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Optimizing reaction efficiency: Microwave-supported synthesis of quinoxaline-based compounds

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ABSTRACT

The chemistry of chloroquinoxalines has garnered significant interest owing to the potential applications of this nitrogen-containing heterocyclic class in various fields. This manuscript delves into the investigation of heteroaromatic nucleophilic substitution reactions (S_NAr) involving quinoxaline substrates, specifically 2-chloroquinoxaline and 2-chloro-3-methylquinoxaline, in the presence of thiols (mercaptan). The documented findings present the outcome of these reactions, which proceed experimentally under mild and metal-free conditions and lead to the selective formation of mono- and di-substituted products with commendable yields. Employing microwave-assisted synthesis for the preparation of compounds **1**, **4,** and **5** was crucial for optimizing reaction efficiency and maximizing product formation. The experimental findings revealed an increase in the overall yield of compounds **1**, **4**, and **5** by approximately 15–20%, accompanied by a significant reduction in reaction time by 75%.

Introduction

Thioethers are important motifs in synthetic organic chemistry, biochemistry and materials science. Several synthesized thioethers exhibit significant biological activity and serve as drug candidates for various diseases [1,2]. Transition metals such as palladium, copper, nickel, cobalt, indium, gold, rhodium, iron, manganese have been shown to catalyze C-S bond cross-coupling reactions between arylthiols and aryl halides. In particular, Migita and coworkers pioneered the transition metal-catalyzed C—S bond reaction [3,4], which is widely used in coupling reactions with aryl chlorides and alkyl/aryl thiols. Despite its usefulness, reports indicate challenges in reactions involving aryl thiols with chloroheteroarenes, due to the coordinating and adsorptive properties of sulfur-containing compounds, which act as catalyst poisons and limit their effectiveness [5,6]. Aerial oxidation of thiols poses another common hurdle in thioetherification reactions, leading to facile conversion of sulfide to disulfides [7]. Bandaru and colleagues have developed a highly effective catalytic protocol, the Pd/PTABS system, which operates at only 50 °C and enables the thioetherification of heteroaryl chlorides [2]. This system demonstrated remarkable efficiency, even at low temperatures, and facilitated the cross-coupling of numerous chloroheteroarenes (e.g. 2-chloroquinoxalines, 2-chloropyrazines). In addition, Gehrtz et al. (2018) presented a novel approach using Ni (0) precatalysts for the cross-coupling of chloro (hetero)arenes with thiolates [8]. The oxidative addition of Ni (0) complexes to electrophiles was found to be more facile than for Pd (0) complexes [9]. However, the use of Pd- or Ni-based catalysts has its own drawbacks, including high cost, environmental pollution and limited availability. The use of transition metal catalysts is often expensive and necessitates their complete removal from products, especially in the production of synthetic pharmaceuticals [10,11].

We attempted to solve this problem by circumventing the use of transition metal-based catalysts and instead using solvent systems [DMF/K_2CO_3 (condition A) or acetone/0.1 N NaOH (condition B)] for the synthesis [21,22]. Two sets of chloro(hetero)arenes, a class of quinoxalines, were used in the study, namely 2-chloroquinoxalines (2-CQ) and 2-chloro-3-methylquinoxalines (3-MCQ). Chloroquinoxalines are valuable building blocks due to their involvement in many chemical reactions, including nucleophilic aromatic substitution and cross-coupling catalyzed by transition metals. The reaction proceeds in a

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one-pot system, bypassing extensive separation procedures associated with the isolation of intermediates, saving both time and financial resources, towards the synthesis of chloroquinoxalines (**1**–**6,** Scheme 1). In addition to conventional methods, we have attempted to synthesize 3-(quinoxalin-2-ylthio) benzoic acid (**1**), 3-(3-methylquinoxalin-2-ylthio) benzoic acid (**4**) and 2-(3-methylquinoxalin-2-ylthio) benzoic acid (**5**) using microwave-assisted synthesis to allow comparative analysis between the two methodologies.

Various fields have increasingly adopted microwave synthesis, including medicine, pharmaceutical chemistry, polymer science, plant protection, fragrances and cosmetics, colour protection, biotechnology, biomedical chemistry and the development of nanoparticles. More than a thousand peer-reviewed articles are published annually on microwave-assisted synthesis in a wide spectrum of topics, including addition reactions, condensation reactions, metal-catalyzed processes, nanomaterials, the preparation of ionic liquids and substitution reactions. Microwaves have also been shown to be useful in conducting several palladium-catalyzed carbon–carbon coupling reactions (e.g. Heck, Negishi, Suzuki-Miyaura) [12].

The efficiency of heat transfer by dielectric heating is crucial for microwave-assisted organic synthesis (MAOS), leveraging the solvent's or reagent's capacity to absorb microwave energy [13]. Dielectric heating enables a rapid temperature increase that occurs in less than a nanosecond (10–9 s), which is a significant advantage over conventional heating methods. This is the main advantage over conventional heating methods, as microwaves interact directly with dipoles or ionic molecules in the reaction mixture. Moreover, minimal wall effects enable volumetric heating as the electromagnetic field from microwave irradiation comes into direct contact with the molecules in the reaction mixture [14]. The higher reaction speed achieved by microwave irradiation often leads to a higher product yield. The shortened reaction durations diminish the probability of unwanted side reactions and thus promotes the formation of the desired substitution product (Fig. 1) [15]. Subsequently, it was found that the product yield increased during microwave-assisted synthesis, while the overall duration of the synthesis was shortened. In addition, the likelihood of di-sulfide formation as a by-product is eliminated for compounds **1**, **4** and **5**.

Results and discussions

The significance of the specific structural C-S-C motif in economically relevant compounds drives researchers to search for sustainable methods to access these moieties, emphasizing the importance of thiol-etherification reactions. In our experiment, we explored various solvent solutions to forge C-S-C patterns without relying on catalysts or elevated temperatures. We investigated common laboratory solvent systems to facilitate the cost-effective synthesis of compounds for researchers.

The experiment was started with the use of 2-CQ (1 mmol) and mercaptan (1.5 mmol) for the conventional synthesis of 2-(arylthiol) quinoxaline derivatives (compounds **1**–**3**) in the presence of DMF/K_2CO_3 (condition A) or acetone/0.1 N NaOH (condition B), as shown in Scheme 1. The reaction mixture was refluxed for 1–2 h until the reaction was complete, which was monitored by TLC (hexane/ethyl acetate, 7:3 or 8:2). The resulting reaction mixture was then filtered, quenched with cold water and treated with 3 N NaOH to remove the residual disulfide content, while the use of caustic soda (NaOH) assisted the decomposition of the disulfide bonds. The results show that the use of both solvent systems A and B clearly prevents the formation of disulfides, particularly for the synthesis of compound **1** [16].

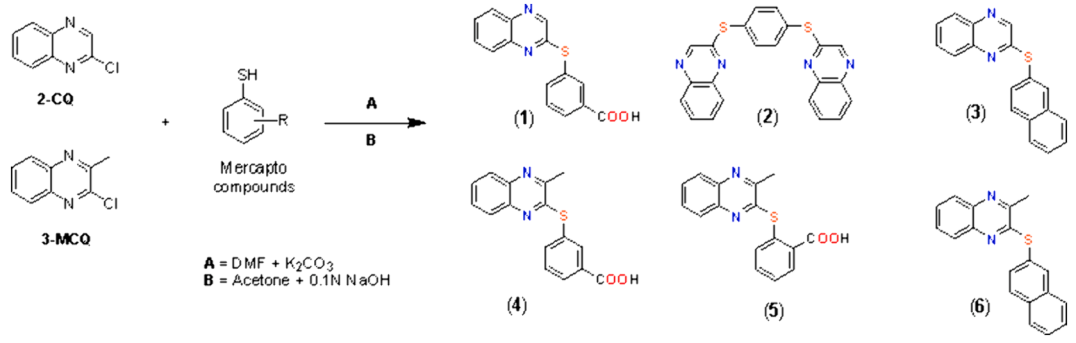
Originally, the amounts of 2-CQ and mercaptans up to 1 mmol were used based on the stoichiometric ratio and the computations of the individual reactions. However, it turned out that 2CQ and 2-MCQ remained unreacted and were identified in the spectrum of the NMR analysis. It is important to emphasize that the complete use of 2-CQ and 2-MCQ in the reaction was necessary due to their high solubility in almost all solvents, which made their removal a challenge. The amount of mercaptans was then optimized to 1.5 mmol to use the starting reactants CQ and MCQ as limiting reagents.

Table 1 shows that the synthesis of 2-CQ and 3-MCQ derivatives in the two solvent systems A and B yielded 50 % and 55 % of compound **1** after about one hour, respectively. It was postulated that the increased production of compound **1** in solvent system B could be due to the use of a stronger base, NaOH, which is well suited for acid/base reactions with the –COOH functional group.

The different connection of the thiol group with the quinoxaline group in compound **2** distinguishes it from compounds **1** and **3**. The unexpected reaction between 2-CQ and 1,4-benzenedithiol led to the synthesis of compound **2** (Scheme 2). This compound **2** was obtained within five minutes under reflux in the presence of solvent solutions (A and B). However, TLC analysis confirmed the formation of disubstituted chloroquinoxaline and by-products (including disulfides) despite the targeted mono-substituted compound. In this particular reaction, it was postulated that 2-CQ attaches to the thiol group on both sides due to the presence of two SH groups at the *para*-positions of the mercaptan. The lower electronegativity of the thiol group destabilizes HS-, a stronger nucleophile, leading to accelerated attack compared to Cl-. Moreover, Cl- serves as a better leaving group compared to SH-, since SH- itself is unstable in its transition state.

Meanwhile, compound **3** was exclusively synthesized using solvent system A. Solvent system A was considered optimal because the combination of DMF/K_2CO_3 effectively suppressed the formation of disulfides, while solvent system B showed a notable presence of disulfides in the reaction mixture. Although the disulfides could potentially be eliminated by treating the crude product with the caustic soda treatment, this method was avoided due to the reported negative effects on the overall yield. Therefore, solvent system A was chosen as the preferred option for the synthesis of compound **3**.

The synthesis of 3-MCQ based quinoxaline derivatives, compounds **4** and **5**, was compatible with both solvent systems A and B. Similar to compound **1**, the yield of both compounds was slightly higher in the



Scheme 1. Synthesis of 2-(arylthiol)quinoxalines (compounds **1**–**3**) and 3-methyl-2-(arylthiol)quinoxalines (compounds **4**–**6**). The compound **2** is disubstituted quinoxaline.

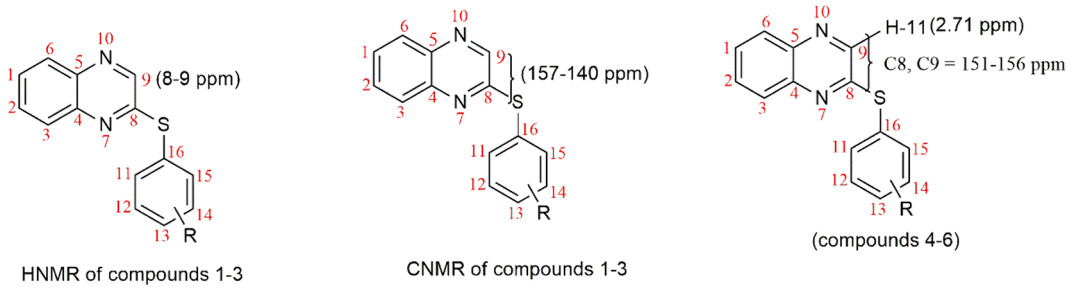


Fig. 1. General representation of the 1H and 13C NMR signals for compounds **1**–**6** (in particular the distinctive peak of C8 and C9).

Table 1
The experimental conditions for the synthesis of 2-(arylthiol)quinoxalines (compounds **1**–**3**) and 3-methyl-2-(arylthiol)quinoxalines (compounds **4**–**6**).

2-CQ + mercaptan compounds					2-MCQ + mercaptan compounds				
DMF + K_2CO_3 (**A**)			Acetone + 0.1 N NaOH (**B**)		DMF + K_2CO_3 (**A**)			Acetone + 0.1 N NaOH (**B**)	
	Time (min)	Yield (%)	Time (min)	Yield (%)		Time (min)	Yield (%)	Time (min)	Yield (%)
1	60	50	60	55	**4**	60	50	60	56
2	5	50	5	53	**5**	60	51	60	52
3	30	51	–	–	**6**	30	52	–	–

solvent acetone/0.1 N NaOH (system B). This observation was rationalized due to the involvement of acid-base reactions between a weak acid, –COOH, and a strong base, NaOH, creating favourable conditions for the reaction. The crude compounds **4** and **5** were first treated with dilute hydrochloric acid, before recrystallization in a methanol–water mixture (1:1) resulting in the pure products. Similar to the synthesis of compound **3**, compound **6** was also obtained exclusively in DMF/K_2CO_3 (system A) to limit the formation of disulfides, as already explained for compound **3**.

Following the successful synthesis of quinoxaline derivatives (compounds **1**–**6**) using conventional methods, we aimed to explore alternative approaches to synthesize these compounds aiming to improve the yield and reduce synthesis time. Both batch and continuous microwave (MW) organic synthesis have gained popularity due to their precise temperature and pressure control (Martina et al., 2021). Microwave devices offer a wide range of chemical synthesis possibilities, with the S_NAr reaction being particularly feasible in this setup. Initially, we focused on determining the optimal reaction conditions for arylthiols with a –COOH group, which were selected due to their higher melting points and longer synthesis time (Table 2). Compound **1** was used as a test subject to determine the ideal temperature and duration for a complete synthesis. We gradually increased the temperature and reaction time until the reaction was complete, which was confirmed by detectable changes using TLC analysis. In the MW synthesis experiments, solvent system A was used due to the higher boiling point of DMF (154 °C).

A comparative study was conducted between the conventional and microwave synthesis methods to determine their respective efficiencies. The results showed that microwave synthesis yielded a higher percentage of pure compounds (ranging from 75 % and 86 %) than the conventional heating method, which yielded a lower percentage of pure compounds (approximately 50 %). In addition, microwave synthesis significantly shortened the reaction time, with an initial reaction time of one hour for the formation of compound **1**; however, after MW irradiation, this time was reduced to 15 min, which corresponds to a remarkable 75 % reduction in reaction time. Table 3 provides a comprehensive summary of the details for each reaction.

In traditional heating, an external heat source, often an oil or water bath, is used to heat the organic reaction mixture. Whilst, the reflux is established and controlled based on the boiling point of the solvent. This technique of energy transfer is inert and inefficient as it relies on convection currents and the thermal conductivity of materials and results in the temperature in the reaction vessel exceeding that of the reaction mixture. In contrast, microwave heating enables rapid, in-core

Table 2
Optimizing reaction conditions for the microwave synthesis of chloroquinoxaline (compound **1**).

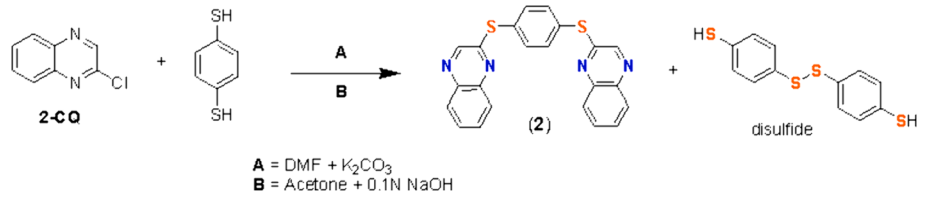
Time (min)	Temp. (°C)	Solvent system	Formation of compound 1
5	50	A (DMF + K_2CO_3)	*NF
10	80	A (DMF + K_2CO_3)	*NF
10	100	A (DMF + K_2CO_3)	*NF
15	100	A (DMF + K_2CO_3)	Precipitates observed

*NF = not finished.

Table 3
Comparative analysis of the percentage yield and reaction time for quinoxalines (compounds **1**, **4** and **5**) using the classical reflux and microwave-assisted methods.

Compounds	Conventional method		Microwave assisted method		Increase in yield (%) MW/CR**	Decrease in reaction time (%) MW/CR***
	Time (min)	Yield (%)	Time (min)	Yield (%)		
1	60	50	15	80	20	75
4	60	50	15	86	26	75
5	60	51	15	75	15	75

**: Microwave over Classical Reflux increase in yield (%) = *MW yield/ CR yield* (%).
***: Microwave over Classical Reflux decrease in reaction time= (*CR time-MW time/CR time*) × 100.



Scheme 2. Synthesis of disubstituted product, 2-(4-(quinoxaline-2-ylthio) phenylthiol) quinoxaline (2).

volumetric or internal heating by allowing the microwave radiation to interact directly with the chemical reaction mixture, including solvents and catalysts. Microwave containers are typically made of microwave-transparent materials such as borosilicate glass, Teflon and quartz, resulting in a reverse heating gradient compared to conventional methods.

Indeed, reaction mixtures prepared in the laboratory are heated extremely rapidly, reaching temperatures well above the boiling point of the solvent when heated normally. This temperature level is difficult, if not impossible, to achieve with conventional thermal heating methods. Consequently, reactions that used to take hours or days can now be carried out within minutes or seconds using a sealed vessel microwave [17,18].

However, the products synthesized with microwave irradiation technology were clean and pure, making further purification unnecessary. Microwaves require less energy to break a chemical bond compared to other types of radiation because it's electromagnetic radiation in the molecular scaffold remains unaffected, consequently [19,20]. Using the microwave-assisted approach to synthesize the quinoxaline derivatives, compounds **1**, **4**, and **5**, offers numerous advantages, including a lower activation barrier, faster reactions with minimal byproducts, and a highly purified final product. Following the successful preparation of the chloroquinoxalines (compounds **1**–**6**), the pure compounds were structurally characterized using various spectroscopic methods, including 1H nuclear magnetic resonance (NMR), 13C NMR, Fourier transform infrared (FT-IR) and direct injection MS (DIMS).

The location of attachment for 2-CQ and 3-MCQ is at C-8, where arylthiols undergo S_NAr interactions with the parent quinoxalines. Due to their asymmetry, the proton spectra of 2-CQ and 3-MCQ show significant variations at C-8 and 9. The derivatives of 2-CQ feature a distinct singlet at approximately 8–9 ppm corresponding to H-9. The proton spectra show characteristic peaks for 2-chloroquinoxaline, in particular a single peak at 8.67 ppm for H-9 (compound **1**). The standard singlet for H-9 is also observed for other compounds, for compound **2** at 8.59 ppm and for compound **3** at 8.65 ppm. The absence of the -SH signal (around 2–3 ppm) and the presence of the –COOH signal as a broad singlet (at 3.5 ppm) suggest an S_NAr reaction between 2-chloroquinoxaline and 2-mercaptobenzoic acid (compound **1**). No -SH signal was detected for compounds **1**–**6**, providing definitive evidence for S_NAr reactions. The absence of the typical signal for C-9 in compounds **4**–**6** is attributed to the presence of the methyl group H-11, which is located at approximately 2.71 ppm (Fig. 1).

Meanwhile, the 13C- NMR spectrum showed the peak for the carbonyl group (C-18) at 167.0 ppm (compound **1**). The C-8 peak, which is the attachment point for the formation of the sulfide bond at 156.0 ppm, confirms the formation of 3-(quinoxalin-2-ylthio)benzoic acid. The absence of the -S-bond shifts the C-8 peak more upfield, approaching 148 ppm. The carbonyl functionalities exhibited chemical shifts of 167 and 168 ppm for compounds 4 and 5, respectively. A similar pattern of carbon peaks is observed for compounds **2** and **3**. For instance, the C-8 and C-9 peaks are at values of 155.3 and 142.3 ppm (compound **2**) and 156.7 and 144.3 ppm (compound **3**), respectively. The difference in the carbon signals for C-8 and 9 emphasizes the asymmetric nature of the substitution.

Conclusion

In summary, this research paper provides a comprehensive investigation of the use of arylthiols in the heteroaromatic nucleophilic substitution reaction (S_NAr) for the synthesis of chloroquinoxaline derivatives. A comparative study was conducted to illustrate the differences in time and yield between the processes carried out using traditional and microwave-assisted approaches. The results revealed an overall improvement in the yield of compounds **1, 4** and **5** by approximately 15–20 %, accompanied by a reduction in reaction time of approximately 75 %. The results presented herein hold significant promise for advancing organic synthesis, and our esteemed research group intends to utilize these methods in various applications in the future.

CRediT authorship contribution statement

Hena Khatoon: Conceptualization, Formal analysis, Methodology, Writing – original draft. **Emilia AbdulMalek:** Supervision. **Siti Munirah Mohd Faudzi:** Writing – review & editing. **Tabrej Khan:** Project administration. **Omar Shabbir Ahmed:** Project administration.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Hena Khatoon reports financial support and equipment, drugs, or supplies were provided by University Putra Malaysia Faculty of Science. Hena Khatoon reports a relationship with Universiti putra Malaysia faculty of science department of chemistry that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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