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DEVELOPMENT OF SYNTHETIC METHODS FOR BENZOXAZOLE AND QUINOXALINE HETEROCYCLIC DERIVATIVES

SUMMARY OF DOCTORAL DISSERTATION ON MATERIALS SCIENCE

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INTRODUCTION

1. Rationale of the Dissertation

Benzoxazole- and quinoxaline-containing compounds have attracted great attention in medicinal chemistry due to their diverse biological activities and potential applications in the treatment of various diseases. Benzoxazole derivatives have been reported to exhibit antibacterial, antifungal, anti-inflammatory, and antioxidant activities, largely attributed to their free radical scavenging ability. Notably, some of these compounds also demonstrate inhibitory effects on the proliferation of cancer cells in the liver, lung, and colon. Similarly, quinoxaline is another important heterocyclic framework found in numerous pharmacological agents. Quinoxaline derivatives have shown strong anticancer activity and, in addition, possess antiviral, anti-inflammatory, and enzyme-modulating properties, thereby offering promising prospects for therapeutic applications in complex diseases. With their versatile chemical properties and wide spectrum of pharmacological activities, both benzoxazole and quinoxaline are considered strategic scaffolds in modern drug design.

In the context of sustainable development and the demand for minimizing adverse environmental impacts in chemical production, green synthesis has become an inevitable trend in contemporary chemistry. In this field, sulfur and sulfur-containing compounds play an important role, not only due to their chemical versatility but also because of their potential for use in environmentally friendly processes. Organic compounds containing sulfur are often biodegradable or recyclable, thereby reducing the persistence of chemical residues in the environment. Thanks to these advantages, sulfur has gained increasing

interest as a valuable element in green synthetic strategies, contributing to the advancement of more efficient, safer, and sustainable chemistry.

Based on these research foundations and the urgent need, this dissertation entitled: "***Development of Synthetic Methods for Benzoxazole and Quinoxaline Heterocyclic Derivatives***" was carried out with the objective of developing new, simple, efficient, and environmentally friendly methods for the synthesis of benzoxazole and quinoxaline heterocycles.

2. Research Objectives of the Dissertation

- To develop a new synthetic method for benzoxazole heterocycles using a sulfur-based catalytic system.
- To develop a new synthetic method for quinoxaline heterocycles using a sulfur-based catalytic system.

3. Research Contents of the Dissertation

- Synthesis of benzoxazole derivatives using a sulfur-based catalytic system and characterization of their structures.
- Synthesis of quinoxaline derivatives using a sulfur-based catalytic system and characterization of their structures.

CHAPTER 1. LITERATURE REVIEW

1.1. Introduction to Benzoxazole Compounds

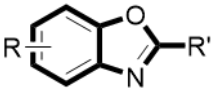


Figure 1.1. Chemical structure of benzoxazole

Benzoxazole is a fused aromatic heterocycle consisting of a benzene ring attached to an oxazole ring (a five-membered ring containing nitrogen and oxygen), forming a stable conjugated π-system with high aromaticity. This unique structure imparts benzoxazole with diverse chemical properties: it possesses both thermal and chemical stability while being reactive enough to undergo condensation, substitution, and metal complexation reactions due to the presence of heteroatoms. Benzoxazole is an important aromatic heterocycle in medicinal chemistry, receiving widespread attention thanks to its broad spectrum of biological activities and potential pharmaceutical applications. Many benzoxazole derivatives have been demonstrated to exhibit antibacterial, antifungal, antiviral, and anti-inflammatory effects, as well as strong antioxidant activity due to their free radical scavenging ability. Particularly, recent studies have shown that some benzoxazole-containing compounds possess significant anticancer activity by inhibiting the proliferation of cancer cells. With such properties, benzoxazole is considered a promising framework for the development of next-generation therapeutic agents targeting a variety of diseases, including cancers.

Beyond pharmaceuticals, benzoxazole derivatives also find applications in advanced materials. Owing to their outstanding optical and electronic properties, benzoxazole serves as a key scaffold in the design of luminescent polymers, fluorescent probes for bioimaging, OLEDs, and chemical–biological sensors. These properties not only expand its application potential

in optoelectronic technology but also support the development of modern biomedical diagnostic tools. Thus, with its unique combination of biological activity and material-related characteristics, benzoxazole is regarded as a highly valuable heterocyclic framework with versatile applications in both medicinal chemistry and materials science.

1.2. Selected Drugs Containing Benzoxazole Moieties

The benzoxazole framework is present in many biologically active and pharmacologically relevant compounds, as well as in substances possessing physical properties suitable for functional material applications. Benzoxazole derivatives are employed as antitumor agents, antihypertensive drugs, antiviral drugs, antifungal agents, anticancer drugs, and antihistamines.

Flunoxaprofen is a non-steroidal anti-inflammatory drug (NSAID) with a benzoxazole heterocyclic structure linked to a 4-fluorophenyl group and a propanoyl moiety. It belongs to the arylpropanoic acid derivatives and exhibits anti-inflammatory, analgesic, and antipyretic activities comparable to indomethacin (with greater efficacy than aspirin). Its mechanism of action differs from many classical NSAIDs: flunoxaprofen primarily inhibits leukotriene biosynthesis (inflammatory mediators) rather than prostaglandins..

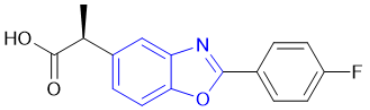


Figure 1.2. Chemical structure of Flunoxaprofen

In clinical practice, flunoxaprofen has been tested for the treatment of rheumatoid arthritis. Comparative studies with naproxen have shown that the two drugs possess equivalent therapeutic efficacy. In summary, flunoxaprofen is a benzoxazole-based NSAID with effective anti-

inflammatory and analgesic activities, while causing fewer gastric injuries compared to conventional NSAIDs.

Benoxaprofen is another NSAID belonging to the propanoic acid class, structurally similar to flunoxaprofen, but containing a 4-chlorophenyl group instead of a 4-fluorophenyl group. It has been used in the treatment of rheumatoid arthritis and osteoarthritis, typically administered at a daily dose of 300–600 mg once a day.

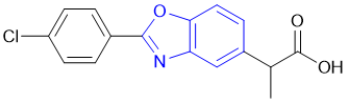


Figure 1.3. Chemical structure of Benoxaprofen

Boxazomycin B is a natural product belonging to the antibiotic group, isolated from Streptomyces species. It possesses a benzoxazole scaffold that plays an essential role in its broad biological activities. Boxazomycin B is particularly known for its strong inhibitory effect against Gram-positive bacteria, especially drug-resistant strains such as Staphylococcus aureus and Enterococcus faecalis. In addition, some preliminary studies have also indicated its potential antifungal activity, making this compound an important candidate for the development of new antibacterial and antifungal drugs.

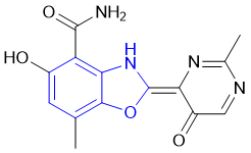


Figure 1.4. Chemical structure of Boxazomycin B

1.3. Introduction to Quinoxaline Compounds

Quinoxaline is an aromatic heterocyclic compound consisting of two fused rings: a benzene ring and a pyrazine ring (1,4-diazine). Its molecular formula is $C_8H_6N_2$. Quinoxaline derivatives have attracted much attention due to their broad range of potential applications in biology, medicine, and pharmacology. They act as antiprotozoal, antiviral, anti-inflammatory, and antibacterial agents, as well as kinase inhibitors. Beyond pharmaceuticals, quinoxaline compounds are also applied as DNA cleaving agents, dyes, organic semiconductors, cavitands, efficient electroluminescent emitters, dihydroannulenes, and building blocks for the synthesis of anion receptors. Quinoxaline derivatives display diverse pharmacological activities such as anticancer, antimalarial, antibacterial, analgesic, anticonvulsant, antidiabetic, antitubercular, and anthelmintic properties.

1.4. Selected Drugs Containing Quinoxaline Frameworks

Varenicline is a prescription medication used to aid smoking cessation in adults. It is marketed under the trade name Chantix (in the United States) or Champix (in some other countries). Mechanistically, varenicline acts as a partial agonist of the α4β2 nicotinic acetylcholine receptor, mildly stimulating these receptors to reduce cravings and withdrawal symptoms. At the same time, it prevents nicotine from binding to the receptor, thereby reducing the rewarding effects of smoking. Varenicline remains one of the most effective pharmacological options for smoking cessation.

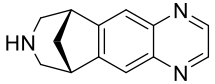


Figure 1.5. Chemical structure of Varenicline

Glecaprevir is an antiviral drug that inhibits RNA replication in the hepatitis C virus (HCV), thereby preventing HCV-related diseases. Viral mutations and amino acid sequence changes can impair the binding of

conventional NS3/4A protease inhibitors; however, glecaprevir effectively targets this binding site. In oral combination with pibrentasvir, it is marketed under the brand name Mavyret. In 2017, the FDA approved this fixed-dose combination for patients with comorbidities such as cirrhosis or kidney disease.

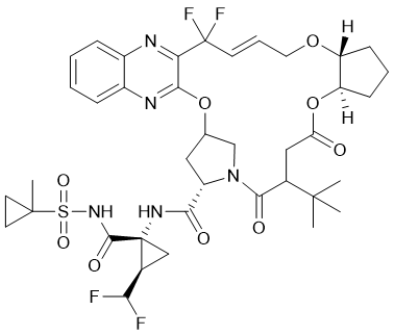


Figure 1.6. Chemical structure of Glecaprevir

Voxilaprevir is another NS3/4A protease inhibitor, acting directly on the single-stranded RNA of HCV to block its replication mechanism. Typically, voxilaprevir is used in combination regimens for immunocompromised patients with chronic HCV infection, especially in advanced liver disease.

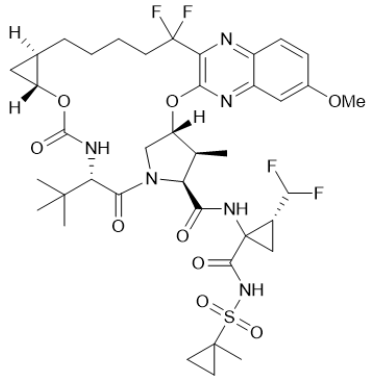


Figure 1.7. Chemical structure of Voxilaprevir

Olaquindox is a synthetic chemical compound belonging to the quinoxaline-1,4-dioxide class. It was first developed in the 1960s for veterinary use, particularly to prevent bacterial infections and promote growth in pigs and poultry. Olaquindox is effective in preventing and treating gastrointestinal infections caused by Gram-negative bacteria such as Escherichia coli and Salmonella. After oral administration, it is rapidly absorbed in the gastrointestinal tract, distributed mainly in the liver and kidneys, and metabolized via deoxygenation to less active metabolites before being excreted through urine and feces.

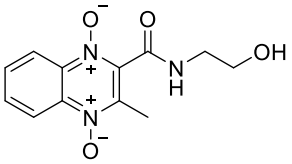


Figure 1.8. Chemical structure of Olaquindox

CHAPTER 2. RESEARCH METHODS

2.1. Thin-Layer Chromatography (TLC)

Thin-layer chromatography (TLC) was employed to qualitatively analyze the starting materials and products. Typically, the starting materials and products exhibit different R_f values, colors, and fluorescence. TLC was used to determine whether the reaction occurred, whether it had completed, based on the appearance of spots on the plate and their corresponding Rf values. The Rf values of compounds depend on their intrinsic properties as well as on the solvent system used as the mobile phase. Based on this property, appropriate solvents or solvent mixtures can be selected to achieve effective separation (well-differentiated R_f values) or to identify the solvent system required for product purification.

2.2. Column Chromatography

Column chromatography was applied to isolate products from the reaction mixtures. A column (20 × 50 mm) packed with silica gel (particle size 240–400 mesh) was used for separation. The solvent systems employed included n-hexane : ethyl acetate, heptane : ethyl acetate, and dichloromethane : methanol.

2.3. Structural Determination Methods

^{1}H-NMR spectra (500 MHz and 600 MHz) and ^{13}C-NMR spectra (125 MHz and 150 MHz) of the investigated compounds were recorded on a Bruker XL-500 spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard. Measurements were performed at the Nuclear Magnetic Resonance Center, Institute of Chemistry, Vietnam Academy of Science and Technology (VAST).

Mass spectra of the studied compounds were recorded on a SCIEX X500 QTOF mass spectrometer in both ESI+ and ESI– modes at the Laboratory of Heterocyclic Chemistry, Institute of Chemistry, VAST.

X-ray diffraction (XRD) analyses were performed on an MM007 HF diffractometer (Rigaku, Japan) at the Institute of Natural Product Chemistry – CNRS, France.

CHAPTER 3. RESULTS AND DISCUSSION

3.1. Synthesis of Benzoxazole Derivatives from 2-Nitrophenol and Isothiocyanate

We report a novel method - a direct redox-condensation reaction between 2-nitrophenol and isothiocyanate catalyzed by an in situ generated Fe/S system, enabling the synthesis of 2-aminobenzoxazoles in a single step. This strategy represents a completely new reaction mechanism that simultaneously exploits the reducing ability of the sulfur moiety in isothiocyanates and the oxidizing ability of the nitro group to construct the desired heterocycles under simple and environmentally benign conditions. This work marks an important advance toward the development of green and efficient synthetic methodologies for nitrogen-containing heterocycles.

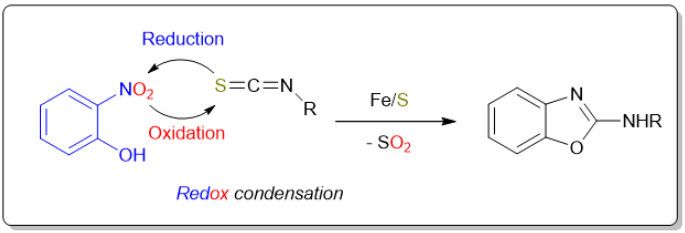
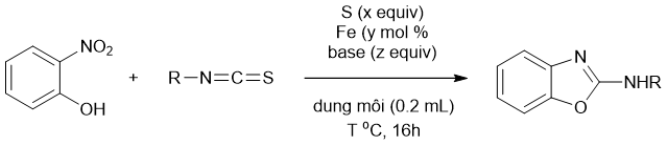


Figure 3.1. Synthesis of 2-aminobenzoxazole

In a typical experiment, 2-nitrophenol (1 mmol) was reacted with phenyl isothiocyanate (1.5 equiv) in *N*-methylpyrrolidin-2-one (NMPone) under an inert atmosphere, in the presence of elemental sulfur and

$FeCl_2 \cdot 4H_2O$ as the catalytic system, at 100 °C for 16 hours. The detailed results are summarized in Table 3.1.



Scheme 3.1. Synthesis of 2-aminobenzoxazole from isothiocyanates

Table 3.1. Influence of solvent, temperature, and catalyst on the yield of 2-aminobenzoxazole synthesis

Entry	Catalyst		Base (eq)	Solvent	T (°C)	Yield (%)
	S (eq)	Fe salt (% mol)				
1	-	-	NMP (0)	NMPone	100	0
2	1	-	NMP (0)	NMPone	100	0
3	-	$FeCl_2.4H_2O$ (5)	NMP (0)	NMPone	100	0
4	1	$FeCl_2.4H_2O$ (5)	NMP (0)	NMPone	100	0
5	-	$FeCl_2.4H_2O$ (5)	NMP (1)	NMPone	100	0
6	1	$FeCl_2.4H_2O$ (5)	NMP (2)	NMPone	100	62
7	1	$FeCl_2.4H_2O$ (5)	NMP (0.5)	NMPone	100	58
8	1	$FeCl_2.4H_2O$ (5)	NMP (1)	NMPone	100	32
9	**1.5**	**$FeCl_2.4H_2O$ (5)**	**NMP (1)**	**NMPone**	**100**	**72**
10	2	$FeCl_2.4H_2O$ (5)	NMP (1)	NMPone	100	68
11	0.5	$FeCl_2.4H_2O$ (5)	NMP (1)	NMPone	100	45
12	0.2	$FeCl_2.4H_2O$ (5)	NMP (1)	NMPone	100	42
13	1.5	$FeCl_2.4H_2O$ (1)	NMP (1)	NMPone	100	55
14	1.5	$FeCl_2.4H_2O$ (10)	NMP (1)	NMPone	100	68

15	1.5	$FeCl_2.4H_2O$ (5)	NMP (1)	NMPone	110	67
17	1.5	$FeCl_2.4H_2O$ (5)	NMP (1)	-	100	46
18	1.5	$FeCl_2.4H_2O$ (5)	NMP (1)	DMAc	100	65
19	1.5	$FeCl_2.4H_2O$ (5)	NMP (1)	DMF	100	67
20	1.5	$FeCl_2.4H_2O$ (5)	NMP (1)	Pyridine	100	62
21	1.5	$FeCl_2.4H_2O$ (5)	NMP (1)	DMSO	100	55
22	1.5	$FeCl_3.6H_2O$ (5)	NMP (1)	NMPone	100	70
23	1.5	$FeCl_2.4H_2O$ (5)	DIPEA (1)	NMPone	100	67
24	1.5	$FeCl_2.4H_2O$ (5)	DABCO (1)	NMPone	100	69
25	1.5	FeS	NMP (1)	NMPone	100	0

We conducted experiments in the absence of one of the three key components — sulfur, $FeCl_2 \cdot 4H_2O$, or NMPone. The results showed that both starting materials were fully recovered after heating at 100 °C for 16 h (experiments 1–5). This indicates that all three components are indispensable for initiating and sustaining the reaction; the absence of any one of them prevents the condensation from taking place. In contrast, when all three components were present and the Fe/S catalytic system was generated in situ, the desired 2-aminobenzoxazole product was obtained in 62 % yield (experiment 6). First, the influence of the base was examined. When the amount of NMP was decreased or increased (experiments 7 and 8 compared to experiment 6), the yields dropped significantly with too little base (32 % with 0.5 equiv) and did not improve further at higher loading (58 % with 2 equiv). Second, investigation of the sulfur amount (experiments 9–12) revealed that the optimal condition was 1.5 equiv (experiment 9, 72 % yield). Using lower amounts (0.2–0.5 equiv) significantly decreased the yield (42–45 %), while an excess amount (2.0 equiv) did not enhance the yield and

complicated purification due to sulfur-derived impurities. This demonstrates that the sulfur amount must be carefully controlled to ensure both high efficiency and ease of post-reaction workup.

For the iron catalyst, decreasing the $FeCl_2.4H_2O$ loading to 1 mol% (experiment 13) reduced the yield to 55 %, while increasing it to 10 mol% (experiment 14) only slightly improved the yield to 68 %. These results suggest that 5 mol% is the optimal loading, balancing catalytic efficiency and cost. Regarding temperature, increasing the reaction temperature to 110 °C (experiment 15) did not significantly improve the yield (67 %) compared to 100 °C (72 %, experiment 9). It was also noted that commercially available FeS showed no catalytic activity in this transformation (experiment 25).

In addition to catalyst components, solvent effects were examined. Replacing NMPone with DMAc, DMF, or pyridine (experiments 17–20) still allowed the reaction to proceed but gave lower yields (46–67 %) compared to NMPone (72 %). Interestingly, the use of DMSO — a mildly oxidizing solvent — afforded the product in 55 % yield. Furthermore, replacing $FeCl_2.4H_2O$ with $FeCl_3.6H_2O$ (experiment 22) resulted in a lower yield. Finally, several tertiary amine bases such as DIPEA and DABCO (experiments 23 and 24) were tested in place of NMP; however, they provided lower yields compared to NMP.

3.2. Synthesis of Benzoxazole Derivatives from 2-Nitrophenol, Amines, and Carbon Disulfide

In addition to the methods employing pre-formed or commercially available isothiocyanates, we also investigated an alternative approach. Instead of isolating or using pre-synthesized isothiocyanates, we generated the isothiocyanate in situ directly in the reaction mixture by reacting the corresponding amine with carbon disulfide (CS_2). This method not only

reduces the number of synthetic steps and minimizes intermediate purification, but also improves the product purity since the freshly generated isothiocyanate reacts immediately, thus avoiding decomposition or side reactions during storage.

To determine the optimal reaction conditions, we first stirred a solution of *p*-toluidine and CS_2 in *N*-methylpyrrolidin-2-one (NMP) at 40 °C for 30 minutes in the presence of solid K_2CO_3. Subsequently, o-nitrophenol and the catalytic additives were added, and the reaction mixture was heated at 100 °C for 16 hours. The detailed results are summarized in Table 3.2.

Table 3.2. Effect of solvent, temperature, and catalyst on the yield of 2-aminobenzoxazole synthesis from amine and CS_2

Entry	**Solvent**	**Catalyst**	**T (°C)**	**Yield (%)**
1	NMP	$FeCl_2.4H_2O$ (0.05 mmol)	110	54
2	NMP	$FeCl_2.4H_2O$ (0.05 mmol)	80	58
3	NMP	$FeCl_2.4H_2O$ (0.05 mmol) + S (1 eq)	100	69
4	NMP	$FeCl_2.4H_2O$ (0.05 mmol) + S (2 eq)	100	65
5	NMP	$FeCl_2.4H_2O$ (1 mol %)	100	46
6	NMP	-	100	0
7	NMP	$FeCl_2.4H_2O$ (10 mol %)	100	65
8	NMP	$FeCl_3.6H_2O$ (5 mol %)	100	67
9	NMP	$FeSO_4.7H_2O$ (5 mol %)	100	64
10	DMF	$FeCl_2.4H_2O$ (0.05 mmol)	100	67
11	DMAc	$FeCl_2.4H_2O$ (0.05 mmol)	100	65
12	DMSO	$FeCl_2.4H_2O$ (0.05 mmol)	100	58

13	PhCl	$FeCl_2.4H_2O$ (0.05 mmol)	100	0
14	xylene	$FeCl_2.4H_2O$ (0.05 mmol)	100	0
15	NMP	$FeCl_2.4H_2O$ (0.05 mmol)	100 under argon	70

We carried out the standard reaction at 100 °C using $FeCl_2.4H_2O$ (0.05 mmol, 10 mg) as the catalyst, affording the product in 71% yield. Increasing the reaction temperature to 110 °C decreased the yield to 54 % (experiment 1), likely due to the undesired conversion of the dithiocarbamate salt into *N*,*N*'-di(*p*-tolyl)thiourea. In contrast, lowering the temperature to 80 °C led to incomplete conversion, resulting in a reduced yield of 58 % (experiment 2).

We also examined the effect of combining elemental sulfur with iron to promote the redox-condensation of nitroarenes. However, this modification did not significantly affect the reaction outcome (experiments 3 and 4). On the other hand, the reaction did not proceed at all in the absence of iron catalyst (experiment 6). Varying the amount of $FeCl_2.4H_2O$ (either increasing or decreasing relative to the standard condition) also resulted in reduced yields (experiments 5 and 7). Using other iron salts such as $FeCl_3 \cdot 6H_2O$ or $FeSO_4.7H_2O$ gave lower yields compared to $FeCl_2.4H_2O$ (experiments 8 and 9).

To better understand the role of the solvent, we tested a range of polar solvents including DMF, DMSO, and *N*,*N*-dimethylacetamide (DMAc) (experiments 10–12). These solvents allowed the reaction to proceed but afforded lower yields than with NMP (*N*-methyl-2-pyrrolidone). When weakly polar solvents such as chlorobenzene or xylene were used, the reaction did not occur (experiments 13 and 14). NMP was therefore selected

as the optimal solvent due to its favorable characteristics, which significantly contributed to the overall efficiency of the reaction. With its high polarity and strong solubilizing ability for both organic substrates (e.g., amines, 2-nitrophenol) and inorganic reagents (e.g., K_2CO_3 and dithiocarbamate intermediates), NMP created a homogeneous reaction medium that facilitated effective interactions between the reactants. Furthermore, its high thermal stability (boiling point ca. 202 °C) ensured that it remained intact under the reaction conditions (100 °C for 16 h). Importantly, NMP supported the formation and stabilization of the dithiocarbamate salts—key intermediates in the nitro group reduction pathway. Although DMF, DMSO, and DMAc are also highly polar solvents, their use gave lower yields. This may be attributed to their lower chemical stability compared to NMP in the presence of CS_2 and strong bases such as K_2CO_3. For instance, DMSO, despite its high polarity, is more susceptible to reduction or oxidation under such conditions, potentially leading to side reactions or by-products that reduce the efficiency of the process.

In the presented synthesis of 2-aminobenzoxazoles, $FeCl_2.4H_2O$ plays a pivotal role throughout the redox and cyclization process. First, Fe^{2+} ions catalyze the reduction of the nitro group ($–NO_2$) of 2-nitrophenol to an amino group ($–NH_2$), which is crucial for the subsequent heterocyclization. Although the dithiocarbamate salts generated from amines and carbon disulfide can act as reducing agents, efficient reduction only occurred in cooperation with Fe^{2+}. Iron coordinates with the reactive species, particularly dithiocarbamates and 2-nitrophenol, stabilizing intermediates and directing the intramolecular reduction pathway of the nitro group through nitroso and hydroxylamine stages. After this reduction, Fe^{2+} further facilitates SO_2 elimination and ring closure to form the benzoxazole core. The essential role

of Fe^{2+} was further confirmed experimentally: decreasing the concentration of $FeCl_2$ led to significantly lower yields, while the absence of $FeCl_2$ completely inhibited the reaction. Additionally, the formation of FeS as a by-product indicated that iron not only served as a catalyst but also directly participated in the reaction mechanism. With its low cost, low toxicity, and environmentally benign nature, iron catalysis ensures both high synthetic efficiency and alignment with the principles of green chemistry

3.3. Synthesis of Quinoxaline Derivatives

We developed a redox-condensation reaction model of o-nitroaniline **69** with acetophenone **70** using $Na_2S.3H_2O$ as the catalyst. For reaction optimization, we selected the initial molar ratio of o-nitroaniline : acetophenone : $Na_2S.3H_2O$ as 1 : 1.2 : 1 and examined conditions around this ratio. The reaction was typically carried out for 4 hours..

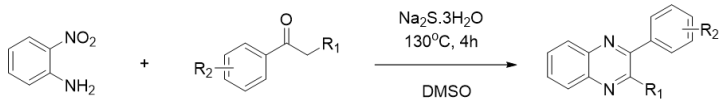


Table 3.3. Effect of Solvent, Temperature, and Catalyst on the Yield of Quinoxaline Synthesis

Entry	**Catalyst (eq)**	**Solvent**	**T (°C)**	**Yield (%)**
1	$Na_2S.3H_2O$ (1)	-	120	36
2	$Na_2S.3H_2O$ (0.5)	-	120	14
3	-	-	120	0
4	$Na_2S.3H_2O$ (1)	*p*-xylene	120	15
5	$Na_2S.3H_2O$ (1)	*n*-pentanol	120	10
6	$Na_2S.3H_2O$ (1)	$EtOCH_2CH_2OH$	120	7
7	$Na_2S.3H_2O$ (1)	pyridine	120	13

8	$Na_2S.3H_2O$ (1)	DMF	120	14
9	$Na_2S.3H_2O$ (1)	DMSO	120	40
10	$Na_2S.3H_2O$ (1)	DMSO	130	54
11	$Na_2S.3H_2O$ (1)	DMSO	100	40
12	$Na_2S.3H_2O$ (1)	DMSO	80	32
13	$FeCl_3.6H_2O$ (1)	DMSO	130	0
14	S (1)	DMSO	130	0

We began our study by examining the role of $Na_2S.3H_2O$ as the catalyst. Under solvent-free conditions, using 1.0 equivalent of $Na_2S.3H_2O$ at 120 °C for 4 hours, the reaction afforded the desired product in 36% yield (experiment 1). This result demonstrates that $Na_2S.3H_2O$ is capable of promoting the transformation under medium-temperature conditions without the need for a solvent, which is an important advantage in the context of green synthesis. When the catalyst loading was reduced to below 1 equivalent (experiment 2), the yield decreased significantly to only 14 %, indicating a strong dependence of the reaction efficiency on the amount of catalyst employed. Notably, in the absence of $Na_2S.3H_2O$ (experiment 3), the reaction did not proceed and no product was formed. This finding confirms the essential catalytic role of $Na_2S.3H_2O$ in the reaction mechanism and rules out the possibility of the transformation occurring spontaneously or being driven solely by heating.

Next, we extended our investigation to evaluate the effect of different solvents on the reaction yield, with the aim of identifying the optimal medium. Six solvents were selected as representatives of polar and non-polar classes: p-xylene, n-pentanol, ethylene glycol monoethyl ether ($EtOCH_2CH_2OH$), pyridine, *N*,*N*-dimethylformamide (DMF), and dimethyl

sulfoxide (DMSO) (experiments 4–9). All reactions were conducted under identical conditions (120 °C, 4 h, 1.0 equiv of $Na_2S.3H_2O$). The results revealed that DMSO provided the highest yield (experiment 9) among the tested solvents. This can be attributed to its high polarity and strong solubilizing ability for both inorganic and organic substrates, including $Na_2S.3H_2O$, which facilitates efficient reduction and condensation. Moreover, DMSO can stabilize charged or highly polar intermediates (such as o-nitrosoaniline or imine intermediates), thereby maintaining the selectivity and efficiency of the mechanism. In contrast, other solvents such as *p*-xylene or *n*-pentanol afforded only very low yields or failed to support the reaction, clearly indicating that solvent polarity and solvation capacity play decisive roles in the reaction efficiency.

After identifying the appropriate catalyst and solvent, we further examined the effect of reaction temperature in DMSO. Increasing the temperature to 130 °C (experiment 10) improved the yield to 54 %, suggesting that higher thermal energy facilitates the transformation. Conversely, lowering the temperature to 100 °C and 80 °C (experiments 11 and 12) decreased the yields to 40 % and 32 %, respectively. This can be rationalized as follows: the reaction involves imine formation and subsequent cyclization, generating water as a by-product. Excess water promotes hydrolysis of intermediate imine B, leading to loss of selectivity and lower yields. At higher temperature (130 °C), water is efficiently removed from the system, thus reducing the likelihood of hydrolysis and favoring product formation.

CONCLUSION

1. The dissertation has successfully developed a novel reaction for the synthesis of 2-aminobenzoxazole derivatives under the following conditions: *o*-nitrophenol (1.5 equiv), PhNCS (1.5 equiv), $FeCl_2.4H_2O$ (5 mol%), *N*-methylpiperidine (1 equiv), *N*-methylpyrrolidone (0.2 mL), at 100 °C for 16 hours. Using this new method, 39 2-aminobenzoxazole derivatives bearing various substituents were synthesized. Their structures were elucidated by spectroscopic techniques including ^{1}H NMR, ^{13}C NMR và HRMS. Among them, eight compounds were identified as new: 08 hợp chất mới **(145az, 145ca, 145ea, 145fa, 145ga, 145ha, 145ia, 145la).**

2. The dissertation has successfully developed a new "*one-pot*" method for the synthesis of 2-aminobenzoxazole derivatives under the following conditions: amine (1 equiv), o-nitrophenol (1 equiv), CS_2 (1.5 equiv), K_2CO_3 (1 equiv), $FeCl_2.4H_2O$ (5 mol%), *N*-methylpyrrolidone (0.2 mL), at 100 °C for 16 hours. By applying this new strategy, 31 2-aminobenzoxazole derivatives were synthesized. Their structures were elucidated by ^{1}H NMR, ^{13}C NMR và HRMS. Among them, twenty compounds were completely new: **(148ac, 148ad, 148ae, 148ag, 148ah, 148ak, 148an, 148aq, 148ar, 148as, 148at, 148av, 148aw, 148ax, 148ay, 148ba, 148ca, 148da, 148ea, 148fa**).

3. The dissertation has successfully developed a novel reaction for the synthesis of quinoxaline derivatives under the following conditions: *o*-nitroaniline (1 equiv), acetophenone (1.2 equiv), $Na_2S.3H_2O$ (1 equiv), DMSO (0.4 mL), at 130 °C for 4 hours. Using this method, 34 quinoxaline derivatives were synthesized. Their structures were elucidated by ^{1}H NMR, ^{13}C NMR và HRMS. Among them, two compounds were identified as entirely new quinoxaline derivatives: 6-Methyl-2-phenyl-3-(*p*-tolyl)quinoxaline **(151as)**, 2-(3-Bromophenyl)-3-methylquinoxaline **(151ea)**.

NEW CONTRIBUTIONS OF THE DISSERTATION

- Established two successful synthetic protocols for heterocyclic compounds with benzoxazole scaffolds and one synthetic protocol for heterocyclic compounds with quinoxaline scaffolds.
- Proposed a direct redox-condensation mechanism from *o*-nitrophenol to synthesize benzoxazole-based heterocycles without going through the *o*-aminophenol intermediate. This transformation proceeds in a single step (*one-pot*) via the participation of Fe/S, eliminating separate reduction steps and improving atom economy, step economy, and electron efficiency.
- Proposed a novel mechanism for the synthesis of quinoxaline heterocycles, involving the selective partial reduction of o-nitroaniline to *o*-nitrosoaniline, followed by regioselective cyclization. This process affords only one regio-defined product even when using asymmetrically substituted starting materials.
- Successfully synthesized 70 benzoxazole derivatives, among which 28 compounds have not been previously reported in the literature.
- Successfully synthesized 34 quinoxaline derivatives, among which 2 compounds have not been previously reported in the literature.

LIST OF PUBLICATIONS RELATED TO THE DISSERTATION

1. Le Anh Nguyen, Supasorn Phaenok, **Duc Long Le**, Thi Thu Tram Nguyen, Quoc Anh Ngo, Thanh Binh Nguyen, 2023, Fe/S-Catalyzed Redox Condensation of *o*-Nitrophenols with Isothiocyanates to 2-Aminobenzoxazoles. *Organic Letters*, *25*, 5145-5150.

2. **Duc Long Le**, Thi Yen Tran, Le Anh Nguyen, Quoc Anh Ngo, Dinh Hung Mac, Thanh Binh Nguyen, 2024, Iron-Promoted Redox Access to 2-Aminobenzoxazoles from Amines, Carbon Disulfide and 2-Nitrophenols. *Asian Journal of Organic Chemistry*, *13*, e202400212.

3. **Duc Long Le**, Ngoc Binh Vo, Thi Thu Tram Nguyen, Quoc Anh Ngo, Patailleau Retailleau, Thanh Binh Nguyen, 2024, Sodium sulfide-promoted regiodefined redox condensation of *o*-nitroanilines with aryl ketones to benzo [*a*] phenazines and quinoxalines. *Organic & Biomolecular Chemistry*, *22*, 1167-1171.