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Efficient Synthesis of Aromatic Quinoxaline Derivatives

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Honors Thesis

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Abstract

Quinoxaline and its derivatives have many antimicrobial properties that make them possible substitutes for current medication, with abilities including antibacterial, anticancer, antiviral, and antifungal among others [1]. It is important to be able to quickly and effectively develop new compounds. Current methods to synthesize quinoxaline derivatives are cumbersome, with long reaction times, low yields, and required solvents that add hazards and costs. Microwave-assisted synthesis is a novel methodology to synthesize quinoxaline derivatives in only 5 minutes with no solvent. This study analyzes microwave irradiation as a synthesis technique.

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Introduction

Quinoxaline Derivatives and Applications

Quinoxaline derivatives are a class of nitrogen-containing heterocyclic compounds of the structure seen in Figure 1. The compounds have a large variety of biological activities, with different types of quinoxaline derivatives having antibacterial, antifungal, antiviral, antidepressant, anticancer, antiparasitic, and even anti-HIV 1 properties, among others [1]. The antimicrobial property of the quinoxaline derivative depends on what R is in compound 1 below in Figure 1. The two Rs can be the same group of molecules, they can be completely different, or they can even attach to the same structure and form a ring structure.

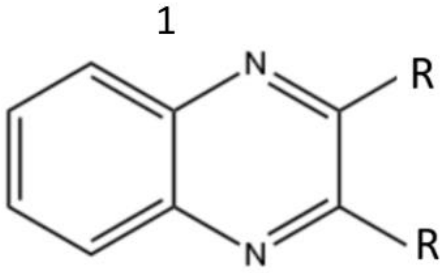
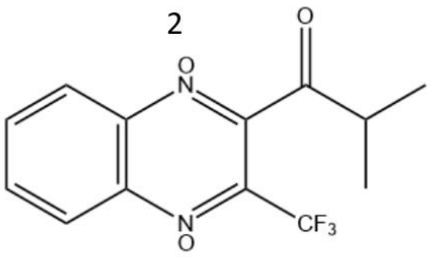


Figure 1: Structure of Quinoxaline Derivatives

For example, 3-benzyl-2-substituted quinoxalines are very effective against neurological disorders like depression and Parkinson, 2-(3-methylbut-1-en-2-yl)-3-(trifluoromethyl)quinoxaline-1,4-di-N-oxide, compound 2 in Figure 2, is very active against cancer, pyrrolo(3,4-b)quinoxalines are effective at treating candidiasis fungal infections [2] and pyrazino(3,4-b)quinoxaline derivatives, such as compound 3 below in Figure 3, show activity against tuberculosis [3]. Quinoxaline derivatives inhibit the growth of gram-positive bacteria and also attack tumors [5].



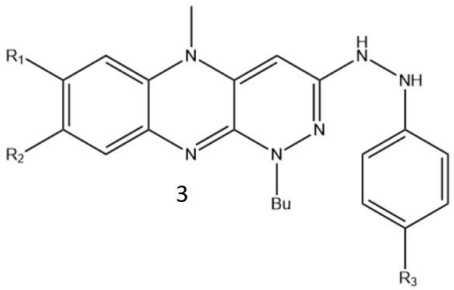


Figure 2: Compound 2 [2]

Figure 3: Compound 3 [3]

Metal complexes of these derivatives display even more properties [1]. Quinoxaline derivatives having these activities is important because extensive misuse and abuse of current medication has allowed pathogenic microorganisms to develop resistances to certain medications, making their treatments less effective. This is in turn causing an increase in allergies and respiratory issues worldwide, and more drug resistant pathogens are appearing more frequently over time [4]. Quinoxaline derivatives, due to their extensive properties, are a possible substitute for current medications. The quinoxaline ring is already widely used in various antibiotics including echinomycin and levomycin [5].

Quinoxaline derivatives also have non-medical applications. For example, some pyridazinoquinoxalines, such as compound 4 in Figure 4 below, are food additives [3].

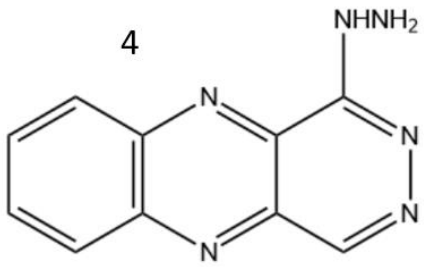


Figure 4: Compound 4 [3]

Quinoxaline bases can be reacted to form different compounds with specific medicinal applications. For example, in a study by Khan, Mullick, and Manchanda, quinoxaline-2,3-dione was prepared and reacted to yield 2,3-bis-quinoxalines. Different functional groups can then be added to the bis quinoxalines to give the desired medical application. Figure 5 below gives the scheme for these reactions. Species 5 is quinoxaline-2,3-dione, and species 1a is the 2,3-bis quinoxaline, in this case 2,3-dichloroquinoxaline. Species 1a can then be reacted with different nucleophiles of the form of species 6 to create different variations of species 7 with unique medical applications. For example, it was observed that an unsubstituted phenyl ring shows effective antimicrobial activity, nitro groups and methyl groups improve antibacterial activity, and chlorine and nitro substituted phenyl derivatives improve antifungal activity [6].

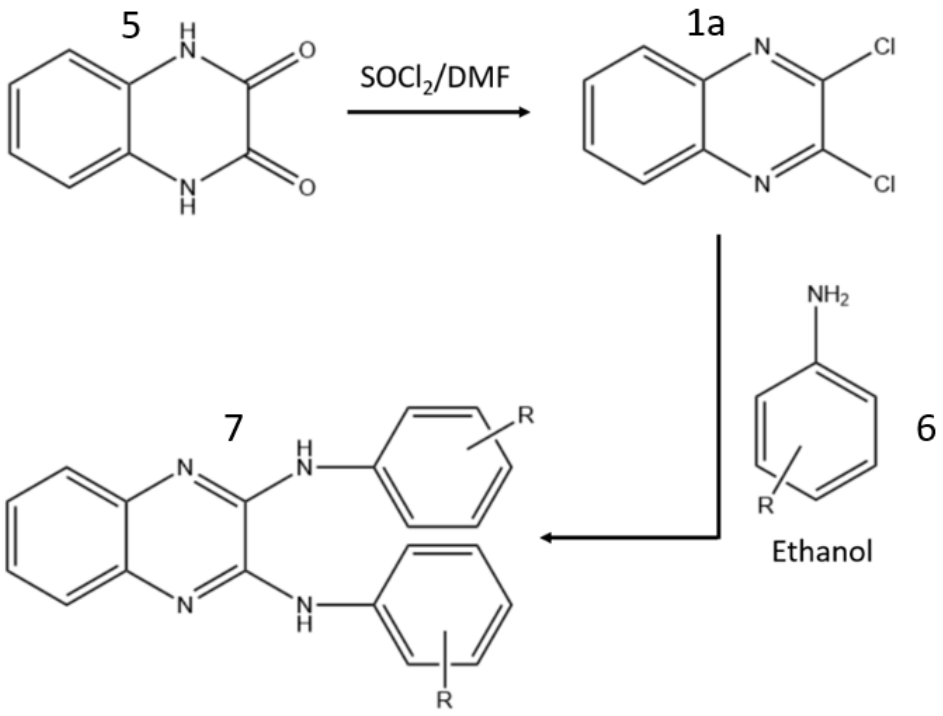


Figure 5: Reaction scheme of 2,3-bis-quinoxalines

SNAr Reactions and Complications

There are many methods for developing quinoxaline derivatives. The method of note in this paper is the nucleophilic aromatic substitution (SNAr) of 2,3-dichloroquinoxaline. A nucleophile is a compound that donates an electron pair to another species to form a covalent bond between them during a reaction. In SNAr, a nucleophile donates its electrons to an electron-deficient aromatic ring, the electrophile, which contains a leaving group. The nucleophile replaces the leaving group on the aromatic ring. Electron withdrawing groups (EWGs) on the aromatic ring can speed up the reaction; they make the ring more electron deficient by moving the electron density to

one side of the ring near the EWG. SNAr is a convenient method to produce new compounds by switching one functional group on an aromatic ring with another.

2,3-dichloroquinoxaline was used as the quinoxaline base and electrophile in this study. With 2,3-dichloroquinoxaline, the presence of chlorine at the C2 and C3 positions make the substrate an electrophile in SNAr reactions, as chlorine is a very effective leaving group and leaves the aromatic ring electron deficient. SNAr of 2,3-dichloroquinoxaline allows for the formation of carbon-heteroatom bonds, such as C-O, C-N, and C-S, at the C2 and C3 positions directly, making it a very versatile compound [7]. This allows researchers to easily develop multiple derivatives with different antimicrobial properties. 2,3-dichloroquinoxaline is also commercially available and can be easily prepared from low-cost materials [7].

The SNAr reaction of 2,3-dichloroquinoxaline is a thermal reaction, requiring a lot of heat in order to complete. With traditional heating techniques such as reflux, it can be very cumbersome and time-consuming. In a study by Dhanaraj and Johnson, N^2,N^3-bis(4-nitrophenyl)-quinoxaline-2,3-diamine (7a) was synthesized by the reaction between quinoxaline-2,3-(1,4H)-dione (5) and 4-nitroaniline (6a). Figure 6 below gives the reaction scheme. The reaction was conducted on the mmol scale and was refluxed for approximately six hours [8].

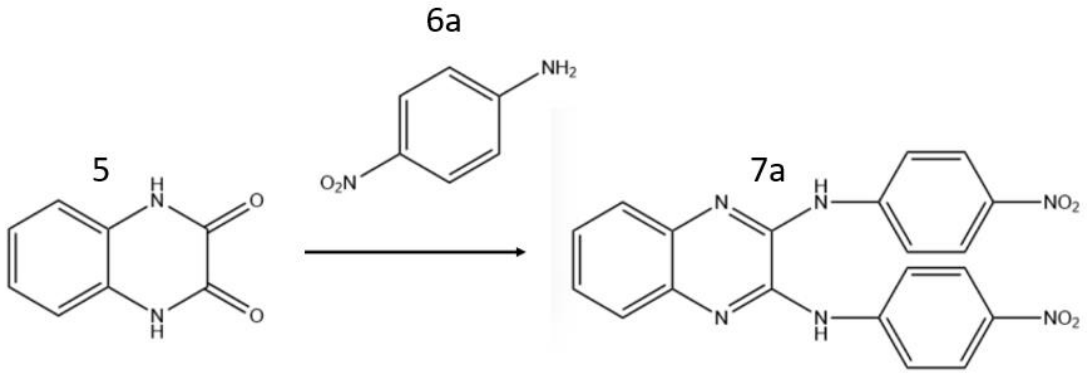


Figure 6: Reaction scheme

Microwave Assisted Synthesis

Microwave irradiation is an alternative heating method for thermal chemical reactions. Microwaves are a part of the electromagnetic spectrum with frequencies between 300 and 300,000 MHz, and wavelengths between 1 m and 1 mm. Figure 7 shows microwaves on the electromagnetic spectrum.

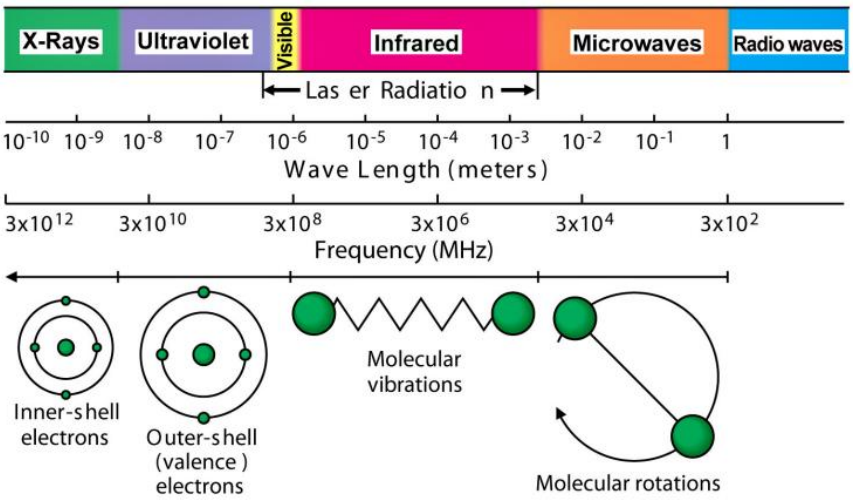


Figure 7: Electromagnetic spectrum [9]

Microwaves consist of both an electrical and magnetic field, though only the former contributes to heating the species. Microwave heating involves microwaves coupling with molecules in the reaction and directly increasing the species temperature. This heating does not depend on the thermal conductivity of the reaction vessel. When the microwave source is turned off, the species will no longer be heated and the latent heat will remain; this makes microwave irradiation easy to control [9]. This is in contrast to conventional heating, which relies on thermal conduction. A heating medium is heated up to a specific temperature, and then this transfers heat to the redaction mixture through the vessel walls, so the rate of heat transfer depends on the thermal conductivity of the vessel. Furthermore, heating will not immediately stop when the heating device is turned off, as the heating medium will still be at a high temperature and will continue to transfer heat. Figure 8 below gives a schematic of conventional conduction heating. Figure 9 gives a schematic of microwave irradiation heating.

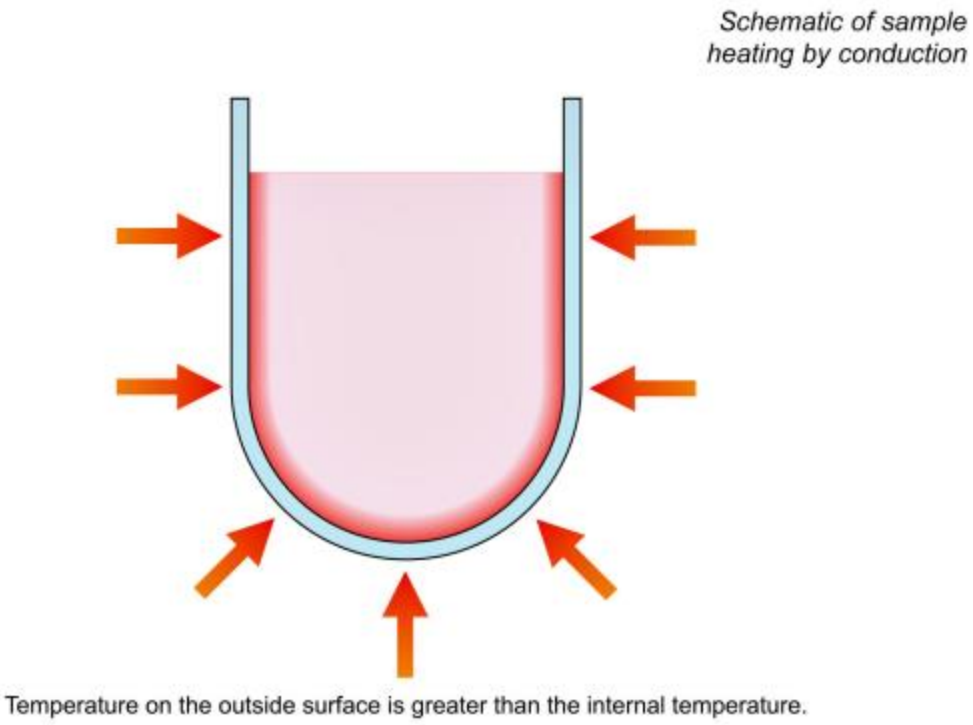


Figure 8: Schematic diagram of conventional heating via conduction [9]

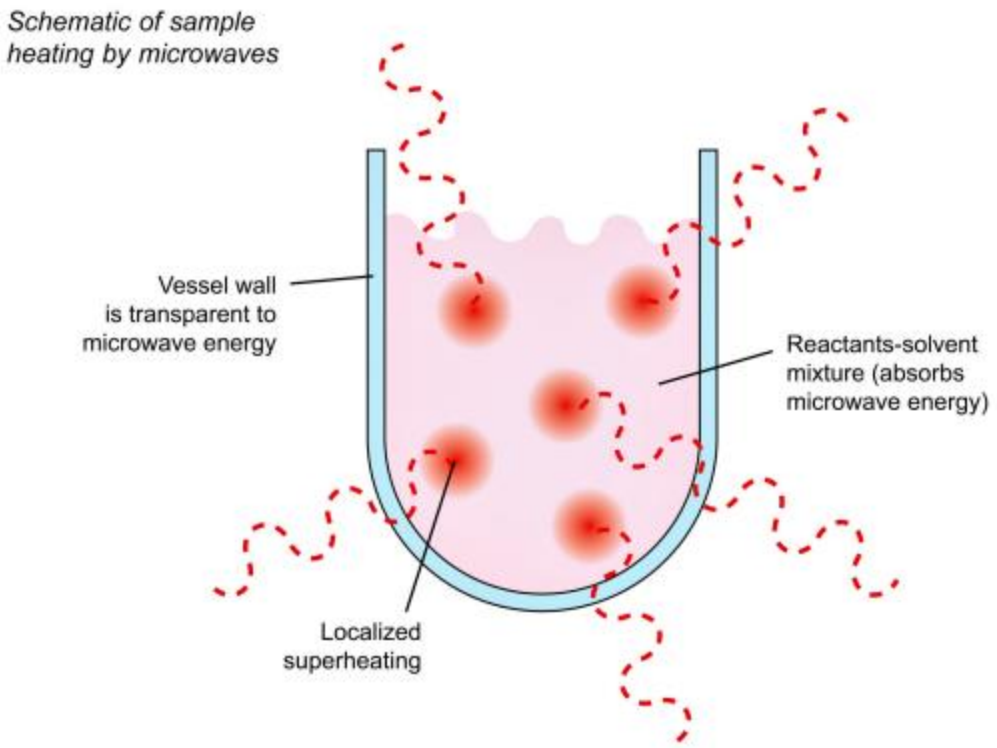


Figure 9: Schematic diagram of heating via microwave irradiation [9]

Furthermore, microwave radiation does not contain enough energy to break chemical bonds, so microwave irradiation will not change the structure of the species [9]. However, overheating with microwaves can cause a species to decompose.

Microwaves transfer energy to molecules through two mechanisms: dipole rotation and ionic conduction. Dipole rotation involves polar molecules aligning with the rapidly changing electric field of the microwave. This rotational motion of the molecule results in a transfer of energy. With ionic conduction, if free ions are present in the reaction mixture, the electric field will cause ionic motion, resulting in localized superheating. As the temperature of the species increases, ionic conduction becomes more efficient and the energy transfer rate increases [9].

Microwave irradiation can dramatically increase reaction rates over conventional heating methods, such as reflux. While microwaves do not impact the activation energy of the reactions, they provide enough momentum to quickly reach this point and complete the reaction quicker than conventional methods. In typical microwave hardware supplying 300 W, more microwave energy is supplied than is needed to reach the activation energy, resulting in increased reaction rates and greater yields than conventional heating [9]. According to Hayes, microwaves transfer energy in 10E-9 seconds with each cycle of energy, while the kinetic molecular relaxation from the energy is around 10E-5 seconds. Therefore, energy is transferred to the species faster than its molecules can relax, resulting in increased reaction rates, high instantaneous temperatures necessary for the SNAr reactions, and higher product yields [9].

According to Hayes, studies have found that microwave irradiation can increase reaction rates by approximately 1000-fold versus conventional heating methods [9].

Microwave irradiation is very useful with slow reactions with high activation energies [9]. Microwave irradiation has been shown to expedite SNAr reactions. With conventional heating methods such as reflux, SNAr reactions are very time-consuming and inefficient, with some taking more than six hours such as the one presented by Dhanaraj and Johnson, and yields are typically around 60%. Microwave irradiation can perform the same reactions in only one hour or less, and with yields above 80-90% [9].

Literature Preparation Techniques

There are many techniques discussed in various literature to develop quinoxaline derivatives. This section of the report details many of them and compares them.

Ruiz et al report a room temperature synthesis of quinoxaline derivatives using recyclable alumina-supported heteropolyoxometalates. They mixed Keggin heteropolyoxometalates as catalysts with 1 mmol of o-phenylenediamine and 1 mmol of a 1,2-dicarbonyl carbonyl compound in toluene, and stirred at room temperature. This procedure has the advantage of running at room temperature, so there are no high temperature or pressure hazards. Furthermore, high yields of above 90% were reported. However, in order to achieve high yields, reaction times of above 2 hours and catalyst amounts above 100 mg were required. The high amounts of catalyst required could drive up costs. Furthermore, the reaction requires a solvent, adding costs and waste [10].

Reflux is a widely used technique to synthesize quinoxaline derivatives. Reflux involves heating a chemical reaction while continuously cooling the vapors to prevent material from leaving the reaction vessel. A paper by Khatoon and Abdulmalek detail three different procedures to develop quinoxaline derivatives that use reflux. In one procedure to develop anticancer derivatives, Rayes et al reacted phenylquinoxalines-2(1*H*)-thione and triethylamine with acrylic acid derivatives. They refluxed the mixture for 4 to 6 hours and attained 88% yield. In another procedure, Singh at al. used reflux to develop antibacterial and antifungal derivatives. They refluxed 2-chloro-3-methyl quinoxaline and 4-hydroxy benzaldehyde in acetonitrile for 30 hours to get yields of 60% to 70%. In a third procedure, Baashen synthesized quinoxaline-2,3(1H,4H)-dithione derivatives as general antimicrobial agents. They produced the products by the thionation

of quinoxaline-2,3(1H,4H)-dione with a crystalline zwitterionic dipyridine-diphosphorus pentasulfide complex, and refluxed it in pyridine for 1 hour. The highest yield of 86% resulted from a 5 hour reflux [11]..

Reflux reactions are effective, and they can lead to high yields as seen by the above procedures, but they have a few issues. Because they heat through conduction, the heating can be difficult to control. They also take a very long time, with some requiring 30 hours just for moderate yields. They also require solvents, and some of these can be dangerous both to humans and the environment, such as acetonitrile. This also makes it more difficult to waste the solvent, adding additional costs and safety procedures.

Goal

This study aims to synthesize various quinoxaline derivatives using microwave assisted synthesis. The goal is to show that the technique is a feasible technique for this synthesis, and to get higher yields than other literature preparation methods. Yields of 80% to 90% are desirable. This study also aims to test the various properties of these quinoxaline derivatives.

Results and Discussion

2,3-dichloroquinoxaline, compound 1a, is the starting material for the microwave-assisted synthesis due to its versatility outlined above. Before the microwave-assisted synthesis, a large quantity of this starting material was developed using the procedure outlined in Figure 10 below.

Figure 10: Synthesis of Starting Material

Figure 11 below shows the synthetic procedure for the synthesis of quinoxaline derivatives using microwave irradiation. Table 1 below gives the amounts of each reactant used in this procedure.

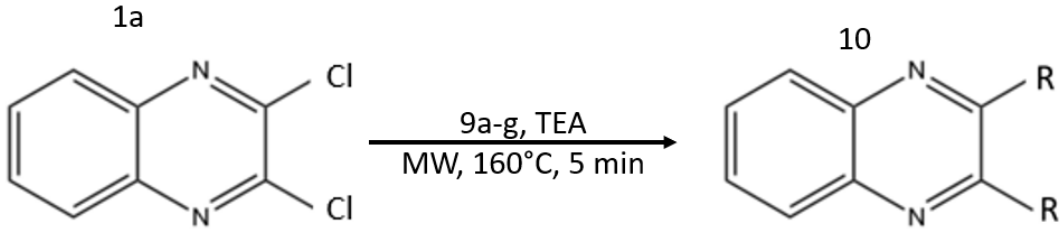


Figure 11: Microwave-Assisted Synthesis Procedure

Table 1: Molar Equivalents of Reagents in Microwave-Assisted Synthesis

Species	Molar Equivalent
2,3-dichloroquinoxaline (Compound X)	1 mmol
Nucleophile (R)	2 mmol
Triethylamine (TEA)	3 mmol

The reaction in Figure 11 was performed with a variety of nucleophiles, including both oxygen and nitrogen-containing compounds. All reactions used the molar amounts

given in Table 1. After each microwave reaction, TLC was used to determine the purity of the product; if some starting material was still present, then another microwave reaction under the same conditions was performed. This was repeated until no starting material was left. Only a maximum of three microwave cycles were used, as more can lead to decomposition of the product. After TLC, the product was extracted, washed, dried, and filtered, and all solvent was boiled off. NMR was used to verify the final product. Table 2 below shows all synthesized compounds produced, along with their yields.

Table 2: Summary of Results

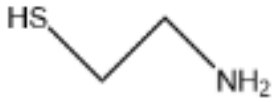
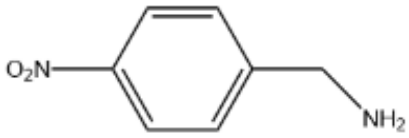
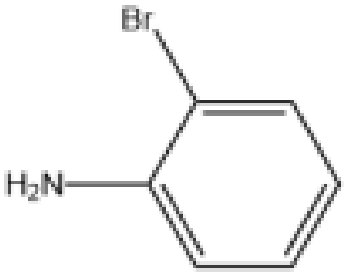
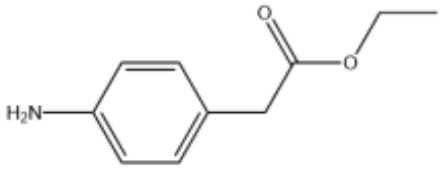
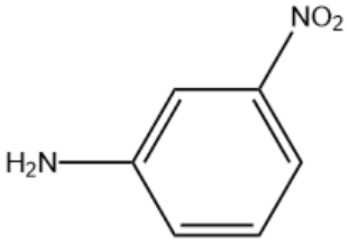
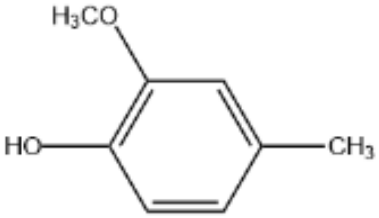
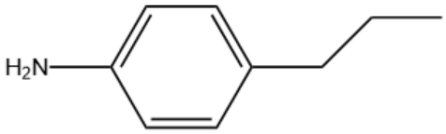
Compound	Nucleophile	Nucleophile Schematic	Yield, %
10a	Cysteamine-Hydrochloride (9a)		65
10b	4-nitrobenzylamine hydrochloric acid (9b)		89
10c	2-bromoaniline (9c)		10

Table 2 Continued

10d	Ethyl (4-aminophenyl) acetate (9d)		26
10e	3-nitroaniline (9e)		30
10f	2-methoxy-4-methylphenol (9f)		35
10g	4-propylaniline (9g)		53

The average yield for all compounds was 44%, which is below the desired range of above 80%. 10a and 10b are the only aliphatic quinoxaline derivatives, and they had the highest yields of 65% and 89% respectively. The aliphatic derivatives had an average yield of 77%, while the aromatic derivatives had an average yield of 31%.

Electron donating groups (EDGs) are groups on the aromatic ring that add electron density to the ring. This acts to make the nucleophile stronger. Of the aromatic derivatives, 10c, 10d, and 10e all feature electron withdrawing groups (EWGs), which

pull electron density from the ring. 10f and 10g both feature exclusively EDGs. The compounds with EDGs have a higher average yield than those with EWGs; the EDG compounds have an average yield of 44%, while the EWG compounds have an average yield of 22%. This leads to a key finding that the use of EDGs on the nucleophile can increase the yield of quinoxaline derivatives by making the nucleophile stronger.

Conclusion

Microwave-assisted synthesis is an effective technique for synthesizing quinoxaline derivatives. This is advantageous over traditional methods due to the lack of solvents, which remove costs and hazards associated with them, and there are shorter reaction times. However, this study recorded moderate yields.

Future Work

Future work will focus on optimizing the current procedure so that higher yields of 80% to 90% can be achieved while still maintaining low reaction times below 30 minutes. Future work will also involve testing the different synthesized species for their properties.

Experimental Methods and Data

NMR spectra were obtained in $CDCl_3$ or DMSO-d_6. Operating at 400 MHz with TMS as the internal standard. All microwave assisted reactions were carried out with a single mode cavity CEM Discovery Microwave Synthesizer. Purification was accomplished using Teledyne-Iso Combiflash flash chromatography system. All commercially available materials were used without further purification.

General procedure for compound **1a**

Oxalic acid (25 mmol) was added to a 100 mL round-bottom flask with thionyl chloride (172 mmol, 12.5 mL) and a catalyst DMF (0.5 mL). The materials were dissolved fully and placed into a heating bath of oil. The mixture was heated to 100°C and refluxed for approximately 1 hour. This generated 2,3-dichloroquinoxaline with a yield of 96%.

General procedure for compound **10**

2,3-dichloroquinoxaline (0.2g, 1mmol) was added to a microwave tube with the nucleophile (2mmol) and triethylamine (0.4mL, 3mmol). The reaction mixture was added to a microwave for 5 minutes at 160°C. TLC was used to determine product purity. If starting material was present, the mixture was reacted in the microwave again at the same conditions. The resulting mixture was extracted with water and dried using anhydrous magnesium sulfate and evaporated under reduced pressure. If needed, compounds were purified by column chromatography (hexane/ethylacetate) to give compounds 10a-g.

2,2'-(quinoxaline-2,3-diylbis(sulfanediyl))bis(ethan-1-amine) (10a): color solid (65% yield), mp, 1H-NMR ($CDCl_3$) δ: 2.78 (t, J = 4 Hz, 4H), 3.38 (t, J = 4 Hz, 4H), 7.61-7.78 (m, 4H)

N^2,N^3-bis(4-nitrobenzyl)quinoxaline-2,3-diamine (10b): color solid (89% yield), mp, H-NMR ($CDCl_3$) δ: 4.36 (s, 4H), 7.59-7.81 (m, 12H)

N^2,N^3-bis(2-bromophenyl)quinoxaline-2,3-diamine (10c): color solid (10% yield), mp, H-NMR ($CDCl_3$) δ: 7.07 - 7.55 (m, 8H), 7.61-7.79 (4H)

Diethyl 2,2'-((quinoxaline-2,3-diylbis(azanediyl))bis(4,1-phenylene))diacetate (10d): color solid (26% yield), mp, H-NMR ($CDCl_3$) δ: 1.18 (t, J = 2 Hz, 6H), 3.56 (s, 4H), 4.12 (q, J = 2 Hz, 4H), 3.36 - 3.40 (m, 8H), 7.68 - 7.79 (m, 4H)

N^2,N^3-bis(2-nitrophenyl)quinoxaline-2,3-diamine (10e): color solid (30% yield), mp, H-NMR ($CDCl_3$) δ: 7.45 - 7.8 (m, 10H), 7.82 (d, J = 3Hz, 2H)

2,3-bis(2-methoxy-4-methylphenoxy)quinoxaline (10f): color solid (35% yield), mp, H-NMR ($CDCl_3$) δ: 2.31 (s, 6H), 3.85 (s, 6H), 6.59 - 6.74 (m, 6H), 7.56 -7.69 (m, 4H)

N^2,N^3-bis(4-propylphenyl)quinoxaline-2,3-diamine (10g): color solid (53% yield), mp, H-NMR ($CDCl_3$) δ: 0.94 (t, J = 3.5 Hz, 6H), 1.62 - 1.66 (m, 4H), 2.48 (t, J = 3.2 Hz, 4H), 7.22 - 7.38 (m, 8H), 7.56 -7.74 (m, 4H)

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