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A Green and Efficient One-Pot Synthesis of 2,3-Diphenylquinoxaline Using Sodium Hypochlorite as a Sustainable Oxidant †

Nitin R. Deore [1], Vivek P. Shewale [2] J. Oscar C. Jimenez-Halla [3], Pragya [4], Arun Gabaji Dholi [1], Darien I. Martinez-Valencia [3] Tushar Janardan Pawar [5,*] and Sachin V. Patil [1,*]

[1] Department of Chemistry, HPT Arts and RYK Science College, Affiliated to Savitribai Phule Pune University, Nashik 422005, India; nitinrdeore@gmail.com (N.R.D.); dholi.arun@gmail.com (A.G.D.); sachin.dhokare@gmail.com (S.V.P.)
[2] Department of Chemistry, Indian Institute of Technology Bombay, Powai 400076, Mumbai, India; shewalevivek2@gmail.com
[3] Departamento de Química, División de Ciencias Naturales y Exactas, Universidad de Guanajuato, Noria Alta S/N, Guanajuato 36050, Mexico; jjimenez@ugto.mx (J.O.C.J.-H.); di.martinezvalencia@ugto.mx (D.I.M.)
[4] Department of Chemistry, Birla Institute of Technology and Science Pilani, Pilani Campus, Pilani 333031, Rajasthan, India; p20190013@pilani.bits-pilani.ac.in
[5] Red de Estudios Moleculares Avanzados, Instituto de Ecología A.C. (INECOL), Carretera Antigua a Coatepec 351, CP. 91073, El Haya, Xalapa, Veracruz, México; tushar.janardan@inecol.mx (T.J.P.).
* Correspondence: tushar.janardan@inecol.mx (T.J.P.), sachin.dhokare@gmail.com (S.V.P.)

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Abstract

A highly efficient and sustainable one-pot method for the synthesis of 2,3-diphenylquinoxaline (DPQ) is presented. The reaction employs sodium hypochlorite as an inexpensive and eco-friendly oxidant for the conversion of benzoin, followed by condensation with o-phenylenediamine in an ethanol/water system. This green approach demonstrates remarkable versatility, affording excellent yields under photochemical (96%), reflux (92%), and electrochemical (83%) conditions. To provide mechanistic insight, computational studies were conducted, revealing the reaction pathway and identifying key energetic barriers. This work offers a practical and environmentally benign alternative for synthesizing important quinoxaline derivatives.

Keywords: green chemistry; one-pot synthesis; 2,3-diphenylquinoxaline; sodium hypochlorite as oxidant

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1. Introduction

Quinoxaline derivatives represent a class of organic compounds with diverse applications, including their utilization as pharmacophores, organic semiconductors, and molecular recognition agents [1,2]. Among these derivatives, 2,3-diphenylquinoxaline (DPQ) stands out as a molecule of particular interest due to its unique structural features and potential for various biological and material science applications [3,4]. While the Synthesis of DPQ has been previously reported using different methodologies, the existing approaches often suffer from drawbacks such as the use of volatile and environmentally harmful solvents, low product yields, and harsh reaction conditions [5,11]. The development of a sustainable and efficient synthetic strategy for the preparation of DPQ is therefore of significant interest.

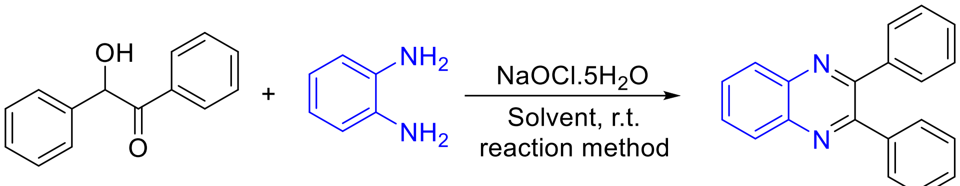
In recent years, the increasing emphasis on sustainable and environmentally friendly chemical processes has spurred the exploration of alternative synthetic methodologies that minimize the use of toxic reagents and solvents, reduce energy consumption, and generate minimal waste [12]. The integration of green chemistry principles in the Synthesis of complex organic molecules has emerged as a crucial area of research, aiming to address the challenges posed by conventional synthetic protocols [13].

In this context, our study focuses on the development of an innovative and eco-friendly approach for the Synthesis of DPQ, employing Sodium Hypochlorite ($NaOCl.5H_2O$) as a key reagent. The proposed method involves a one-pot synthesis, starting with the oxidation of benzoin, an α-hydroxyketone, to benzil, followed by its condensation with o-phenylenediamine in a water/ethanol solvent system. This synthetic pathway not only minimizes the use of hazardous organic solvents but also ensures an efficient conversion of the starting materials to the desired product. The utilization of $NaOCl.5H_2O$ offers several advantages, including its low cost, ready availability, and its eco-friendly nature compared to conventional catalysts. Furthermore, using a water/ethanol solvent system adds to the sustainable aspects of the process, as it reduces the generation of harmful waste and offers the potential for recycling and reuse.

The green Synthesis of DPQ described in this study presents a significant advancement in the field of sustainable organic Synthesis. By utilizing a benign catalytic system and a sustainable solvent, the approach not only offers a more environmentally friendly alternative to conventional methods but also demonstrates a high yield of the target compound, ranging from 83% to 96%. The mild reaction conditions provided by this methodology contribute to the preservation of the structural integrity of the desired product, ensuring its suitability for further functionalization and application in various fields. Notably, the versatility of the reaction conditions allows for its execution using reflux, photochemical, or electrochemical methods, thereby providing flexibility and adaptability to different laboratory setups and preferences. The ability to perform the Synthesis using multiple methodologies further enhances the practicality and accessibility of this green synthetic approach.

2. Results and Discussion

The successful Synthesis of 2,3-diphenylquinoxaline **3** using 2-hydroxy-1,2-diphenylethan-1-one **1** and benzene-1,2-diamine **2** under various conditions underscores the adaptability and efficiency of the green synthesis method. In this study, a systematic exploration of various parameters on the yield of the targeted reaction was conducted, as elucidated in the Table 1. We investigated different combinations of factors, including the amount of $NaOCl.5H_2O$, choice of solvent, and reaction conditions. Initially, the optimization of the photochemical reaction commenced with the use of 0.5 equivalent $NaOCl.5H_2O$ (Entry 1). Subsequent increments in the amount of $NaOCl.5H_2O$ to 1.0, 1.5, 2.0, and 2.5 equivalents (Entries 2 to 5) revealed that 1.5 equivalents and above consistently provided the same yield. Further exploration involved different solvents (Entries 6 to 9), unveiling varied yields in the photochemical setting. Notably, DMF and DMSO yielded relatively higher percentages, whereas Ethanol/Water emerged as the optimal solvent. Reflux conditions in Ethanol/Water resulted in a notable yield of 92% (Entry 10). Lastly, grinding and sonication, yielded 75% and 83% respectively (Entries 11 and 12), suggesting the influential role of mechanical processes on the reaction outcome.



1 **2** **3**

Scheme 1. Optimization of the reaction.

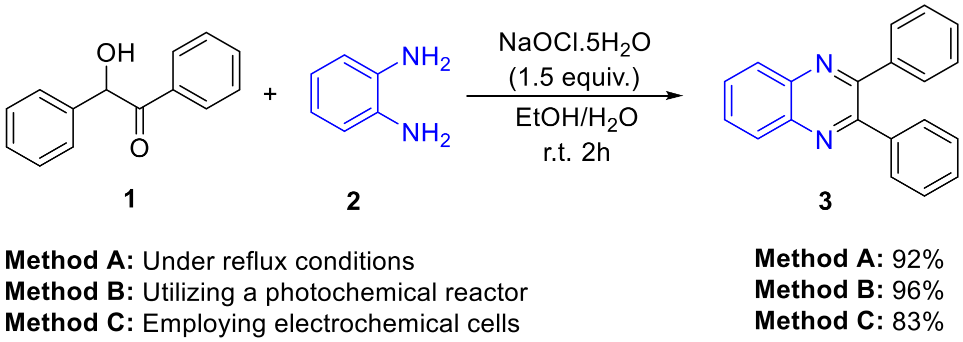
Table 1. Optimization of the reaction.

Entry	Amount of NaOCl.5H2O	Solvent	Reaction Condition	Yield (%)
1	0.5	EtOH/H2O	Photochemical	60
2	1.0	EtOH/H2O	Photochemical	70
3	1.5	EtOH/H2O	Photochemical	96
4	2.0	EtOH/H2O	Photochemical	96
5	2.5	EtOH/H2O	Photochemical	96
6	1.5	DMF	Photochemical	70
7	1.5	DMSO	Photochemical	72
8	1.5	THF	Photochemical	60
9	1.5	DCM	Photochemical	50
10	1.5	EtOH/H2O	Reflux	92
11	1.5	EtOH/H2O	Grinding	75
12	1.5	EtOH/H2O	Electrochemical	83

2.1. Reaction Methods

2.1.1. Refluxing at 65 °C

The Synthesis involved refluxing a mixture of alpha-hydroxy ketone (Benzoin) **1**, o-phenylenediamine **2**, and Sodium Hypochlorite in Ethanol/Water at 65 °C for 2 h. The reaction progress was monitored by TLC. After completion, the mixture was processed, yielding 92% pure quinoxaline 3 (Scheme 2). Identity confirmation included melting point comparison, Carbonyl functional group test, and a negative primary amine test. Additionally, the compound was identified by ^{1}H NMR Spectroscopy.



Scheme 2. Reaction strategies with three different methods.

2.1.2. Photochemical Reactor

In the photochemical Synthesis, a Pilot photocatalyticreactor was used for reaction [Capacity (1 KL), Voltage 230 V, Frequency 50 Hz, Size 600 mm (H) × 480 mm (W) × 480 mm (D), UV lamp type Medium Pressure Mercury vapour lamp] immersion mixture of Benzoin **1**, o-phenylenediamine **2**, and Sodium Hypochlorite in Ethanol/Water was stirred in a UV Tube for 2 h. The progress was monitored by TLC, and the resulting yield improved to 96% (Scheme 2).

2.1.3. Electrochemical Cell

Utilizing an electrochemical cell, a mixture of Benzoin **1**, o-phenylenediamine **2**, and Sodium Hypochlorite in Ethanol/Water was subjected to deep well graphite electrodes for 2 h. The reaction progress was monitored by TLC, and the yield of the product was 83% (Scheme 1). Identity confirmation included various tests, and the electrochemical cell parameters included a cell potential of 30 V.

2.2. Characterization

2,3-Diphenylquinoxaline **(3):** White Crystalline Powder; m.p.: 127 °C; FT-IR (ν_{max}, cm^{-1}): 3045.0 (C-H, st), 1566.5 (C=N, st), 1330.0 (C-N, st) 771.53 (C-H, b); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.21 (2H, dd), 7.81 (2H, dd) 7.55 (4H, dd) 7.38 (6H, m); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 153.51, 141.24, 139.08, 130.00, 129.85, 129.22, 128.83, 128.30.

2.3. Computational Calculations

In order to shed light into the reaction mechanism for the formation of quinoxaline, we performed theoretical calculations with Gaussian 09, Rev. D.01 [Frisch, M. J. et.al. Gaussian 09 Rev. D.01, Gaussian, Inc., Wallingford CT, 2010]. Gas-phase geometries were optimized without constraints or symmetry restrictions using ωB97X-D [J.-D. Chai, M. Head-Gordon, Phys. Chem. Chem. Phys. 2008, 10, 6615–6620] and the def2-SVPP basis set [F. Weigend, R. Ahlrichs, Phys. Chem. Chem. Phys. 2005, 7, 3297–3305]. Harmonic frequency analyses confirmed the nature of each stationary point (0 imaginary frequencies for minima; 1 for transition states). Thermal and entropic corrections (298 K, 1 atm) were taken from the standard thermochemistry output. Solvation was modeled by single-point PCM/SMD calculations [M. Cossi, V. Barone, B. Mennucci, J. Tomasi, Chem. Phys. Lett. 1998, 286, 253–260; A. V. Marenich, C. J. Cramer, D. G. Truhlar, J. Phys. Chem. B 2009, 113, 6378–6396] on the gas-phase geometries with toluene (ε = 2.3741) as solvent. Electronic energies were refined by single-point calculations with def2-TZVPP [F. Weigend, Phys. Chem. Chem. Phys. 2006, 8, 1057–1065]. Final reported energies correspond to SMD(toluene):ωB97X-D/def2-TZVPP//ωB97X-D/def2-SVPP.

The calculated reaction mechanism (Figure 1), for the Synthesis of 2,3-dyphenylquinoxaline **3**, starts with the dehydration reaction between benzoin **1** and $NaOCl\cdot5H_2O$ to produce benzoil and $NaCl\cdot6H_2O$ as subproduct. Then, *o*-phenylenediamine is added to form **A1** adduct and all this process was calculated to be highly exergonic (DG_{R1} = −60.1 kcal/mol). Next, the first aminol group is formed through proton transfer assisted by ethanol (**TS**$_{A1\text{->}4\text{-}S}$) with an energy barrier of $DG^{\ddagger}_{1}$ = 26.3 kcal/mol. Generation of intermediate **4-S** is endergonic by DG_{R2} = +10.3 kcal/mol. From here, *anti*-diaminol **5-S** (DG_{R3} = −5.8 kcal/mol) can be obtained via proton transfer (**TS**$_{4\text{-}S\text{->}5\text{-}S}$) with $DG^{\ddagger}_{2}$ = 12.6 kcal/mol. We also found a pathway to *syn*-diaminol (**5SC**, Figure S7) with $DG^{\ddagger}_{2}{}'$ = 14.3 kcal/mol. However, *syn*-diaminol is thermodynamically less favored than *anti*-diaminol by 1.3 kcal/mol so this last isomer is the kinetic and thermodynamically most favored species. Later, we found that an intermolecular proton transfer between two diaminol molecules (from **5-S** to **A2** adduct, DG_{R4} = −5.3 kcal/mol) presents the lowest energy barrier (via **TS**$_{A2\text{->}A3}$ with $DG^{\ddagger}_{3}$ = 26.7 kcal/mol) than ethanol-assistance ($DG^{\ddagger}_{3}{}'$ = 33.3 kcal/mol) as in the previous steps to produce intermediate **A3** and water (DG_{R5} = −5.4 kcal/mol). Finally, a second intermolecular proton transfer via **TS**$_{A3\text{->}3}$ ($DG^{\ddagger}_{4}$ = 18.7 kcal/mol) leads to 2,3-diphenylquinoxaline (**3**) and a second water molecule (DG_{R6} = −25.5 kcal/mol). We also examined the reaction route from **4-S** to the first condensation via **TS**$_{4\text{-}S\text{->}5}$ (Figure S5) but this resulted in a higher energy barrier of 31.8 kcal/mol (see ESI for other explored pathways).

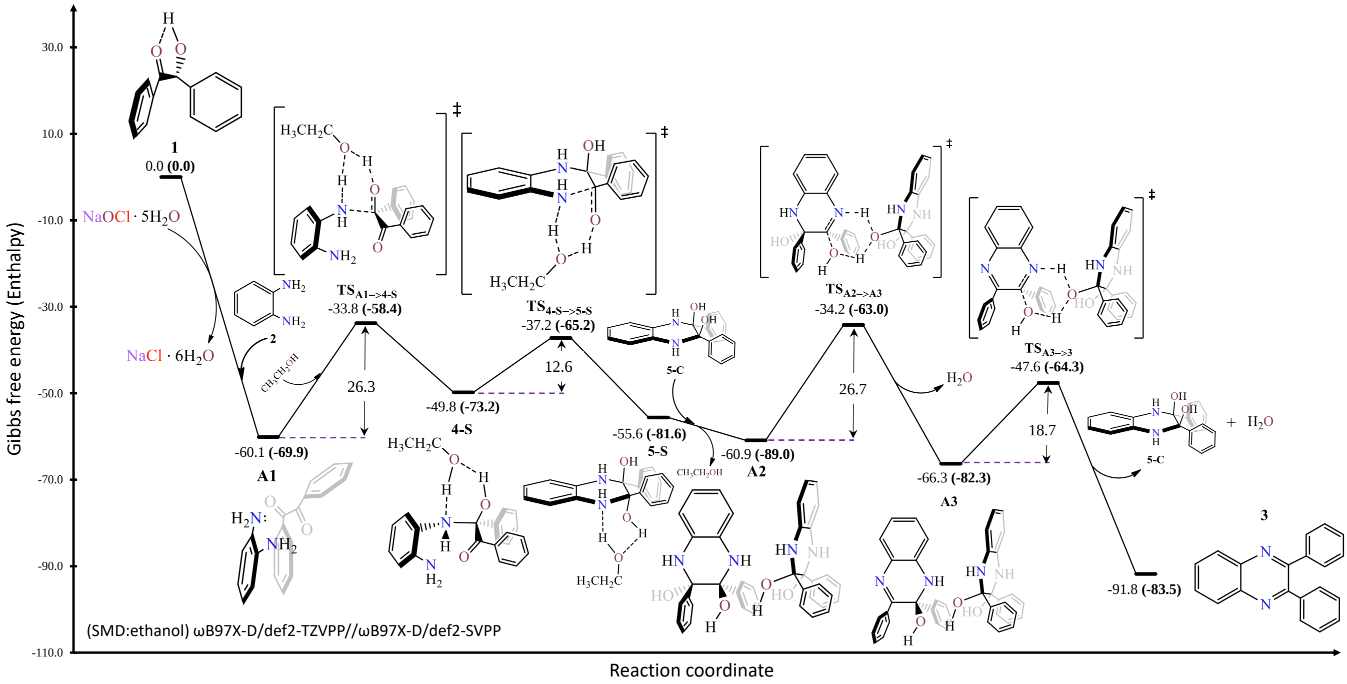


Figure 1. Energy profile of the proposed reaction mechanism to get quinoxaline **3**. Gibbs free energy and enthalpy (in parentheses) values are expressed in kcal/mol.

The diverse synthetic approaches explored in this study showcase the adaptability of the green synthesis method for 2,3-diphenylquinoxaline under various reaction conditions. Refluxing at 65 °C, employing a photochemical reactor, and utilizing an electrochemical cell all demonstrated high yields of the target compound. The environmentally friendly nature of the Sodium Hypochlorite catalyst, combined with the use of Ethanol/Water as a solvent system, aligns with the principles of green chemistry. The versatility of the reaction conditions provides practical options for different laboratory setups, ensuring accessibility and applicability. This study contributes valuable insights into the realm of sustainable organic Synthesis, offering a promising avenue for further advancements and applications in the Synthesis of quinoxaline derivatives.

3. Conclusions

In conclusion, the eco-friendly Synthesis of 2,3-diphenylquinoxaline, using Sodium Hypochlorite, demonstrates exceptional adaptability and sustainability across a range of methodologies. The successful outcomes observed through refluxing at 65 °C, employing a photochemical reactor, and utilizing an electrochemical cell highlight the versatility of this environmentally conscious approach. The adoption of Ethanol/Water as a solvent aligns seamlessly with green chemistry principles, emphasizing the environmentally benign nature of the process. The robustness of the synthetic route is confirmed through rigorous characterization methods. This study contributes to the sustainable synthesis of quinoxaline and sets the stage for broader applications in green organic synthesis, underscoring the significance of environmentally conscious chemical processes.

2,3-Diphenylquinoxaline: Purification with n-Hexane: EtOAc (8:2) as eluent; yellow solid, mp = 125–128^{0}C). 1H NMR (400 MHz, CDCl3) δ 8.22 (dd, J = 6.4 Hz, 3.2 Hz, 2H), 7.88 (dd, J = 6.4 Hz, 3.2 Hz, 2H), 7.52 (d, J = 7.6 Hz, 4H), 7.36–7.34 (m, 6H); 13C NMR (100 MHz, CDCl3) δ (ppm): 153.51, 141.24, 139.08, 130.00, 129.85, 129.22, 128.83, 128.30 HRMS (ESI-TOF) m/z: [M + H+] Calcd for C20H15N2 283.1230, Found 283.1233.

Computational details

All DFT calculations were performed using Gaussian09 rev. E.01 software optimizations were carried out in gas-phase with ωB97X-D [S2], a long-range hybrid functional, in combination with Ahlrichs' def2-sv(p) basis set (written in this paper as def2-SVPP) [S3]. Subsequently, harmonic frequency calculation was done for each optimized geometry to corroborate the kind of each critical point in the Potential Energy Surface (PES), where reactants, intermediates, and products must present all the frequencies as positive values; the transition states must have one and just one negative frequency.

In order to improve our energy calculations, solvent effects were including through the implicit PCM model using the SMD parameters according to the Truhlar's framework with ethanol ($\varepsilon = 24.852$) as solvent [S4,S5]. These calculations were done as single points of the optimized geometry at level of theory mentioned above. Also, we performed single points calculations of each optimized geometry at higher level of theory ωB97X-D/def2-TZVPP to get better accuracy [S6]. Finally, these energy corrections were added to gas-phase values and were reported as our definitive results.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/doi/s1, Figure S1: title; Table S1: title; Video S1: title.

Author Contributions: N.R.D.: Conceptualization, methodology, validation, writing—original draft, resources. V.P.S.: validation, formal analysis. J.O.C.J.-H.: computational resources. P.: writing, design. A.G.D.: data curation. D.I.M.-V.: computing resources, visualization. T.J.P.: conceptualization, resources, writing—original draft. S.V.P.: conceptualization, methodology, writing—original draft, review & editing. All authors have read and agreed to the published version of the manuscript.

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