyl)quinoxaline-6-carboxylic Acid (3h)

Method A: 4,4′-Dibromobenzil (0.6 mmol) and 3,4-diaminobenzoic acid (**2**) (0.6 mmol) were heated at 230 °C for 10 min in 5% HOAc (3 mL). After cooling, the crude product was filtered and dried at room temperature overnight. The crude product was suspended in EtOAc (3 mL) and stirred at r.t. The suspension was filtered to yield the pure product.

Yield: 190 mg (65%); white solid.

Method B: 4,4′-Dibromobenzil and methyl 3,4-diaminobenzoate (**2a**) were reacted according to the general procedure. The crude product was suspended in EtOAc (3 mL) and stirred at r.t. for 5 min. The solid was filtered and dried at r.t.

Yield: 224 mg (77%); beige solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.63 (s, 1 H), 8.33 (d, *J* = 8.5 Hz, 1 H), 8.20 (d, *J* = 6.9 Hz, 1 H), 7.62 (d, *J* = 8.1 Hz, 4 H), 7.46 (d, *J* = 8.2 Hz, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.7, 153.4, 152.8, 142.2, 139.8, 137.1, 133.7, 131.9, 131.9, 131.3, 130.4, 130.1, 129.1, 123.0, 122.9.

Dibenzo[*a*,*c*]phenazine-11-carboxylic Acid (3i)

Method A: 9,10-Phenanthrenequinone (0.6 mmol) and 3,4-diaminobenzoic (**2**) (0.6 mmol) were heated at 230 °C for 10 min in 5% HOAc (3 mL). After cooling, the crude product was filtered and dried at room temperature overnight. The crude product was suspended in EtOAc (10 mL) and heated until it boiled. The mixture was immediately filtered and the solid dried in air to yield the pure product.

Yield: 164 mg (84%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$/CF_3COOD, 9/1): δ = 9.40 (d, *J* = 1.7 Hz, 1 H), 9.34 (d, *J* = 9.5 Hz, 1 H), 9.23 (d, *J* = 7.0 Hz, 1 H), 8.82 (dd, *J* = 9.0, 1.7 Hz, 1 H), 8.78–8.67 (m, 3 H), 8.11 (m, 2 H), 8.00–7.91 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$/CF_3COOD, 9/1): δ = 170.0, 143.8, 139.4, 138.3, 136.7, 135.5, 135.3, 135.1, 134.6, 133.3, 131.0, 130.6, 130.4, 127.5, 127.3, 125.2, 125.0, 124.5, 124.4, 122.4.

2,3-Bis(4-hydroxyphenyl)quinoxaline-6-carboxylic Acid (3j)

Method A: 4,4′-Dihydroxybenzil and 3,4-diaminobenzoic acid (**2**) were reacted according to the general procedure. The obtained solid was filtered and washed with water to yield the pure product.

Yield: 212 mg (98%); yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.89 (s, 1 H), 9.86 (s, 1 H), 8.55 (d, *J* = 1.9 Hz, 1 H), 8.21 (dd, *J* = 8.7, 1.9 Hz, 1 H), 8.10 (d, *J* = 8.7 Hz, 1 H), 7.36 (d, *J* = 8.7 Hz, 2 H), 7.35 (d, *J* = 8.7 Hz, 2 H), 6.75 (d, *J* = 8.7 Hz, 2 H)*, 6.75 (d, *J* = 8.7 Hz, 2 H)*. * Overlapped signals.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.8, 158.6, 158.5, 154.6, 154.0, 142.2, 139.5, 131.5, 131.4, 131.3, 130.6, 129.44, 129.39, 129.0, 115.1.

2,3-Di(pyridin-2-yl)quinoxaline-6-carboxylic Acid (3k)

Method A: 2,2′-Pyridil and 3,4-diaminobenzoic acid (**2**) were reacted according to the general procedure. The obtained solid was filtered and washed with water to yield the pure product.

Yield: 169 mg (86%); pale brown solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.71 (dd, *J* = 1.8, 0.7 Hz, 1 H), 8.37 (dd, *J* = 8.7, 1.8 Hz, 1 H), 8.30 (d, *J* = 0.7 Hz, 1 H), 8.30–8.26 (m, 2 H), 8.05 (m, 1 H), 8.03 (m, 1 H), 7.97 (m, 2 H), 7.37 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.5, 156.6, 153.9, 153.3, 148.1, 148.1, 142.1, 139.6, 137.0, 132.7, 130.8, 130.1, 129.5, 124.0, 123.9, 123.6, 123.5.

2,3-Bis(4-(dimethylamino)phenyl)quinoxaline-6-carboxylic Acid (3l)

Method A: 4,4′-bis(dimethylamino)benzil and 3,4-diaminobenzoic acid (**2**) were heated at 230 °C for 10 min. After cooling, the crude product was filtered and dried at room temperature overnight. The crude solid was dissolved in chloroform (15 mL) and the solution was extracted with 0.1 M NaOH (3 × 5 mL). The aqueous phases were collected and concentrated HCl was added dropwise until neutral pH (7.0, measured with universal indicator paper). The resulting mixture was extracted with EtOAc (3 × 10 mL) and the organic phases were concentrated to yield the pure product.

Yield: 49 mg (20%); orange solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.50 (d, *J* = 1.9 Hz, 1 H), 8.16 (dd, *J* = 8.7, 1.9 Hz, 1 H), 8.04 (d, *J* = 8.7 Hz, 1 H), 7.45 (d, *J* = 8.9 Hz, 2 H), 7.43 (d, *J* = 8.8 Hz, 2 H), 6.68 (d, *J* = 9.1 Hz, 2 H), 6.67 (d, *J* = 9.1 Hz, 2 H), 2.95 (s, 6 H), 2.94 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.9, 154.3, 153.8, 150.7, 150.6, 142.0, 139.2, 130.7, 130.5, 130.2, 128.5, 128.5, 126.0, 125.8, 111.3, 111.2, 34.4.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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