Synthesis of quinoline derivatives by a Döebner-von Miller reaction using a Ag(I)-exchanged Montmorillonite K10 catalyst

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(In Chemistry)

By

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Thesis Declaration

The experimental work described in this dissertation was carried out in the School of Chemistry and Physics, University of KwaZulu-Natal, Pietermaritzburg, under the supervision of Dr Vineet Jeena and co-supervised by Prof. Ross S. Robinson.

The studies represent original work by the author and have not otherwise been submitted in candidature for any other degree.

Signed……..J. Jayram (Candidate)

I hereby declare that the above information is true and correct.

Signed……..Dr V. Jeena (Supervisor)

Signed……Prof R. S. Robinson (Co-supervisor)

School of Chemistry and Physics
University of KwaZulu-Natal
Pietermaritzburg
South Africa
2016

Publication Declaration

My research publication titled “Synthesis of quinoline derivatives by a Döebner-von Miller reaction using a Ag(I)-exchanged Montmorillonite K10 approach – you can teach an old dog new tricks” has been included in the Appendix.

The experimental work discussed in the publication as well as the writing of the publication was performed by myself and was carried out within the School of Chemistry and Physics, University of KwaZulu-Natal, Pietermaritzburg, under the supervision of Dr V. Jeena. I was the primary author for the publication and minor grammatical changes were performed by me under the supervision of my research supervisor.

These studies represent original work by the author and have not otherwise been submitted in candidature for any other degree.

Signed……..J Jayram (Candidate)

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South Africa
2016

Acknowledgments

It is to GOD that I extend my heartfelt thanks for giving me the strength to attempt and complete my Master's degree.

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Abbreviations

^{13}C	Carbon 13
$AlCl_3$	Aluminium chloride
BNCT	Boron Neutron Cancer Therapy
$CDCl_3$	Deuterated chloroform
CH	Conventional Heating
CH_2Cl_2	Dichloromethane
COX-2	Cyclooxygenase-2 Inhibitor
CRT	Cathode Ray Tube
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
EDX	Energy Dispersion X-Ray
EtOAc	Ethyl acetate
FTIR	Fourier Transform Infra-Red
GC	Gas Chromatography
H_2SO_4	Sulfuric acid
HBr	Hydrobromic acid
HCl	Hydrochloric acid
HIV	Human Immunodeficiency Virus
IC_{50}	Half maximal Inhibitory Concentration
IUPAC	International Union of Pure and Applied Chemistry
INH	Isoniazid
IR	Infra-Red
keV	Kilo electron voltage
M	Molar
MDA	Midbrain Dopamine
MDR-TB	Multidrug-resistant Tuberculosis
MeOH	Methanol
MES	Maximal Electroshock
MeV	Mega electron voltage
MIC	Minimum Inhibitory Concentration

MS	Mass Spectroscopy
MTB	*Mycobacterium tuberculosis*
MW	Microwave
nd	Not determined
NMR	Nuclear Magnetic Resonance
Nurr1	Nuclear Receptor Related 1 protein
PDE_4	Phosphodiesterase type 4 Inhibitor
$POCl_3$	Phosphoryl chloride
RMP	Rifampicin
scPTZ	Subcutaneous Pentylenetetrazole
SDD	Silicon Drift Detector
SEM	Scanning Electron Microscopy
TB	Tuberculosis
TBAC	Tetrabutylammonium chloride
THAB	Tetrahexylammonium bromide
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
WHO	World Health Organization
XRD	X-ray Diffraction
ZnO	Zinc Oxide

Abstract

Quinolines play an important role in organic chemistry, as exemplified by their extensive application as biologically and pharmacologically active compounds. However, current methods available to access quinoline compounds employ harsh reaction conditions and expensive starting materials with varying product yields. The Döebner-von Miller reaction is a valuable asset in the synthesis of various natural and biologically active quinoline derivatives; however, there are various challenges associated with this methodology such as harsh reaction conditions, hazardous reagents (10 M hydrochloric acid), tedious isolation procedures, side products and low yields. Consequently, the need to develop a simple and environmentally friendly route to synthesize quinoline derivatives *via* the Döebner-von Miller reaction is essential.

Silver(I)-exchanged Montmorillonite K10 was evaluated as a potential solid acid catalyst towards the synthesis of quinoline derivatives *via* the Döebner-von Miller reaction. Using this approach, the Döebner-von Miller reaction was evaluated under various reaction conditions with solvent-free, conventional heating conditions affording the best results. Using the optimized reaction conditions, a series of substituted quinoline derivatives were synthesized in moderate to excellent yields (42-89%) in 3 hours. The scope of our methodology towards both aromatic and aliphatic α, β-unsaturated aldehydes was also evaluated and the system was found to be equally efficient on both the substrates mentioned above. A recycle and reuse study was conducted in order to gain an accurate assessment of the activity of our catalyst and it was shown that it can be utilized several times without any appreciable loss in activity, thus making this procedure more environmentally benign. A literature comparison study was conducted and the yields obtained using the silver(I)-exchanged Montmorillnoite K10 approach were found to be superior to most previously reported approaches *via* the Döebner-von Miller reaction.

In addition, silver(I)-exchanged Montmorillonite K10, was analyzed by Scanning Electron Microscopy (SEM) and Energy Dispersion X-Ray (EDX) analysis. The results of this study indicated a uniform distribution of silver(I) ions on the surface of Montmorillonite K10 with a total silver(I) content of 3.67 weight %.

Contents

Chapter 2: Results and Discussion

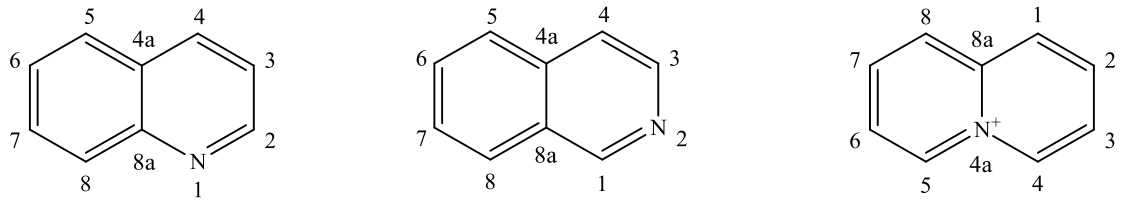
Chapter 4: Experimental

Chapter 1

Introduction

1.1 STRUCTURE AND ISOLATION OF QUINOLINE

Quinolines are interesting compounds for research in the field of chemistry, with numerous derivatives widely distributed in nature.[1] Quinoline (1-*aza*-napthalene or benzo[*b*]pyridine)[2] is a nitrogen-containing heterocyclic aromatic compound with molecular formula C_9H_7N and is characterized by a double-ring structure that comprises a benzene ring fused to pyridine ring at two adjacent carbon atoms.[3] The quinoline ring system **1** is one of the three possible aza-naphthalenes, the former two being isoquinoline **2** and the quinolizium cation **3** (**Figure 1**).[4]

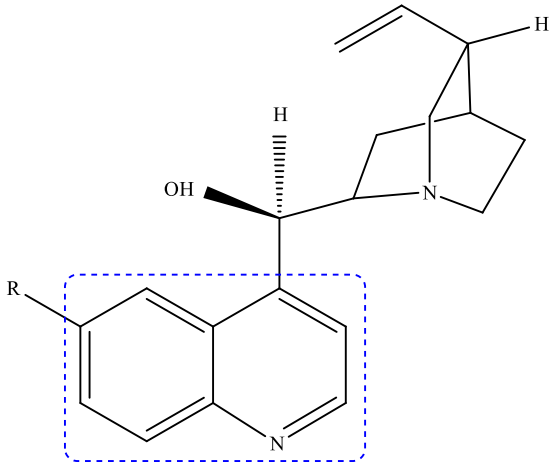


1 **2** **3**

Figure 1

The quinoline ring system is a well-established feature in a variety of naturally occurring compounds, and their isolation and study have led to great advances in the field of heterocyclic chemistry.[5] It was first extracted from coal tar bases in 1834 by Friedlieb Ferdinand Range[6] and in 1842 by Charles Frèderic Grehardt from the alkaloids cinchonine **4** and quinine **5**, from which the name quinoline is derived (**Figure 2**).[7] The word quinine, in turn, derives from

quina a Spanish version of a local South American name for the bark of quinine-containing *Cinchona* species.[8]



4: R = H; cinchona

5: R = OMe; quinine

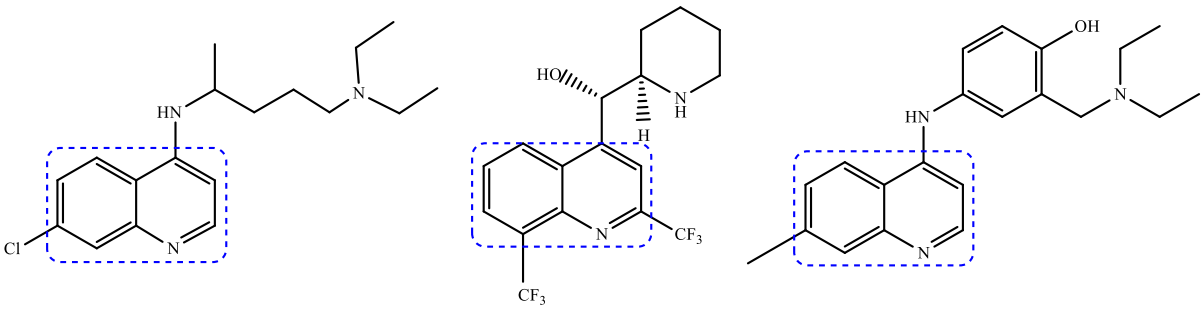
Figure 2

1.2 CHEMICAL AND PHARMACOLOGICAL APPLICATIONS OF QUINOLINE DERIVATIVES

Quinoline and its analogs represent privileged moieties in the field of synthetic and medicinal chemistry because of its diverse chemical and pharmacological properties. The broad spectrum of biological and biochemical activities has been further facilitated by the synthetic versatility of quinoline, which allows the generation of a large number of structurally diverse derivatives.[3] Compounds containing the quinoline ring system were found to be the oldest chemicals for the treatment of various diseases[9] [10] and some medicinal applications of these compounds will be discussed.

1.2.1 Antimalarial activity

Malaria is one of the most widespread diseases in the world, mainly in Sub-Saharan Africa, some parts of Asia and South America.[11] In 2010, it was estimated by the World Health Organization (WHO) that about 40% of the world's population presently lives under malarial threat and an estimated 300 million clinical infections occur each year, leading to approximately 1-3 million deaths annually.[12] The most important use of the quinoline ring is its antimalarial potential, example., Quinine **5** was the first effective drug for malaria caused by *Plasmodium falciparum*, appearing in therapeutics in the 17th century.[13]

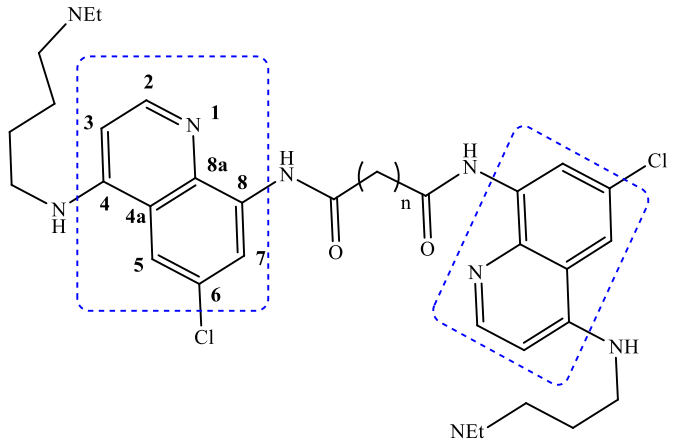


6 **7** **8**

Figure 3

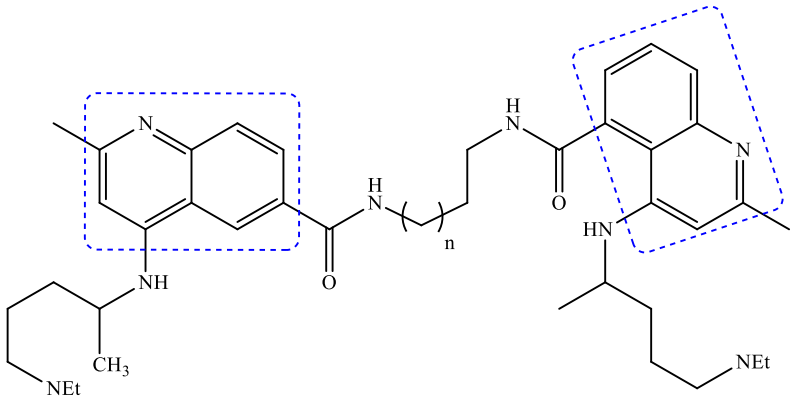
Chloroquine **6** became the most widely used antimalarial drug by the 1940s, however, chloroquine-resistant strains were discovered in 1957.[14] In the late 1970s, subsequent screening for effective analogues of chloroquine identified mefloquine **7** but yet again, mefloquine-resistant strains were quickly identified.[15] During the same era, amidoquine **8** was identified as a widely used antimalarial drug. Raynes and co-workers developed bisquinoline derivatives [**9**, **10**] (**Figure 4**) with promising antimalarial activity against both chloroquine-resistant (the ability of bacteria to withstand a drug that once killed tham) and chloroquine-sensitive (unusual reaction to a drug) parasites.[16] Both chloroquine and mefloquine still are in use today, although sparingly due to resistance.[17] More recently, various aminoquinoline antimalarials[18], [19], [20], [21] were developed and are active against malarial parasites thereby

providing a clinical cure (ability of an individual to show no signs or symptoms of a disease which they previously had).[22]



n = 2, 4, 6

9



n = 2, 4, 6, 8

10

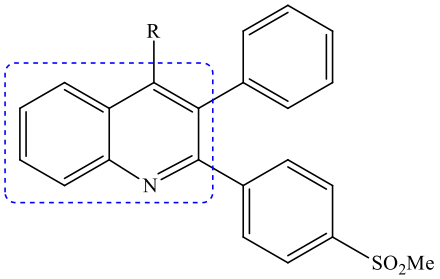
Figure 4

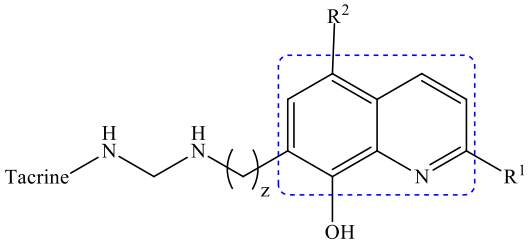
1.2.2 Central Nervous system effects

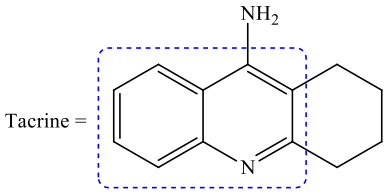
Cognitive dysfunction is a major health problem in the 21st century and is found in various neuropsychiatric and neurodegenerative disorders, such as depression, schizophrenia, Alzheimer's disease, Parkinson's disease and Epilepsy.[23] In view of this, various derivatives containing the quinoline ring system have been synthesized as target structures against neurological disorders.[23]

1.2.2.1 Parkinson's and Alzheimer's disease

Ghodsi and co-workers[24] synthesized and evaluated a number of 4-substituted 2,3-diarylquinoline derivatives **11** bearing a methylsulfonyl group at the *para*-position of the 2-phenyl ring as selective cyclooxygenase-2 inhibitors (COX-2) which are important for the treatment of Parkinson's disease[25] and Alzheimer's disease.[26] Carboxylic acids promote hydrogen bonding interaction therefore 2-(4-(methylsulfonyl)phenyl)-3-phenylquinoline-4-carboxylic acid showed high potency and selectivity as selective COX-2 inhibitors whereas hydrophobic and bulky groups showed reduced potency and selectivity owing to the lack of hydrogen bonding.[24] Bachiller and co-workers developed some novel tacrine-8-hydroxyquinoline hybrids **12** with activity against Alzheimer's disease (**Figure 5**).[27] All tested derivatives showed half maximal inhibitory concentration (IC_{50}) values in the nano- and subnanomolar range (0.5-5.5 nM). Strain II showed a 700-fold greater potency than tacrine (**Figure 5**).







R = COOH > H > NH_2 > Me > Ph

(activity)

11

z = alkyl chain;

Str-I: $R^1 = R^2 = H$ (IC_{50} = 5.5 ± 0.2 nM)

Str-II: $R^1 = CH_3$; $R^2 = H$ (IC_{50} = 0.5 ± 0.02 nM)

Str-III: $R^1 = H$; $R^2 = Cl$ (IC_{50} = 1.0 ± 0.05 nM)

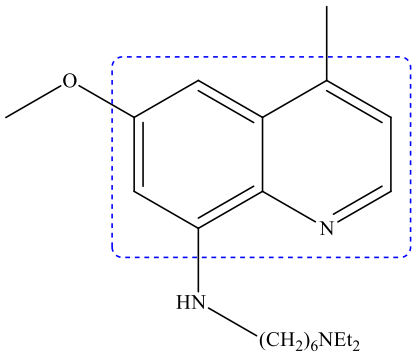
12

Figure 5

The nuclear receptor related 1 (Nurr1) protein is important for cognitive functions and long-term memory in the forebrain areas and is well established in the development and survival of midbrain dopamine (mDA) neurons.[28] Mutations in this gene have been associated with neurological disorders including Parkinson's disease. Recently, Chun-Hyung and co-workers developed a nuclear receptor Nurr1 agonist as a molecular target for neuroprotective therapeutic development for Parkinson's disease. Their results showed that antimalarial drugs chloroquine **6** and amidoquine **8** (**Figure 3**) stimulated the transcriptional function of Nurr1, consequently, significantly improving behavioural deficits in 6-hydroxydopamine lesioned rat model of Parkinson's disease. These findings offered proof that small molecules targeting the Nurr1 ligand binding domain can be used as a mechanism-based and neuroprotective strategy for Parkinson's disease.[29]

1.2.2.2 Chagas' disease

Chagas' disease is a potentially life-threatening illness caused by the protozoan parasite *Trypanosoma cruzy*, affecting the central nervous system resulting in brain lesions and encephalitis[30] and is spread mostly by insects known as Triatominae or kissing bugs. Treatment of Chagas disease focuses on killing the parasite in acute infection and managing signs and symptoms in later stages. The 8-(diethylaminohexylamino)-6-methoxy-4-methyl quinoline **13** developed by Chiari and co-workers showed highly effective activity against the protozoan parasite providing an effective means of controlling the kissing bug population, consequently decreasing the number of Chagas' disease infections (**Figure 6**).[31]



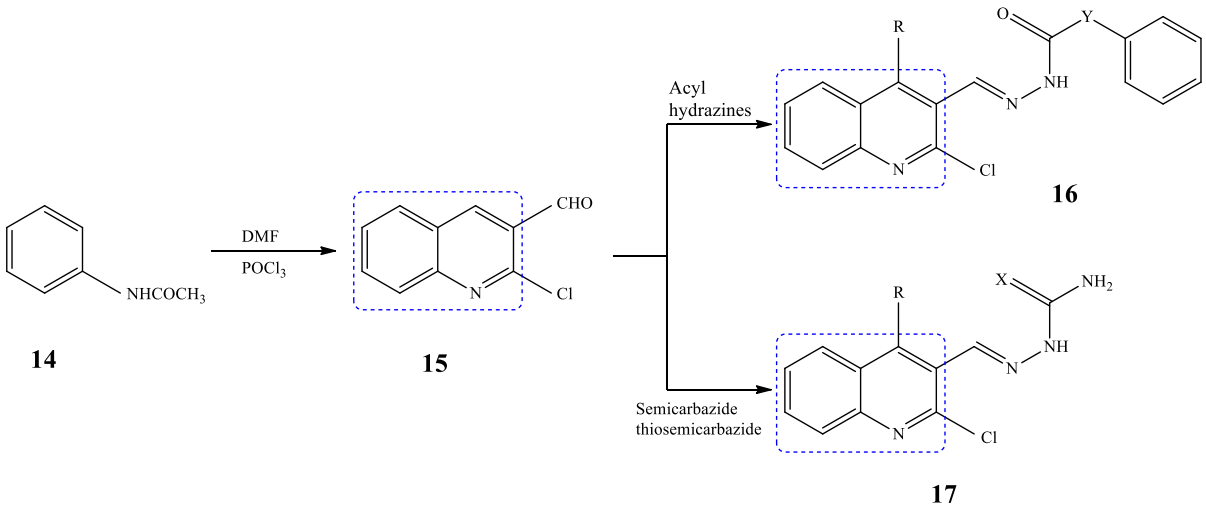
13

Figure 6

1.2.2.3 Epilepsy

Epilepsy is a chronic neurological disorder, the hallmark of which is recurrent, unprovoked seizures.[32] There is an enduring demand for the development of new anticonvulsant agents as it has not been possible to control every kind of seizure with the currently available treatments.[33] In recent years, innumerable modifications of the quinoline ring system have been reported with promising anticonvulsant outcomes.

Kumar and co-workers reported the synthesis and *in vivo* anticonvulsant activity of new 2-chloroquinolinyl-hydrazone. The evaluation of anticonvulsant activity was performed in mice by two models of seizures viz. maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ). Pentylenetetrazole is an agent that displays activity as a central nervous system stimulant (**Scheme 1**).[34]



R = -Cl, -Br, -F

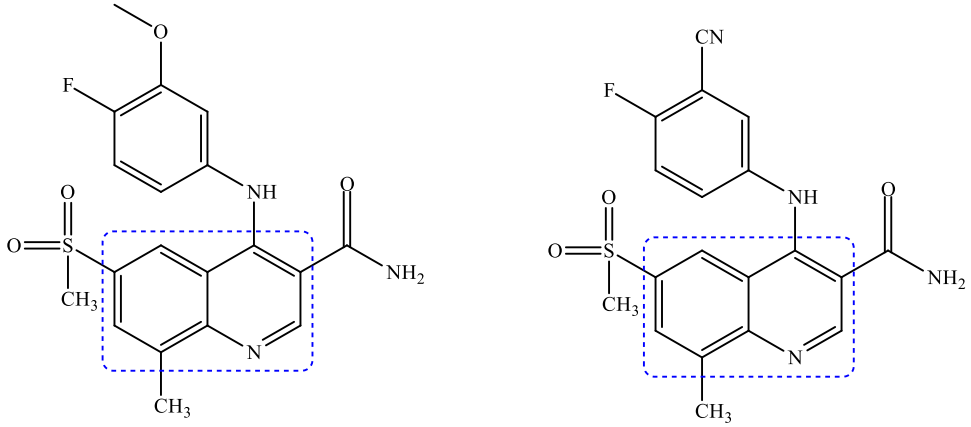
X/Y = CH_2, CH_2O, O, S

Scheme 1

The results of their study showed that electron withdrawing groups (Cl, Br, F) in the benzoyl ring **16** showed good anticonvulsant activity and were long acting. The anticonvulsant activity decreases when CH_2 or CH_2O groups are introduced between the carbonyl group and phenyl ring **16**. Replacement of the phenyl ring in compound **17** with an amino group results in retention of the anticonvulsant activity.

1.2.3 Cardiovascular activity

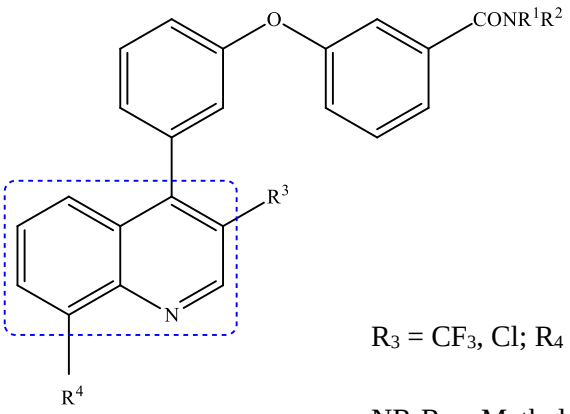
Various chemical modifications of the quinoline ring system have been attempted with positive results and new lead compounds as potential cardiovascular agents. Lunniss and co-workers developed a selective phosphodiesterase type 4 (PDE_4) inhibitor (**18, 19**) with utility in chronic obstructive pulmonary disorder (**Figure 7**).[35]



18 **19**

Figure 7

Bernotas and co-workers developed biarylether amide quinolines **20** which act as liver X receptor agonists, useful in conditions of dyslipidaemia.[36] This condition is marked by the abnormal concentrations of lipoproteins or lipids in the blood plasma. These agents also reverse the conditions of arteriosclerosis (**Figure 8**).[36]



R_3 = CF_3, Cl; R_4 = CH_2Ph

NR_1R_2 = Methyl ester, Pyrrolidine, Piperidine, Morpholine

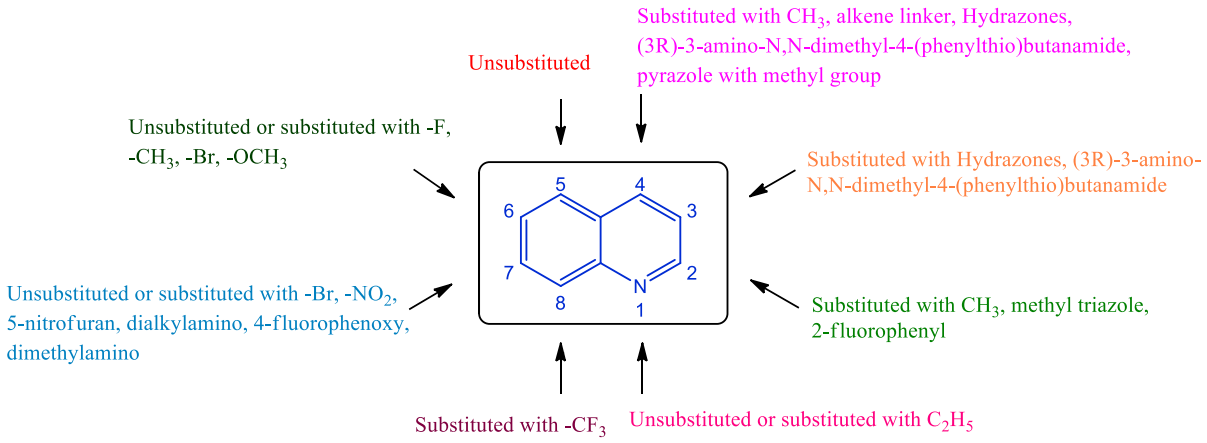
20

Figure 8

1.2.4 Antimycobacterial activity

Tuberculosis (TB) remains as a global endemic that is heightened by a lack of proper therapeutic agents, the spread of Human Immunodeficiency Virus (HIV) and the emergence of multidrug-resistant TB (MDR-TB). Thus, new anti-TB drugs, acting *via* a novel mode of action, are urgently required to shorten the duration of treatment and effectively kill drug resistant *Mycobacterium tuberculosis* (MTB) strains. With this objective in mind numerous quinoline containing derivatives have been synthesized and tested for anti-TB activity.[37]

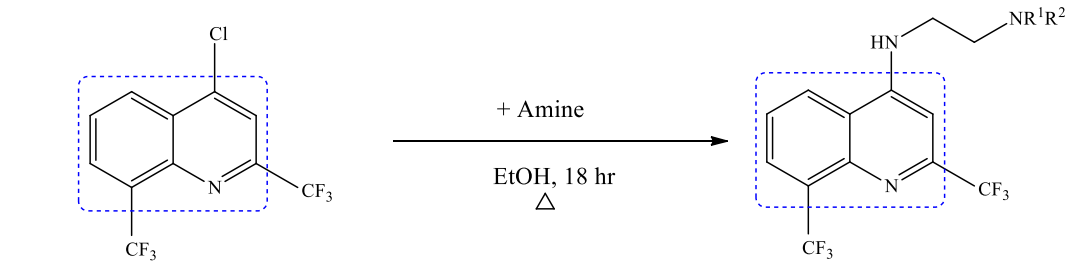
Rangappa and co-worker compiled structural requirements **21** for anti-TB activity from previously published data using a quinoline backbone (**Figure 9**).[38]



21

Figure 9

Mital and co-workers synthesized a number of 4-amino substituted 2, 8-*bis* (trifluoromethyl)quinoline derivatives and evaluated their *in vitro* antimycobacterial activity against MTB strain H37Rv.[39] Preliminary results indicated that most of the compounds demonstrated better in vitro antimycobacterial activity, and are comparable to the first line antituberculosis drugs, streptomycin, isoniazid (INH), ethambutol, pyrazinamide and rifampicin (RMP).[40] The most effective compound **23a** of the series has a Minimum Inhibitory Concentration (MIC) of 3.13 µg/ml and IC_{50} value of 3.9 µg/ml. Biological studies also showed that the presence of a diaminoalkyl chain and trifluoromethyl groups **23 e - j** in the 2- and 8-positions of the quinoline ring displays useful biological activity (**Scheme 2**).



22

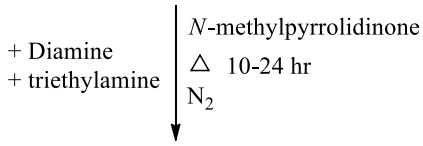
52-65%

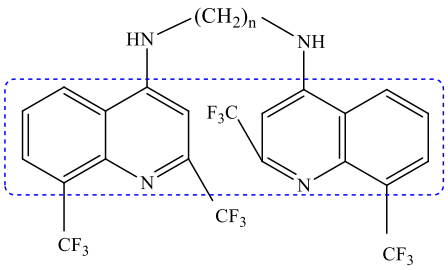
23a R1 = R2 = -(CH2)5-;

23b R1 = R2 = -(CH2)4-;

23c R1 = R2 = -(CH2)2-O-(CH2)2;

23d R1 = H, R2 = -C(CH3)3





38-45%

23 e - j n = 2, 3, 4, 5, 7, 9

Scheme 2

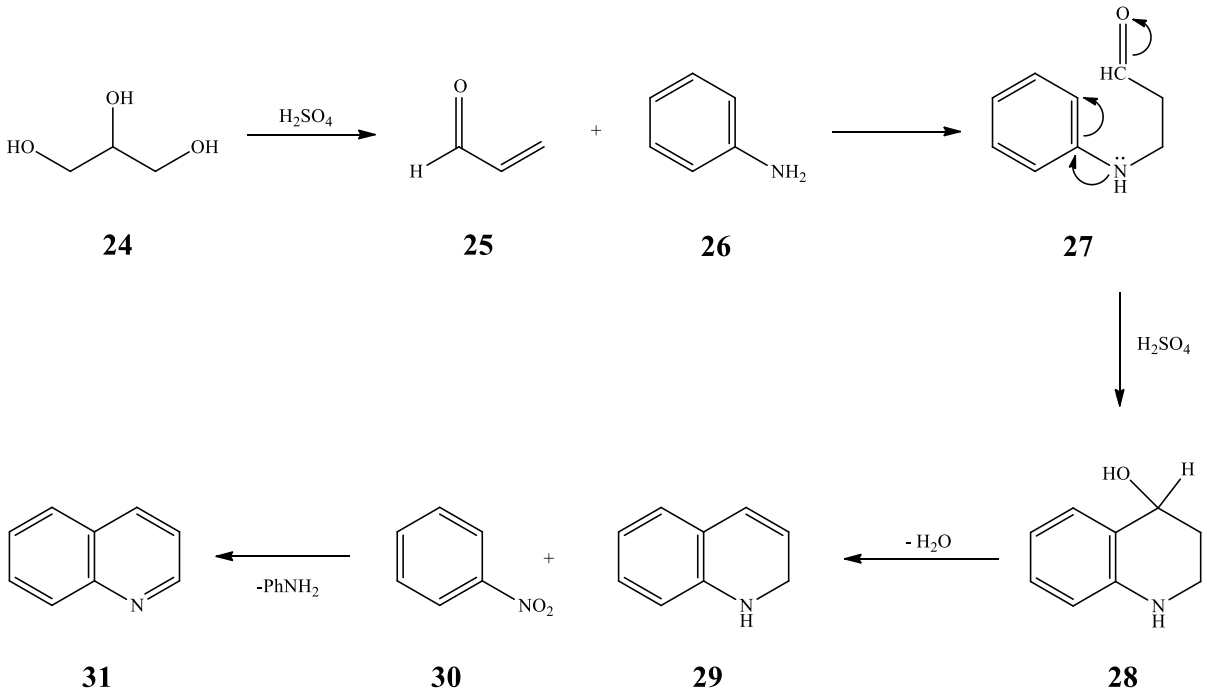
1.3 SYNTHETIC APPROACHES TO ACCESS QUINOLINE DERIVATIVES

The great attention paid by researchers to the study of quinoline derivatives is explained by the broad range of biology activity highlighted above. Owing to such significance, there has been increasing interest in the development of efficient methodologies for the synthesis of quinoline derivatives. A number of established protocols exist for the synthesis of quinoline compounds which are broken down into classes based on the substitution pattern of the starting materials.[41]

1.3.1 The Skraup synthesis

In 1879 Koenigs reported the first synthesis of quinoline in which the vapours of ethylaniline were passed over heated litharge. The yields of quinoline were very low and it was not until the reports of Skraup that quinoline synthesis became practical.[42]

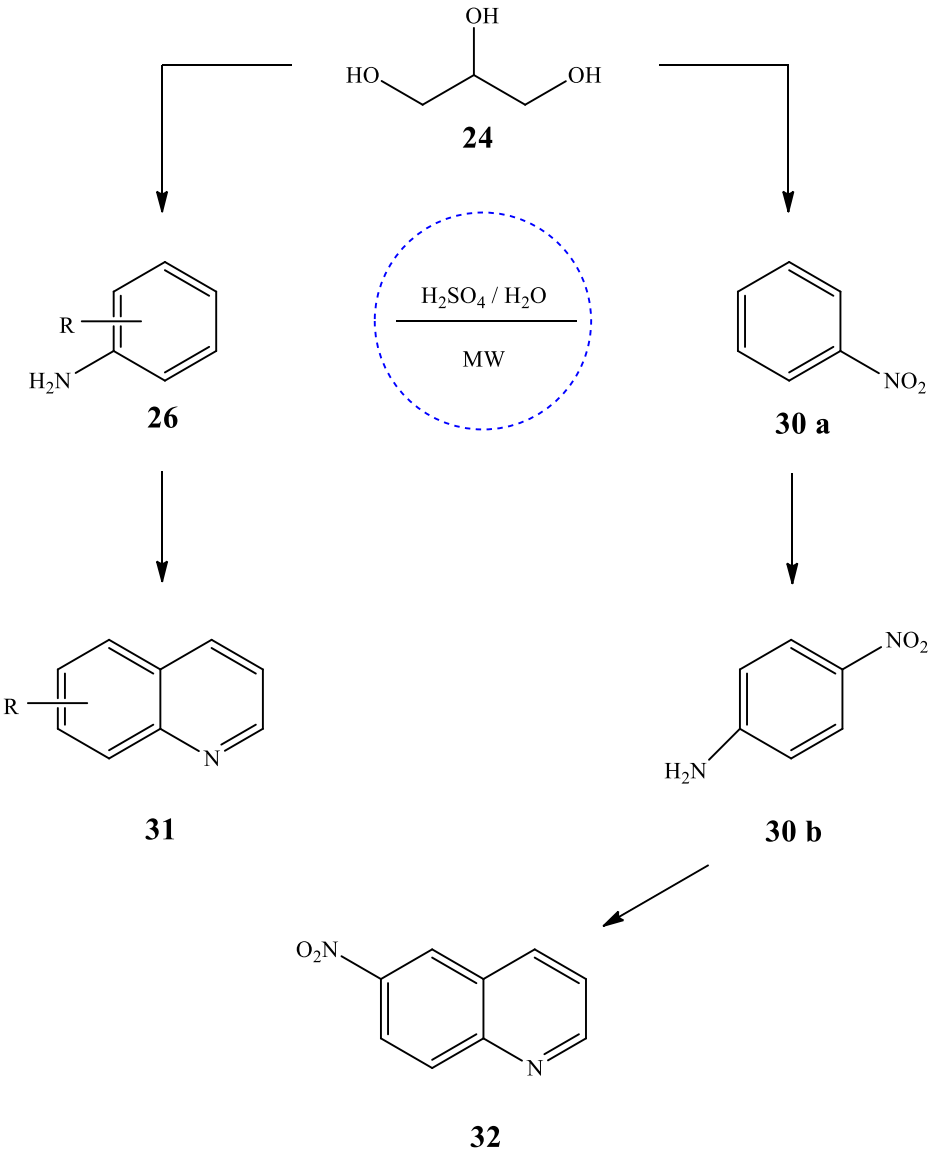
Over a century ago (1880), Zdenko Hans Skraup[43] reported the first formal synthesis of quinoline derivatives. The classical Skraup method involves heating aniline derivatives with glycerol, sulfuric acid and an oxidizing agent. The generally accepted Skraup mechanism involves the initial dehydration of glycerol **24** to give acrolein **25**, which undergoes a conjugate 1, 4-addition by aniline **26** resulting in the formation of a β-anilinopropionaldehyde intermediate **27**. Ring closure then results from the electrophilic attack by the carbonyl carbon at the ring position ortho to the amino group; subsequent dehydration gives the dihydroquinoline **29** which is finally oxidized by nitrobenzene **30** to afford the fully cyclized quinoline **31** (**Scheme 3**).



Scheme 3

Substituted anilines can be used to give quinoline derivatives with substituents in the hetero-ring.[44] In principle, 5- and 7-substituted quinolines are formed from *meta*-substituted anilines whereas symmetrical *para*-substituted arylamines undergo ring closure at either of the *ortho* positions to produce 6-substituted quinolines. In practice, electron-donating substituents direct ring closure *para*, consequently producing 7-substituted quinoline derivatives.[45]

The Skraup approach to quinoline synthesis has been gaining attention well into the 21st century and in 2014 Saggadi and co-workers synthesized 5-, 6-, 7- and 8-substituted quinolines using microwave conditions, aniline derivatives and glycerol in the presence of sulfuric acid and water with the desired quinolines obtained in 10-66% yields.[46] They also synthesized 6-hydroxyquinoline **32** (77%) under similar reactions conditions using nitrobenzene as the sole source of aromatic compound (**Scheme 4**).[47]

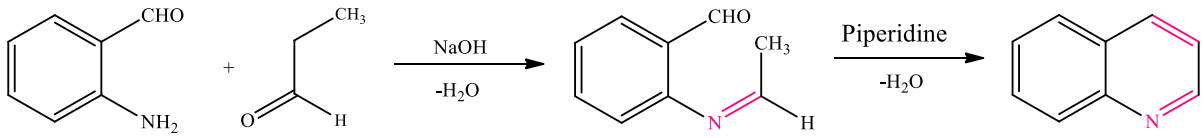


Scheme 4

1.3.2 The Friedländer Synthesis

Paul Friedländer reported the synthesis of quinoline in 1882[48] whereby the reaction occurs by the condensation of *o*-aminobenzaldehyde **31** with acetaldehyde **32** (a carbonyl derivative having α-methylene protons) in the presence of sodium hydroxide. The Friedländer ring closure involves two distinct reactions: 1) the first stage involves the base catalysed formation of a

Schiff base **35** between the amino group of *o*-aminobenzaldehyde and the carbonyl group of acetaldehyde and 2) an internal claisen type condensation between the aryl aldehyde group and the α-hydrogen of acetaldehyde to afford the quinoline derivative **36**. Piperidine is used as a condensing agent (**Scheme 5**).[49]

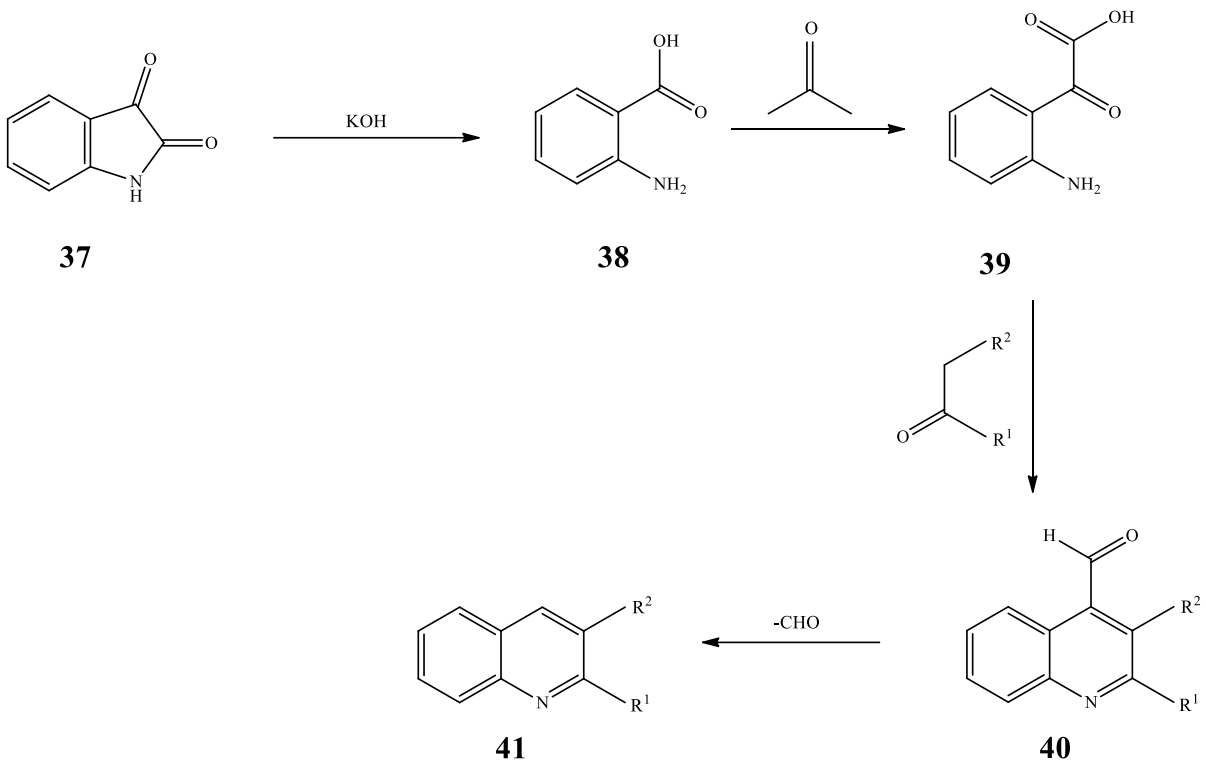


33 **34** **35** **36**

Scheme 5

Although the Friedländer synthesis is quite a versatile method for the synthesis of quinolines, the primary limitation of this method is the preparation and stability of aminobenzaldehyde precursors which are bifunctional and prone to self-condensation.[50] This problem may be controlled either by use of the Pfitzinger,[51] Borsche (proceeds with arylimines),[52] or Niementowski (*o*-aminobenzyl carboxylic acids)[53] modifications.

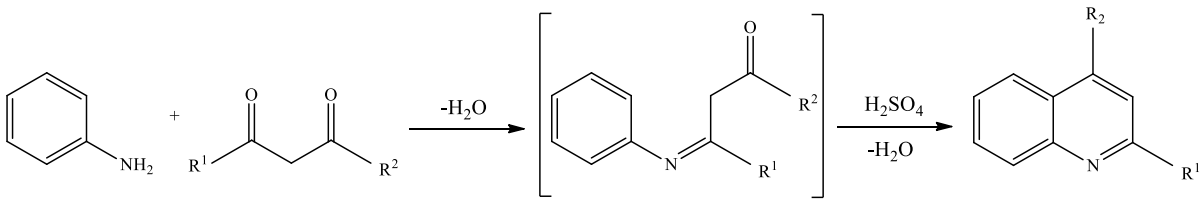
The Pfitzinger extension of the Friedländer protocol relies on the use of isatin **37**, a more stable precursor than 2-aminobenzaldehydes. Isatin is easily hydrolysed to *o*-aminoarylglyoxalate **38** which reacts with ketones to afford quinoline-4-carboxylic acid **40**. This is subsequently decarboxylated to afford the corresponding quinolines **41** (**Scheme 6**).



Scheme 6

1.3.3 The Combes quinoline synthesis

Alphonse-Edmond Combes reported the synthesis of 2, 4-disubstituted quinolines in 1888.[54] The Combes reaction involves the nucleophilic addition of unsubstituted aniline **26** with β-diketones **42** to form an enamine intermediate **43**. Acid-catalyzed cyclization of the Schiff base affords a substituted quinoline **44**. The cyclization step involves electrophilic substitution by the *o*-protonated imino ketone followed by dehydration to give the quinoline. The reaction is impressive because it uses both the technology of turning a ketone into an imine and for the acid cyclized ring closure (**Scheme 7**).[55]

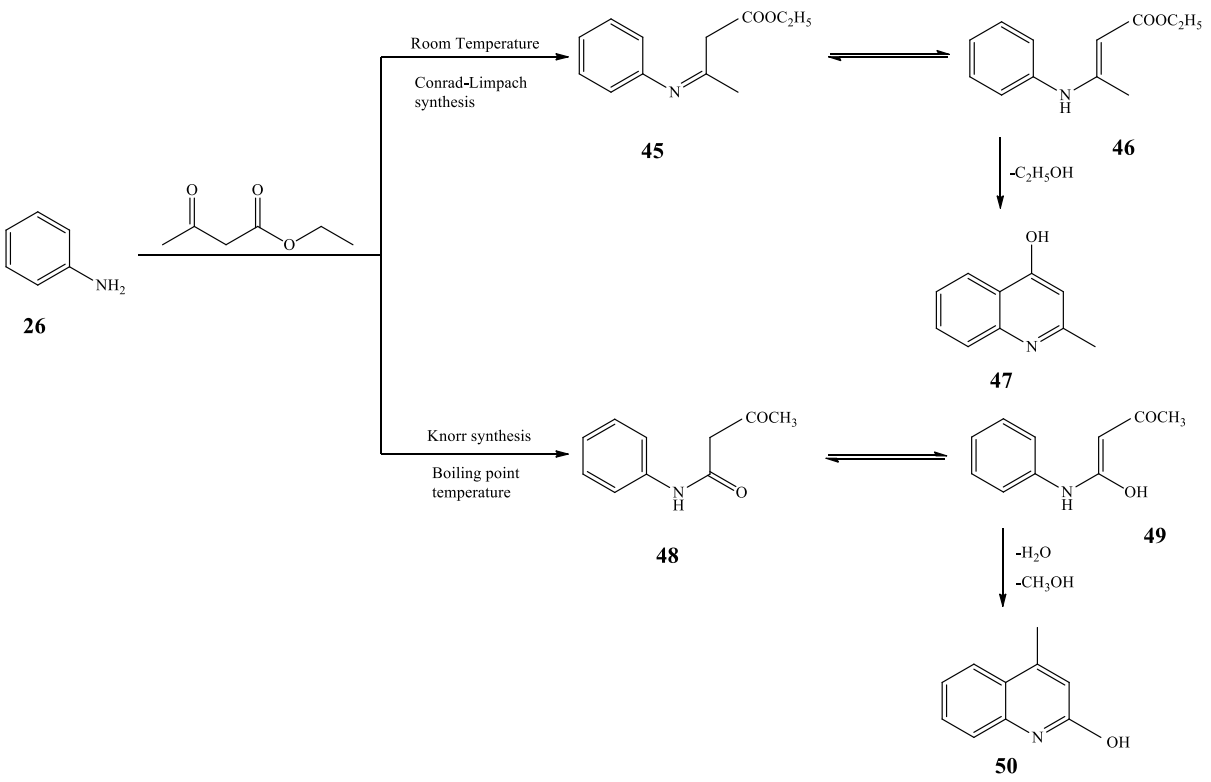


26 **42** **43** **44**

Scheme 7

According to Roberts and Turner[56], cyclization proceeds readily with a strongly *ortho-para* orientating group in the *meta* position to the nitrogen atom. Similar groups in the *para* position inhibit ring closure whereas, nitroanilines do not react in the Combes synthesis. *Meta*-substituted anilines predominantly produce 7-substituted quinoline derivatives.

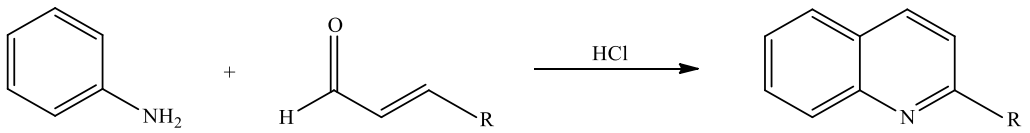
Combes method resembles the Conrad-Limpach-Knorr synthesis of quinolines so closely and should be classed as a variant of this method (**Scheme 8**).[57] The Conrad–Limpach synthesis exploits ketoesters and in a manner similar to that in the Combes reaction, diketones are used. In the Conrad-Limpach-Knorr synthesis, a β-keto ester, such as ethyl acetoacetate reacts with an aromatic amine in two ways. The factors governing the manner in which the condensation takes place has been clarified by Hauser and Reynolds.[58]



Scheme 8

1.4 THE DÖEBNER-VON MILLER SYNTHESIS

In 1881, German scientists Oscar Döebner and Wilhelm von Miller modified the Skraup quinoline synthesis by heating a primary aromatic amine (aniline) with an α, β-unsaturated carbonyl compound in the presence of hydrochloric acid (HCl)[59] however, unlike the Skraup quinoline synthesis, no oxidizing agent is used (**Scheme 9**). The synthesis of quinoline derivatives, when performed in the manner advocated by Skraup, occurs under harsh reaction conditions, which are often violent in nature.[60] The Döebner-von Miller synthesis, however, is experimentally much simpler, and not nearly as hazardous to run, even though the yields are usually not high owing many side-reactions.[61] As a note, glycerol in the Skraup synthesis forms an α, β- unsaturated carbonyl compound, subsequently undergoing a Döebner-von Miller reaction.

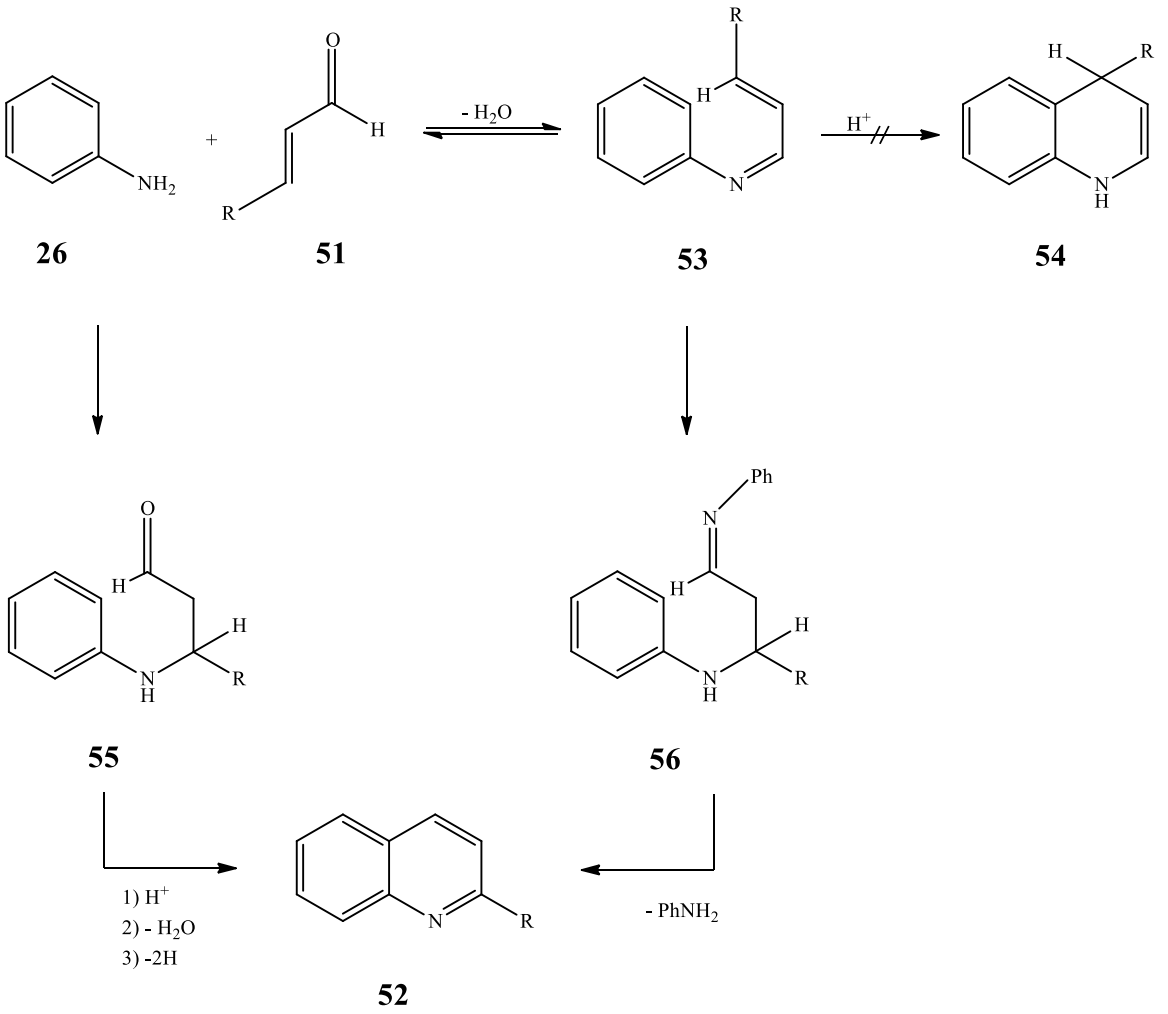


26 **51** **52**

Scheme 9

If we view the Döebner-von Miller syntheses chronologically, many researchers focused on the mechanism of the reactions rather than gaining an insight into the reaction conditions and attempting to increase the yield. Despite the numerous instances of successful quinoline syntheses, the mechanism of the Döebner-von Miller reaction has been a subject of debate and is quite controversial. It is known from the Skraup synthesis (**see section 1.3.1**) that glycerol **24** is dehydrated to form acrolein **25** and, a series of steps open to controversy, the aniline **26** and α, β-unsaturated aldehyde **27** combine to yield the quinoline product. What the nature is of the intermediate steps between **26** and **27** continues to be uncertain. Skraup's proposed mechanism was based on producing Schiff base intermediate **53** (**Scheme 19**), which directly cyclized with the aromatic ring in the presence of an acid.[43] However, this could not explain the regiochemistry found using α, β-unsaturated aldehydes, which led exclusively to 2-substituted quinolines **52** (**Scheme 9** and **10**). Direct cyclization of the Schiff base intermediate **53** should have led to 4-substituted 1, 4-dihydroquinoline **54**.

To accommodate this fact, in 1892, Bischler proposed a mechanism in which the aldehyde or its Schiff base **53** underwent a 1, 4-addition to another molecule of aniline to give the β-anilino aldehyde **55** or imine **56** to afford the 2-substituted quinolines **52** (**Scheme 10**).[62]



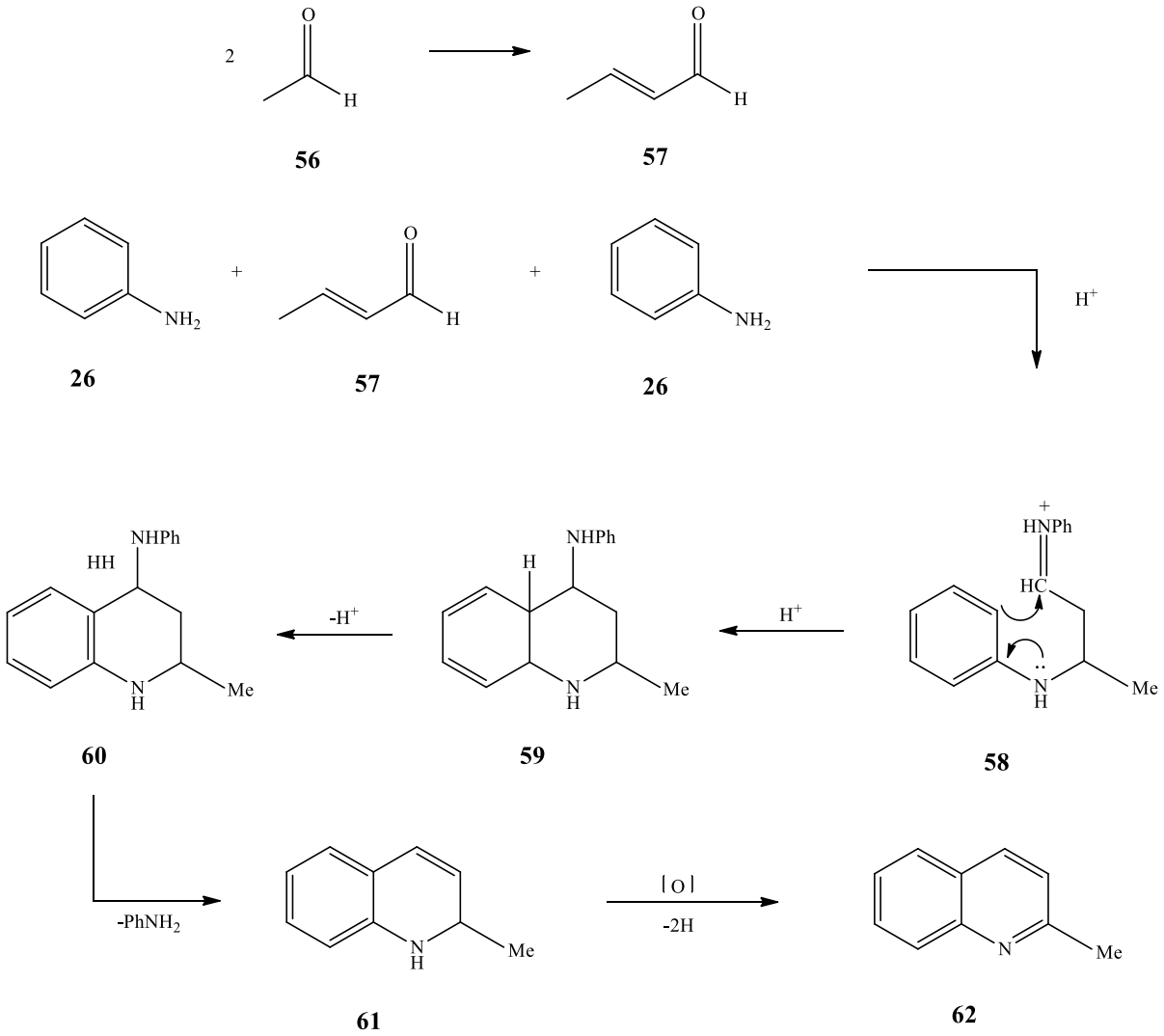
Scheme 10

Despite the limited resources available during this era, the above proposed mechanism is an impressive piece of chemistry forming the foundation for new and improved research. In the following 20 years (1896, 1911, 1912), other researchers[63] [64] [65] employed milder, hydrolyzing conditions to the Döebner-von Miller reaction and detected uncyclized and cyclized derivatives of **52**, **55** and **56** which have been interpreted as support in favour of Bischler's proposed mechanism.

It was not until 1922, that Mills and co-workers studied the yield of the quinoline products in the Döebner-von Miller synthesis using sulfuric acid and hydrochloric acid. As demonstrated by these authors, hydrochloric acid gave better results than sulfuric acid, and the addition of zinc chloride to the reaction mixture increased the yield.[66]

In 1923, König proposed a modification in favour of the mechanism first suggested by Bischler which involved the imine **56** as the key intermediate.[67] König's mechanistic proposal was subsequently supported by deuterium-labeling experiments by Forrest and co-workers in 1969.[68] These studies indicated that anils cannot undergo direct ring closure but must either revert to the β-anilino carbonyl compounds and cyclize or react *via* the conjugate adducts.

At this point, the "most likely mechanism" for the Döebner-von Miller reaction was described as a process in which the first stage is probably a crotonic self-condensation of two molecules of an aldehyde or ketone, resulting in the formation of an α, β-unsaturated carbonyl compound. The latter reacts with aniline to form a Schiff base and the resulting dihydroquinoline undergoes further oxidation to afford a quinoline derivative (**Scheme 11**).[69]



Scheme 11

The Skraup synthesis was regarded as a reaction of substituted aromatic amines not only with glycerol but also with the α, β-unsaturated carbonyl compounds, where the only difference between this and the Döebner-von Miller reaction is the use of different reagents to obtain the quinoline product. Manske[61] and Surrey[70] pointed out the similarity between the mechanisms for the production of quinoline systems by the Skraup and Döebner-von Miller methods. Hence, studies on the Döebner-von Miller reaction mechanism highlighted the importance of the Skraup reaction as an essential component.

A number of different investigators provided insights into the mechanism by isolating various intermediates in the reaction sequence. Badger and co-workers, in 1963, suggested that the conjugate addition is the first step in the annulation sequence.[71] In the same year, Tung claimed the isolation of various ketone anils by the treatment of aniline with mesityl oxide in boiling benzene. The formation of the quinoline led him to speculate a unidirectional ring closure of the intermediate to the quinoline product.[72]

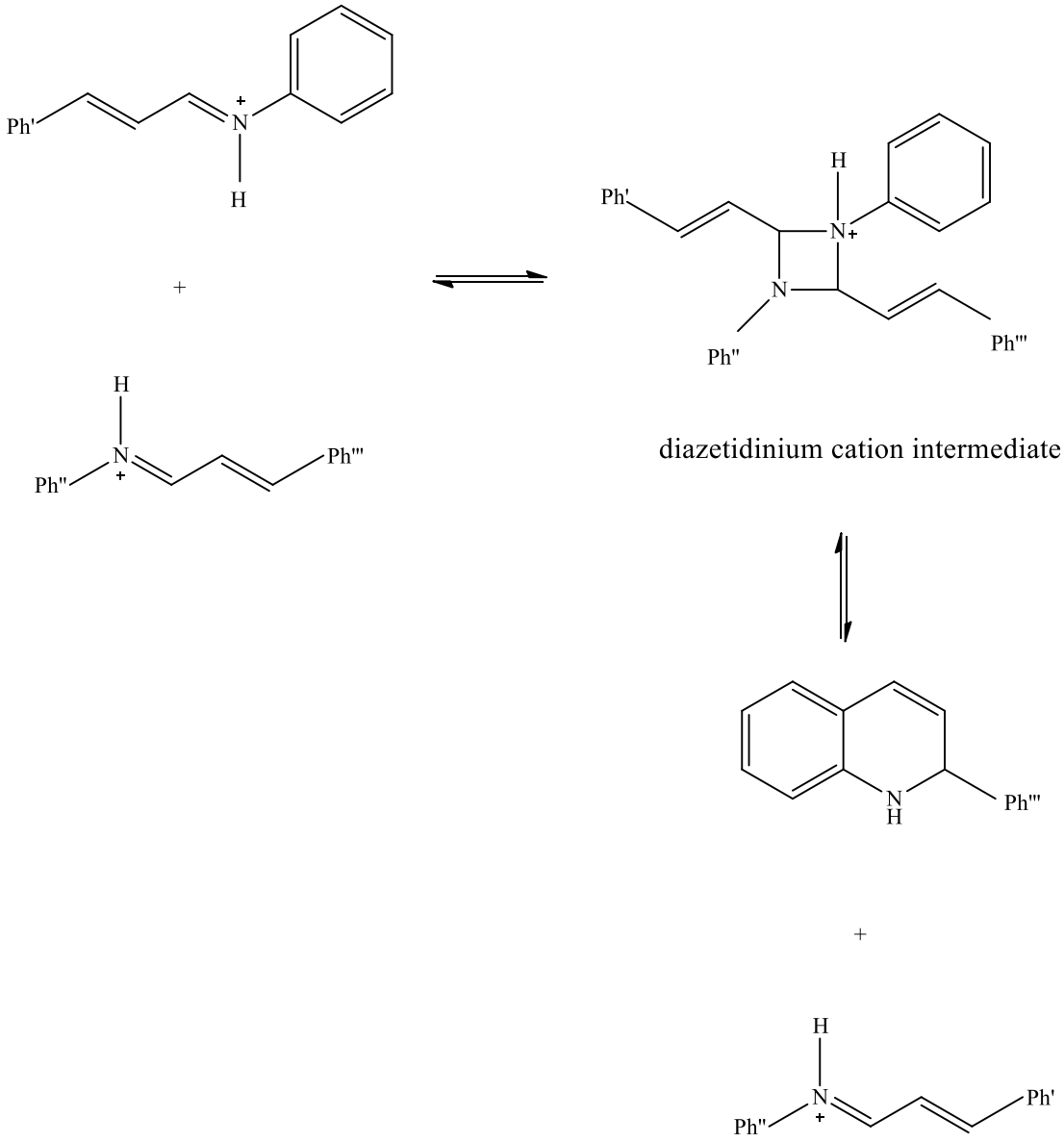
At this point in time, a great deal of research has been conducted focusing on the mechanism of the Döebner-von Miller reaction with many differing opinions. At the dawn of the 1970's, researchers focused their attention on improving the yield of these reactions by varying the reaction conditions. In view of this, one of the major drawbacks surrounding the Döebner-von Miller reaction is the yield, reaction conditions and isolation procedure. The yields reported are usually low owing to the many by-products formed in the reaction and the isolation and purification of quinolines from complex reaction mixtures is often quite tedious, and the many manipulations involved tend to lower the recovery of the desired product.[73]

In 1976, Leir worked on improving such conditions and discovered an improved method of isolation of the quinoline product. It was found that when the reaction of *p*-fluoroaniline with crotonaldehyde under standard Döebner-von Miller conditions was completed, addition of zinc chloride to the reaction mixture caused precipitation. Removal of impurities led to the formation of a bright yellow solid which upon analysis proved to be a 2:1 complex of the desired quinoline hydrochloride and zinc chloride. The yield of various quinoline complexes synthesized was 42-55%.[74] Leir's work is regarded as a significant discovery as the yield increased compared to the original yield obtained in 1881 by Döebner and von Miller. It would have been useful to know the yield obtained by Döebner-von Miller as many publications cite the improvement in Leir's work, however, the article is unavailable due to the year of publication.

In view of the increased interest in the Döebner-von Miller quinoline synthesis, it is not surprising that many mechanistic studies are already on record. Even though Leir conducted a

study focusing on improving the yield of the Döebner-von Miller reaction, in the coming years (1978 and 1985) Dauphinee and co-workers continued with studies on the mechanism by isolating the imine formed from the reaction of aniline with acetaldehyde suggesting that the self-condensation of the Schiff base followed by cyclization gave the quinoline product.[75] [76]

In 1989 Eisch and co-worker studied the mechanism of the Doebner-von Miller quinoline synthesis and proposed that direct Schiff base formation might be the critical step in the reaction mechanism.[77] Their results showed that heating a Schiff base under strictly anhydrous conditions or in dimethylsulfoxide (DMSO) led to a diazetidinium cation intermediate which subsequently rearranged rapidly to a 2-substituted quinoline. This proposed mechanism also explained the observed regiochemistry of generating 2-phenylquinoline, with no observed 4-phenylquinoline (**Scheme 12**).[77]

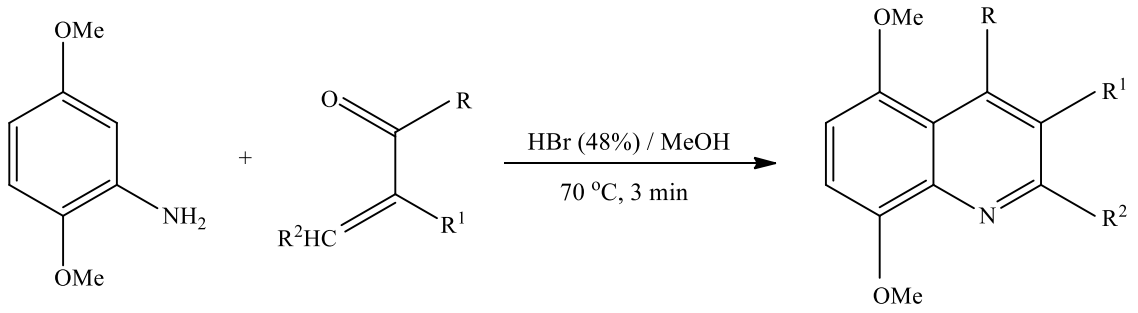


Scheme 12

As stated previously, one serious shortcoming of the Döebner-von Miller reaction is the laborious procedure for the isolation of the quinoline from the complex reaction mixture. This is due to the polymerization of the α, β-unsaturated aldehydes under the strongly acidic conditions, consequently the yields are often low. Investigations of recent decades have therefore been devoted to the search for better reaction conditions. A recent modification of the Döebner-von Miller reaction is a two-phase solvent system consisting of an organic and

aqueous acidic part allows the clean preparation of the desired product thereby avoiding polymerization of the unsaturated carbonyl compounds.

Choi and co-workers, in 1998, utilized a two-phase system (HCl/dioxane, HCl/dichloromethane (CH_2Cl_2), hydrobromic acid (HBr)/methanol(MeOH), aluminium chloride ($AlCl_3$)/CH_2Cl_2) in the synthesis of quinolines from 2, 5-dimethoxyaniline **63** and crotonaldehyde **57**. The highest yield (52%) was obtained with hazardous 48% HBr in 15 minutes at 70 °C (**Scheme 13**).[78]

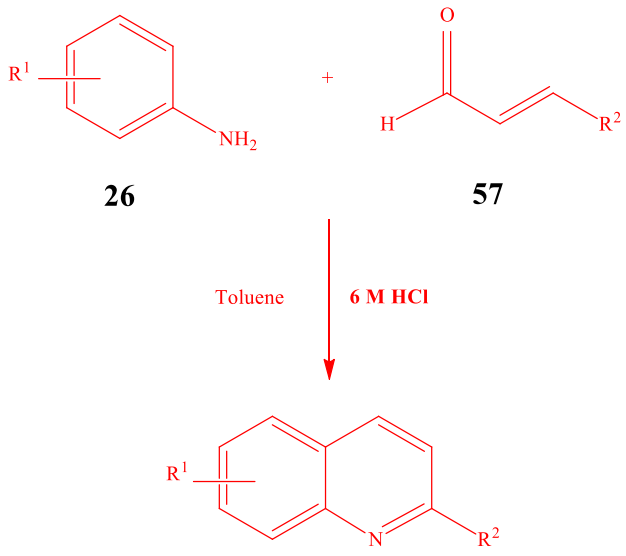


63 **57 a-d** **64 a-d**

49, 56 **a** R = R_1 = R_2 = H, **b** R = R_1 = H, R_2 = Me, **c** R = R_2 = H, R_1 = Me, **d** = R = Me, R_1 = R_2 = H

Scheme 13

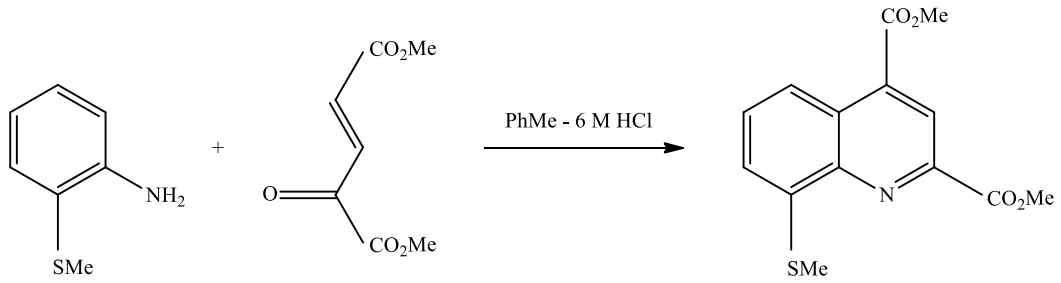
At the turn of the millennium, in 2000, Matsugi and co-workers developed a two-phase protocol for the Döebner-von Miller synthesis. It was established that the most favourable system was a mixture of toluene and 6 M hydrochloric acid producing a maximum yield of 80% (**Scheme 14**).[79] The two-phase system developed as a trend among researchers so as to decrease the polymerization of the α, β-unsaturated aldehyde.[80]



Scheme 14

Li and co-workers also reported a two-phase Döebner-von Miller reaction using similar conditions and their system consisted of 12 M hydrochloric acid and toluene. In their work, 5 mol % of tetrabutylammonium chloride (THAC) as an additive being most successful for the synthesis 2-alkyl-8-quinolinecarboxylic acid (yield 57%).[81]

A similar approach was used for the preparation of **68** from the aniline derivative **66** with α, β-unsaturated compounds of the 2-ketoglutaconate type **67** (**Scheme 15**).[82]



56 %

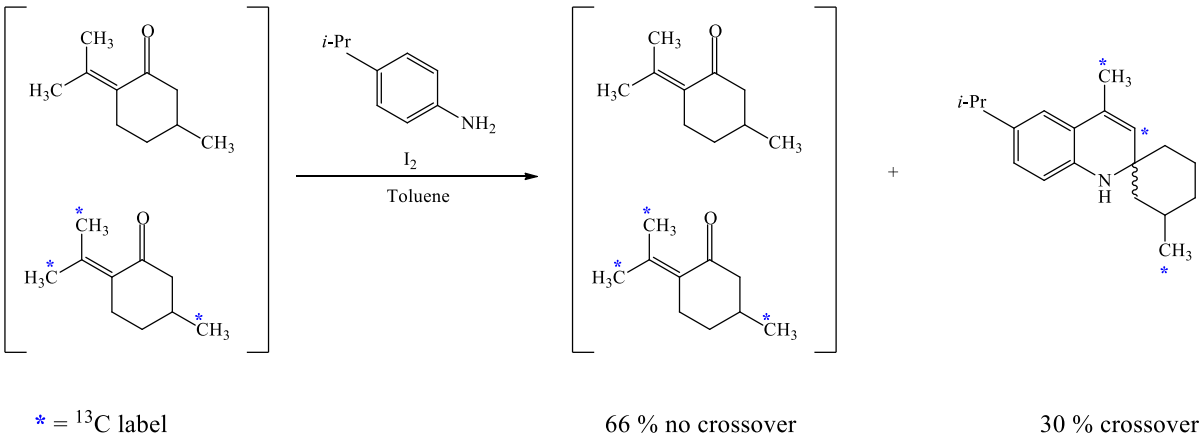
66 **67** **68**

Scheme 15

The above methods using a biphasic system has the following advantages: 1) moderate to high yields (50-80%) compared with the single phase reaction; 2) no strict control over the addition of the unsaturated aldehyde and 3) simply neutralizing the aqueous phase could isolate almost colourless pure product. However, the system displays limited substrate applicability and harsh reaction conditions which does not comply with the principles of green chemistry which is a topical point in the 21st century.[83]

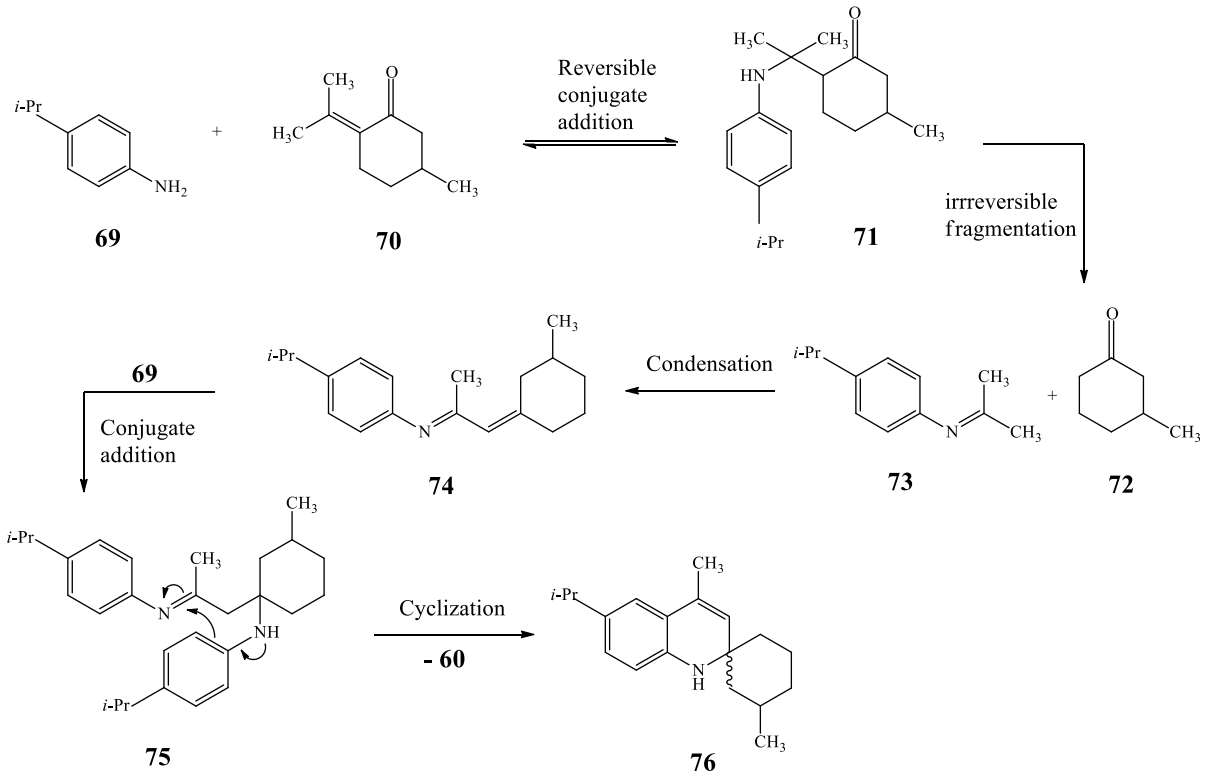
In 2006 Scott Denmark and co-workers believed that further improvements in the reaction yield and reproducibility would occur from a detailed understanding of the mechanism of the Döebner-von Miller reaction. Hence, they studied the formation of substituted quinolines from anilines and α, β-unsaturated ketones mechanistically by conducting a series of isotopic labelling experiments by cyclizing *p*-isopropylaniline with mesityl oxide ^{13}C-labeled once at the 2-position or labelled both at 2- and 4-positions (**Scheme 16**).[84] The results of their study implied that either multiple mechanistic pathways were simultaneously operative, resulting in a mixture of labelled quinoline products or the mesityl oxide acetone subunits were scrambling during, prior to or separate from the cyclization process. Denmark and co-worker concluded, after subsequent tests, that the acetone units of mesityl oxide were separating and recombining

during the cyclization process. On the basis of their studies, a fragmentation-recombination mechanism was proposed.



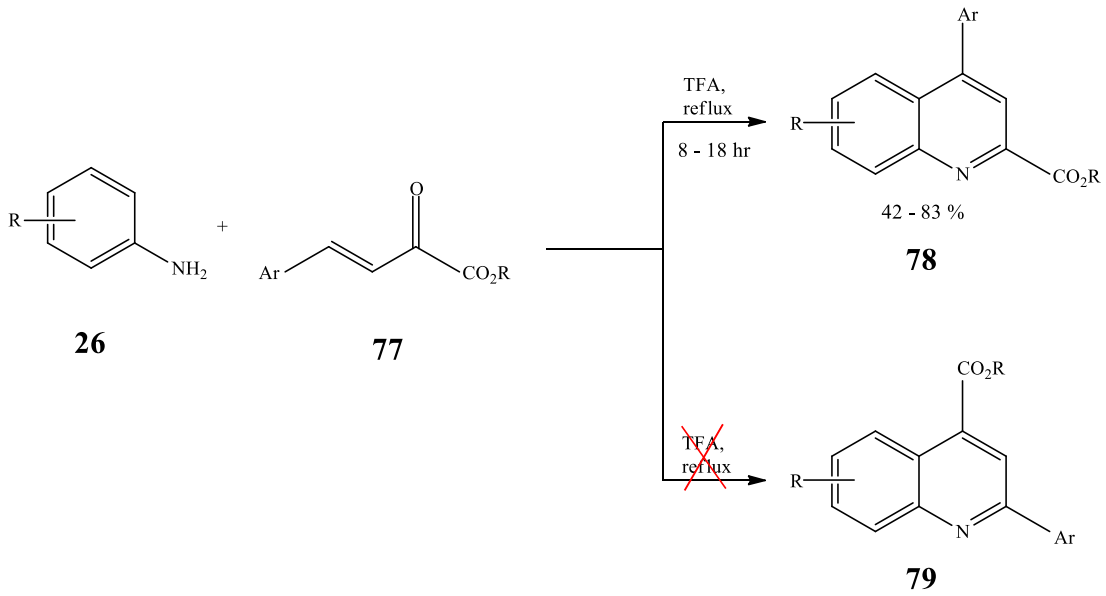
Scheme 16

The proposed mechanism (**Scheme 17**) involves an initial condensation of the aniline moiety **69** with the α, β-unsaturated ketone **70** in a nucleophilic conjugate fashion, followed by a fragmentation to the corresponding imine **73** and the ketone **72** itself in a non-reversible reaction. The fragments recombine in a condensation reaction to form an anil **74**, followed by a nucleophilic conjugate addition of a second aniline molecule which leads to imine **75**. Elimination of one aniline molecule followed by cyclization furnishes the final quinoline product **76**.



Scheme 17

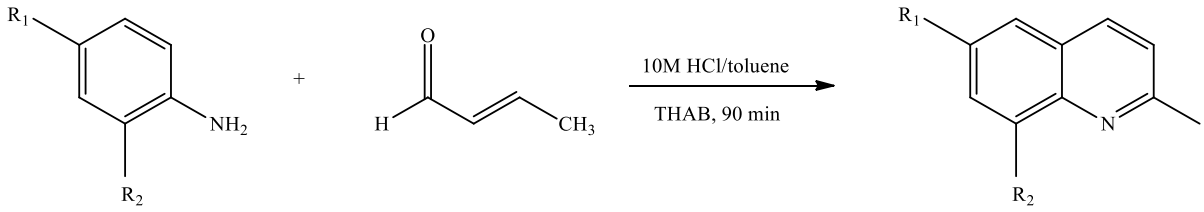
Later that year, Chen and co-worker discovered a reversal of the standard regiochemistry of the Döebner-von Miller quinoline synthesis when anilines were condensed with γ-aryl-β, γ-unsaturated α-ketoesters in refluxing trifluoroacetic acid (TFA). These workers postulated that the reaction involved a 1, 2-addition of aniline to **77** to form a Schiff base adduct with subsequent cyclization and oxidation to yield the quinoline product. Surprisingly, the reaction afforded quinoline-2-carboxylates **78** instead of the expected quinoline-4-carboxylates **79** (**Scheme 18**). Therefore, the regioselectivity of the reaction could reverse in the presence of an electron-withdrawing ester group on the carbonyl compound.[85]



26 **77** **78** **79**

Scheme 18

Recently[86], a Döebner-von Miller strategy was employed for the synthesis of quinolines starting from aniline and crotanaldehyde using a similar approach to Matsugi and co-workers. A 10 M hydrochloric acid/toluene system readily formed 2-methylquinoline derivatives in the presence of tetrahexylammonium bromide (THAB). The experiments showed that the reaction of crotanaldehyde proceeded very well with various anilines bearing electron-donating, electron-withdrawing and halogen groups under the general conditions of the reaction. However, the desired products were obtained in disappointing yields (7-57%) as compared to Matsugi and co-workers, under similar reaction conditions (**Scheme 19**).[86]



26 **57** **80**

$R_1 = R_2 = H$ (40%)

$R_1 = MeO$; $R_2 = H$ (8%)

$R_1 = H$; $R_2 = CH_3$ (7%)

$R_1 = NO_2$; $R_2 = H$ (23%)

$R_1 = H$; $R_2 = CO_2H$ (57%)

Scheme 19

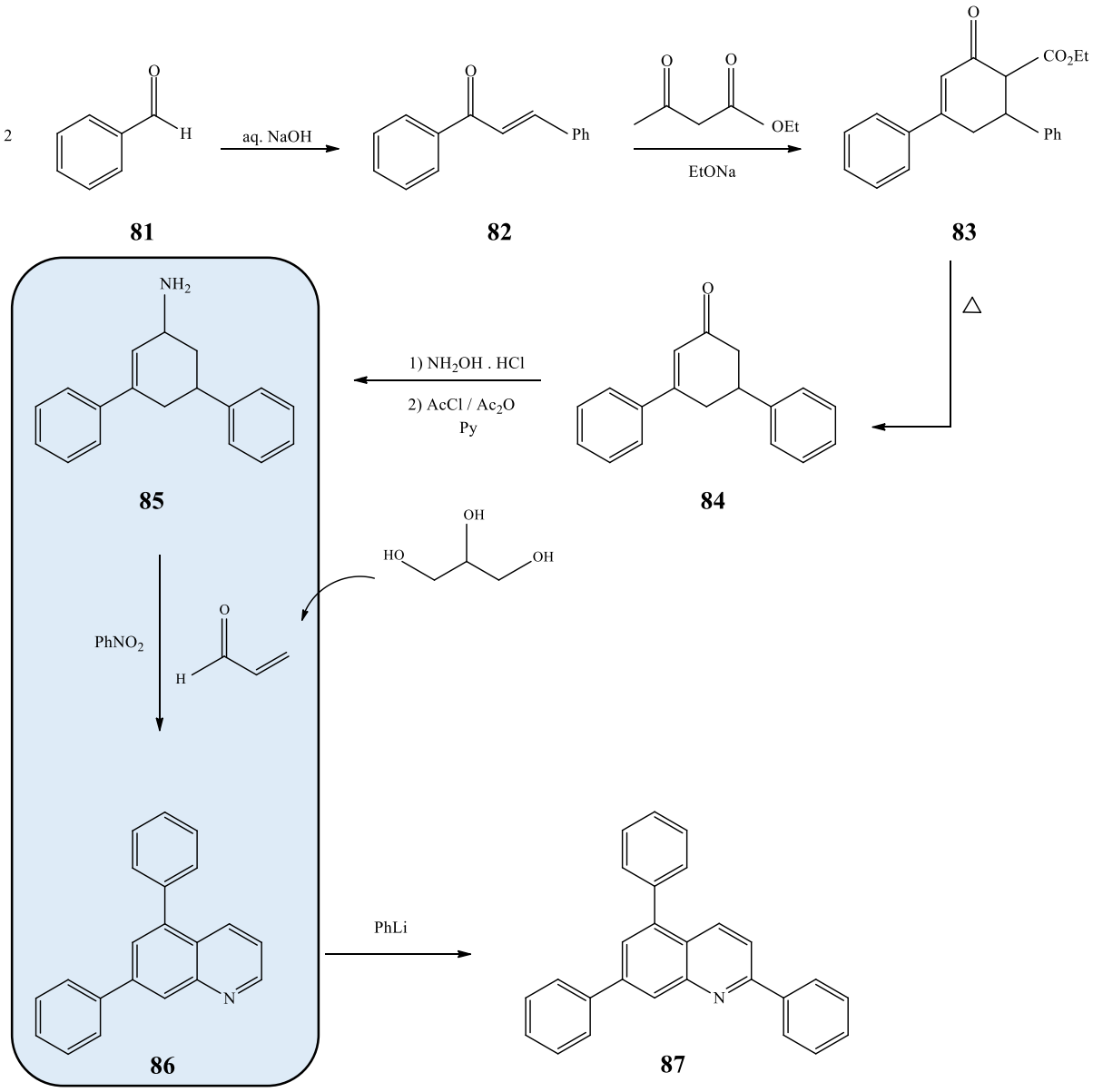
As can be seen from the above literature review, numerous studies focusing on the mechanism, reaction conditions and yield of the Döebner-von Miller reaction has been conducted. Despite the many challenges and conflicting views on the mechanism, the Döebner-von Miller reaction forms part of the many synthetic routes available to access biologically active compounds and some of these will be discussed below.

1.5 APPLICATION OF THE DÖEBNER-VON MILLER REACTION IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

1.5.1 Lead drug evaluation

Qi and co-workers synthesized 2, 5, 7-triphenylquinoline from simple precursors such as benzaldehyde **81** and acetaphenone **82**. The functionality of *m*-terphenylamine as a starting material for the synthesis of functional quinolines for further treatments was considered, and

the synthesis and properties of **85**, **86**, and **87** were also reported (**Scheme 20**). The heterocyclic compounds 5, 7-diphenylquinoline **86** and 2, 5, 7-triphenylquinoline **87** are important due to their biological properties in drug evaluation.[87]

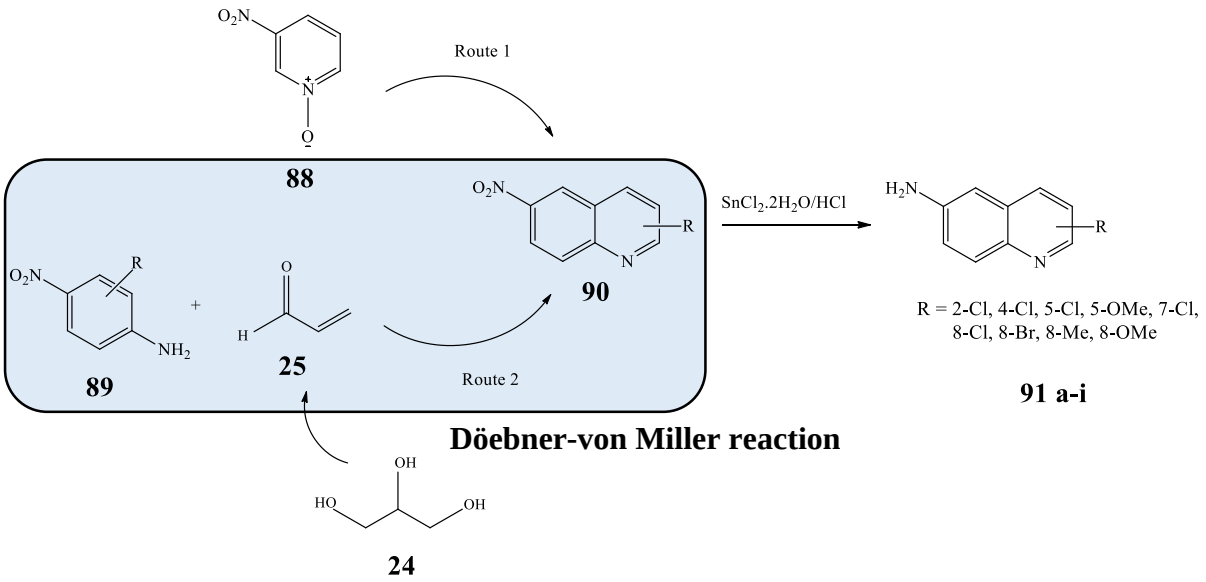


Döebner-von Miller reaction

Scheme 20

As mentioned previously, aminoquinoline derivatives are an important class of heterocyclic compounds showing biological activity. For example, chloroquine[88] and primaquine[89] show potencies against malaria. Two routes for the synthesis of mono-substituted derivatives of 6-aminoquinoline was reported by Yuan and co-workers.[90] In the first route, 6-nitroquinoline **90** was directly converted to substituted quinolines **91**. The halogen reagents stabilized 6-nitroquinoline and the *N*-oxide group activated the pyridine ring, which was subsequently chlorinated by phosphoryl chloride ($POCl_3$). Reduction of the nitro (NO_2) group to amine (NH_2) also removed the *N*-oxide.

In the second route, substituted phenylquinoline derivatives were synthesized *via* the Döebner-von Miller reaction. Soluble *p*-chloroaniline was used as an oxidant and $SnCl_2 \cdot 2H_2O$/HCl was used as a reductant (**Scheme 21**).

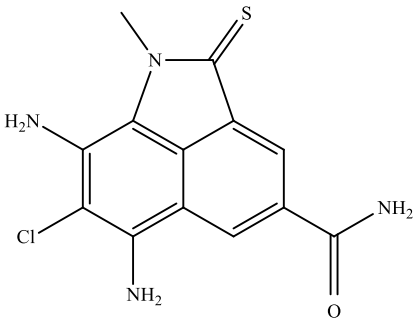


Scheme 21

1.5.2 Ammosamide A and B

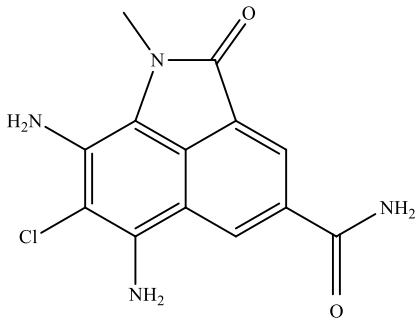
Ammosamides[91] [92] (**Figure 10**) are chlorinated tricyclic pyrroloquinoline alkaloids which exhibits several biological activities, for example, specific cytotoxicity against selected cancer

cell lines. Wu and co-workers[93] synthesized these novel compounds by a Döebner-von Miller reaction *via* a five step total synthesis in the presence of TFA. An electron-rich substituted aniline (1, 3-diamine-4, 6-dinitrobenzene **94**) was reacted with dimethyl-2-oxo glutaconate **95** resulting in the tricyclic pyrroloquinoline **96** (**Scheme 22**). The first step of the total synthesis is important in order to obtain an excellent final yield and the Döebner-von Miller synthesis produces a satisfactory yield of 40% in the presence of harsh reaction conditions and long reaction times.



Ammosamide A

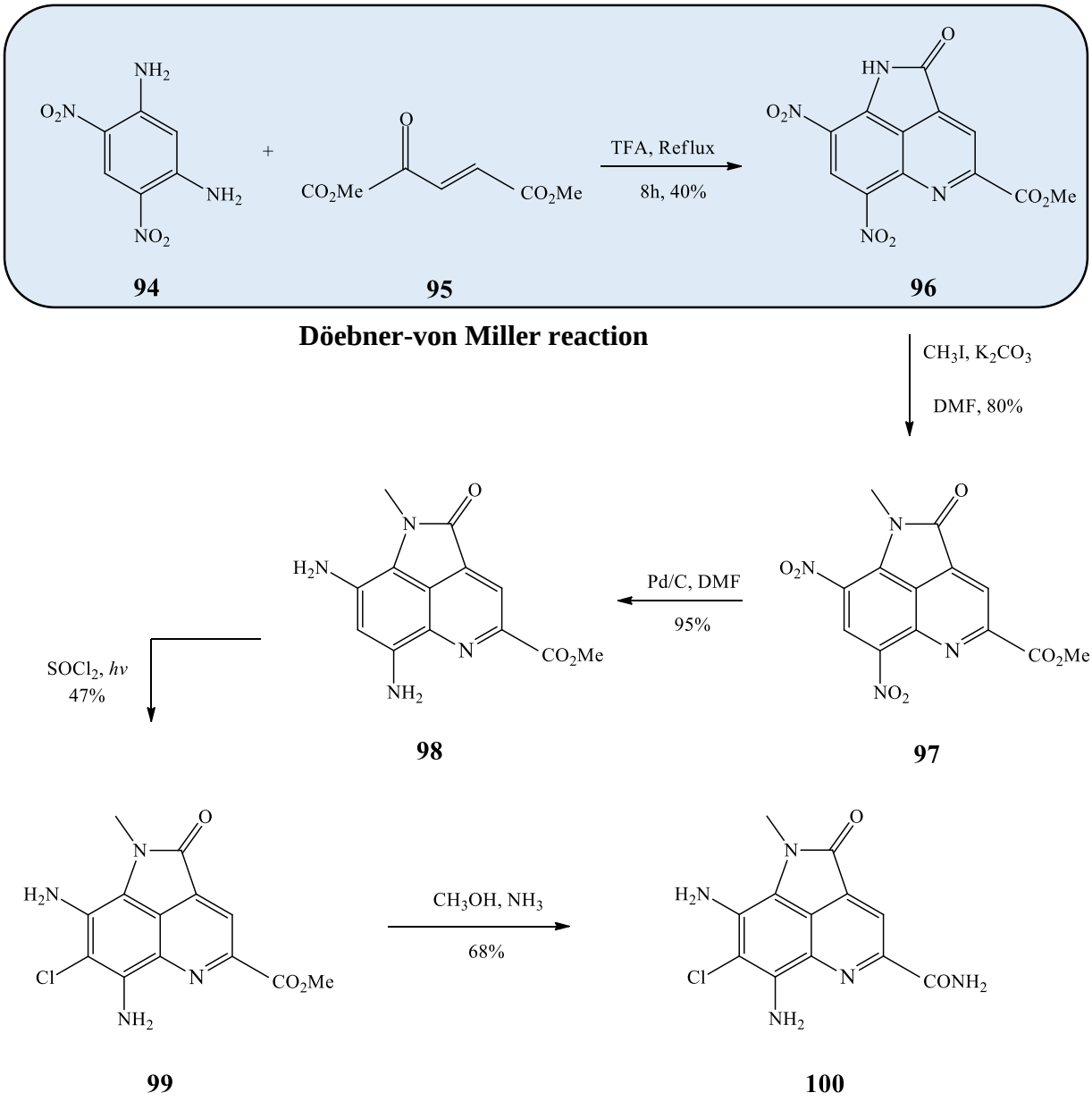
92



Ammosamide B

93

Figure 10

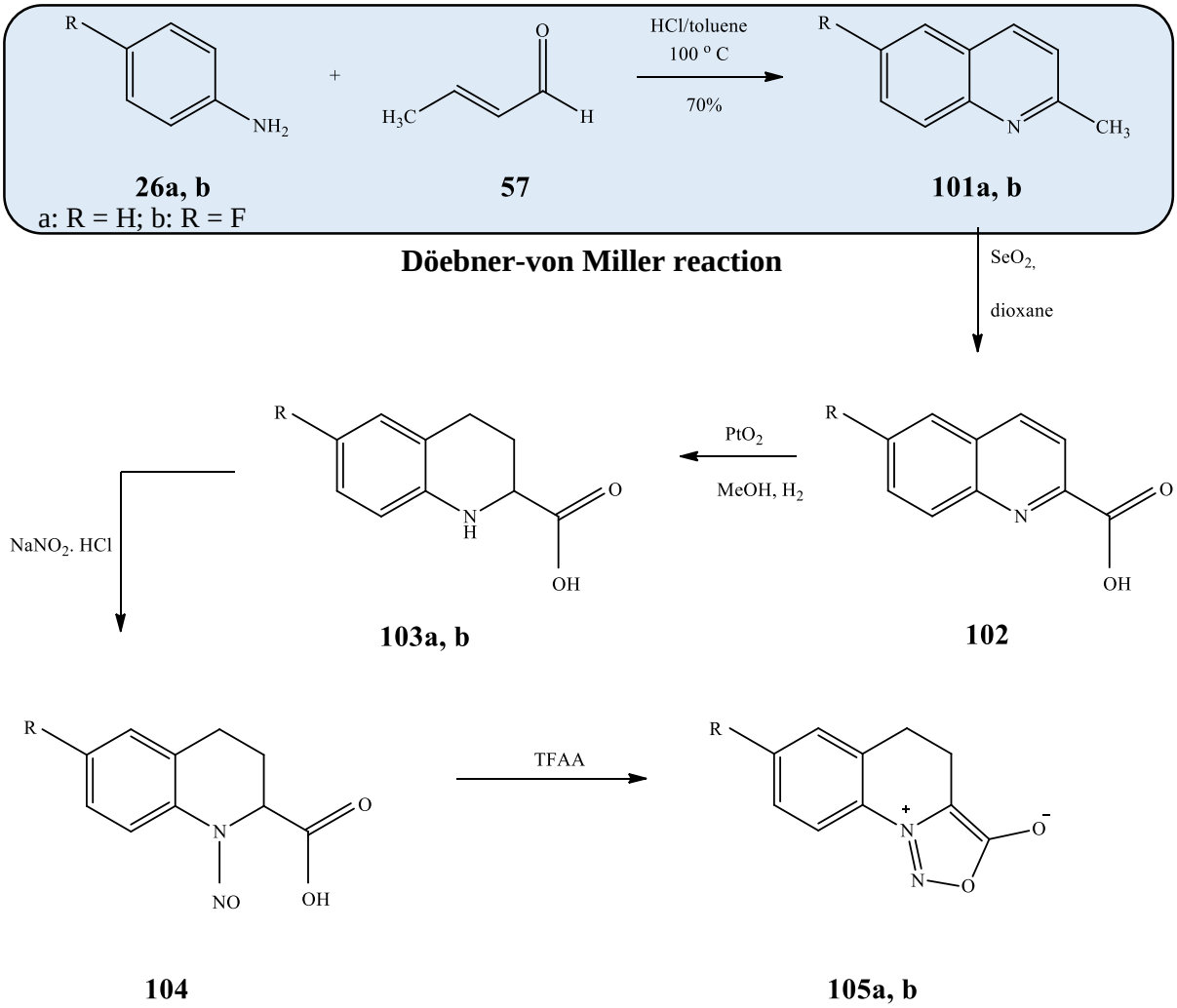


Scheme 22

1.5.3 Syndones

Syndones are biologically active compounds with a meso-ionic character which are shown to exhibit antimicrobial,[94] antineoplastic,[95] anticonvulsant[96] and analgesic[97] properties. Chandrasekhar and co-workers[98] utilized a two-phase (HCl/toluene) Döebner-von Miller reaction to synthesize 1, 2, 3, 4-tetrahydroquinoline-2-carboxylic acid **103a** and its 7-fluoro

derivative **103b** from aniline **26a** or *p*-fluoroaniline **26b** and crotonaldehyde **57**. Selenium dioxide was used as an oxidizing agent. Other syndone derivatives, 3-hydroxy-4, 5-dihydro[1, 2, 3]oxadiazolo[3, 4-*a*]quinoline-10-ium **105a** and its derivative 7-fluoro-3-hydroxy-4, 5-dihydrooxadiazolo[3, 4-*a*]quinoline-10-ium **105b** were prepared by subsequent *N*-nitrosation of **103** in the presence of sodium nitrate and concentrated HCl followed by cyclization with trifluoroacetic anhydride (TFAA) (**Scheme 23**).



Scheme 23

1.6 A GREEN CHEMISTRY APPROACH

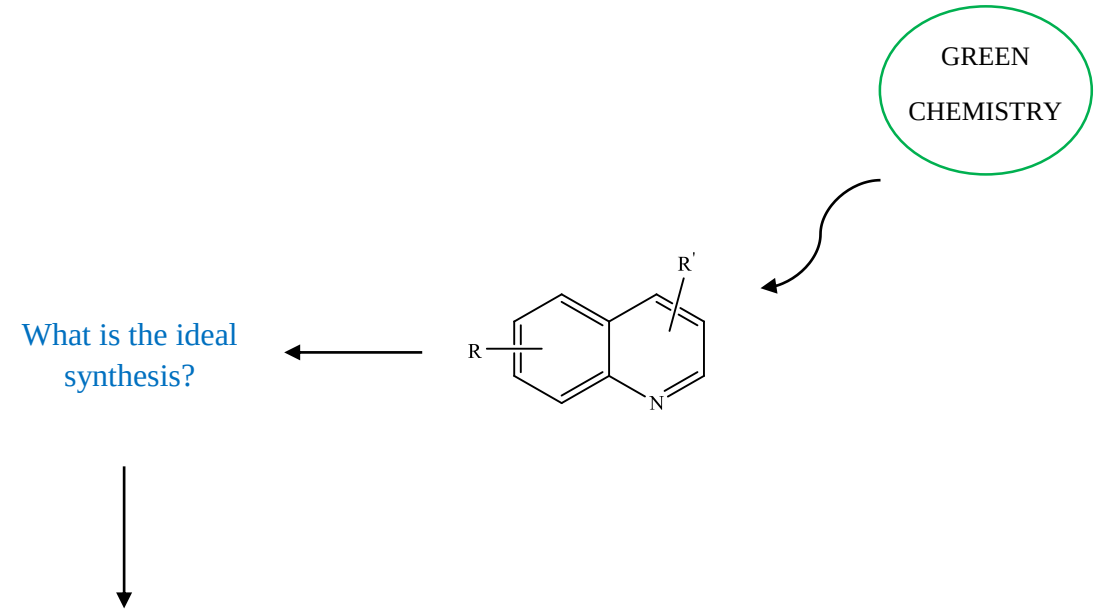
Taking into consideration the above protocols for the synthesis of quinoline derivatives *via* the Döebner-von Miller reaction, it is agreed that the conditions under which each reaction is performed is environmentally unfriendly, even though good to excellent yields are sometimes obtained. However, given the simplicity and use of the Döebner-von Miller in the total synthesis of biologically active compounds, it is essential to devise an environmentally friendly synthetic route to access these quinoline derivatives.

In view of this, the development of environmentally benign and clean synthetic procedures has become the goal of present day organic synthesis.[83] "Green chemistry for chemical synthesis addresses our future challenges in working with chemical processes and products by inventing novel reactions that can maximize the desired products and minimize by-products, designing new synthetic schemes and apparati that can simplify operations in chemical productions, and seeking greener solvents that are inherently environmentally and ecologically benign." [99] There are 12 principles of green chemistry:[100]

1) **Prevent waste:** Design chemical syntheses to prevent waste. Leave no waste to treat or clean up
2) **Atom economy:** Design syntheses so that the final product contains the maximum proportion of the starting materials.
3) **Design less hazardous chemical syntheses:** Use and generate substances that possess little or no toxicity to human health and the environment.
4) **Design safer chemicals and products:** Design chemical products that are fully effective yet have little or no toxicity.
5) **Safer solvents and auxiliaries:** The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and harmless when used.

6) **Increase energy efficiency:** Choose the least energy-intensive chemical route. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7) **Use of renewable feedstock:** Use chemicals which are made from renewable sources, rather than other, equivalent chemicals originating from petrochemical sources.
8) **Reduce derivatives:** Minimize the use of temporary derivatives (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes). Avoid derivatives to reduce reaction steps, resources required and waste created.
9) **Catalysis:** Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10) **Design for degradation:** Chemical products should be designed so that at the end of their function they do not persist in the environment and breakdown into harmful degradation products.
11) **Real-time analysis for pollution prevention:** Analytical procedures need to be further developed to allow real-time, in-process monitoring and control prior to the formation of hazardous materials.
12) **Inherently safer chemistry for accident prevention:** Substances and the form of a substance used in a chemical process should be chosen so as to minimise the potential for chemical accidents, including releases, explosions and fires.

Poliakoff and co-workers have reported a mnemonic, **PRODUCTIVELY**, which captures the essence of the twelve principles of green chemistry which we hoped to apply to the synthesis of quinoline derivatives:[101]



P – Prevent wastes

R – Renewable materials

O - Omit derivatization steps

D – Degradable chemical products

U – Use of safe synthetic methods

C – Catalytic reagents

T – Temperature, pressure ambient

I – In-process monitoring

V – Very few auxiliary substances

E – E-factor, maximize feed in product

L – Low toxicity of chemical products

Y – Yes, it is safe

This set of goals is used as a framework in the development of cleaner and sustainable chemical processes. Though ideally a new process will incorporate all 12 principles, in reality, it may only be possible to optimize a few.

Aims of the project

Quinoline derivatives play an important role in science, particularly, in the field of synthetic and medicinal chemistry. However, various challenges exist within the synthetic routes available to access these compounds, such as harsh reaction conditions and expensive starting materials. The Döebner-von Miller reaction is a valuable route available to synthesize quinoline compounds, however, the tasks associated with this reaction includes harsh conditions, hazardous reagents, numerous side products, tedious isolation procedures and low yields.

The aim of this project is a broad one; to develop the Döebner-von Miller reaction with the following goals in mind:

- Simple and efficient
- Short reaction times
- High yields
- Has a wide substrate applicability
- Environmentally friendly

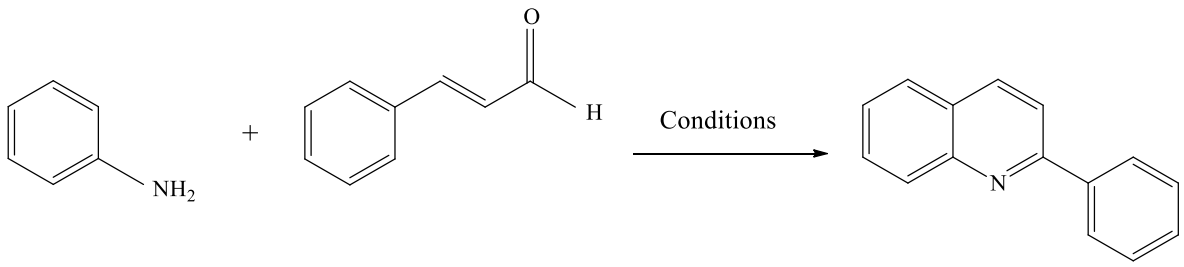
Since the Döebner-von Miller reaction is complex, the secondary goal is to gain an insight into the methodology of quinoline formation using the developed synthetic route.

Chapter 2

Results and Discussion

2.1 PREFACE

The focus of this project was to employ the Döebner-von Miller reaction to the synthesis of quinoline derivatives using an environmentally friendly approach. In the discussion which follows, attention will be focused on establishing the optimum reaction conditions for the synthesis of 2-Phenylquinoline as illustrated in **Scheme 24** which will subsequently be applied to the preparation of a series of quinoline compounds. Selected NMR, IR and GC/MS spectra will be discussed.



26 **106** **107**

Scheme 24

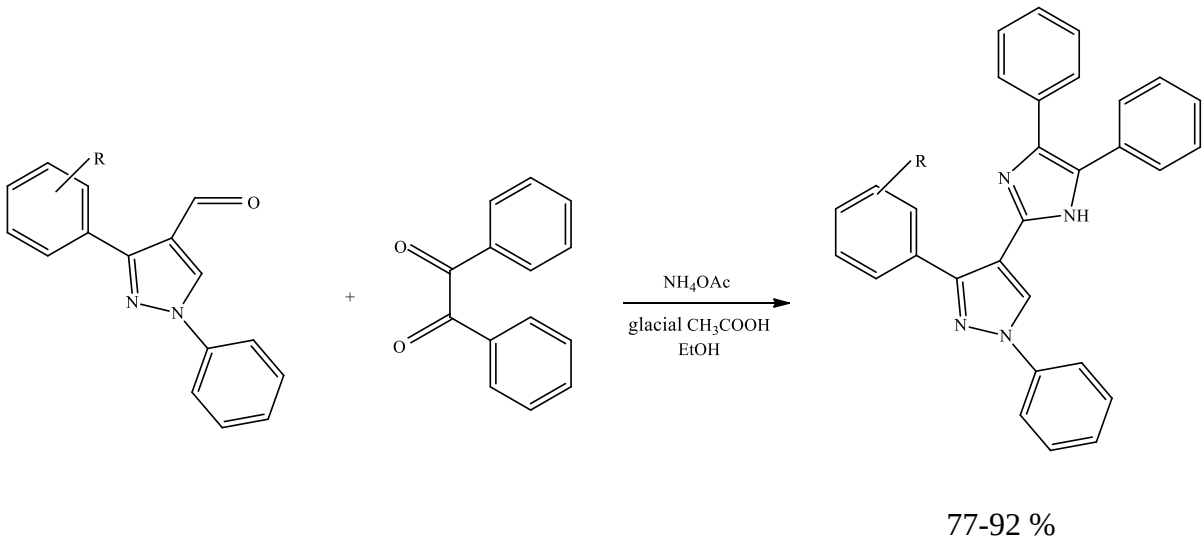
2.2 OPTIMIZING REACTION CONDITIONS USING THE SYNTHESIS OF 2-PHENYLQUINOLINE AS A MODEL REACTION

2.2.1 Application of Acetic acid in the biphasic system for the synthesis of 2-Phenylquinoline

If we consider the harsh reaction conditions employed for the synthesis of quinoline derivatives *via* the Döebner-von Miller reaction, the need for more environmentally friendly synthetic approaches is essential. Taking into account the basic principles of green chemistry, we attempted to improve the harsh biphasic (aqueous/organic) system previously employed in the synthesis of quinoline compounds. In addition, we looked at improving the low yields usually obtained in Döebner-von Miller reaction.

Water makes life as we know it possible and is the solvent of choice for nature to carry out her syntheses.[102] The use of water as a medium for organic syntheses has attracted the attention of organic chemists for many years. The literature now contains a range of important recent books[103], reviews[104] [105] [106] and articles[107] [108] [109] [110] promoting organic synthesis "in" and "on" water.

In search for a more green and efficient biphasic system that comprises both the acidic and aqueous (water) nature led to vinegar as a possible catalyst. Vinegar contains 95% water and 5% acetic acid, thus providing both the acidic and aqueous medium. Acetic and glacial acetic acid has been utilized as a solvent/catalyst in the synthesis of various organic heterocyclic compounds.[111] [112] [113] Baria and co-workers synthesized Imidazolyl-Pyrazole derivatives in the presence of acetic acid (**Scheme 25**).[114] The results of their study demonstrated the easy formation of Imidazolyl-Pyrazole derivatives in excellent isolated yields (77-92 %). Out of a range of other acid catalysts, acetic acid has attracted much attention owing to its suitable acidity, easy availability, and low cost thereby acting as a promising top table reagent.

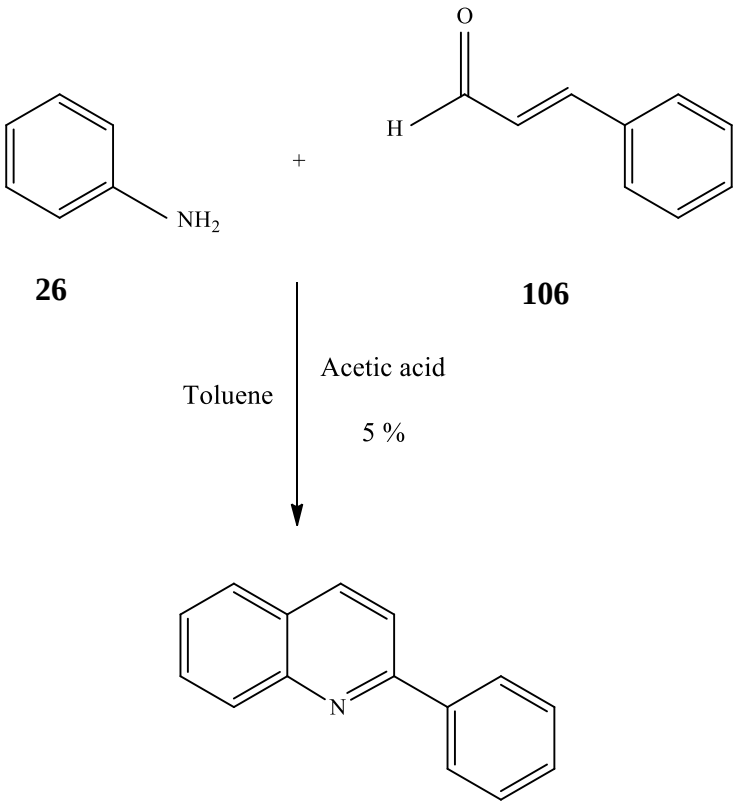


77-92 %

108 **109** **110**

Scheme 25

Inspired by these results, we were interested in applying this to the two-phase system for the synthesis of 2-phenylquinoline using commercially available acetic acid (vinegar, 5% acetic acid) under conventional heating and microwave conditions at 100 °C (**Scheme 26**). Aniline was dissolved in the aqueous phase and cinnamaldehyde formed part of the organic phase, toluene.



Scheme 26

The resulting mixture was filtered through a silica plug and the solvent removed *in vacuo* to produce a crude product which was analyzed by ^{1}H NMR spectroscopy. In both cases, the ^{1}H NMR spectra revealed the presence of a complex reaction mixture showing unreacted starting material and other unidentifiable peaks (**Figure 11**). For comparison reasons, glacial acetic acid was used in the synthesis of 2-phenylquinoline under the same reaction conditions, however, a similar NMR spectrum was obtained.

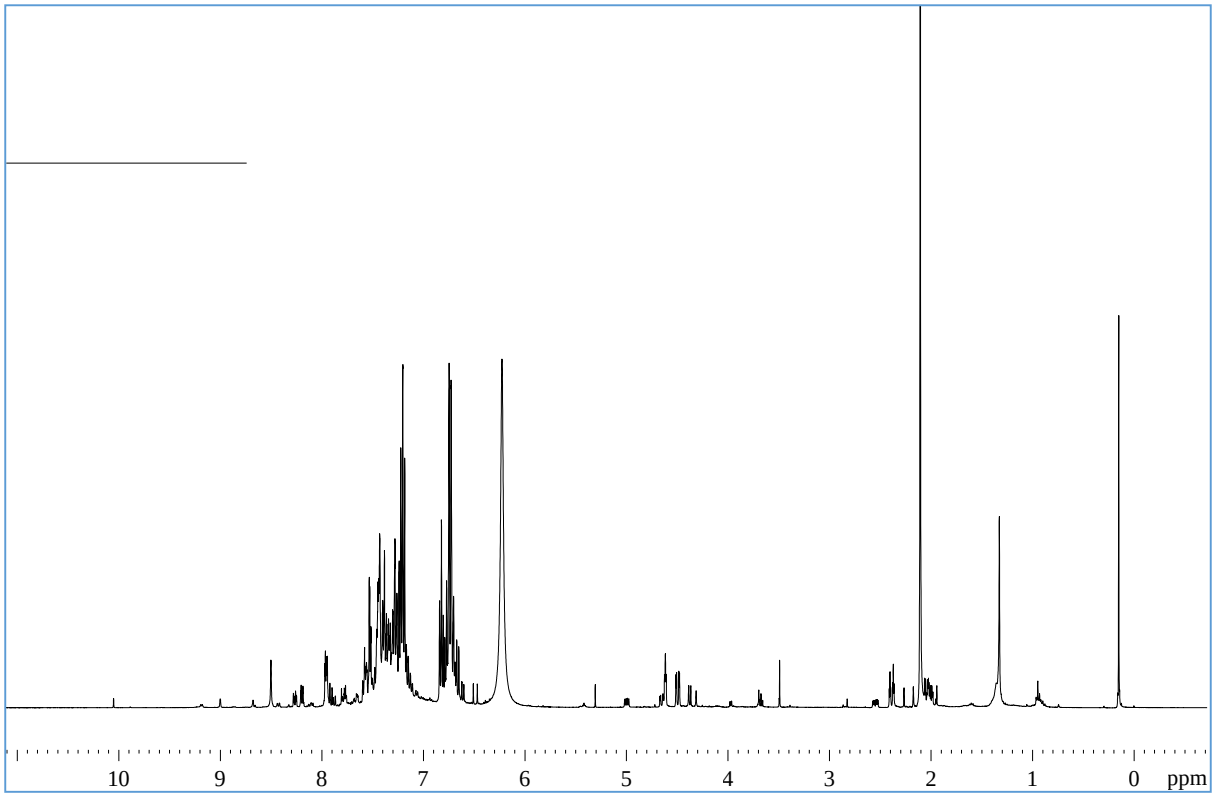


Figure 11

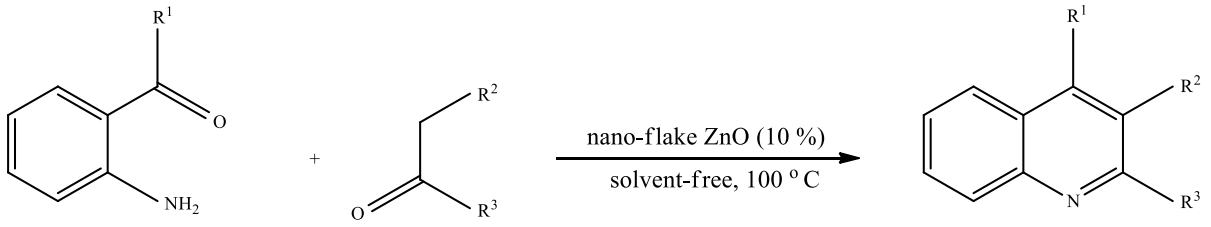
Dastan and co-workers[115] provided an interesting reasoning explaining the failure of these reactions. These authors stated that the use of solvents has an adverse effect on such reactions; the solvent keeps the reactants in the solution phase, making mass transfer an important, often limiting factor. It is known that heterogeneous reactions, in general, suffer from mass transport limitations due to the necessary transport of reactants from one phase to another. We then sought a new avenue to the Döebner-von Miller reaction by using a heterogeneous solid support as a catalyst.

Despite the success and advantages of using a biphasic system to access quinoline derivatives as mentioned previously, the central objective of synthetic organic chemistry during the last decades has been to develop greener and more economically competitive processes for efficient synthesis of heterocyclic compounds. In this context, solid acid catalysts under solvent-free

conditions carry a number of benefits. As all heterogeneous catalytic reactions occur on the surface of catalysts as it is the most direct and selective heating that one can provide.[115] Acidic and basic solid mineral oxides such as alumina, montmorillonite clay, bentonite, silica gel , dowex and amberlite act both as catalysts and supports.[116] The reactants, preadsorbed on the surface of the catalyst, are mobile[117] and react without serious mass transport limitations usually observed in liquid/liquid and liquid/solid systems.[118]

2.2.2 Application of nano-zinc oxide as a solid acid catalyst under solvent-free conditions

At this juncture, our attention was drawn to a number of interesting publications citing the development of zinc oxide (ZnO) as a catalyst for a diverse range of organic transformations in solvent free conditions.[119] [120] [121] [122] More inspiring was the application of nano zinc oxide in the synthesis of quinolines using the Friedlander heteroannulation method (**Scheme 27**).[123] In this synthetic procedure, substituted quinolines were obtained in moderate to excellent yields (43-98 %) presenting this as an efficient and eco-friendly process.



108 **109** **110**

R^1 = Me, Ph

R^2 = CO_2Me, CO_2Et, CO_2CH_2Ph, COMe, COcycloalkyl, $-COCF_3$ 43-98 %

R^3 = Me, $-CF_3$, cycloalkyl

Scheme 27

Zinc oxide was applied as an acidic solid support in the Döebner-von Miller synthesis of 2-phenylquinoline under solvent-free conventional heating conditions. Aniline and cinnamaldehyde were added to diethyl ether followed by the addition of nano-zinc oxide. The solvent was removed by rotary evaporation to obtain a free flowing powder which was heated at 100 ° C for 24 hours. Subsequent reactions followed by varying the time and the resulting crude products were submitted for ^{1}H NMR analysis. Once again, a complex reaction mixture was obtained for this series of experiments indicating the presence of starting material and other unidentifiable peaks (**Figure 12**, spectra showing reaction performed for 24 hours). With the limited success obtained from using zinc oxide, we moved onto silica as a possible solid acid catalyst.

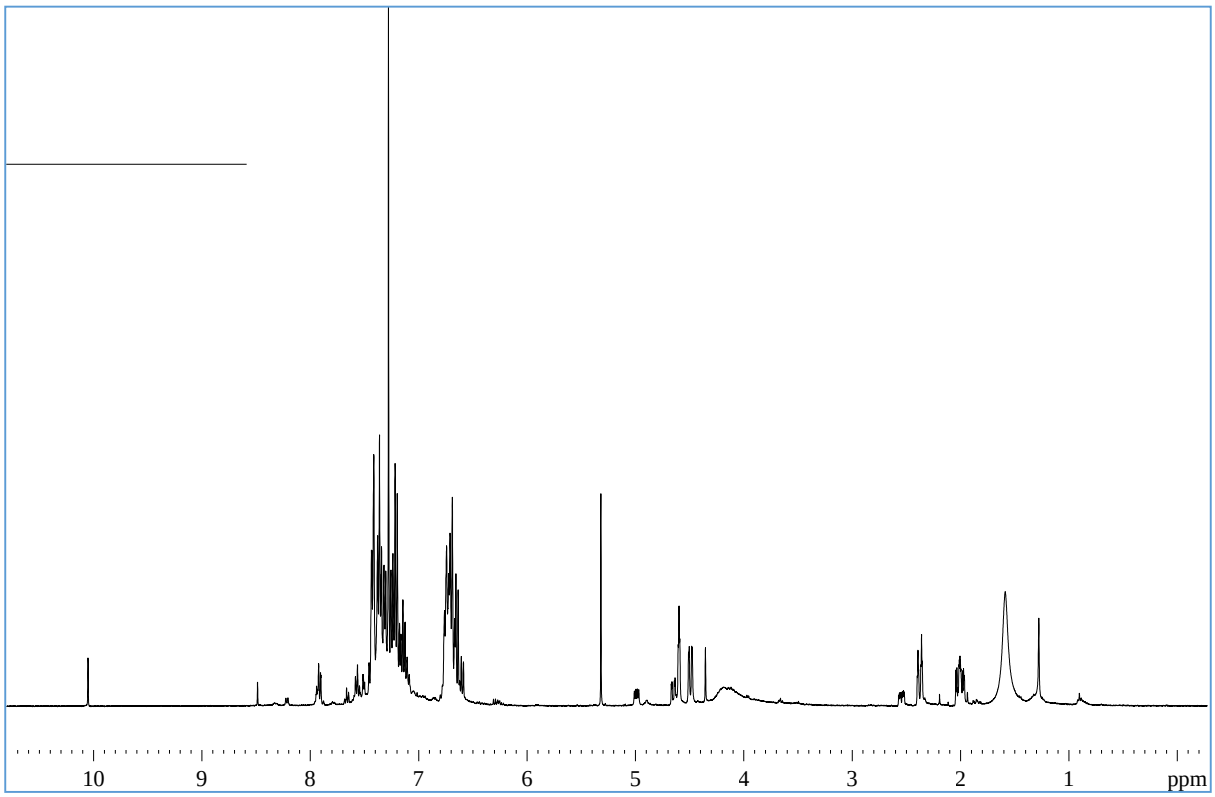
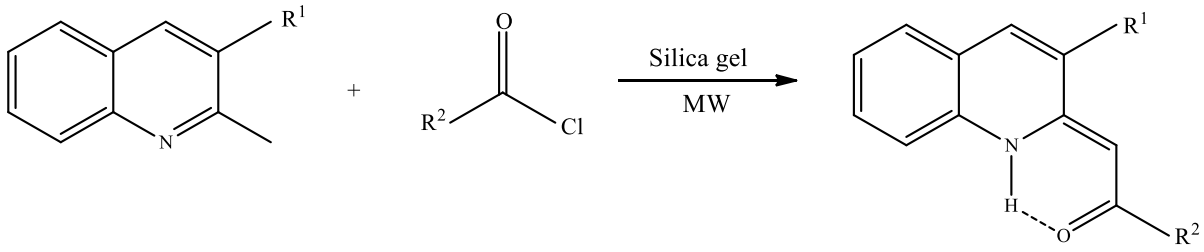


Figure 12

2.2.3 Application of Silica gel as a solid acid catalyst under solvent-free conditions

Silica gel has widely been utilized, not only as an effective adsorbent for chromatography, but also as a mild catalyst and reaction medium which is easily separable from the products after a reaction.[124] Recently, the use of silica-based heterogeneous catalysis has been reported in a number of organic transformations.[125] [126] [127] [128] The attractive features of this catalyst include (a) a thermally and chemically stable surface during the reaction process, (b) an abundant and inexpensive material, (c) easy to handle and low toxicity, (d) noncorrosive nature and air tolerant, and (e) reusability.[129]

Khouzani and co-workers[130] reported the synthesis of 2-ketomethylquinolines using silica gel as an efficient catalyst under solvent-free microwave irradiation conditions (**Scheme 28**). 2-Methylquinoline and 2, 3-dimethylquinoline were reacted with acyl chlorides affording the desired 2-ketoquinolines in yield of 60-90 %.



111 **112** **113**

R^1 = H, Me 60-90 %

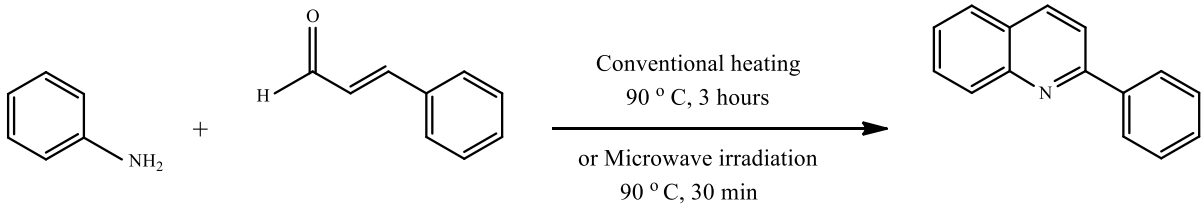
R^2 = C_6H_5, C_6H_5, 4-MeC_6H_4, 4-MeC_6H_4,

4-$MeOC_6H_4$, 2-ClC_6H_4, 4-BrC_6H_4, 2-pyridyl, 1-naphthyl, Bu^t

Scheme 28

In another study, Maleki and co-workers[131] reported a silica-based sulfonic acid catalyst as practical and efficient for the synthesis of highly substituted quinolines under solvent-free conditions at ambient temperature. The results of their study indicated the easy formation of quinoline derivatives in good to excellent yields (61-96 %). Ranu and co-workers[132] developed a microwave-assisted simple synthesis of quinolines from anilines and alkyl vinyl ketones on the surface of silica gel in the presence of indium(III) chloride. The easy formation of quinoline derivatives resulted in yields in the range of 55-87 %.

Since silica gel was readily available in our laboratory and based on the success enjoyed by the authors above, the Döebner-von Miller reaction was attempted using silica gel under solvent-free conventional and microwave conditions. In both cases, aniline and cinnamaldehyde were adsorbed onto the surface of silica gel and subjected to the respective reaction conditions (**Scheme 29**).



26 **106** **107**

Scheme 29

Conventional heating conditions yielded a complex reaction mixture with no identifiable peaks indicating product formation. In contrast, microwave irradiation showed a complex ^{1}H NMR spectra with trace amounts of product, mostly unreacted starting material and other unidentifiable peaks (**Figure 13**). Longer microwave irradiation (60 minutes) reactions were conducted and similar NMR spectra were obtained.

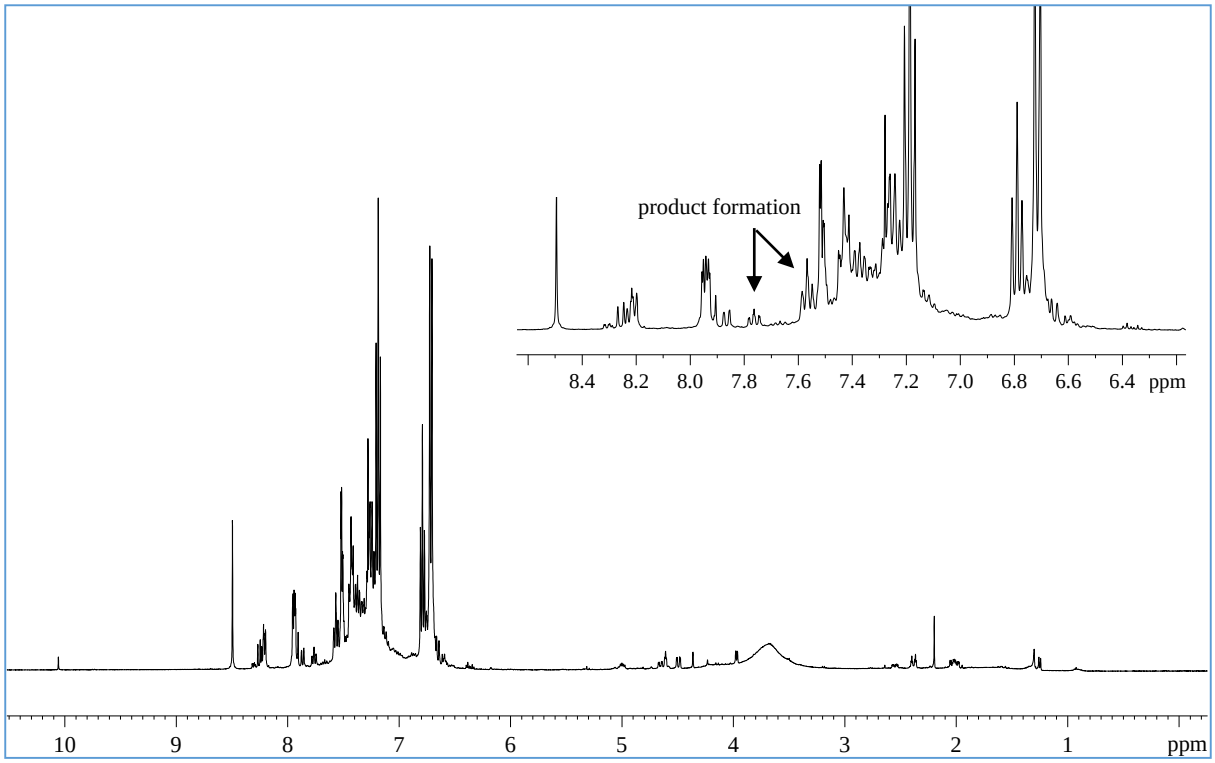


Figure 13

At this point, it was realized that the most likely successful route to the Döebner-von Miller reaction occurs on the surface of a solid support which acts as a catalyst and reaction medium. It was in this search for an alternative solid acid catalyst that our attention became focused on Montmorillonite K10 as a possible acidic solid support for the reaction of aniline with cinnamaldehyde under solvent-free conditions.[133]

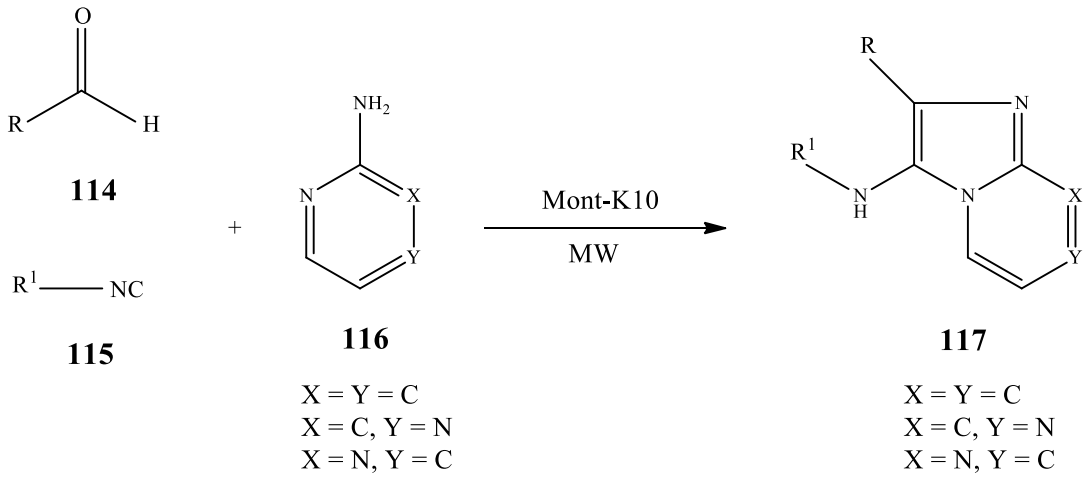
2.2.4 Application of natural and modified Montmorillonite K10 as a catalyst/solid support in heterocyclic chemistry

Recent years have witnessed a phenomenal growth in the use of mineral solid acids such as clays as a catalyst and reaction medium for various organic transformations.[134] The future of synthetic organic chemistry rests with heterogeneous media (clay minerals) rather than the

currently predominant homogeneous systems due to certain specific advantages of using solid surfaces. Solid clay catalysts have a broad range of functions including use as catalytically active agents (usually as solid acids), as bifunctional or inert supports and as filters to give solid catalysts with required physical properties.[134]

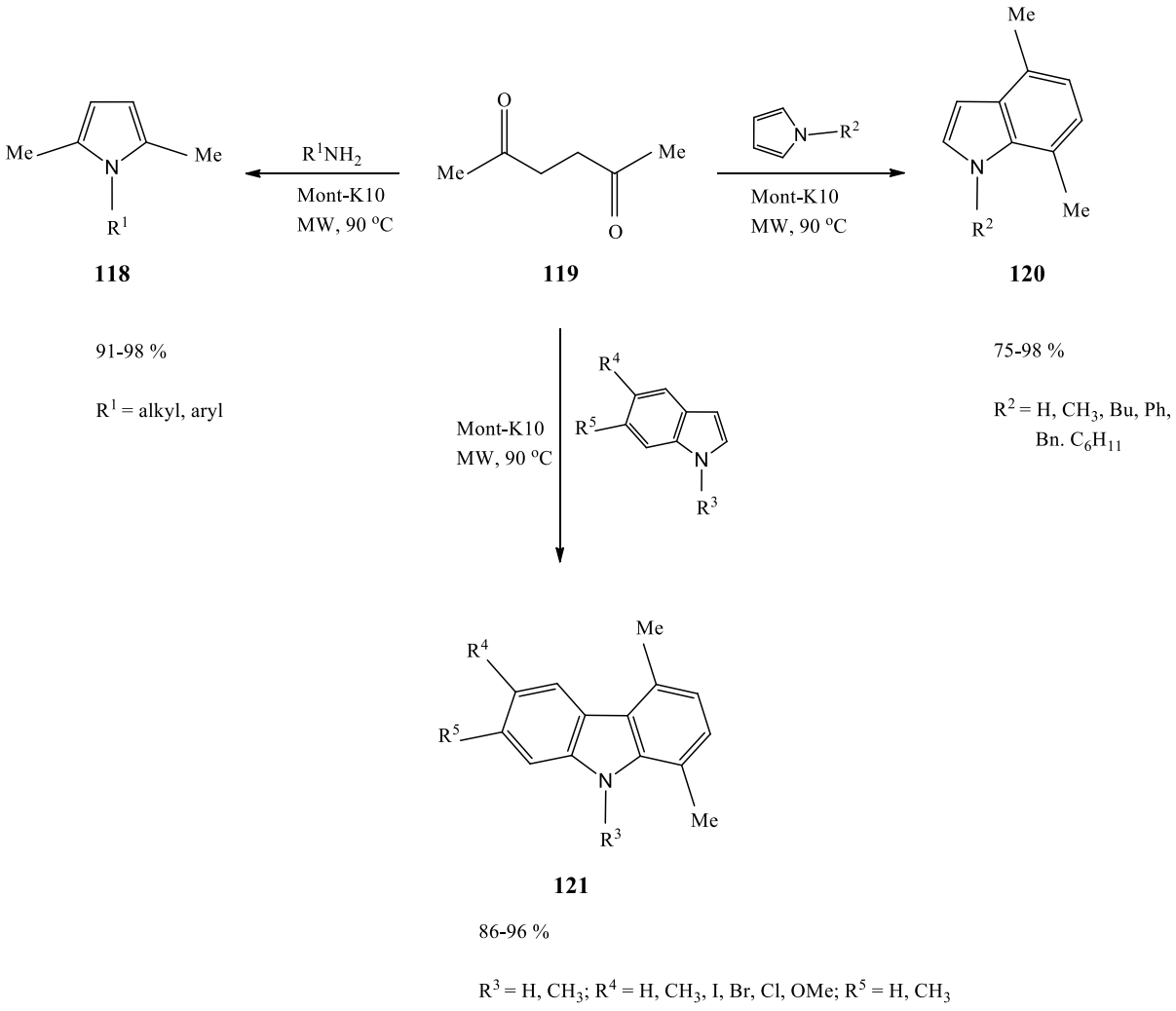
The application of natural clays as solid acid catalysts for chemical reactions constitutes an exciting component of green chemistry.[134] The common solid acid catalyst, Montmorillonite K10, $Al_2Si_4O_{10}(OH)_2.nH_2O$, has been used as a catalyst for various organic syntheses[115] [134] [135] [136] [137] [138] and offer several advantages over classical acids. For example the strong acidity, non-corrosive properties, cheapness, mild reaction conditions, high yields and selectivity and the ease of setting and working-up.[139]

The imiazo[1, 2-*a*] annulated nitrogen heterocycles bearing the pyridine, pyrazine, and pyrimidine moieties constitute a class of biologically active compounds that are potent anti-inflammatory agents, antibacterial agents, inhibitors of gastric acid secretions and calcium channel blockers.[140] Varma and co-worker developed a rapid one-pot microwave synthesis of imidazo[1, 2-*a*] annulated pyridines, pyrazines and pyrimidines (56-88 %) in the presence of recyclable Montmorillonite K10 under solvent free conditions, a process that is adaptable for the parallel assembly of a library of compounds (**Scheme 30**).[141] Their study showed that this process is general for all the three components, e.g. aldehydes (aliphatic, aromatic and vinylic), isocyanides (aliphatic, aromatic and cyclic) and amines (2-aminopyridine, 2-aminopyrazine and 2-aminopyrimidine).



Scheme 30

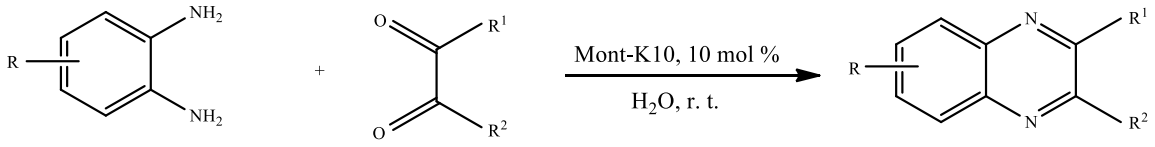
Montmorillonite K10 has been shown to act as a solid-acid catalyst in the solvent-free catalyzed electrophilic reactions for the synthesis of pyrroles, indoles and carbazoles from primary amines, pyrroles and indoles respectively (**Scheme 31**).[142] A wide variety of primary amines, pyrroles and indoles were reacted with 2, 5-hexandione (alkylating agent) to obtain the corresponding heterocyclic products in excellent yields.



Scheme 31

In another study, Montmorillonite K10 has shown application in the synthesis of quinoxaline derivatives which find use in areas such as medicine, dyes, electron luminescent materials, organic semiconductors and others[143] and is commonly prepared by the condensation of 1, 2-diketones with *o*-phenylene diamines. A variety of catalysts are used, particularly acidic or oxidizing reagents and in most cases, an organic solvent is used. Huang and co-workers have overcome the eco-disadvantages associated with using such catalysts and organic solvents by making use of Montmorillonite K10 in water at room temperature (**Scheme 32**).[144] The reaction yields the quinoxaline derivatives in excellent yields (90-100 %, 70 % when the

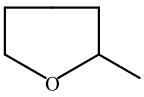
diamine has an electron withdrawing NO_2 group) and the catalyst can be reused without much loss in activity.



122 **123** **124**

R = H, CH_3, NO_2

$R^1 = R^2 = C_6H_5$

$R^1 = R^2 =$ 

$R^1 = C_6H_5$; $R^2 = CH_3$

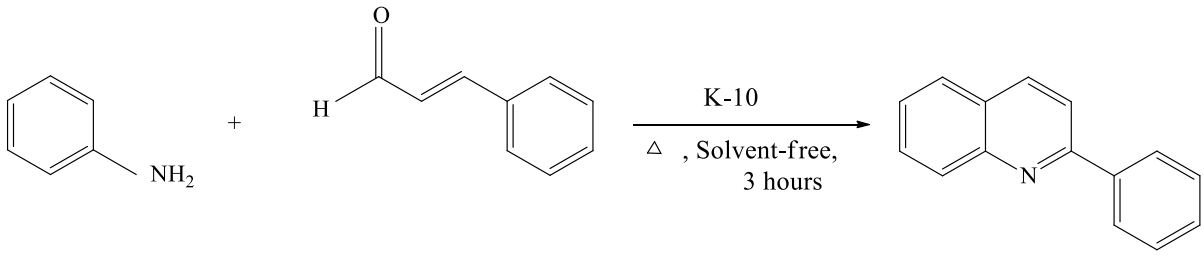
$R^1 = R^2 = CH_3$

90-100 % when R = H, CH_3

70 % when R = NO_2

Scheme 32

Inspired by the results obtained by the authors above, we attempted to apply Montmorillonite K10 to the synthesis of 2-phenylquinoline using the Döebner-von Miller reaction under conventional heating conditions. In the first experiment, aniline and cinnamaldehyde were added to toluene followed by the addition of Montmorillonite K10 and the reaction was heated for 3 hours (**Scheme 33**).



26 **106** **107**

Scheme 33

After purification by column chromatography, a clean ^{1}H (**Figure 14**) and ^{13}C (**Figure 15**) NMR was obtained corresponding to the correct chemical shifts and integration as indicated by literature,[145] and only a 21% yield achieved. The yield obtained is low however, in the realm of the Döebner-von Miller reaction, this is a satisfactory yield. Based on these results, attention was focused on optimizing the reaction conditions using Montmorillonite K10 as a source of solid support to optimize the reaction conditions.

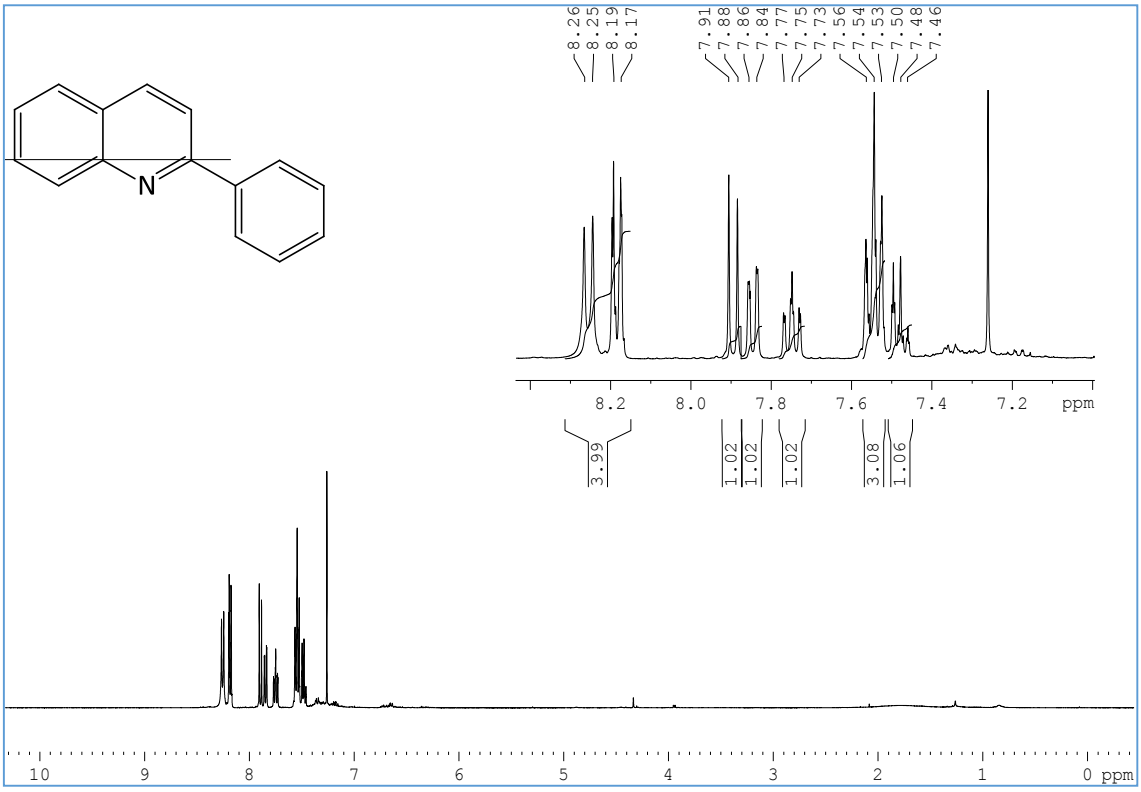


Figure 14

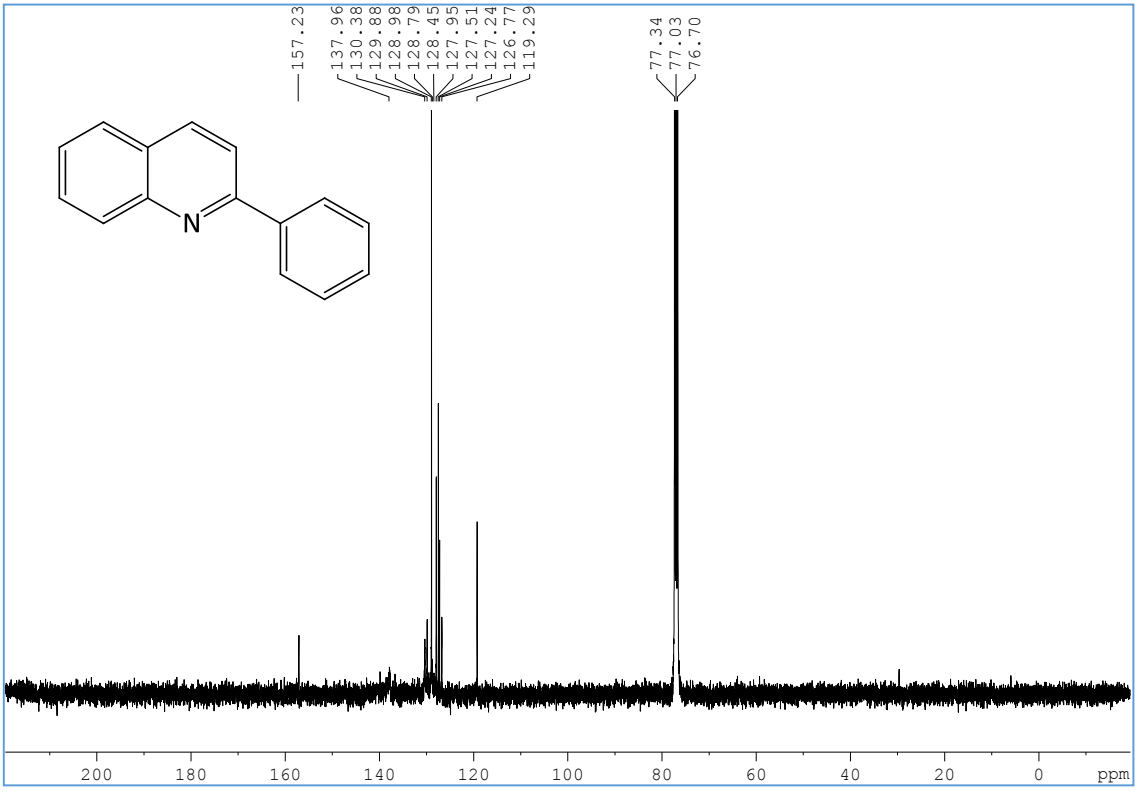


Figure 15

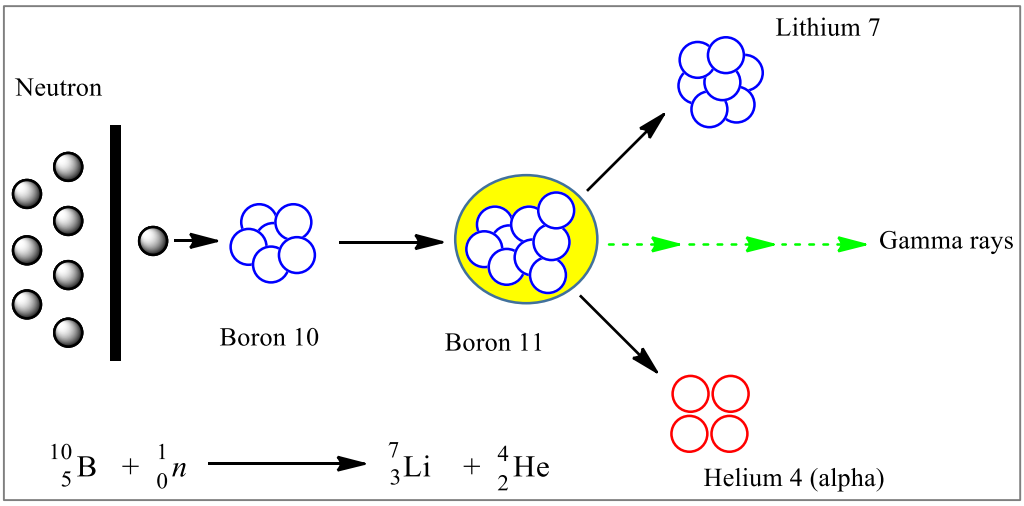
Natural Montmorillonite K10 being a negatively charged silicate has excellent cation exchange properties[146] [147] allowing alteration of the acidic sites by a simple ion-exchange procedure.[148] Cationic-exchanged catalysts, e. g. Fe^{n+}-Mont K10,[149] [150] Pd-Cu^{n+}-Mont K10,[151] Pd/C-Mont-K10,[152] [153] Zn^{n+}-Mont K10,[154] [155] Al^{n+}-Mont K10,[156] [157] Ni^{n+}-Mont K10[149] [158] [159] and Cu^{n+}-Mont K10[149] [151] have recently been shown to have great potential as solid-acid catalysts for various organic transformations. Owing to the vast nature of cationic-exchanged catalysts used in the synthesis of many organic compounds, we attempted to incorporate boron due to its application in Boron Neutron Capture Therapy (BNCT) so that the compounds synthesized, together with boron, could be used as a possible drug in the treatment of many cancer types.

2.2.5 Boron Neutron Capture Therapy (BNCT) and the application of boron modified Montmorillonite K10 in the synthesis of 2-phenylquinoline

An ideal treatment for cancer would be one whereby tumor cells are selectively destroyed altogether, without damaging normal tissue cells.[160] The treatment itself or the help of the body's immune system should destroy most of the cancer cells, preventing the danger that exists – the tumor cells may re-establish itself. Although today's standard approaches to treating cancer – surgery, radiation therapy and chemotherapy – have successfully cured many classes of cancers, many treatment failures still exist. The possibilities of a new experimental cancer therapy with some indication of its potential efficiency has led many scientists to work on an approach known as Boron Neutron Capture Therapy (BNCT).[160]

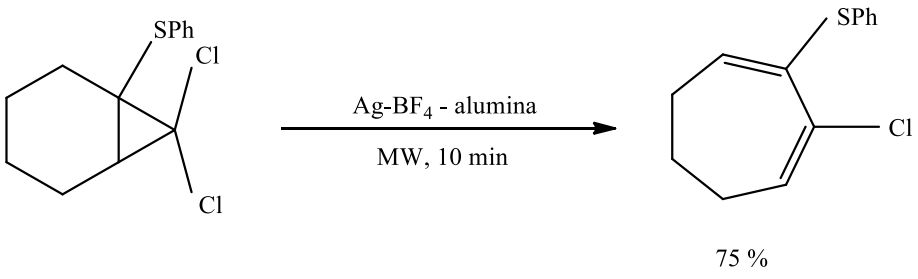
Boron Neutron Capture Therapy (BNCT) is a promising treatment for many cancer types, a form of binary radiotherapy that brings together two components that when kept separate have only minor effects on cells.[161] The principle of BNCT depends upon two factors: a selective concentration of a suitable neutron capture element within or near the tumor cells and the delivery of an adequate thermal neutron fluence to the tumor region.[162]

BNCT treatment consists of two key stages: the first is the preferential accumulation in tumor cells, with the isotope boron – 10 (^{10}B) which has a suitable affinity for neutrons at a certain energy.[163] Secondly, the tumor is irradiated with thermal neutrons at an energy such that their probability for capture is maximized.[163] When a thermal neutron is captured by a ^{10}B atom, the resulting reaction produces an alpha (^{4}He) and lithium (^{7}Li) particle. Consequently, the alpha and lithium particle, in principle, can break the deoxyribonucleic acid (DNA) strands of the tumor cell resulting in cancer cell death (**Scheme 34**).[164]



Scheme 34

A simple application of boron in organic synthesis was described by Villenim and co-worker.[165] These authors described an efficient ring expansion transformation under solvent-free conditions in the presence of silver tetraflouroborate ($AgBF_4$) adsorbed alumina. The reaction occurs under microwave conditions producing the desired product in good yields (**Scheme 35**).



125 **126**

Scheme 35

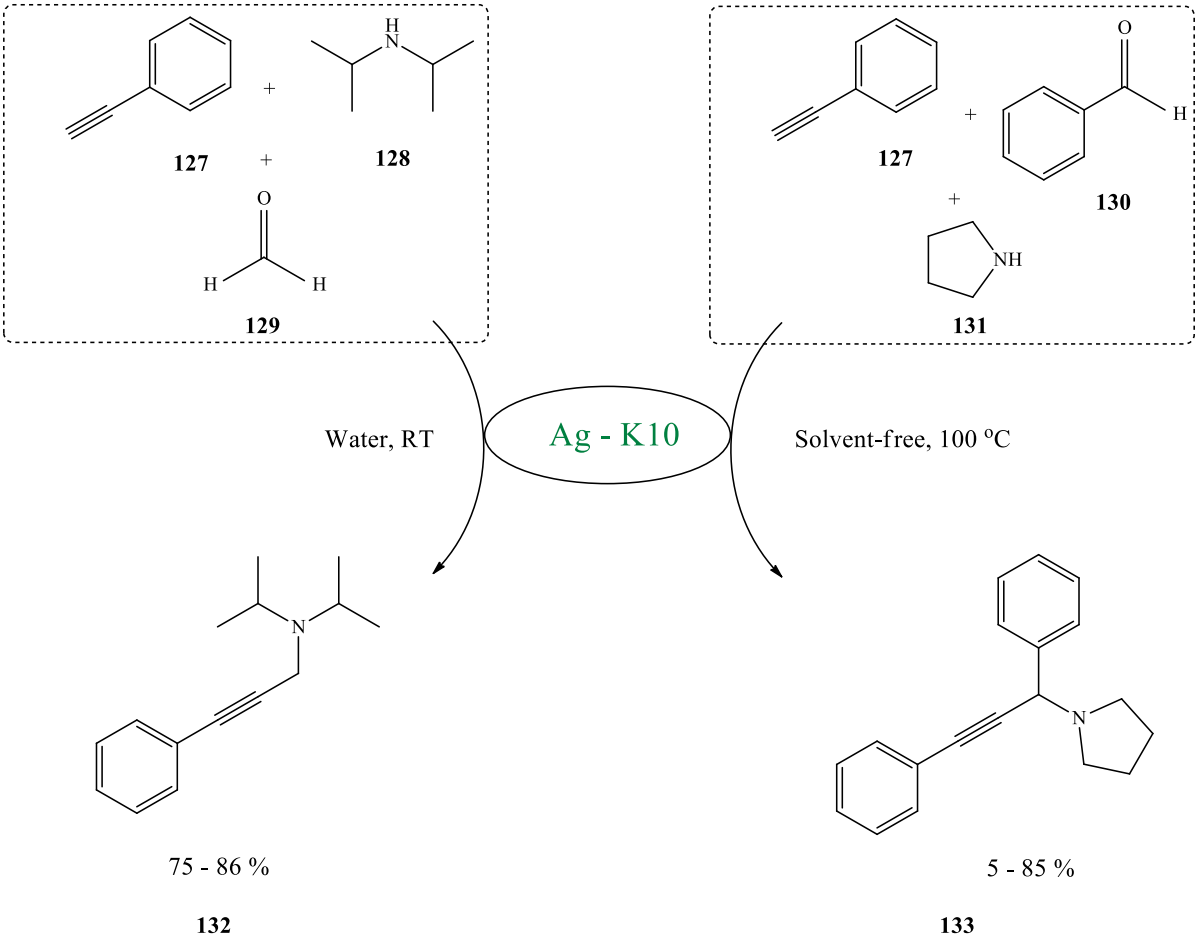
While we are still uncertain how this would progress, we wanted to apply boron to the synthesis of 2-phenylquinoline and its derivatives for a long term application in BNCT.

Using the above protocol as a guide, the synthesis of 2-phenylquinoline was attempted using boron exchanged Montmorillonite K10 under solvent-free, conventional heating conditions. The crude mixture was passed through a silica plug, the solvent removed *in vacuo*, and analyzed by ^{1}H NMR spectroscopy. The results showed a complex ^{1}H NMR spectra with unreacted starting material and no product peaks.

2.2.6 Application of Silver(I)-exchanged Montmorillonite K10 in the synthesis of 2-phenylquinoline

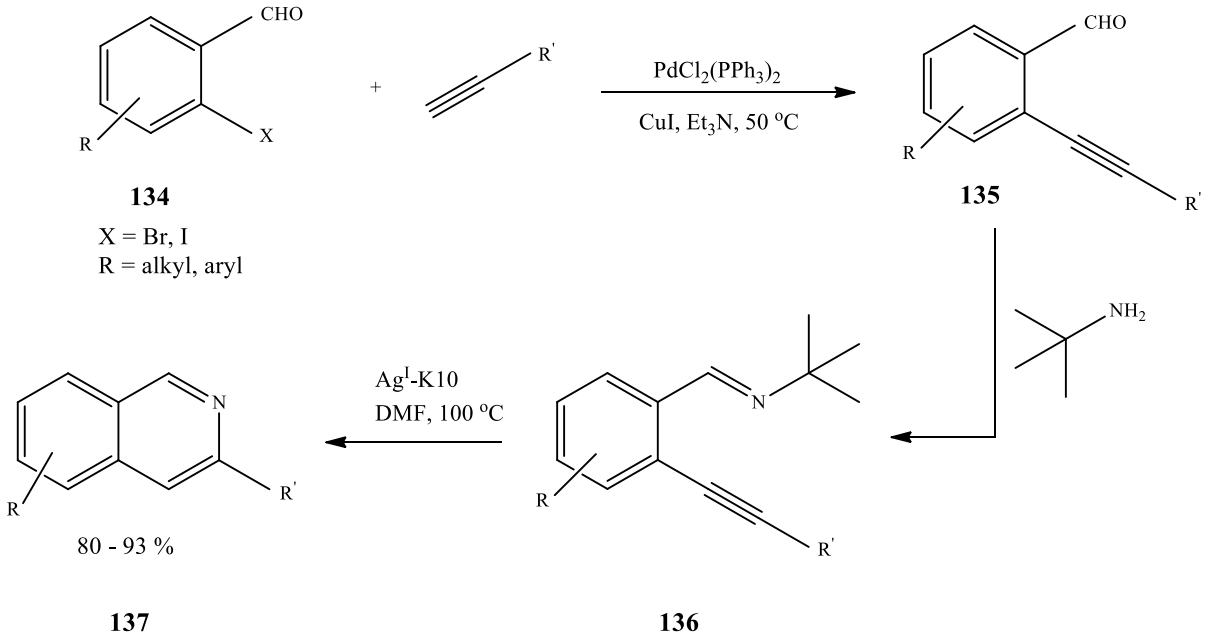
Whilst looking at optimizing the reaction conditions two significant findings to the success of this project was discovered. Jeganathan and co-workers[166] had reported the use of silver(I)-exchanged Montmorillonite K10 for the synthesis of propagylamines under room temperature conditions. They reported that 50 mg of Ag(I)-exchanged Montmorillonite K10 (4.57 % silver content) can be used to synthesize propagylamines in good to excellent yields (**Scheme 36**).

More importantly, they stated that the reaction can also be performed under solvent-free conditions in the case of aromatic and aliphatic aldehydes, affording propagylamines in higher yields.[166]



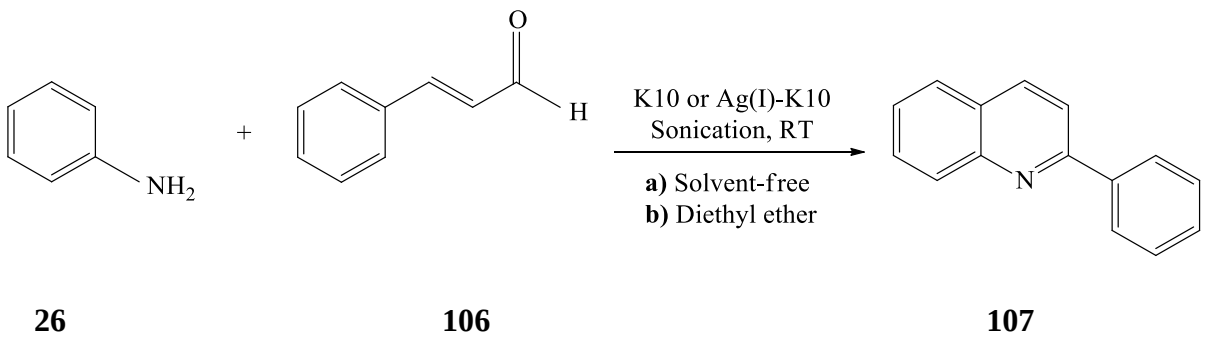
Scheme 36

In another study, Jeganathan and co-worker reported the synthesis of substituted isoquinolines *via* iminoalkyne cyclization using silver(I)-exchanged Montmorillonite K10 as a recyclable catalyst.[167] A reported 20 mg of Ag(I)-exchanged Montmorillonite K10 in the presence of dimethylformamide (DMF) was used to synthesize isoquinoline derivatives in excellent yields (**Scheme 37**).



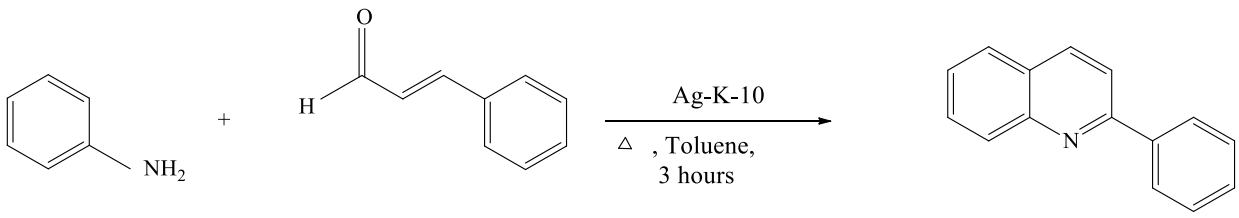
Scheme 37

Notably, in the above two syntheses, no additional base, co-catalyst or other activator is required and the reactions proceed smoothly and tolerates various functional groups. Based on the above, we decided to employ silver(I)-exchanged Montmorillonite K10 in the synthesis of quinoline derivatives hoping to achieve positive results. Montmorillonite K10 and silver(I)-exchanged Montmorillonite was used to optimize the reaction conditions under various sonication conditions (**Scheme 38**) and in all cases, the yield of the desired product was disappointing (trace to 10%).



Scheme 38

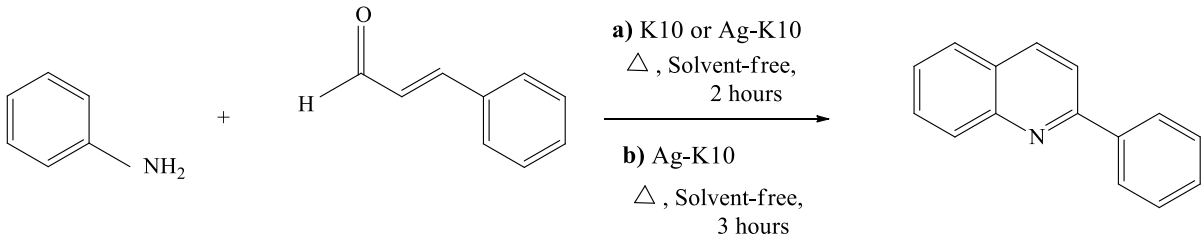
The results of the sonication experiments showed that conventional heating conditions are necessary for the reaction to proceed. Moreover, blank control experiments showed the absence of product indicating that a catalyst is required. The general quinoline reaction was then repeated using silver(I)-exchanged Montmorillonite K10 in the presence of toluene under conventional heating conditions for 3 hours (**Scheme 39**). Crude ^{1}H NMR spectroscopy revealed the presence of product, thus the reaction was repeated to obtain an isolated yield. Hence, 2-phenylquinoline was obtained in an isolated yield of 29 % compared to natural Montmorillonite K10 under the same reaction conditions.



26 **106** **107**

Scheme 39

This most promising result enabled us to optimize the reaction conditions using silver-exchanged Montmorillonite K10 as a solid acid catalyst. In addition, we decided to compare the yields of subsequent reactions to those obtained using natural Montmorillonite K10 in order to confirm the superior activity of Ag-K10. Thus, the reaction was repeated for two hours under solvent-free conditions using Montmorillonite K10 and silver-exchanged Montmorillonite K10, respectively. The crude sample was purified using column chromatography to give the desired product in an isolated yield of 43% and 65%, respectively. At this point, we were confident that Ag-K10 is a superior catalyst to natural Montmorillonite K10, the reaction was repeated for three hours using Ag-K10. The contents were purified using column chromatography and, to our delight, the desired product was isolated in a yield of 89% (**Scheme 40**).

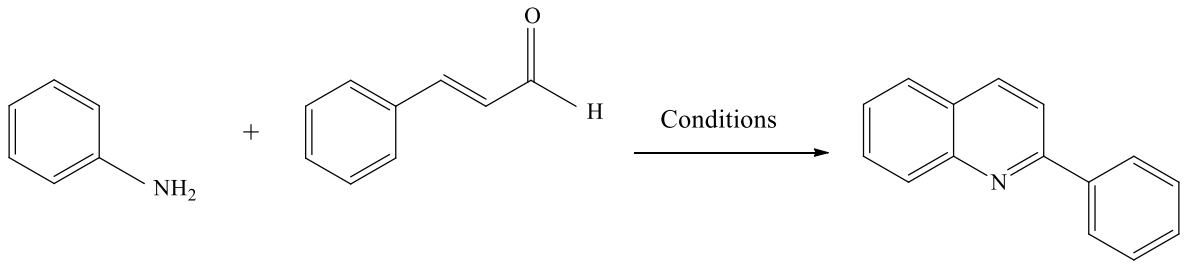


26 **106** **107**

Scheme 40

2.2.7 Summary of results of optimization study

Natural and silver-exchanged Montmorillonite K10 mediated 2-phenylquinoline synthesis was evaluated under various reaction conditions. The best results were obtained under solvent-free conventional heating conditions using Ag-K10. A summary of the results from this study is given in **Table 1**.



26 **106** **107**

Entry	Method[a]	Catalyst	Solvent	*T* (°C)[b]	Time (min)	Isolated Yield (%)
1	Sonication	Mont-K10	neat	RT	180	trace
2	Sonication	Mont-K10	Diethyl ether	RT	180	trace
3	Sonication	Ag(1)-K10	neat	RT	180	trace
4	Sonication	Ag(1)-K10	Diethyl ether	RT	180	trace
5	CH	None	Neat	90	180	0
6	CH	Mont-K10	Toluene	110	180	21
7	CH	Ag(1)-K10	Toluene	110	180	29
8	CH	Mont-K10	neat	120	180	43
9	CH	Ag(1)-K10	neat	120	120	65
10	**CH**	**Ag(1)-K10**	**neat**	**120**	**180**	**89**

[a] CH- Conventional heating

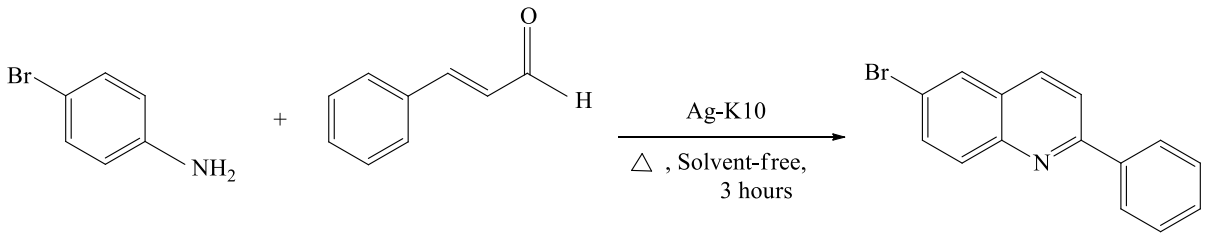
[b] RT – Room temperature

With the optimized procedure in hand, the scope and limitations of Ag(I)-exchanged Montmorillonite K10 were further evaluated using a series of substituted anilines with cinnamaldehyde.

2.3 SYNTHESIS OF QUINOLINE DERIVATIVES USING SILVER-EXCHANGED MONTMORILLONITE K10 UNDER SOLVENT-FREE CONDITIONS

2.3.1 Synthesis of 6-Bromo-2-phenylquinoline

This study commenced with *p*-Bromoaniline **137** and the corresponding quinoline was synthesized by reacting with cinnamaldehyde **106** in the presence of Ag-K10 under the optimized reaction conditions described earlier (**Scheme 41**).



138 **106** **139**

Scheme 41

The resulting crude mixture was purified by column chromatography to afford the title compound **139** in an isolated yield of 42%. The ^{1}H NMR spectrum (**Figure 16**) revealed the presence of the product with the expected peaks obtained at the correct chemical shifts. The GC-MS analysis (**Figure 17**) showed the product to be relatively pure with one major peak at a retention time of 6.74 minutes corresponding to the target compound mass of 284 g.mol^{-1}.

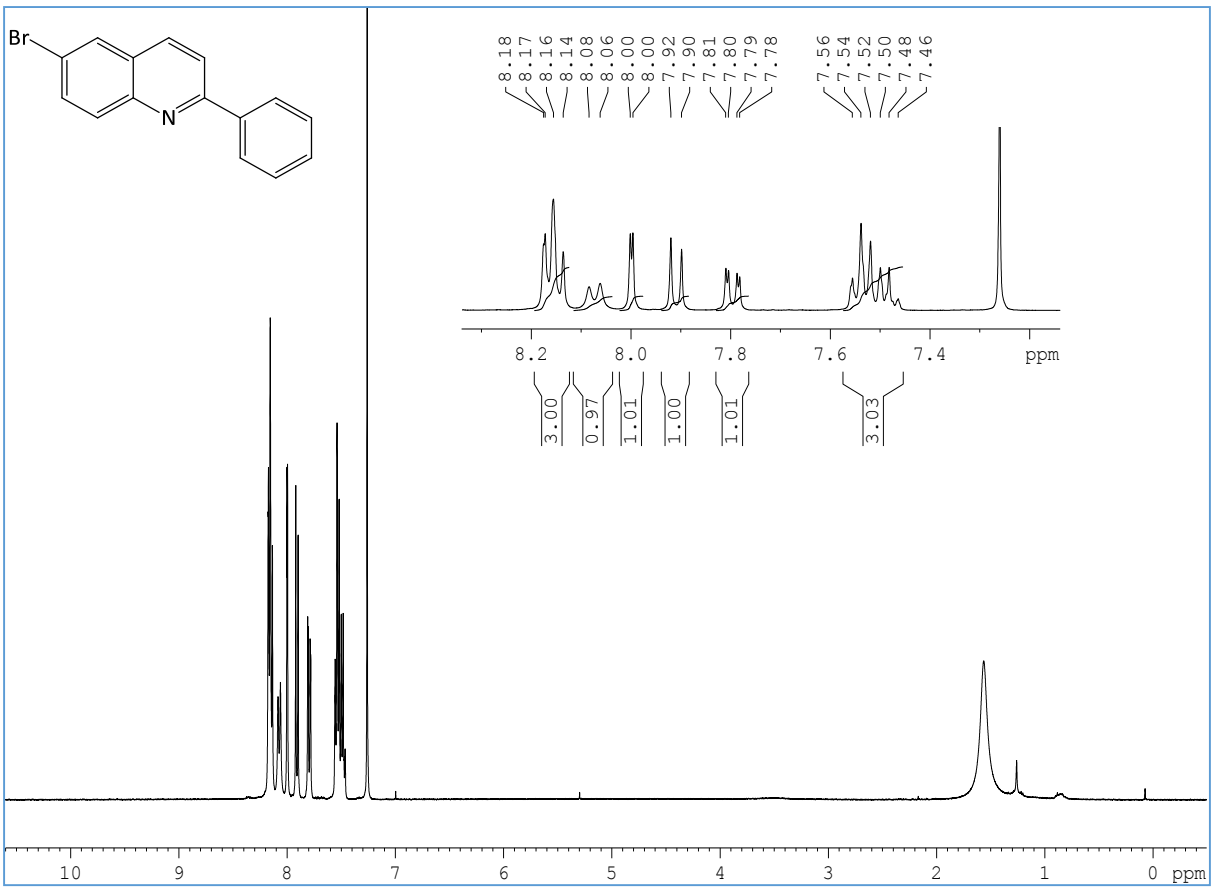


Figure 16

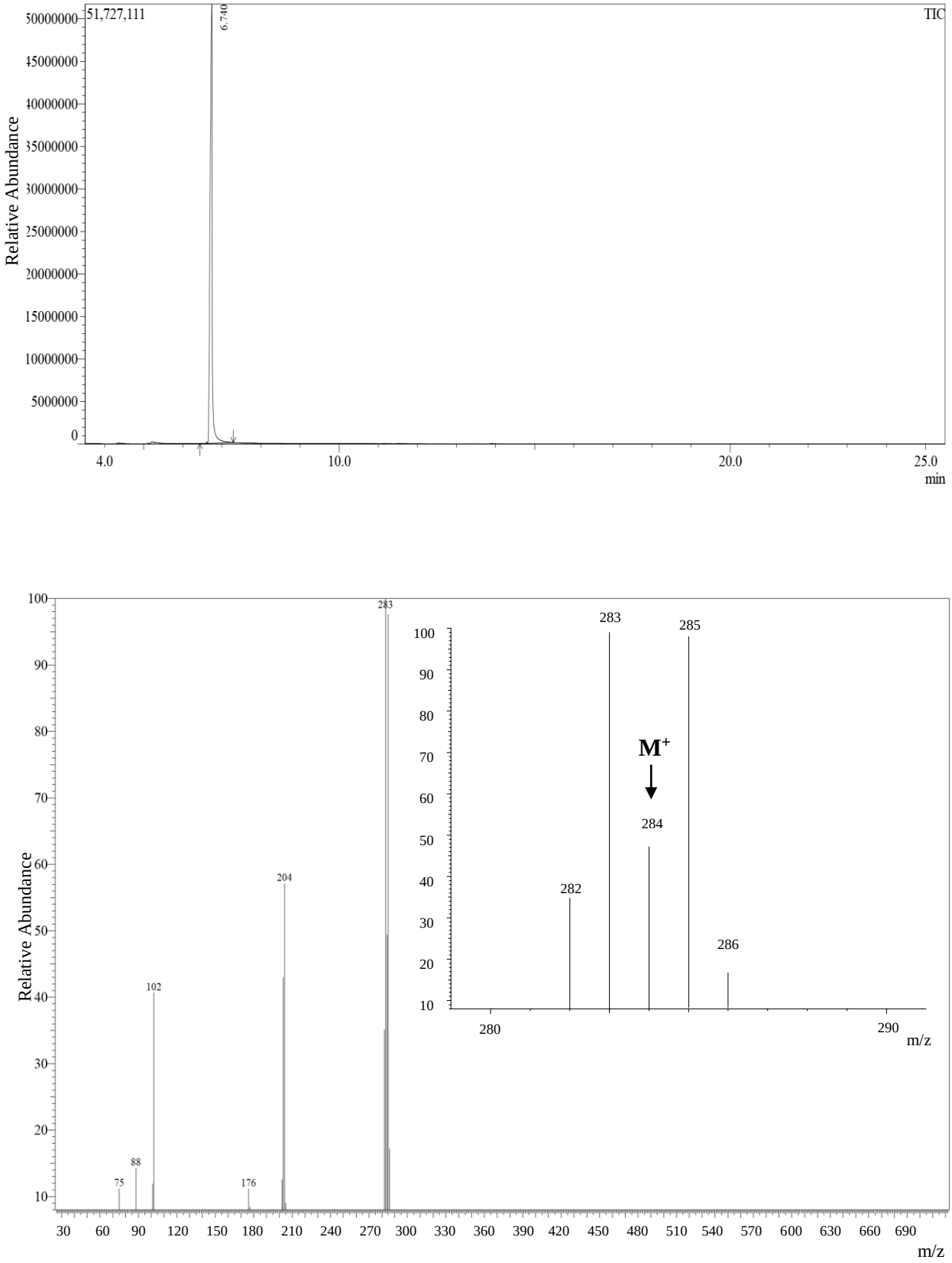
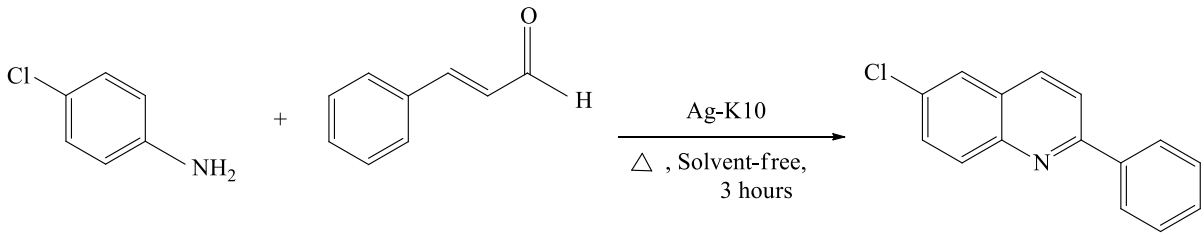

51,727,111
6.740
TIC
Relative Abundance
50000000
45000000
40000000
35000000
30000000
25000000
20000000
15000000
10000000
5000000
0
4.0
10.0
20.0
25.0
min
100
90
80
70
60
50
40
30
20
10
Relative Abundance
283
204
102
88
75
176
30 60 90 120 150 180 210 240 270 300 330 360 390 420 450 480 510 540 570 600 630 660 690
m/z
283
285
M+
284
282
286
280
290
m/z

Figure 17

2.3.2 Synthesis of 6-Chloro-2-phenylquinoline

The second substrate on which silver-exchanged Montmorillonite K10 was examined was the reaction of *p*-Chloroaniline **140** with cinnamaldehyde for three hours under solvent-free conditions (**Scheme 42**).



140 **106** **141**

Scheme 42

After this time period, the resulting crude mixture was analyzed for the presence of 6-Chloro-2-phenylquinoline using ^{1}H NMR spectroscopy. The reaction mixture was purified by column chromatography yielded the desired product in 56%. Analysis of the proton NMR confirmed the presence of the desired product. Further analysis of the Infra-red (IR) spectrum (**Figure 18**) revealed absorption bands at υ_{max} 3055 (=C–H, aromatic), 2918 (–C–H, aromatic), 1464 (C–C, in ring, aromatic), 1330 (C–N, aromatic amine), 831 (C–Cl, alkyl halide) cm^{-1} consistent with literature.[168] [169] Moreover, the melting point (108-111 ℃) temperature compares favourably with literature (108-110 °C),[168] [169] indicating a pure sample.

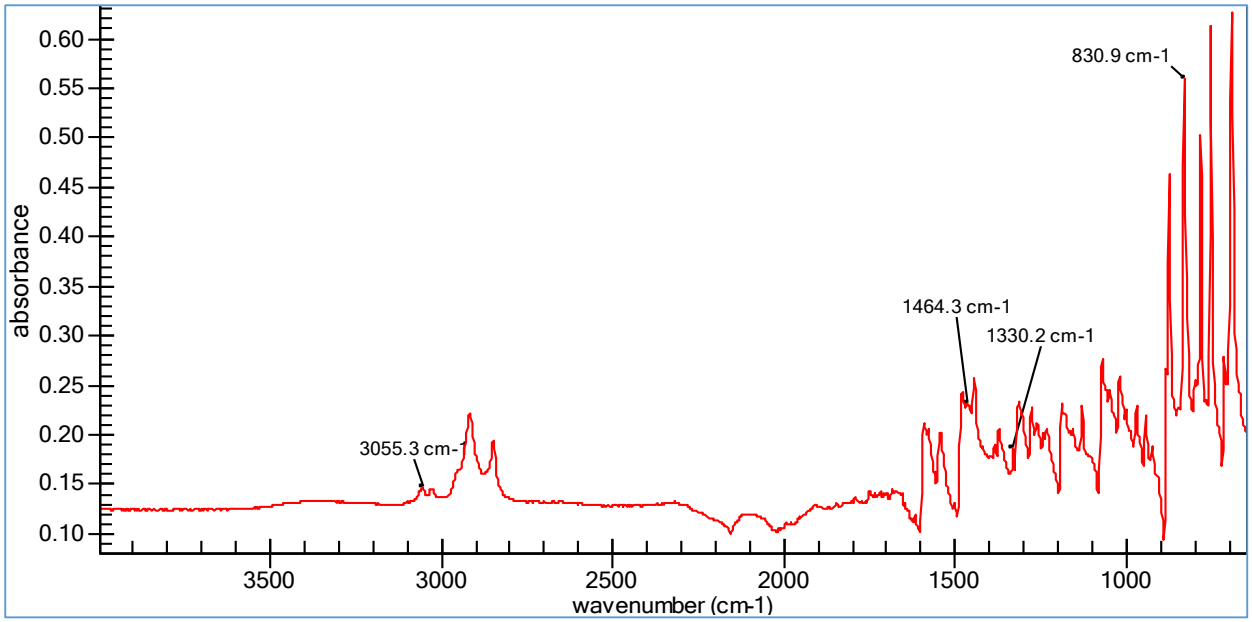
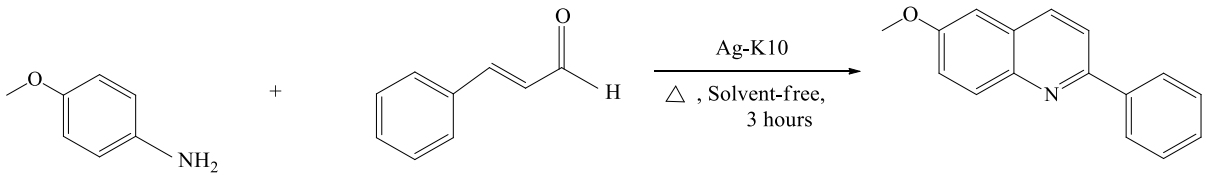

absorbance
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
3500
3000
2500
2000
1500
1000
wavenumber (cm-1)
830.9 cm-1
1464.3 cm-1
1330.2 cm-1
3055.3 cm-1

Figure 18

2.3.3 Synthesis of 6-Methoxy-2-phenylquinoline

The amine, *p*-anisidine, **142**, and cinnamaldehyde **106** was synthesized using the optimum reaction conditions to produce the desired product, 6-Methoxy-2-phenylquinoline **143**, in an isolated yield of 46% (**Scheme 43**).



142 **106** **143**

Scheme 43

The ^{1}H NMR spectrum was assigned (**Figure 19**) and compared to Demaude and co-workers[170] and all the expected peaks were obtained. The GC-MS analysis (**Figure 20**) revealed the product to be relatively pure with one major peak at a retention time of 6.52 min corresponding to the target compound mass of 235 $g.mol^{-1}$ in an isolated yield of 46%.

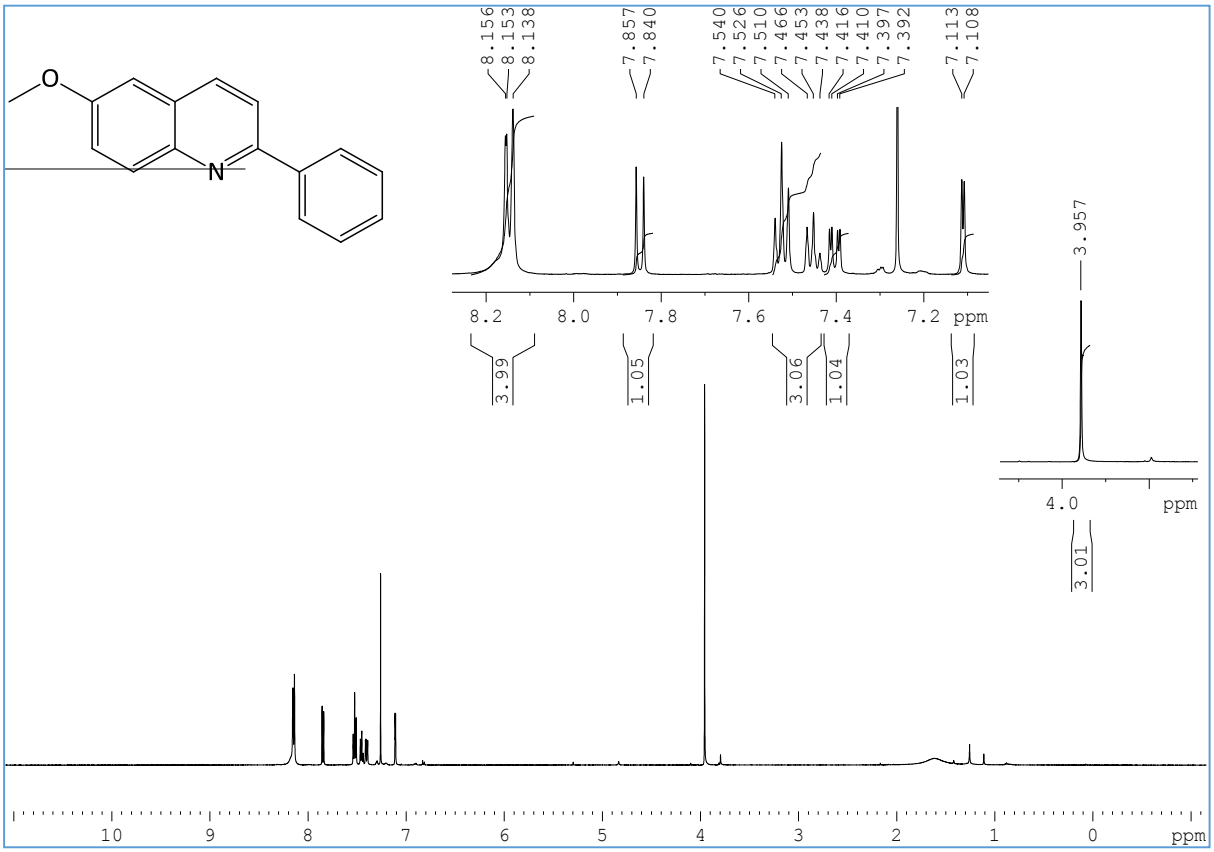

O
N
8.156
8.153
8.138
7.857
7.840
7.540
7.526
7.510
7.466
7.453
7.438
7.416
7.410
7.397
7.392
7.113
7.108
8.2
8.0
7.8
7.6
7.4
7.2 ppm
3.99
1.05
3.06
1.04
1.03
3.957
4.0
ppm
3.01
10
9
8
7
6
5
4
3
2
1
0
ppm

Figure 19

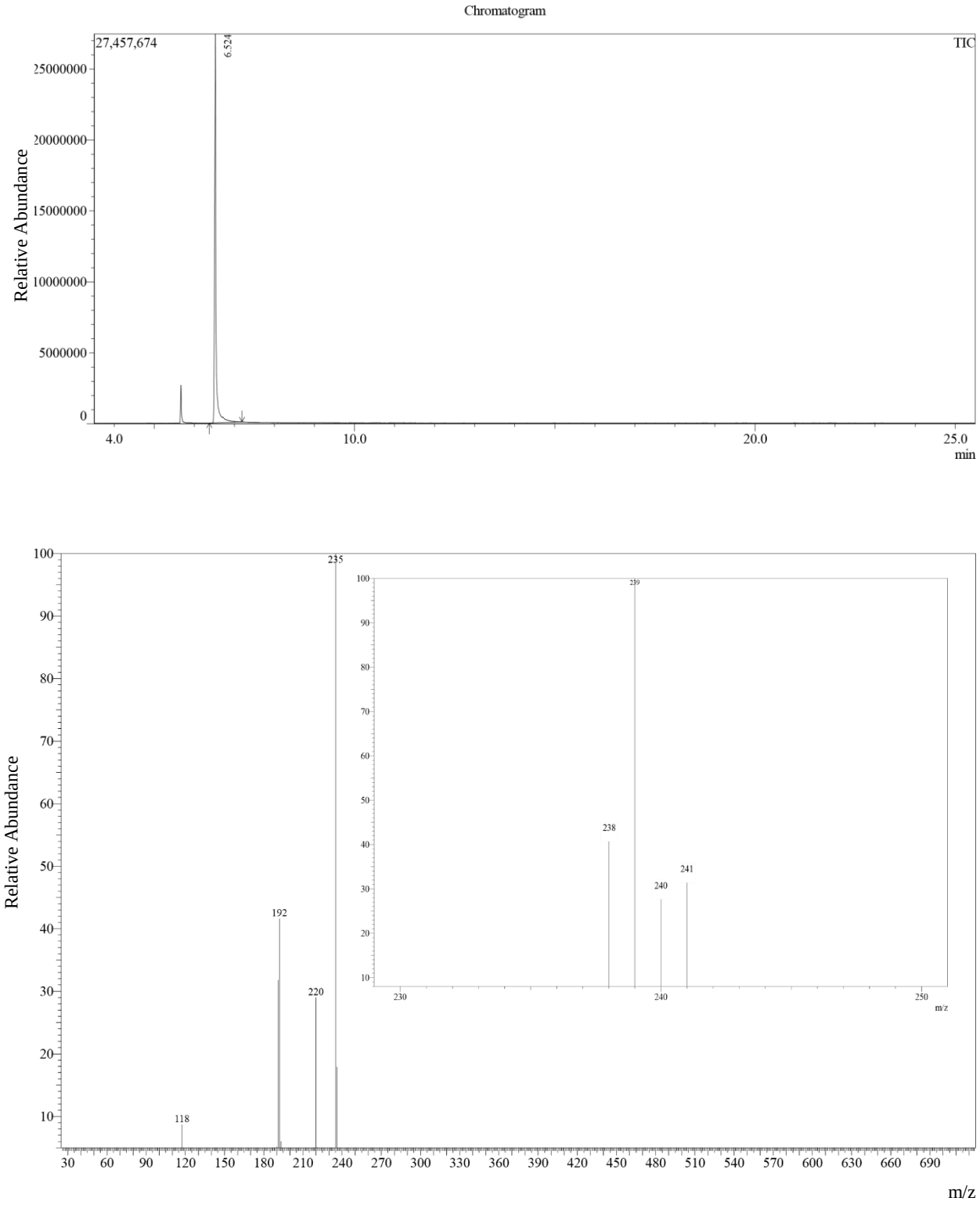
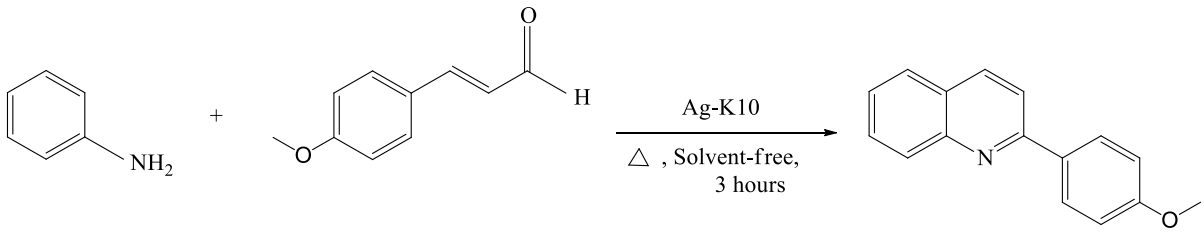

Chromatogram
27,457,674
6.524
TIC
Relative Abundance
25000000
20000000
15000000
10000000
5000000
0
4.0
10.0
20.0
25.0
min
100
90
80
70
60
50
40
30
20
10
235
192
220
118
239
238
240
241
230
240
250
m/z
30 60 90 120 150 180 210 240 270 300 330 360 390 420 450 480 510 540 570 600 630 660 690
m/z

Figure 20

2.3.4 Synthesis of 2-(4-methoxyphenyl)quinoline

The aldehyde component was then varied by using trans-*p*-methoxycinnamaldehyde **144** coupled with aniline **26** and the system was equally efficient producing the desired quinoline derivative **145** in an isolated yield of 60% (**Scheme 44**).



26 **144** **145**

Scheme 44

On comparison with 6-Methoxy-2-phenylquinoline **143**, 2-(4-Methoxyphenyl)quinoline **145** produced the same mass fragments in the GC-MS trace irrespective of position of the methoxy (-OCH_3) substituent but differed in the ^{1}H NMR spectrum (**Figure 21**). Moreover, the expected IR spectrums (**Figure 22**) are closely related and the retention time (6.71 minutes) is bordering on that of quinoline **143** indicating that these two derivatives are very similar in spectroscopic data.

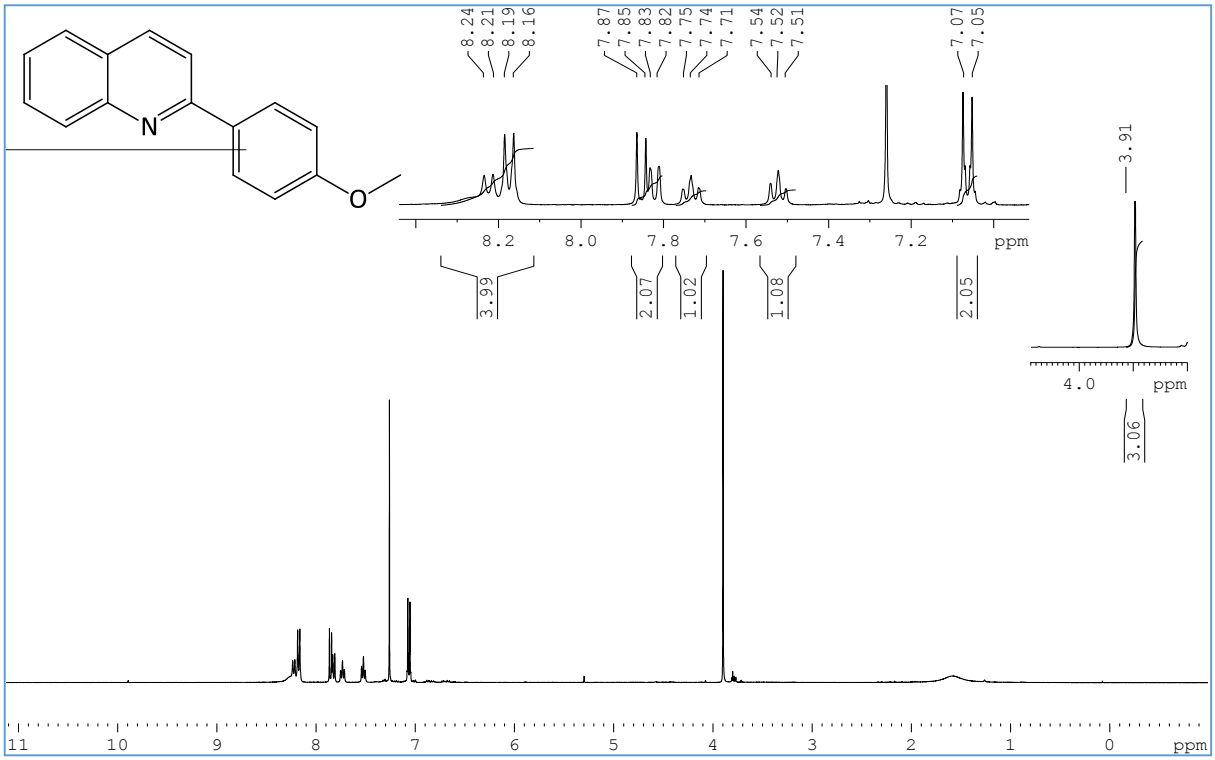


Figure 21

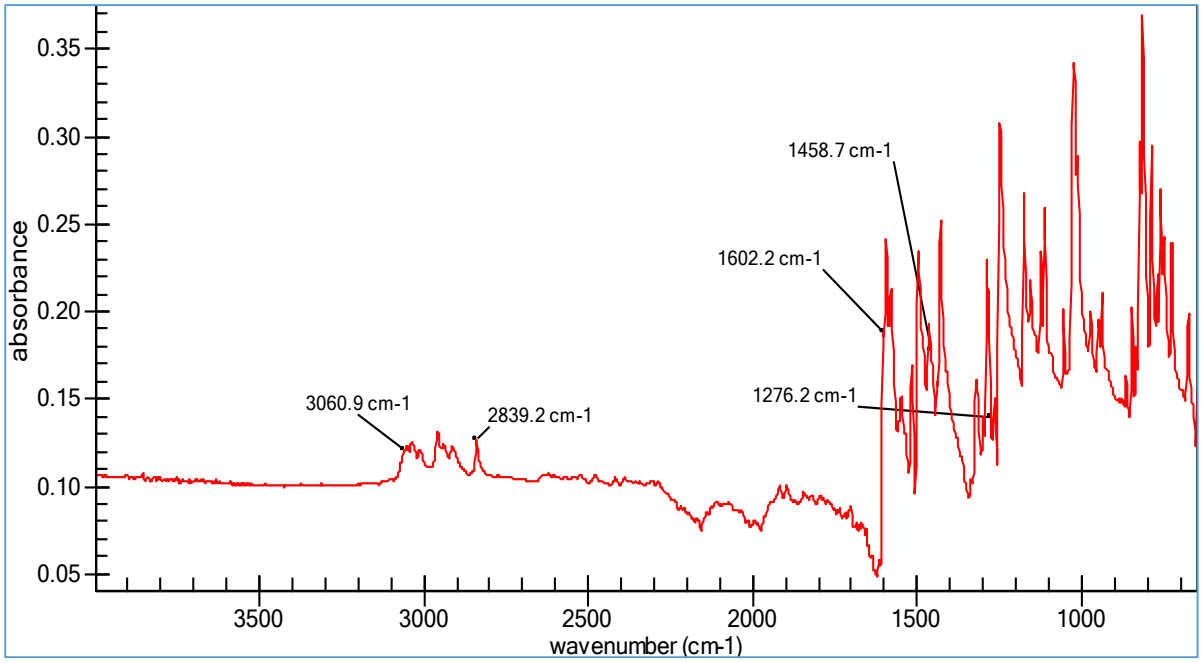
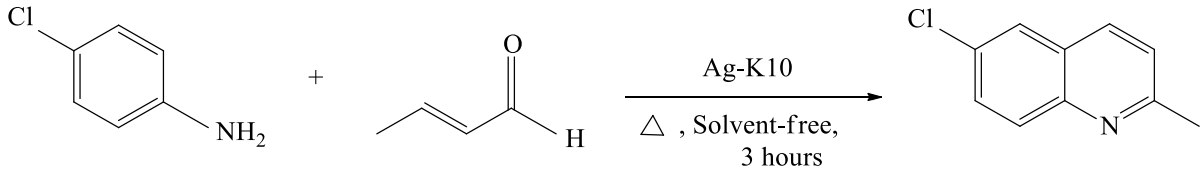


Figure 22

2.3.5 Synthesis of 6-Chloro-2-methylquinoline

In an attempt to further widen the applicability of our system, we have selected the reaction between *p*-Chloroaniline **140** and crotonaldehyde **57** (**Scheme 45**).



140 **57** **146**

Scheme 45

The crude mixture obtained was analyzed by ^{1}H NMR spectroscopy and the results revealed trace amounts of unreacted starting material. Much to our excitement, the reaction was repeated and purified by column chromatography to obtain the desired quinoline compound in an excellent yield of 80%. On comparison with literature,[171] all the expected peaks were obtained and a ^{1}H NMR spectrum depicting these assignments is shown in **Figure 23**.

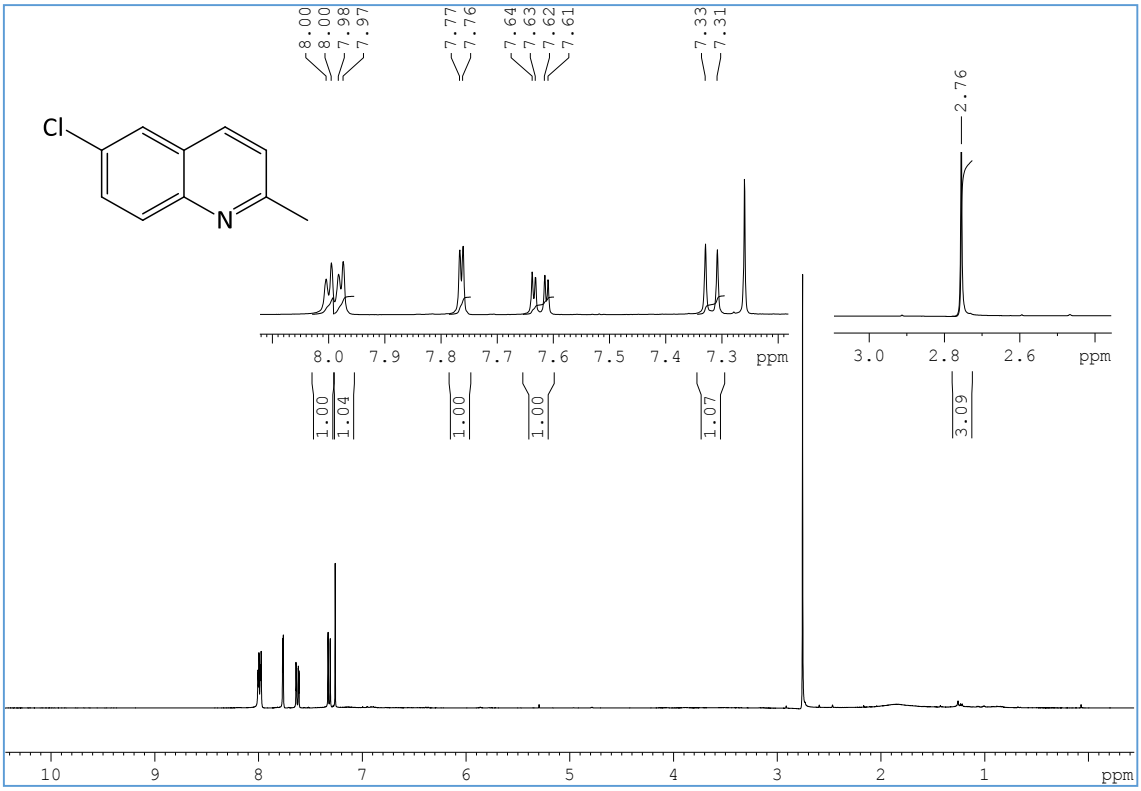
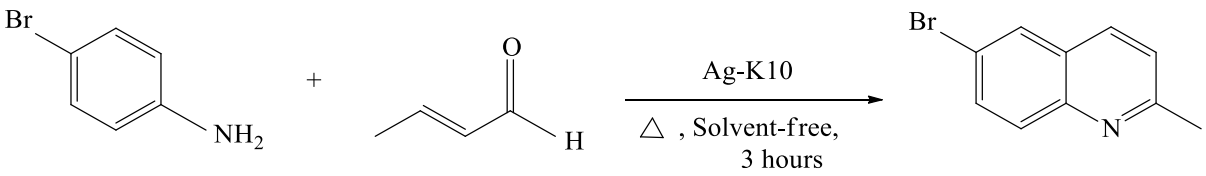


Figure 23

2.3.6 Synthesis of 6-Bromo-2-methylquinoline

Silver-exchanged Montmorillonite K10 was further examined in the synthesis of 6-Bromo-2-methylquinoline **147** from *p*-Bromoaniline **138** and crotonaldehyde **57** under solvent-free conditions (**Scheme 46**).



138 **57** **147**

Scheme 4

Once again, the crude mixture was analyzed for the presence of the desired product showing that crotonaldehyde readily underwent cyclization to form 6-Bromo-2-methylquinoline, after purification, in an excellent yield of 81%. The ^{1}H and ^{13}C spectra were compared with literature[171] and all the expected peaks were obtained at the correct chemical shifts and integral ratios (**Figure 24** and **Figure 25**).

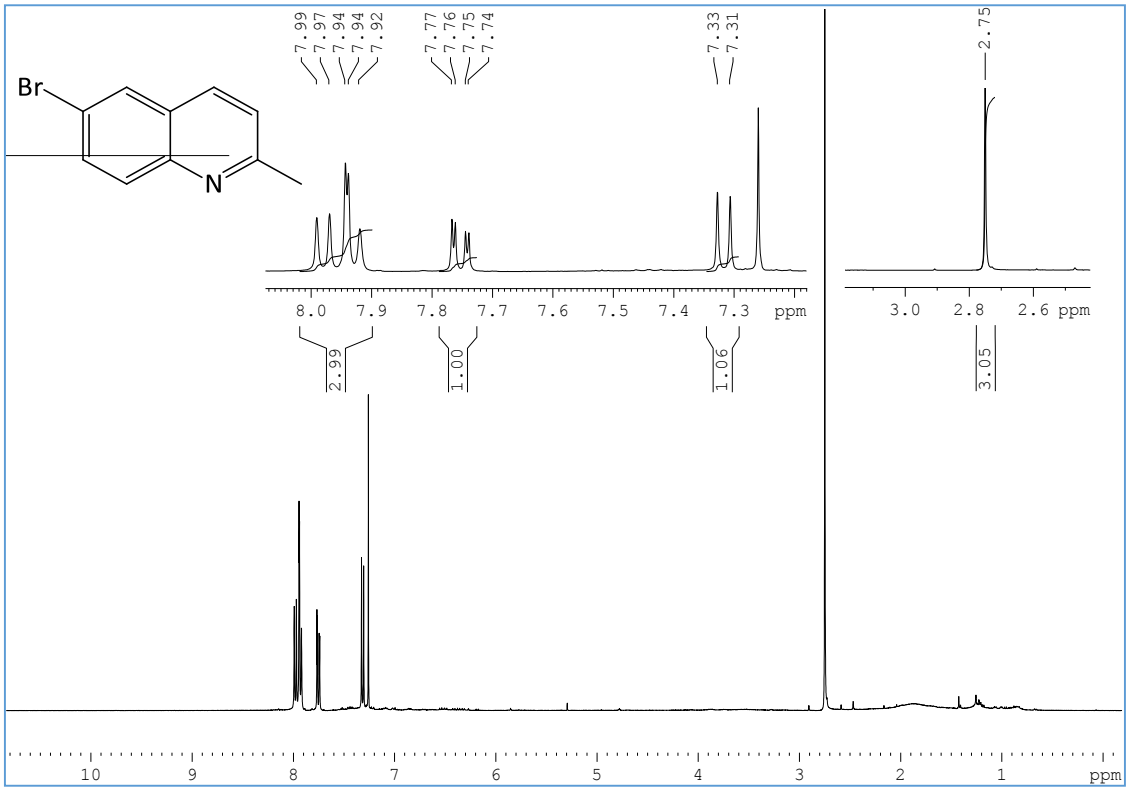


Figure 24

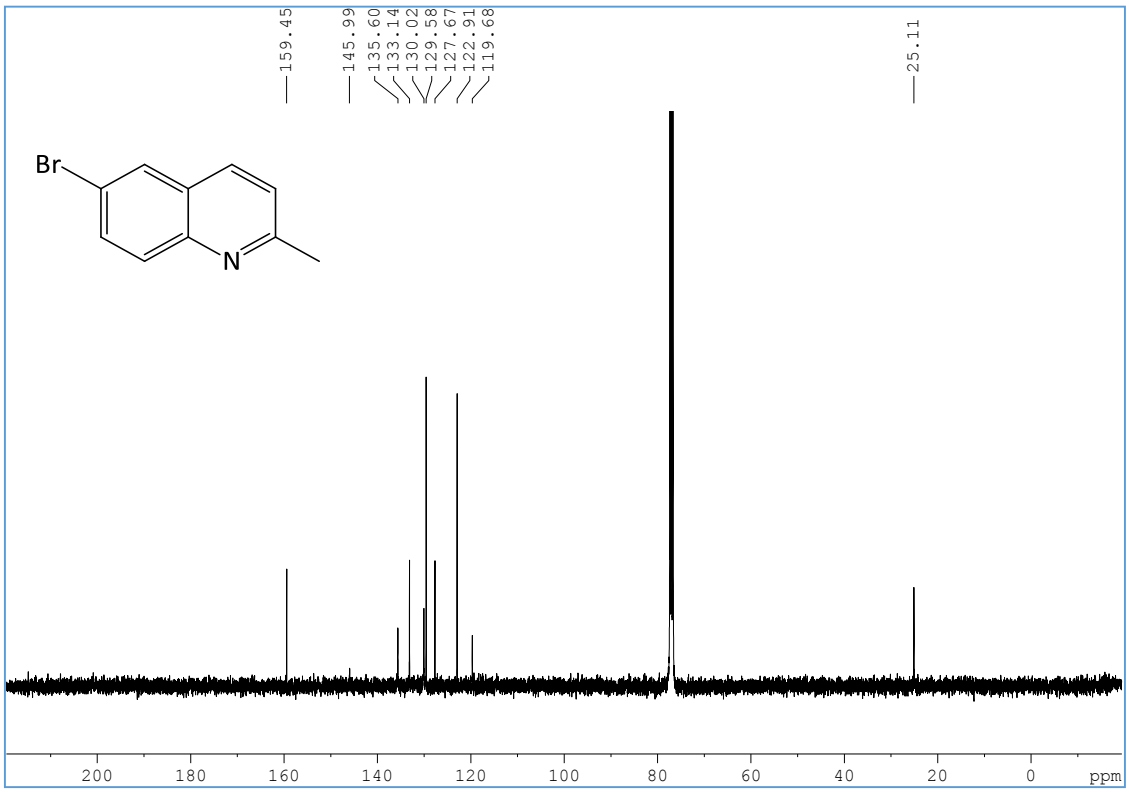


Figure 25

2.4 SUMMARY OF RESULTS OBTAINED FOR THE SYNTHESIS OF 2-PHENYLQUINOLINE DERIVATIVES UNDER SOLVENT-FREE CONDITIONS

The application of silver-exchanged Montmorillonite K10 in the synthesis of substituted quinoline derivatives was explored under the optimized reaction conditions. Under these conditions, a range of quinoline derivatives were isolated in yields ranging from 42-89% in 3 hours. The procedure was also effective when varying the aldehyde component with the quinolines isolated in satisfactory yields of 60-81%. The results of this study is summarized in **Table 2**.

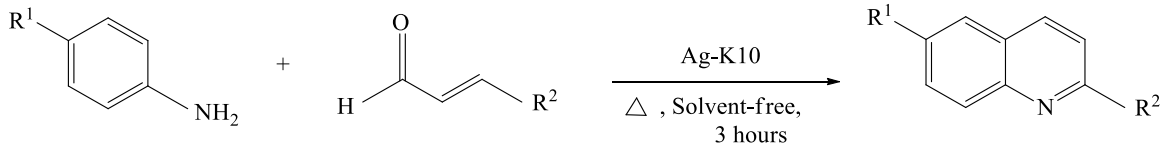
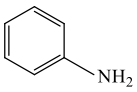
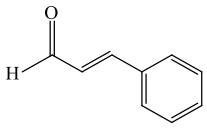
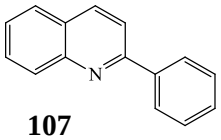
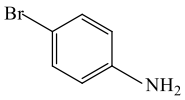
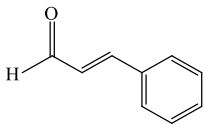
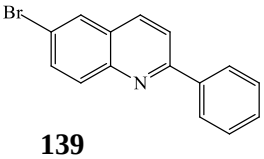
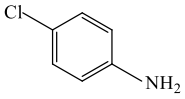
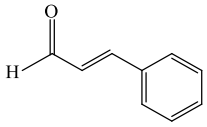
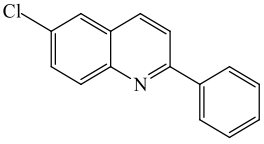
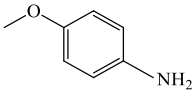
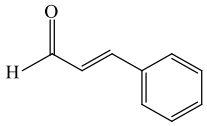
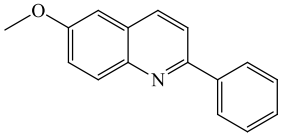
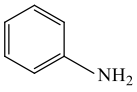
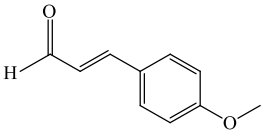
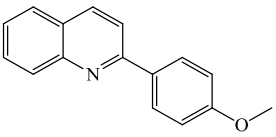
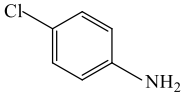
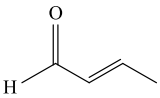
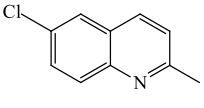
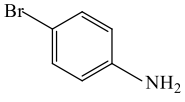
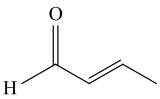
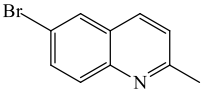


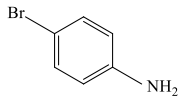
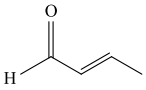
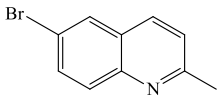
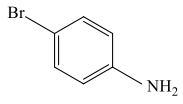
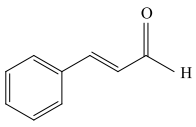
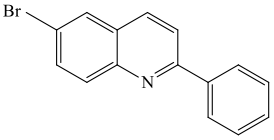
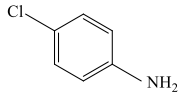
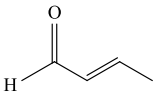
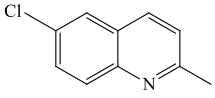
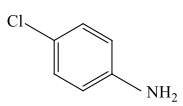
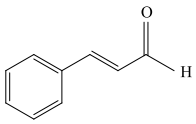
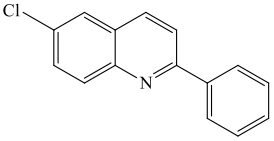
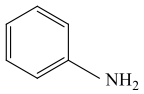
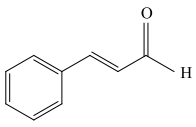
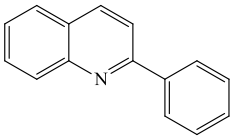
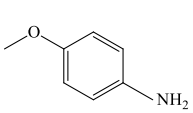
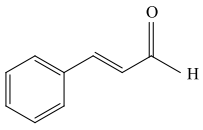
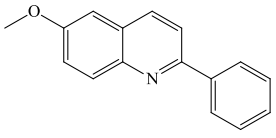
Table 2: Summary of results obtained for the synthesis of quinoline derivatives

Entry	Amine	α, β-unsaturated aldehyde	Quinoline	Yield
I.			 **107**	**89**
II.			 **139**	**42**
III.			 **141**	**56**
IV.			 **143**	**46**
V.			 **145**	**60**
VI.			 **146**	**80**
VII.			 **147**	**81**

2.5 LITERATURE REVIEW COMPARISON STUDY OF SUBSTITUTED 2-PHENYLQUINOLINE DERIVATIVES

Numerous examples in literature deal exclusively with either aromatic α, β-unsaturated aldehydes[133] or aliphatic α, β-unsaturated aldehydes.[172] To the best of our knowledge, studies of the Döebner-von Miller reaction that is equally efficient on both aromatic and aliphatic α, β-unsaturated aldehydes has not been reported. A literature review comparison study (**Table 3**) was conducted to evaluate our system and in most cases, a vast improvement in yield was obtained highlighting the scope of our methodology to both aromatic and aliphatic α, β-unsaturated aldehydes. As the data indicates, low to moderate yields are mostly observed under harsh reaction conditions in literature. Moreover, in a number of literature cases, a limited number of substrates were evaluated and, where no comparison was possible, this was indicated with 'not determined'. In addition, the Ag(I)-exchanged Montmorillonite K10 approach is milder than previously reported syntheses.

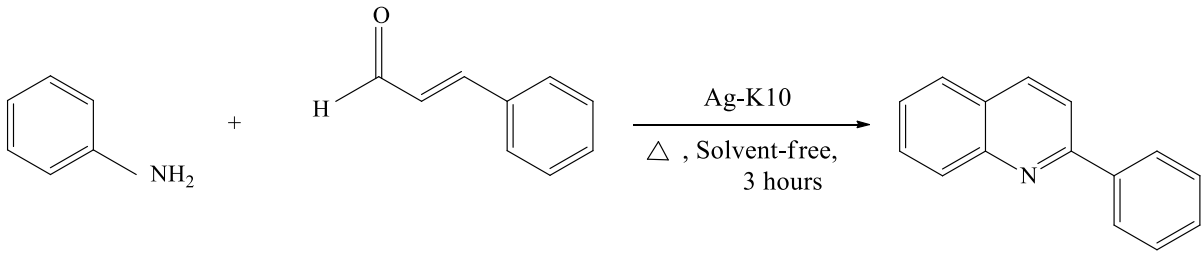
Table 3: Comparison study for the synthesis of quinoline derivatives

Amine	α, β-unsaturated aldehyde	Quinoline	Isolated Yield (%)		Reported reaction conditions
			This work	Reported	
			81	16[86] 86[172]	10 M HCl/toluene Phosphotungstic acid/toluene
			42	nd[86], [172]	-
			80	53[74] 84[172]	6 M HCl/$ZnCl_2$ Phosphotungstic acid/toluene
			56	nd[172] nd[74]	Phosphotungstic acid/toluene 6 M HCl/$ZnCl_2$
			89	<1[86] nd[172]	10 M HCl/toluene Phosphotungstic acid/toluene
			46	<1[86] nd[172]	10 M HCl/toluene Phosphotungstic acid/toluene

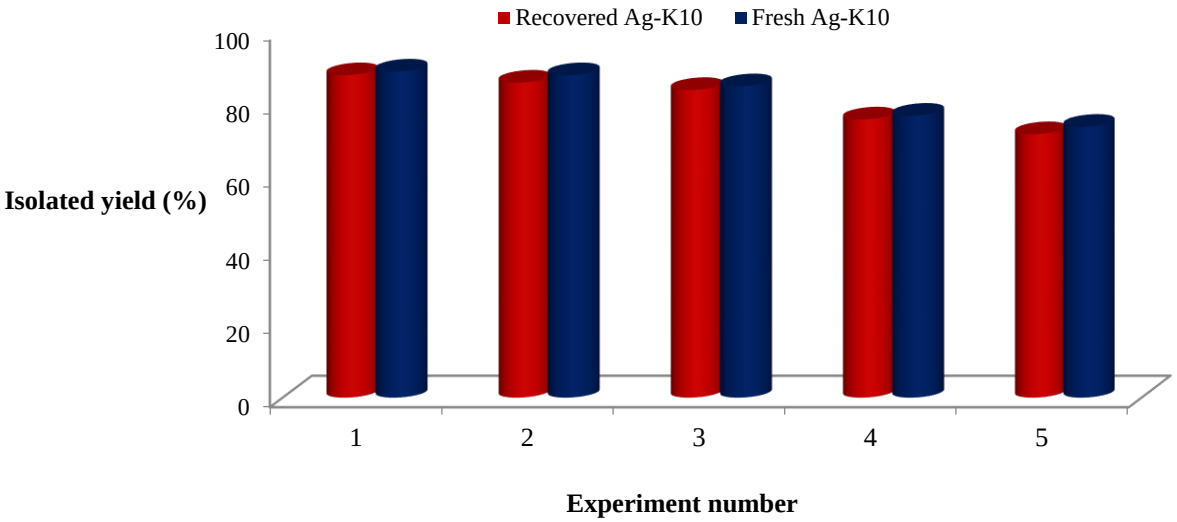
nd = not determined

2.6 RECYCLE/REUSE STUDY OF SILVER(I)-EXCHANGED MONTMORILLONITE K10 UNDER SOLVENT-FREE CONDITIONS

The possibility of recycling the catalyst by simple filtration, without the loss of activity is one of the key advantages of heterogeneous catalysis over the homogeneous counterpart.[173] Thus, the recovery and reusability of the catalyst was investigated in the quinoline formation using the optimized test reaction (**Table 1, experiment 10**). After completion of the reaction, the catalyst was recovered by simple filtration and dried at 100 °C. The recovered catalyst was weighed after each run and its activity examined using the test reaction (**Figure 26**).



26 **106** **107**



Reusability of Ag(I)-exchanged Montmorillonite K10 in the reaction of aniline **26** and cinnamaldehyde **106** under solvent-free conditions: Reused cycle 1, 0.487 g recovered (R, 88%) and fresh Ag(I)-exchanged Montmorillonite K10 (F, 89%); Reused cycle 2, 0.474 g (R, 86% and F, 88%); Reused cycle 3, 0.460 g (R, 84% and F, 85%); Reused cycle 4, 0.446 g (R, 76% and F, 77%); Reused cycle 5 0.430 g (R, 72% and F, 74%)

Figure 26

In order to gain an accurate assessment of the activity of the catalyst, each run was repeated using fresh Silver(I)-exchanged Montmorillonite K10. We observed that the yields of the product remained comparable irrespective of whether recovered or fresh Silver(I)-exchanged Montmorillonite K10 was used. These results also indicated that the catalyst loading of 0.5 g

was critical for a successful reaction as lower catalyst loadings resulted in diminished yields (0.5 g, 89% vs 0.43 g, 74%).

To compliment the studies above, Scanning Electron Microscopy (SEM) and Energy Dispersion X-Ray (EDX) analysis was conducted to characterize the silver(I)-exchanged Montmorillonite K10 catalyst.

Chapter 3

Scanning Electron Microscopy (SEM) and Energy Dispersion X-Ray (EDX) studies

3.1 PREFACE

A thorough characterization of the prepared catalyst was undertaken using Scanning Electron Microscopy (SEM) and Energy Dispersion X-Ray (EDX) techniques. A brief discussion of the characterization methods adopted along with the experimental and discussion aspects is given in the following section.

3.2 SCANNING ELECTRON MICROSCOPY (SEM)

Scanning Electron Microscopy (SEM) is a powerful technique uniquely suited for the examination and analysis of solid objects because it affords a magnified, three-dimensional view of the natural and modified clay surface with great depth of focus. This technique can be used to yield information about the topography (surface features of an object), morphology (shape and size of the particles making up the object) and crystallographic information (how the atoms are arranged in the object).[174]

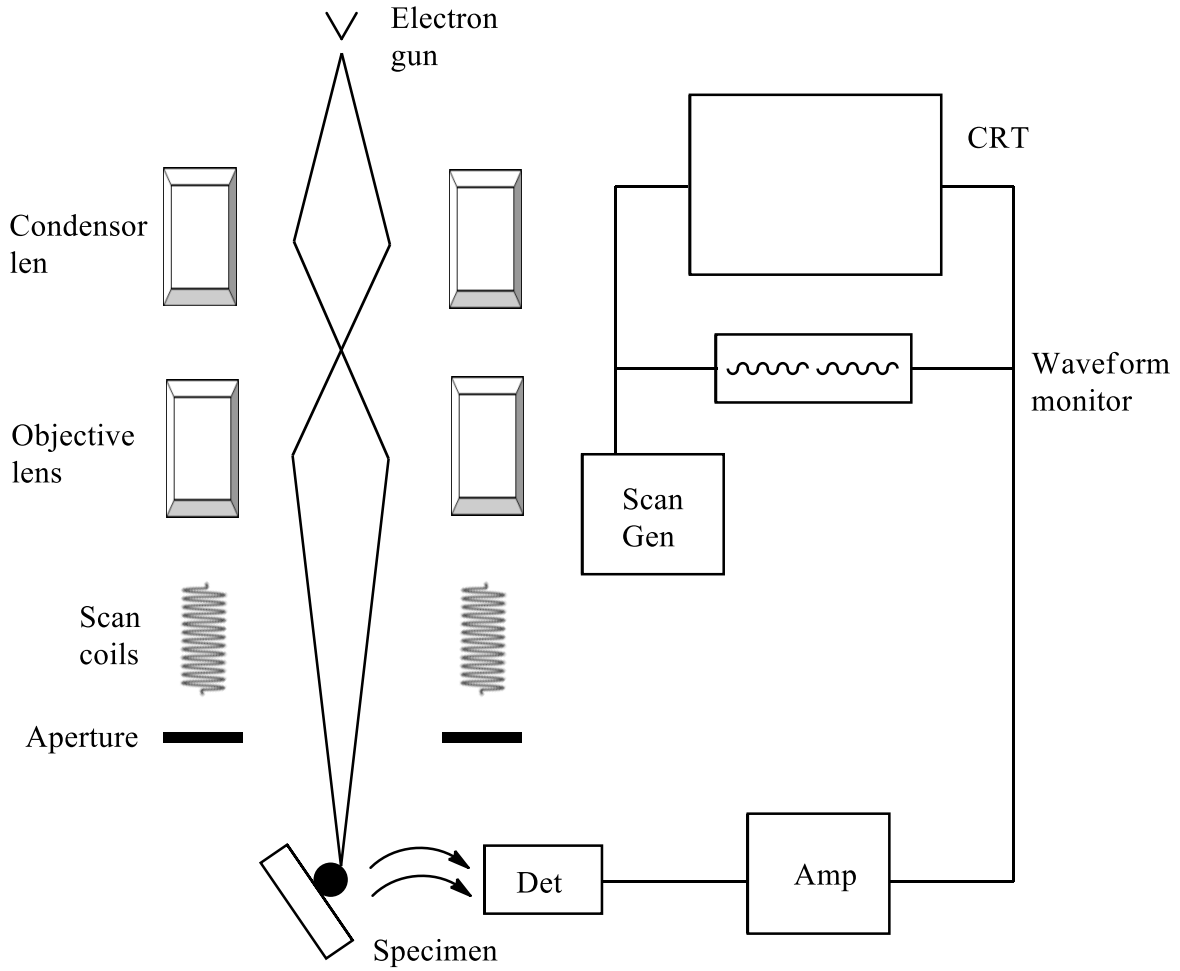


Figure 27

The diagram[175] illustrates the main components and mode of operation of a simple Scanning Electron Microscope. The electron source, usually fitted with a tungsten filament, produces a stream of monochromatic electrons to an energy between 1 keV and 30 keV. The stream is condensed by a series of condenser lenses producing a demagnified image of the source, which in turn is imaged by the probe forming lens (objective lens) onto the specimen. The electron path and sample chamber are evacuated. Scanning coils deflect the probe over a rectangular raster, the size of which, relative to the display screen, determines the magnification. Detectors collect the emitted electron signals, which after suitable amplification can be used to modulate the intensity of the beam of the display video screen, which is scanned in synchronism with the probe.

Before the beam moves to the next point on the specimen, the instrument counts the number of electron interactions and displays a pixel on the cathode ray tube (CRT) whose intensity is determined by this number (the more reactions, the brighter the pixel). This process is repetitive until the grid scan is complete and then repeated. The entire pattern can be scanned 30 times/sec.[176]

In this work, SEM is applied in the morphological characterization of natural Montmorillonite K10 catalyst prior to and following the adsorption of silver (I) ions.

3.3 ENERGY DISPERSION X-RAY (EDX)

Energy Dispersion X-Ray (EDX) spectroscopy is a quantitative and qualitative micro-analytical technique, used in conjunction with SEM, for the elemental analysis or chemical characterization of a sample. It makes use of the X-ray spectrum emitted by a solid sample bombarded with a focused beam of electrons to obtain a localized chemical analysis.[177]

A solid state X-Ray detector, usually lithium drifted Silicon, and pulse counting electronics are used. An electron beam of energy strikes the surface of a conducting beam causing X-rays to be emitted. The detector converts the incoming X-ray photon into an electronic pulse of amplitude proportional to the energy of the X-ray. The interaction of the X-rays with the object causes secondary (fluorescent) X-rays to be generated, which can be detected and displayed as a spectrum of intensity against energy. Each element present in the object produces X-rays with different energies. The X-ray energies allow atom identification and relative peak intensities are used to identify how much of each element is present.[178]

Due to the use of Li-Si detectors, EDX allows multi-elemental analysis and the use of mega electron volt (MeV) protons as the incident particle gives a crucial advantage over the technologically simpler use of kilo electron volts (keV) electrons in an electron microscope. In

addition, X-ray sampling is non-destructive, natural heterogeneity is retained and analysis can be conducted on microgram quantities. Moreover, EDX analysis is fast and accurate and the effort for sample preparation is minimal.[179]

3.4 MODIFICATION OF CLAY MATERIALS

In the past two decades, different types of surface and interlayer modifications have been done to increase the acidity, thermal stability and catalytic properties of clay materials. The most important modifications reported in literature are acid activation,[180] [181] intercalation,[182] [183] pillaring by inorganic polycations[184] [185] and cation-exchange by inorganic[186] and organic[187] cationic species.

3.4.1 Cation-exchange of clay materials

Clay minerals are very reactive because of their large surface area and because they carry a charge. Ion exchange in clays and other minerals is dependent on the:[188]

- crystalline nature of the clay material
- chemical composition of the solution in contact with the clay
- nature of the cation, e. g., hydration energy, size, valency, pH
- concentration of the electrolyte
- population of exchange sites on the clay

Clay has an interlamellar water layer containing dissolved cations sandwiched between extended aluminosilicate sheets. By replacing the interlayer ions with high charge density cations like Al^{3+}, Zn^{2+}, Fe^{2+} and Ag^{+} acidity can be imparted in the clay and can be utilized for a broad range of organic transformations (**Figure 28**)[151] [154] [189] In Montmorillonite K10,

some of the aluminium ions are substituted by magnesium ions, resulting in a negative charge on the two surfaces. The negative charge is neutralized by an interlayer of cations (e. g., Na^+, K^+, Ca^{2+}, and Mg^{2+}) that separate the two layers. The bonding strength between the negative charge on the surfaces and the interlayer cations of montmorillonite is low. Therefore, when montmorillonite is in contact with a solution containing another ion, the interlayer cations and in-solution cations are exchanged with each other.[190]

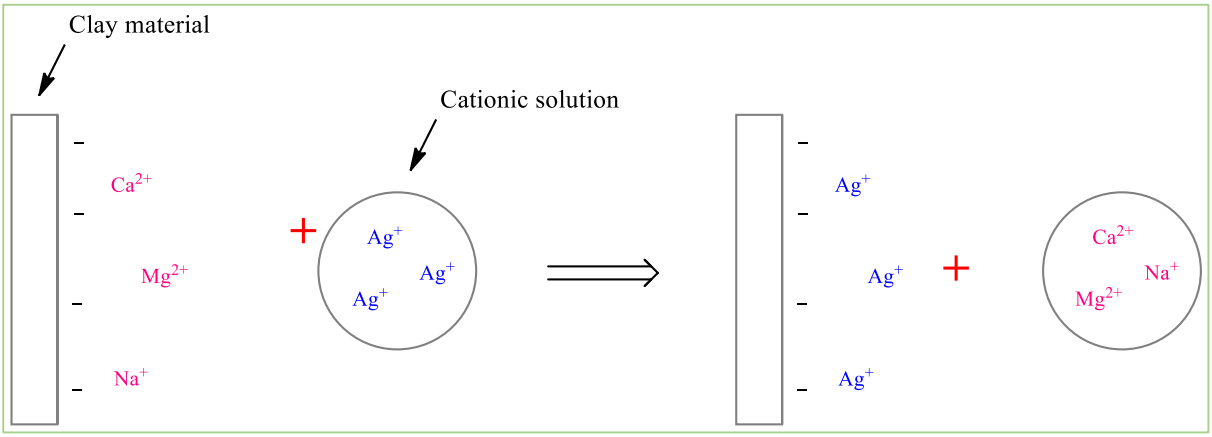


Figure 28

3.5 PREPARATION OF SILVER (I)-EXCHANGED MONTMORILLONITE K10 CATALYST

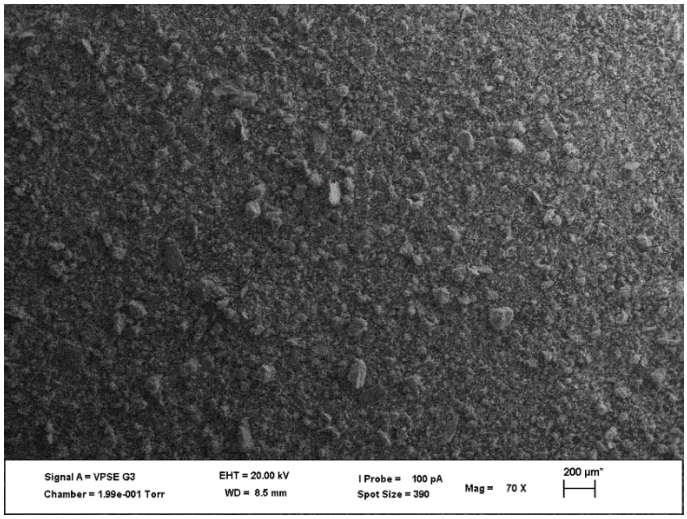
The Ag(I)-exchanged Montmorillonite clay was prepared using an ion-exchange method. Silver nitrate (5 g) was mixed with distilled water (100 ml) and Montmorillonite K10 (10 g). The mixed suspension was stirred for 4 days at room temperature. The clay was filtered under vacuum and washed with water several times. The resulting powder was dried and subsequently ground to a fine powder to produce the Ag(I)-exchanged montmorillonite K10 catalyst.

3.6 ANALYSIS AND DISCUSSION OF SCANNING ELECTRON MICROSCOPY (SEM) AND ENERGY DISPERSION X-RAY (EDX) OF SILVER (I) – EXCHANGED MONTMORILLONITE K10

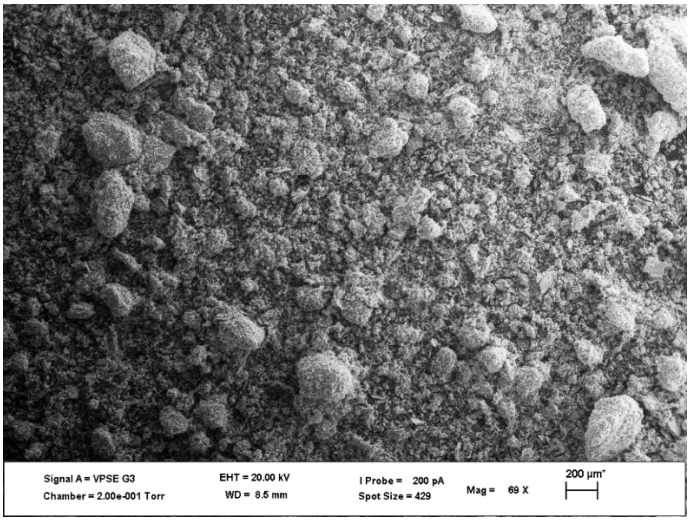
Figure 29

Figure 29 shows the physical appearance of Montmorillonite K10 (left) and Ag(I)-exchanged Montmorillonite K10 (right). Natural Montmorillonite-K10 appears as a dark grey solid and as seen in figure 1, the change in the physical appearance of modified Montmorillonite K10 indicates a change in the chemical composition of the clay. This is confirmed in the SEM and EDX analysis of both catalysts that follow.

The SEM images of Montmorillonite K10 clay and Ag(I)-exchanged Montmorillonite K10 are represented in **Figure 30**. Natural Montmorillonite K10 **(a)** shows some smooth regions in its structure. There is a distinct change in the surface morphology brought about by the addition of silver **(b)**.


Signal A = VPSE G3
Chamber = 1.99e-001 Torr
EHT = 20.00 kV
WD = 8.5 mm
I Probe = 100 pA
Spot Size = 390
Mag = 70 X
200 µm

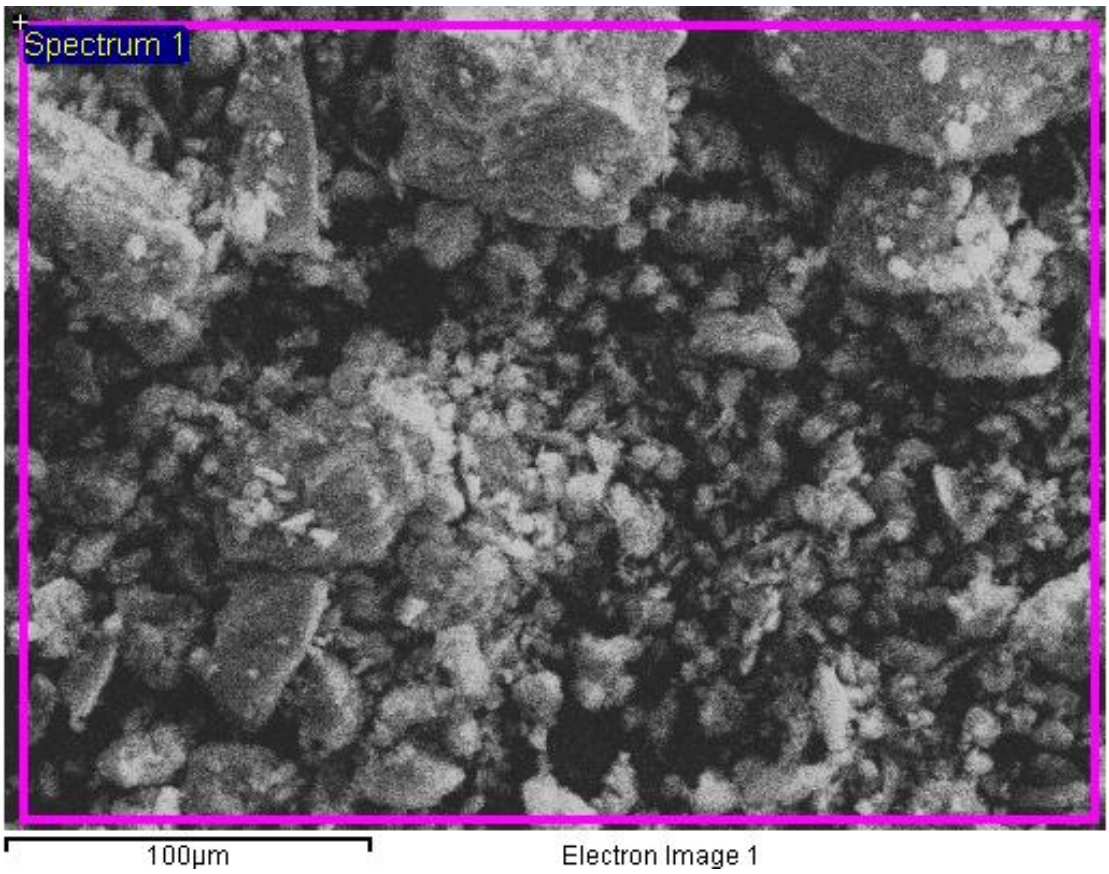
(a)


Signal A = VPSE G3
Chamber = 2.00e-001 Torr
EHT = 20.00 kV
WD = 8.5 mm
I Probe = 200 pA
Spot Size = 429
Mag = 69 X
200 µm

(b)

Figure 30

Natural Montmorillonite K10 (**Figure 31-34**) and silver (I) – exchanged Montmorillonite K10 (**Figure 35-38**) was 'mapped' in order to gain an understanding of the elemental distribution in the powder and provide conclusive proof for the presence of silver. This process involves taking an SEM image and scanning that image for elemental distribution. The dots indicate the distribution of the various elements across that image. For this study, the image, elemental mix and each elements distribution is provided separately for a clear and definite element distribution.



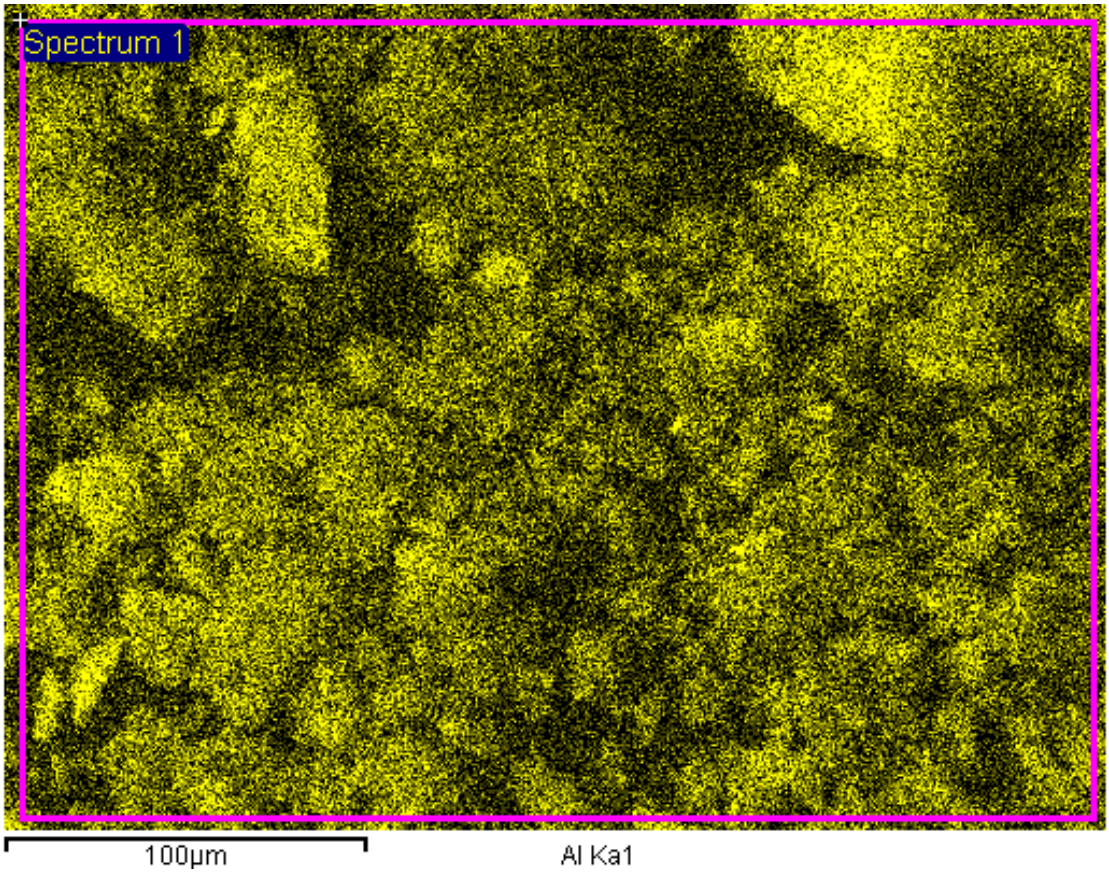


Figure 31 (Al-mapped Mont-K10)

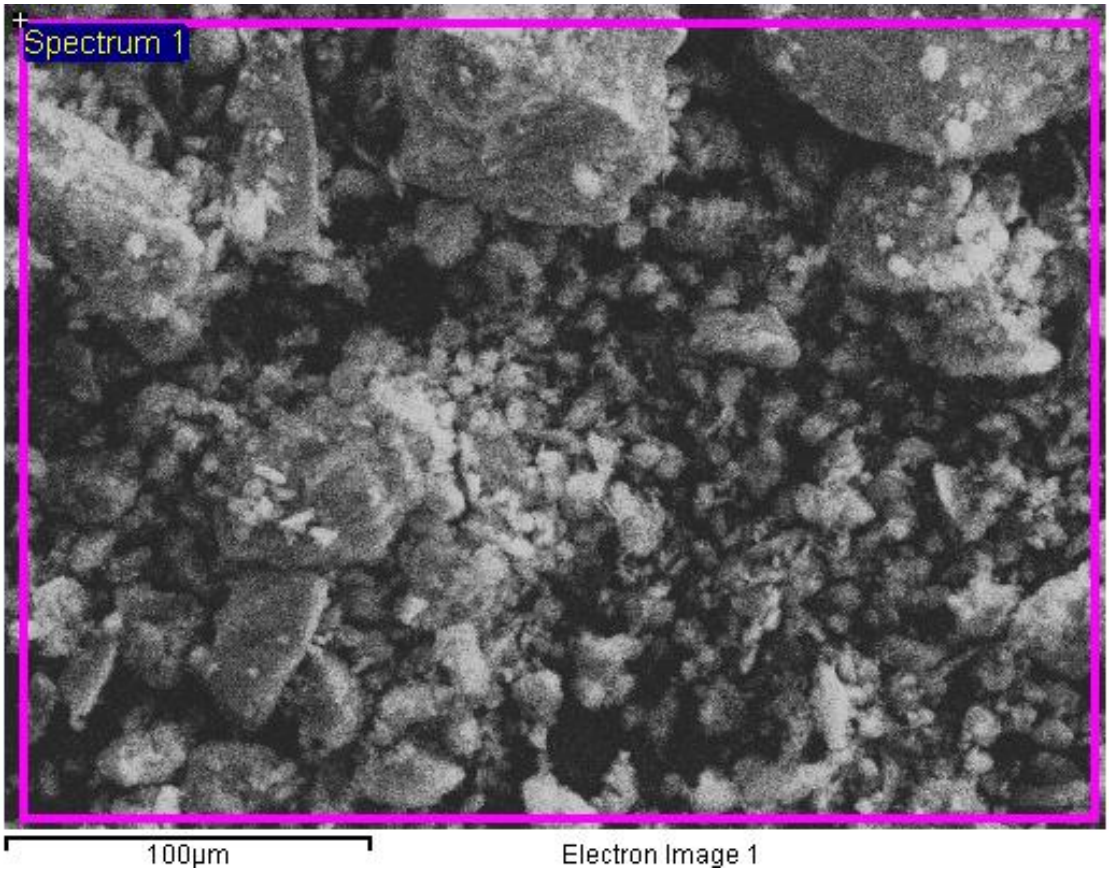
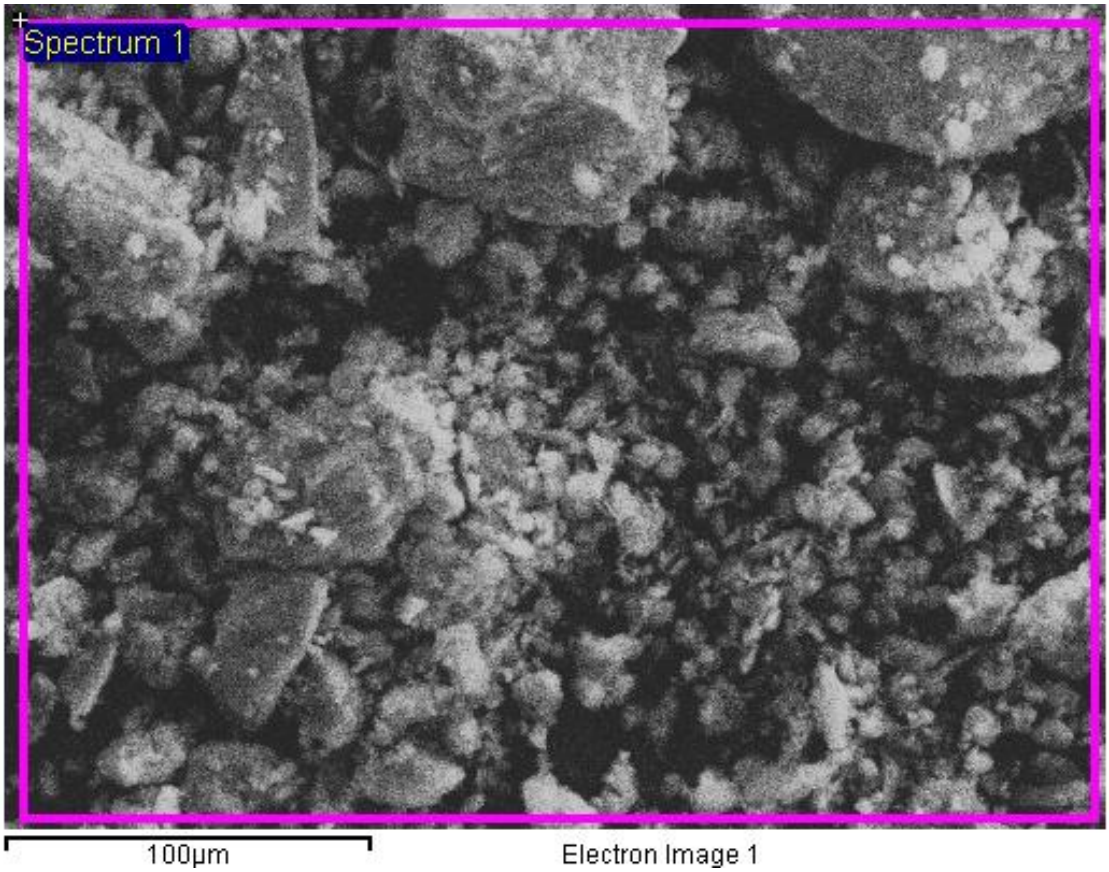


Figure 32 (Si-mapped Mont-K10)



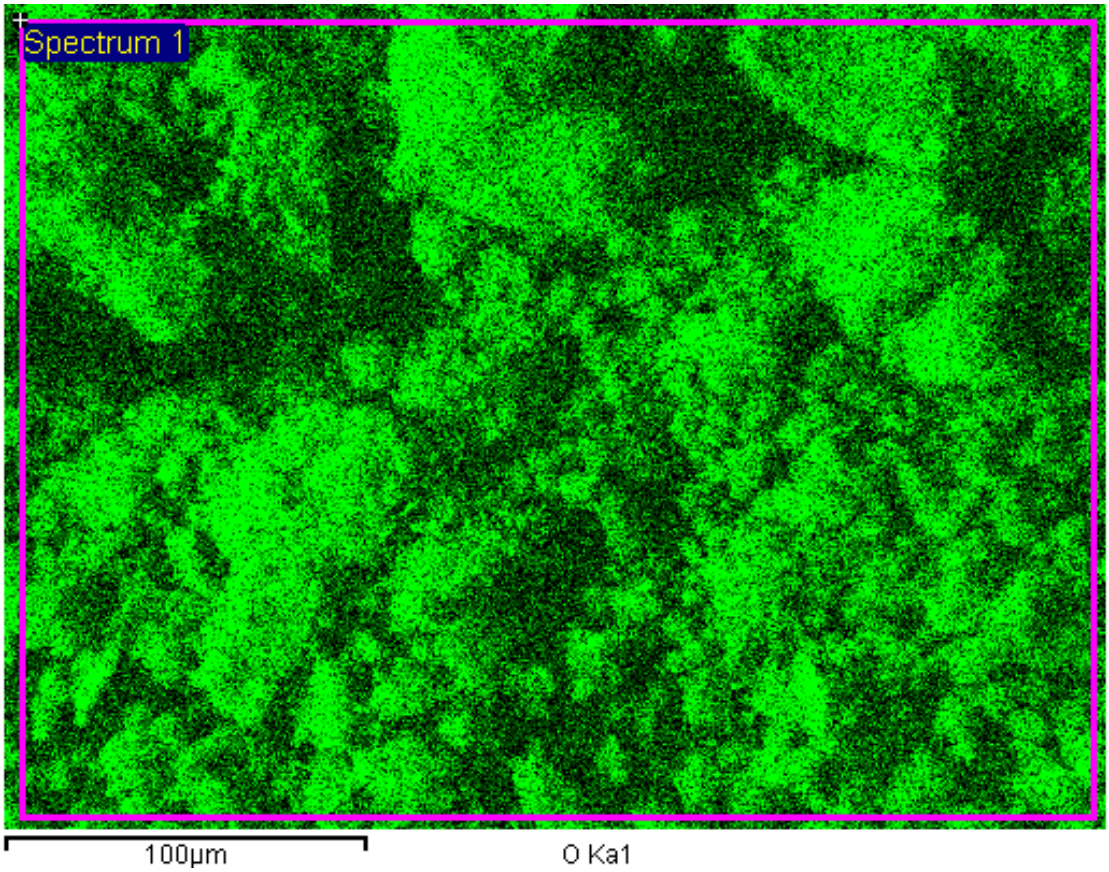
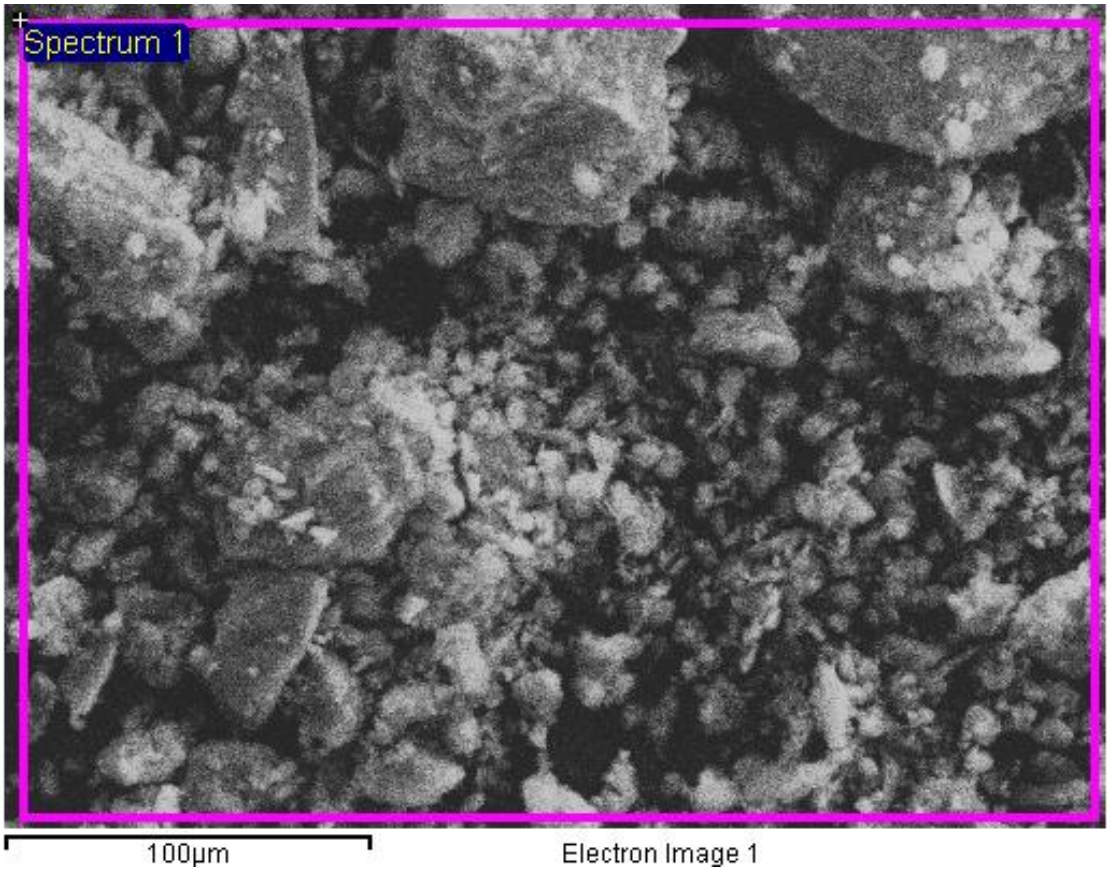


Figure 33 (O-mapped Mont-K10)



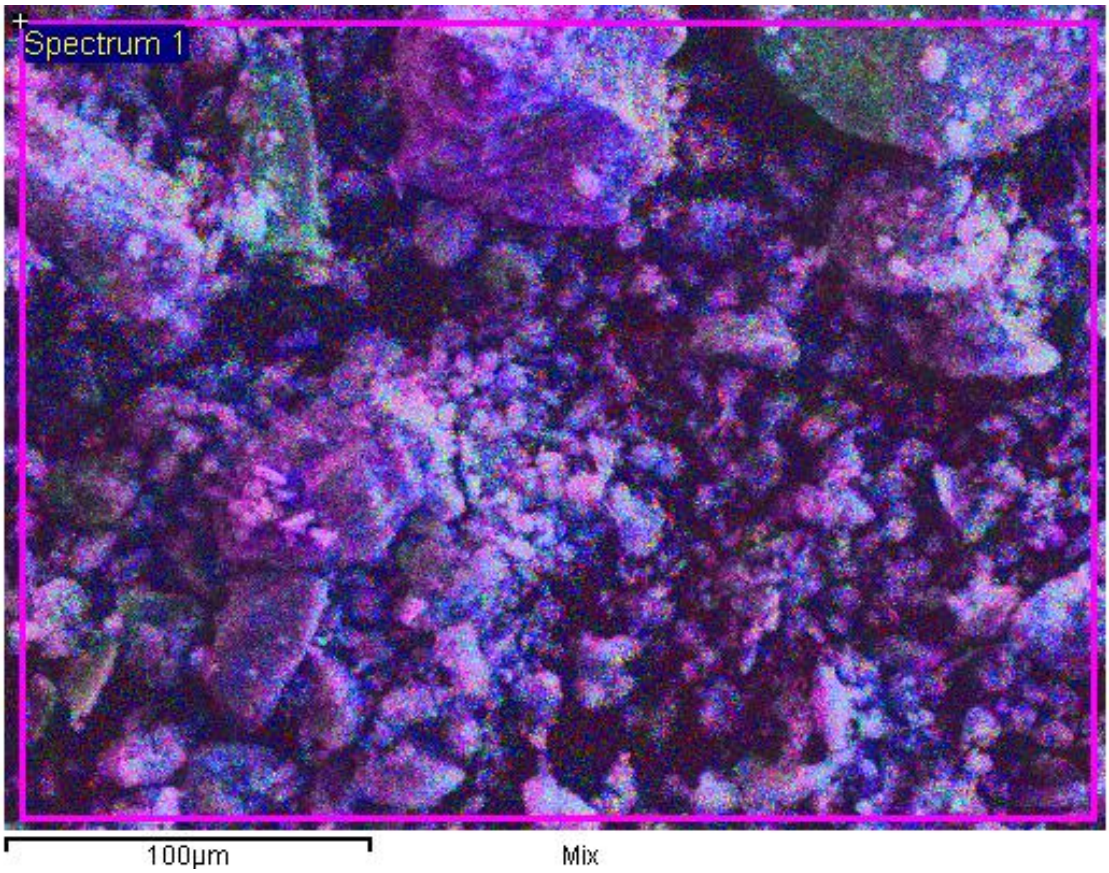


Figure 34 (Mixed element mapping – Mont K10)

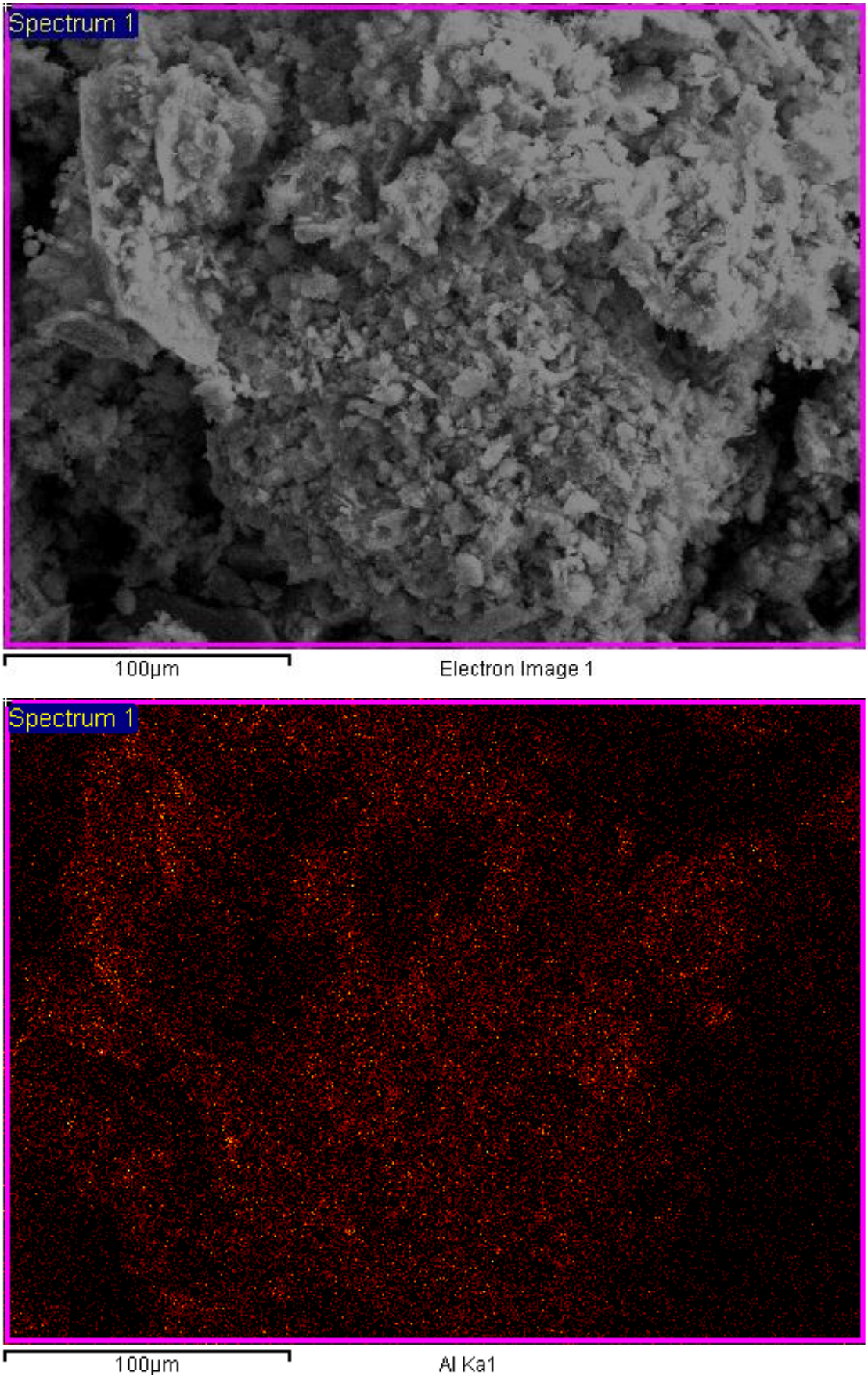


Figure 35 (Al-mapping Ag-Mont K10)

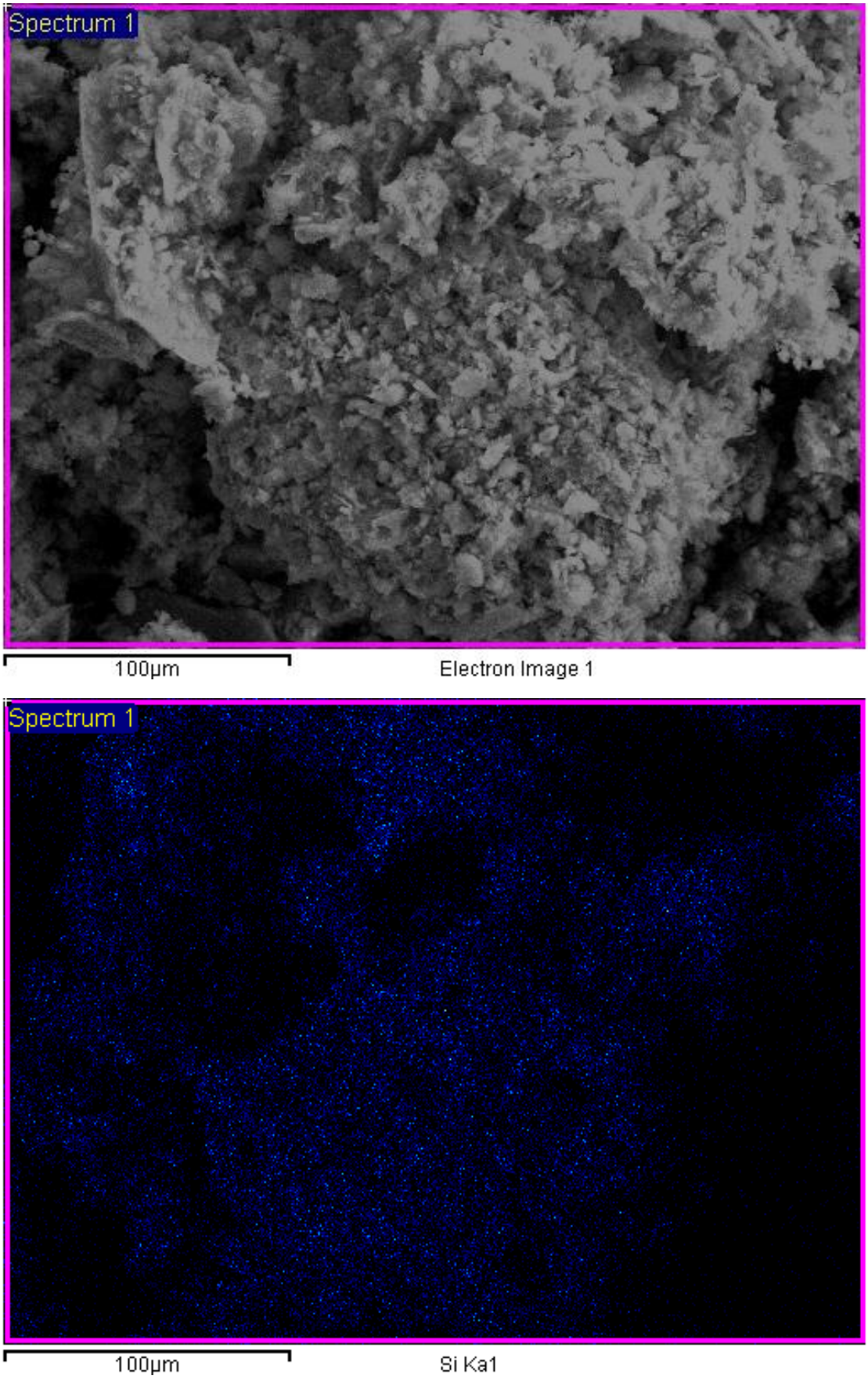


Figure 36 (Si-mapping Ag-Mont K10)

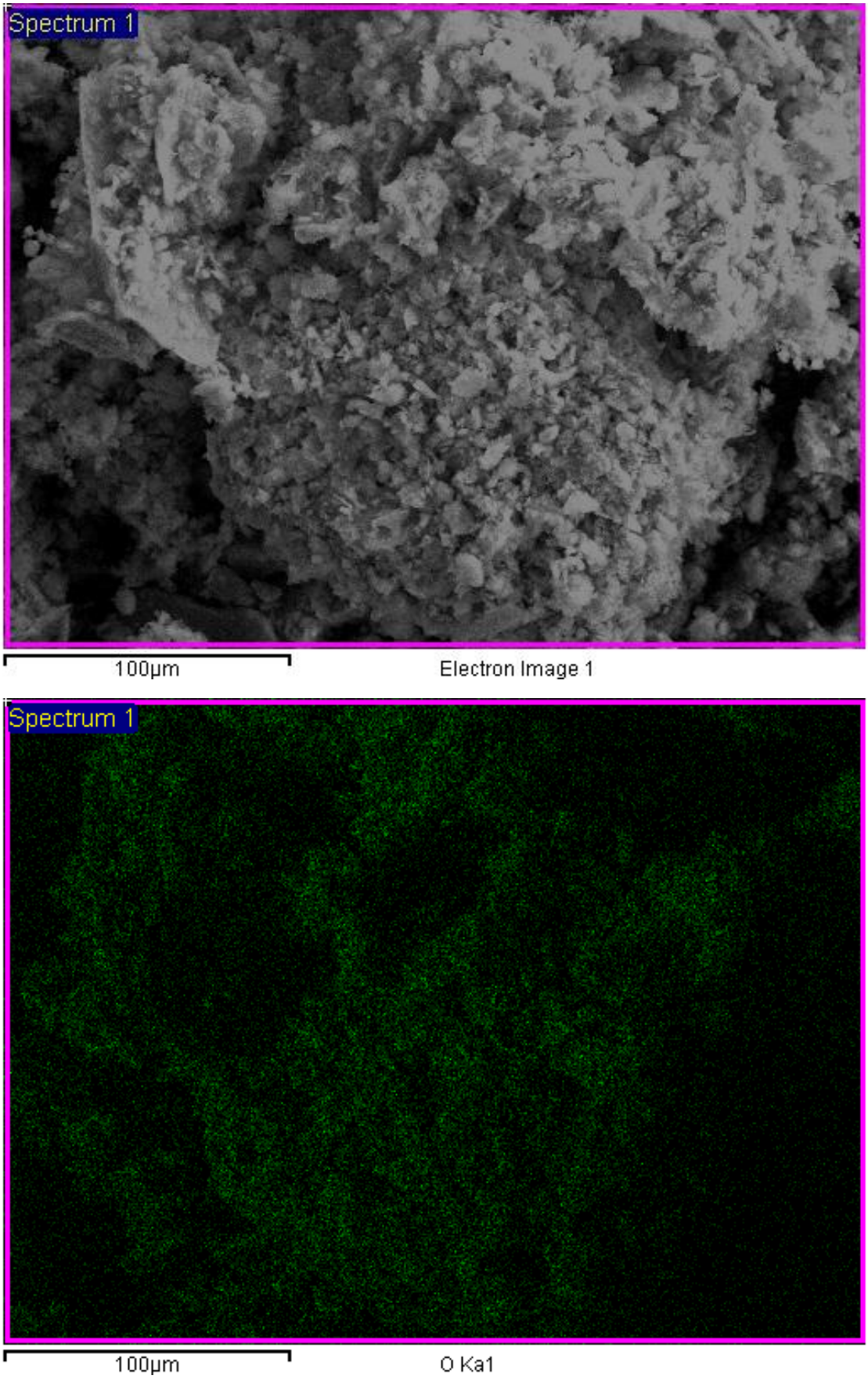


Figure 37 (O-mapping Ag-Mont K10)

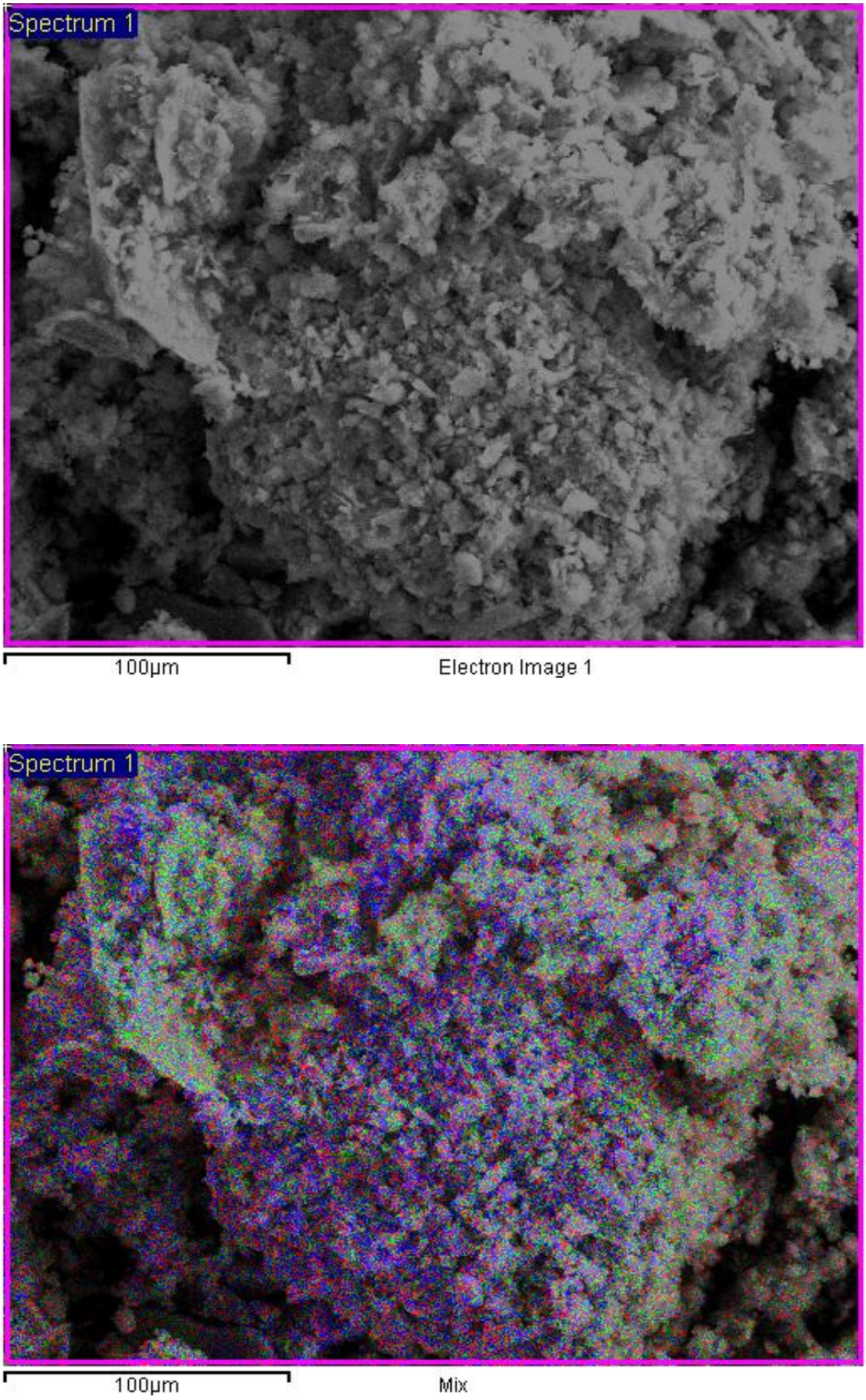
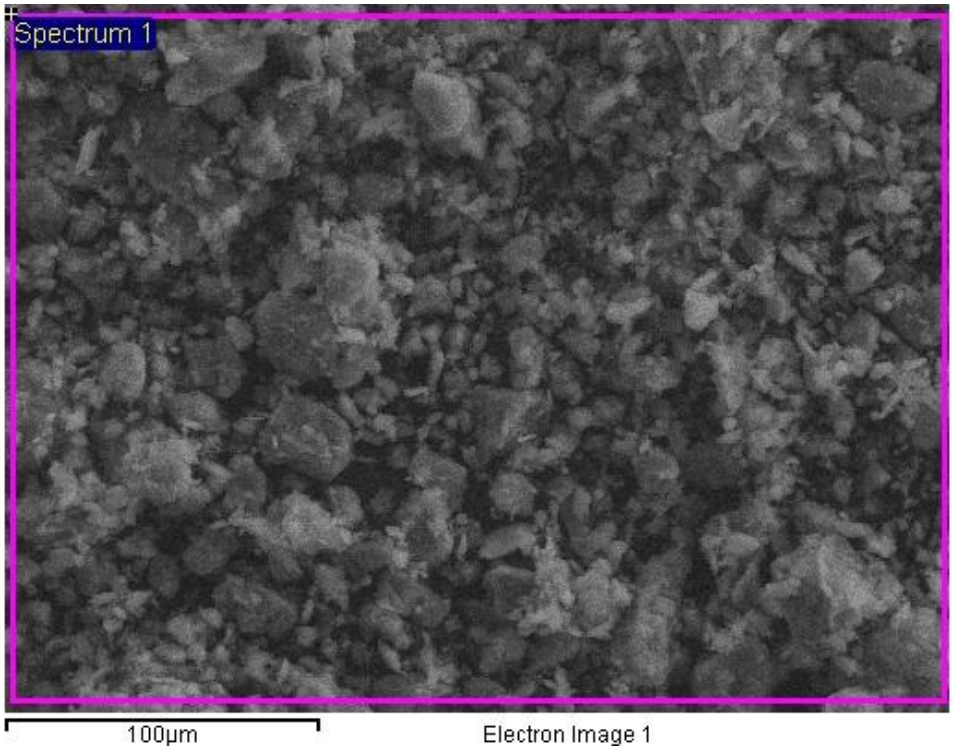
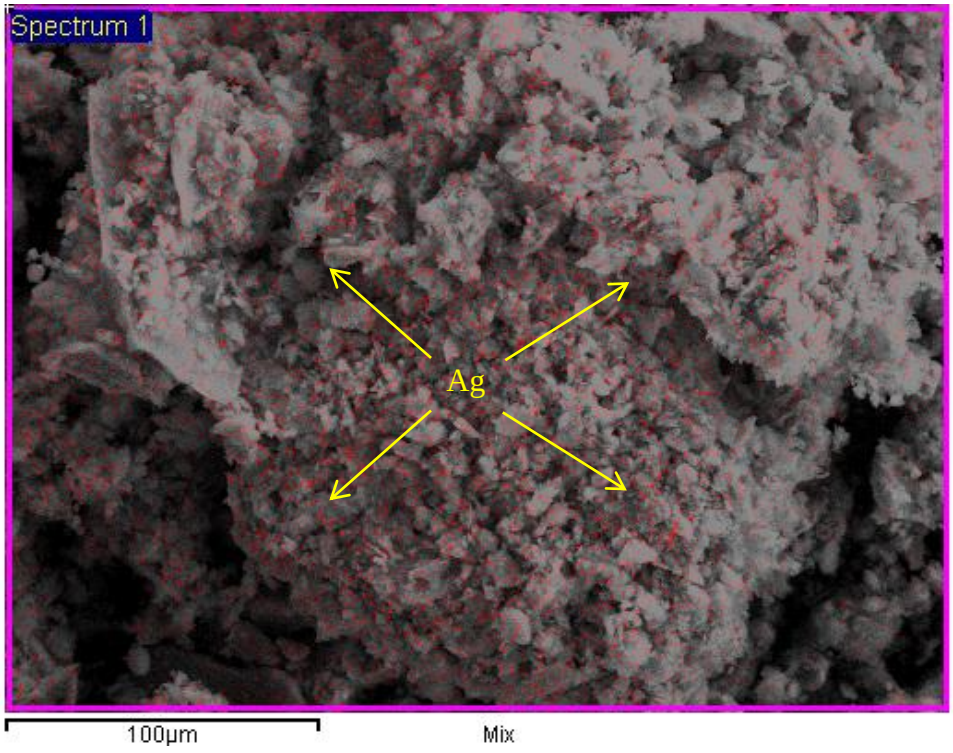


Figure 38 (Mixed element mapping – Ag-Mont K10)

The surface of Ag(I)-exchanged Montmorillonite K10 was analysed by Scanning Electron Microscopy (SEM) for the presence of silver ions and compared to unmodified natural Montmorillonite K10. As can be seen in the data below (**Figure 39**), no silver ions are present in natural Montmorillonite K10 **(a)** while Ag(I)-exchanged Montmorillonite K10 shows a uniform distribution of silver ions as indicated by the pink dots **(b)**.



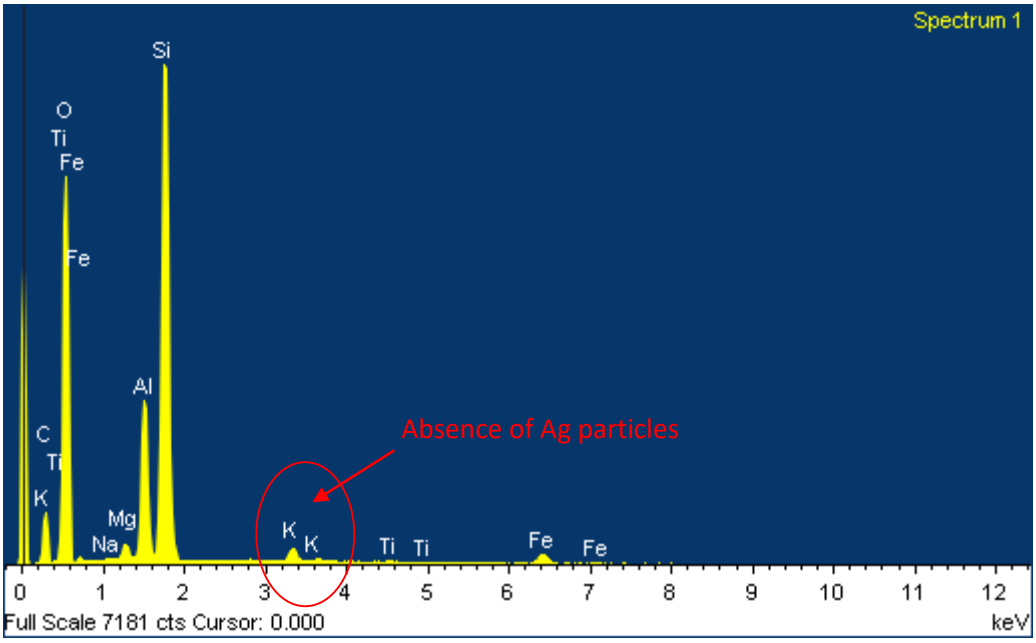
(a)



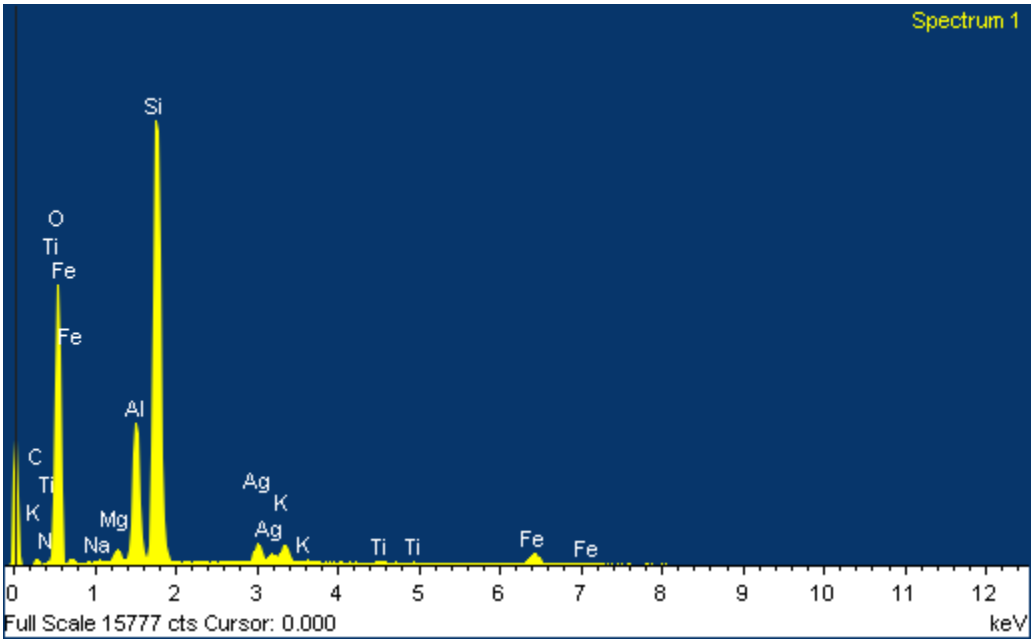
(b)

Figure 39

The SEM results are also supported by EDX analysis (**Figure 40**). According to **Figure 40**, it can be seen that silver ions are adsorbed onto natural Montmorillonite K10. Numerical values are given in **Table 4** indicating the main elemental composition. In both cases, surface composition consists mainly of oxygen, aluminium and silicon and the total silver content, in Ag(I)-exchanged Montmorillonite K10 was found to be 3.67%.


Spectrum 1
Si
O
Ti
Fe
Fe
Al
C
Ti
K
Mg
Na
K
K
Ti
Ti
Fe
Fe
Absence of Ag particles
0
1
2
3
4
5
6
7
8
9
10
11
12
Full Scale 7181 cts Cursor: 0.000
keV

(a)


Spectrum 1
Si
O
Ti
Fe
Fe
Al
C
Ti
K
N
Mg
Na
Ag
K
Ag
K
Ti
Ti
Fe
Fe
0
1
2
3
4
5
6
7
8
9
10
11
12
Full Scale 15777 cts Cursor: 0.000
keV

(b)

Figure 40

Table 4: Elemental analysis of Montmorillonite K10 and Ag-K10 (Main Element Composition)

Element (wt%)	O	Na	Mg	Al	Si	K	Ti	Fe	Ag
Mont-K10	**52.90**	**0.05**	**0.56**	**5.02**	**17.81**	**0.74**	**0.14**	**1.56**	**-**
Ag-K10	**54.33**	**0.13**	**0.72**	**6.85**	**25.22**	**1.25**	**0.30**	**2.77**	**3.67**

If we look back at the 12 principles of green chemistry mentioned in the introduction, the following highlighted statements have been abided by:

1) **Prevent waste:** Design chemical syntheses to prevent waste. Leave no waste to treat or clean up
2) **Atom economy:** Design syntheses so that the final product contains the maximum proportion of the starting materials.
3) **Design less hazardous chemical syntheses:** Use and generate substances that possess little or no toxicity to human health and the environment.
4) **Design safer chemicals and products:** Design chemical products that are fully effective yet have little or no toxicity.
5) **Safer solvents and auxiliaries:** The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and harmless when used.
6) **Increase energy efficiency:** Choose the least energy-intensive chemical route. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7) **Use of renewable feedstock:** Use chemicals which are made from renewable sources, rather than other, equivalent chemicals originating from petrochemical sources.
8) **Reduce derivatives:** Minimize the use of temporary derivatives (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes). Avoid derivatives to reduce reaction steps, resources required and waste created.
9) **Catalysis:** Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10) **Design for degradation:** Chemical products should be designed so that at the end of their function they do not persist in the environment and breakdown into harmful degradation products.
11) **Real-time analysis for pollution prevention:** Analytical procedures need to be further developed to allow real-time, in-process monitoring and control prior to the formation of hazardous materials.
12) **Inherently safer chemistry for accident prevention:** Substances and the form of a substance used in a chemical process should be chosen so as to minimise the potential for chemical accidents, including releases, explosions and fires.

The results of this study has been drawn up for publication and is currently under consideration by New Journal of Chemistry (NJC). The submitted publication has been attached for your perusal.

Conclusions

Silver(I)-exchanged Montmorillonite K10 was evaluated as a potential solid acid catalyst in the synthesis of a series of quinoline derivatives *via* the Döebner-von Miller reaction. The developed synthetic route was found to be more environmentally friendly (solid support, recyclable, solvent-free) than previously reported protocols (boiling 10 M hydrochloric acid). A series of substituted 2-phenylquinoline derivatives were synthesized in moderate to excellent yields ranging from 42-89% in 3 hours. This project also illustrated the scope of our methodology to both aromatic and aliphatic α, β-unsaturated aldehydes which is a valuable addition to the Döebner-von Miller reaction realm. The yields obtained under the silver(I)-exchanged Montmorillonite K10 mediated quinoline synthesis were compared with other established Döebner-von Miller synthetic protocols (**Scheme 15**) and, in most cases, were shown to be significantly superior.

In an attempt to gain an accurate assessment of the activity of our catalyst, a recover and reuse study was conducted using the optimized test reaction. The results indicated that the yields of the product remained comparable irrespective of whether recovered or fresh silver-exchanged Montmorillonite K10 was used. In addition, a catalyst loading of 0.5 g was critical for a successful and high yielding reaction as lower catalyst loading resulted in diminished yields (0.5 g, 89% vs 0.43 g, 74%). The success of this study further supports our environmentally friendly approach and the developed system adheres to some of the 12 principles of green chemistry such as (prevent waste, less hazardous chemical syntheses, safer solvents and auxilliaries and inherently safer chemistry for accident prevention).

Lastly, in order to gain insight into the methodology of the reaction and to complement the studies done above, the silver-exchanged Montmorillonite K10 catalyst was analyzed by SEM/EDX spectroscopy. The results showed a uniform distribution of silver(I) ions with a total silver(I) content of 3.67 weight %.

Future work

Silver(I)-exchanged Montmorillonite K10 has been shown in this study to be a highly efficient solid acid catalyst for the synthesis of quinoline derivatives *via* the Döebner-von Miller reaction. The future work involving the Döebner-von Miller reaction includes the following:

- Preliminary investigations into and further decreasing the silver(I) content of the silver(I) exchanged Montmorillonite K10 catalyst and applying it to the synthesis of simple quinoline derivatives.

- Preliminary investigations into further recycling the catalyst to determine the maximum times it can be recycled.

- Further insight into the structure and morphology of the silver(I)-exchanged Montmorillonite K10 catalyst using other techniques such as Fourier Transform Infra-Red studies, surface area calculations and X-Ray Diffraction studies.

- The Döebner-von Miller reaction is a constant feature in many total syntheses, however, the low yield obtained from this reaction affects the total yield of the final product. One such reaction is the synthesis of biologically active Ammosamide B (**Scheme 22, step 1**). Hence, silver(I)-exchanged Montmorillonite K10 approach will be applied to the total synthesis of Ammosamide B in an attempt to improve the yield the Döebner-von Miller reaction step and consequently improve the overall yield of the target compound.

Chapter 4

Experimental

4.1 GENERAL METHODS

Instrumentation:

NMR spectra were recorded using a Bruker Advance III 400 spectrometer equipped with a 5 mm BBO-Z probe at 30 °C.

^{1}H and ^{13}C spectra were recorded at 400 MHz.

IR spectra were recorded on Smiths IdentifyIR Spectrometer.

Melting points were determined using Kofler hot-stage melting apparatus.

Chromatograms were obtained using Perkin Elmer Clarus 500 Gas Chromatograph.

Scanning Electron Microscope (SEM) images were recorded on EVO LS15, ZEISS.

Energy Dispersion x-Ray (EDX) analysis was performed with an X-max 80 mm^2 Silicone Drift Detector (SDD).

Chemicals:

All chemicals were purchased from Sigma Aldrich and used as such without any further purification.

Explanation of NMR abbreviations:

Spectra were referenced against either the $CDCl_3$ singlet at 7.26 ppm or the central line of the $CDCl_3$ triplet at 77.0 ppm.

s – singlet; d – doublet; dd – doublet of doublet; t – triplet; tt – triplet of triplet; m – multiplet

Spectra:

All spectra referred to in the discussion have been included within the text with supplementary spectra included in an electronic format. NMR spectra have been included as pdf documents. Each folder has been labelled with its IUPAC name and numbered as it appears in the text.

An electronic copy of the spectroscopic data for each compound synthesized is attached at the end of this dissertation.

4.2 PROCEDURES AND SPECTROSCOPIC DATA

OPTIMIZATION OF THE REACTION CONDITIONS USING THE SYNTHESIS OF 2-PHENYLQUINOLINE AS A TEST REACTION

Application of Acetic acid in the synthesis of 2-Phenylquinoline using the biphasic system

Under conventional heating conditions

Aniline (0.140 g, 1.50 mmol) was added to 8 ml of vinegar and placed in an oil bath. Upon heating to a 100 ^{o}C, cinnamaldehyde (0.132 g, 1.00 mmol) in 6.00 ml of toluene was added dropwise and the resulting mixture heated for 3 hours. The mixture was allowed to cool to room temperature and subsequently extracted with ethyl acetate to afford the crude product. The extract was dried over anhydrous magnesium sulphate, concentrated and analyzed by ^{1}H NMR spectroscopy. A complex reaction mixture was obtained showing unreacted starting material and other unidentifiable peaks. For comparison reasons, the reaction was repeated using glacial acetic acid and similar NMR spectra were obtained.

Under microwave conditions

Under microwave heating conditions, the above reactions were repeated for 30 minutes and once again, in the presence of vinegar and glacial acetic acid, similar ^{1}H NMR spectra were obtained.

Application of zinc oxide in the synthesis of 2-Phenylquinoline under conventional heating conditions

In a reaction vial equipped with a magnetic stirrer bar, aniline (0.140 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol) were dissolved in 3.00 ml of diethyl ether followed by the addition of zinc oxide (0.500 g). The resulting mixture was stirred for 5 minutes and the solvent removed by rotary evaporation to obtain a free flowing powder which was heated for 24 hours at 100 ^{o}C. After completion, the reaction mixture was filtered through a short silica plug and the solid residues washed well with ethyl acetate. The solvent was removed *in vacuo* to obtain a crude product which upon analysis by ^{1}H NMR spectroscopy, revealed a complex reaction mixture. Subsequent reactions were performed by varying the time, however, no product peaks were obtained.

Application of silica gel in the synthesis of 2-Phenylquinoline under conventional heating and microwave conditions

Under solvent-free conventional heating conditions

Aniline (0.140 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol) were dissolved in 1.50 ml of diethyl ether in a reaction vial equipped with a magnetic stirrer bar, followed by the addition of silica gel (0.500 g). After 5 minutes of stirring, the solvent was removed *in vacuo* to obtain a dry powder. The reaction mixture was heated at 90 ^{o}C for 3 hours. After completion of the reaction, the mixture was filtered through a short silica plug and the solid residues washed well with ethyl acetate. The solvent was removed *in vacuo* to produce a crude product. Analysis by NMR spectroscopy revealed a complex reaction mixture with unreacted starting material and other unidentifiable peaks.

Under solvent-free microwave conditions

In a reaction vial equipped with a magnetic stirrer bar, aniline (0.140 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol) were dissolved in 1.50 ml of diethyl ether followed by the addition of silica gel (0.500 g). The resulting mixture was stirred for 5 minutes and the solvent removed by rotary evaporation to obtain a free flowing powder which was microwave irradiated for 30 minutes at 90 ^{o}C. After completion, the reaction mixture was filtered through a short silica plug and the solid residues washed well with ethyl acetate. The solvent was removed *in vacuo* to obtain a crude product which upon analysis by ^{1}H NMR spectroscopy, revealed a spectrum showing trace amounts of the desired product and mostly unreacted starting material.

APPLICATION OF MONTMORILLONITE K10 IN OPTIMIZING THE REACTION CONDITIONS FOR THE SYNTHESIS OF 2-PHENYLQUINOLINE

Application of boron-exchanged Montmorillonite K10 in the synthesis of 2-Phenylquinoline

Preparation of boron-exchanged Montmorillonite K10

The boron-exchanged Montmorillonite clay was prepared using an ion-exchange method. A boric acid solution (0.2 M, 100 ml) was mixed with Montmorillonite K10 (10 g) and stirred for 24 hours at room temperature. The clay was filtered under vacuum and washed with water several times. The resulting powder was dried and subsequently ground to a fine powder to produce the boron-exchanged montmorillonite K10 catalyst. Analysis by SEM/EDX revealed a 1% boron content.

Synthesis of 2-Phenylquinoline using freshly prepared B-K10 under solvent-free conditions

Aniline (0.140 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol) were dissolved in 1.50 ml of diethyl ether in a reaction vial equipped with a magnetic stirrer bar, followed by the addition of B-K10 (0.500 g). After 5 minutes of stirring, the solvent was removed *in vacuo* to obtain a dry powder. The reaction mixture was heated at 90 ^{o}C for 3 hours. After completion of the reaction, the mixture was filtered through a short silica plug and the solid residues washed well with ethyl acetate. The solvent was removed *in vacuo* to produce a crude product. Analysis by NMR spectroscopy revealed a complex reaction mixture with mostly unreacted starting material.

Under sonication conditions in the presence of natural Montmorillonite K10

Under solvent-free conditions

Aniline (0.140 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol) were dissolved in 1.50 ml of diethyl ether in a reaction vial equipped with a magnetic stirrer bar, followed by the addition of K10 (0.500 g). After 5 minutes stirring, the solvent was removed *in vacuo* to obtain a dry powder. The reaction mixture was sonicated at room temperature for 3 hours. After completion of the reaction, the reaction mixture was filtered through a short silica plug and the solid residues washed well with ethyl acetate. The solvent was removed *in vacuo* to produce a crude product. Analysis by NMR spectroscopy revealed only trace amounts of the desired product.

Under solvent conditions

Aniline (0.140 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol) were dissolved in 1.50 ml of diethyl ether in a reaction vial equipped with a magnetic stirrer bar, followed by the addition of K10 (0.500 g). After 5 minutes stirring, the reaction mixture was sonicated at room temperature for 3 hours. After completion of the reaction, the reaction mixture was filtered through a short silica plug and the solid residues washed well with ethyl acetate. The solvent was removed *in vacuo* to produce a crude product which was determined by NMR spectroscopy to contain the desired product in less than 10 %.

Under sonication conditions in the presence of Silver-exchanged Montmorillonite K10

Under solvent-free conditions

Aniline (0.140 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol) were dissolved in 1.50 ml of diethyl ether in a reaction vial equipped with a magnetic stirrer bar, followed by the addition of Ag-K10 (0.50 g). After 5 minutes stirring, the solvent was removed *in vacuo* to obtain a dry powder. The reaction mixture was sonicated at room temperature for 3 hours. After completion of the reaction, the reaction mixture was filtered through a short silica plug and the solid residues washed well with ethyl acetate. The solvent was removed *in vacuo* to produce a crude product. Analysis by NMR spectroscopy revealed trace amounts of 2-phenylquinoline.

Under solvent conditions

Aniline (0.140 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol) were dissolved in 1.50 ml of diethyl ether in a reaction vial equipped with a magnetic stirrer bar, followed by the addition of Ag-K10 (0.500 g). After 5 minutes stirring, the reaction mixture was sonicated at room temperature for 3 hours. After completion of the reaction, the reaction mixture was filtered through a short silica plug and the solid residues washed well with ethyl acetate. The

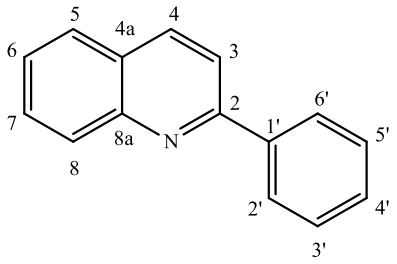
solvent was removed *in vacuo* to produce a crude product which was determined by NMR spectroscopy to contain the desired product in less than 10 %.

Under conventional heating conditions in the absence of a catalyst

Aniline (0.140 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol) were dissolved in 1.50 ml of diethyl ether in a reaction vial equipped with a magnetic stirrer bar. After 5 minutes stirring, the solvent was removed *in vacuo* to obtain a dry powder. The reaction mixture was heated at 90 °C for 3 hours. After completion of the reaction, the reaction mixture was filtered through a short silica plug and the solid residues washed well with ethyl acetate. The solvent was removed *in vacuo* to produce a crude product. Analysis by NMR spectroscopy revealed only the presence of starting material, with no evidence of the desired product.

Under conventional heating conditions in the presence of a solvent (open vessel) and Montmorillonite K10

2-Phenylquinoline 107



Aniline (0.140 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol) were dissolved in toluene in a reaction vial equipped with a magnetic stirrer bar, followed by the addition of K10 (0.50 g). The reaction mixture was heated at a temperature of 110℃ for 3 hours. After completion of the reaction, the crude product was purified by column chromatography over silica gel eluting with a mixture of Hexane : Ethyl acetate (20:1) to produce the title compound

as a yellow solid (0.044 g, 21%); (m.p. 82-84 ℃) (lit. 84-85 °C); R_f 0.67 (20:1 hexane:ethyl acetate);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.46-7.51 (1H, m, *H*-4'), 7.53-7.56 (3H, m, *H*-6, 3', 5'), 7.73-7.77 (1H, m, *H*-7), 7.85 (1H, d, *J* = 8.31 Hz, *H*-5), 7.88-7.91 (1H, d, *J* = 8.31 Hz, *H*-3), 8.18-8.27 (4H, m, *H*-4, 8, 2', 6')

^{13}C NMR (400 MHz, $CDCl_3$) δ_C 119.2 (*C*-3), 126.7 (*C*-6), 127.2 (*C*-4a), 127.5 (*C*-2', 6'), 127.9 (*C*-5), 128.4 (*C*-3', 5'), 128.7 (*C*-4'), 128.9 (*C*-7, 8), 129.8 (*C*-4), 130.3 (*C*-1'), 137.9 (*C*-8a), 157.2 (*C*-2)

ν_{max} (neat): 3033, 2970, 1489, 1319, 1284 cm^{-1};

MS (m/z): 206 $(MH)^+$ (15), 205 (100), 204 (92), 203 (12)

Data consistent with literature.[145]

Under conventional heating conditions in the presence of a solvent (open vessel) and silver-exchanged Montmorillonite K10

Aniline (0.140 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol) were dissolved in toluene in a reaction vial equipped with a magnetic stirrer bar, followed by the addition of Ag-K10 (0.500 g). The reaction mixture was heated at a temperature of 110℃ for 3 hours. After completion of the reaction, the crude product was purified by column chromatography over silica gel eluting with a mixture of hexane:ethyl acetate (20:1) to produce the title compound as a yellow solid (0.059 g, 29%). Spectroscopic data consistent with previously reported data.

Aniline (0.140 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol) were dissolved in 1.50 ml of diethyl ether in a reaction vial equipped with a magnetic stirrer bar, followed by the addition of K10 (0.500 g). After 5 minutes stirring, the solvent was removed *in vacuo* to obtain a dry powder. The reaction mixture was heated at a temperature of 120℃ for 3 hours. After completion of the reaction, the crude product was purified by column chromatography over

silica gel eluting with a mixture of hexane:ethyl acetate (20:1) to produce the title compound as a yellow solid (0.089 g, 43%). Spectroscopic data consistent with previously reported data.

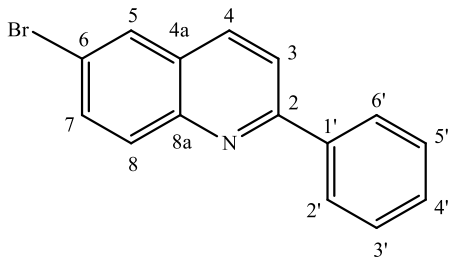
Under solvent-free conventional heating conditions (closed vessel) in the presence of silver-exchanged Montmorillonite K10

Aniline (0.140 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol) were dissolved in 1.50 ml of diethyl ether in a reaction vial equipped with a magnetic stirrer bar, followed by the addition of Ag-K10 (0.500 g). After 5 minutes stirring, the solvent was removed *in vacuo* to obtain a dry powder. The reaction mixture was heated at a temperature of 120℃ for 2 hours. After completion of the reaction, the crude product was purified by column chromatography over silica gel eluting with a mixture of hexane:ethyl acetate (20:1) to produce the title compound as a yellow solid in an isolated yield of 65% (0.0133 g). Analysis of the proton NMR showed the presence of unreacted starting material indicating that the reaction does not go completion. Spectroscopic data consistent with previously reported data.

Aniline (0.140 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol) were dissolved in 1.50 ml of diethyl ether in a reaction vial equipped with a magnetic stirrer bar, followed by the addition of Ag-K10 (0.500 g). After 5 minutes stirring, the solvent was rem oved *in vacuo* to obtain a dry powder. The reaction mixture was heated at a temperature of 120℃ for 3 hours. After completion of the reaction, the crude product was purified by column chromatography over silica gel eluting with a mixture of hexane:ethyl acetate (20:1) to produce the title compound as a yellow solid in an optimized yield of 89% (0.183 g). Spectroscopic data consistent with previously reported data.

Synthesis of quinoline derivatives

6-Bromo-2-phenylquinoline 139



Prepared by the procedure given for 2-phenylquinoline under solvent-free conventional heating conditions (3 hours) in the presence of silver-exchanged Montmorillonite K10 using *p*-Bromoaniline (0.258 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol). Purified using column chromatography (20:1 hexane:ethyl acetate) to produce the title compound as a clear oil: (0.121 g, 42%); R_f 0.54 (20:1 hexane:ethyl acetate);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.46-7.56 (3H, m, *H*-4', 3', 5'), 7.78 (1H, dd, *J* = 8.54, 2.17 Hz, *H*-4), 7.91 (1H, d, *J* = 8.96 Hz, *H*-5), 8.00 (1H, d, *J* = 2.41 Hz, *H*-7), 8.06-8.18 (4H, m, *H*-2', 6', 3, 8)

^{13}C NMR (400 MHz, $CDCl_3$) δ_C 119.8 (*C*-3), 120.1 (*C*-5), 127.5 (*C*-4a), 128.3 (*C*-4'), 128.9 (*C*-2', 6'), 129.5 (*C*-3', 5'), 129.6 (*C*-8), 131.4 (*C*-7), 133.1 (*C*-6), 135.8 (*C*-4), 139.1 (*C*-1'), 146.8 (*C*-8a), 157.7

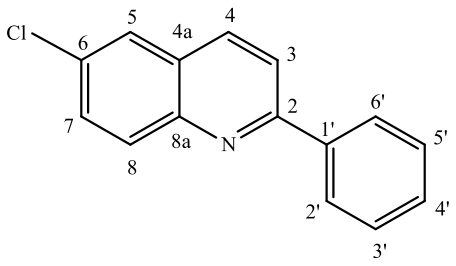
(*C*-2)

ν_{max} (neat): 3055, 2916, 2849, 1459, 1330, 693 cm^{-1};

MS (m/z): 284 $(MH)^+$ (48), 283 (100), 282 (35).

Data consistent with literature.[191]

6-Chloro-2-phenylquinoline 141



Prepared by the procedure given for 2-phenylquinoline under solvent-free conventional heating conditions (3 hours) in the presence of silver-exchanged Montmorillonite K10 using *p*-Chloroaniline (0.191 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol). Purified using column chromatography (20:1 hexane:ethyl acetate) to produce the title compound as a white solid: (0.135 g, 56%); (m.p. 108-111 ℃) (lit. 108-110 °C); R_f 0.38 (20:1 hexane:ethyl acetate);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.48 (1H, t, *J* = 7.02 Hz, *H*-4'), 7.54 (2H, t, *J* = 7.46 Hz, *H*-3', 5'), 7.67 (1H, dd, *J* = 8.96, 2.10 Hz, *H*-4), 7.82 (1H, d, *J* = 2.56 Hz, *H*-5), 7.92 (1H, d, *J* = 9.38 Hz, *H*-7), 8.15 (2H, m, *J* = 8.01 Hz, *H*-2', 6'), 8.15-8.16 (1H, m, *H*-3), 8.16-8.17 (1H, m, *H*-8)

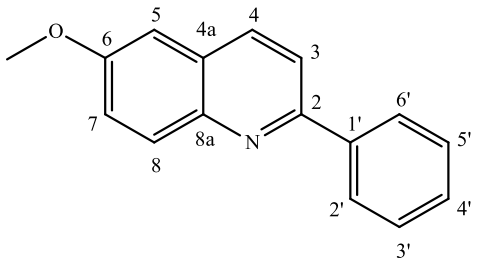
^{13}C NMR (400 MHz, $CDCl_3$) δ_C 119.9 (*C*-3), 126.4 (*C*-5), 127.6 (*C*-4a), 127.8 (*C*-4'), 128.9 (*C*-2', 6'), 129.7 (*C*-3', 5'), 130.7 (*C*-8), 131.4 (*C*-7), 132.0 (*C*-6), 136.0 (*C*-4), 139.3 (*C*-1'), 146.8 (*C*-8a), 157.6 (*C*-2)

ν_{max} (neat): 3055, 2918, 1464, 1330, 831 cm^{-1};

MS (m/z): 240 $(MH)^+$ (28), 239(100), 238 (41).

Data consistent with literature.[168] [169]

6-Methoxy-2-phenylquinoline 143



Prepared by the procedure given for 2-phenylquinoline under solvent-free conventional heating conditions (3 hours) in the presence of silver-exchanged Montmorillonite K10 using *p*-anisidine (0.185 g, 1.50 mmol) and cinnamaldehyde (0.132 g, 1.00 mmol). Purified using column chromatography (20:1 hexane:ethyl acetate) to produce the title compound as a white solid: (0.109 g, 46%); m.p. 127-130 ℃ (lit. 129-130 °C); R_f 0.15 (20:1 hexane:ethyl acetate);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.96 (3H, s, *H*-OCH_3), 7.11 (1H, d, *J* = 2.70 Hz, *H*-5), 7.40 (1H, dd, *J* = 9.18, 3.09 Hz, *H*-4'), 7.43-7.54 (3H, m, *H*-7, 3', 5'), 7.84 (1H, d, *J* = 8.65, *H*-4), 8.13-8.15 (4H, m, *H*-8, 2', 6')

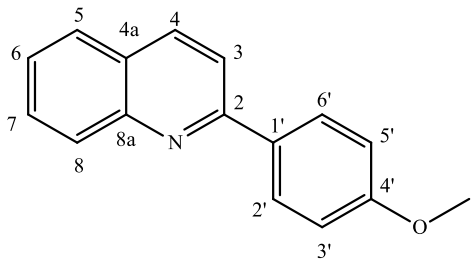
^{13}C NMR (400 MHz, $CDCl_3$) δ_C 55.6 (*C*-OCH_3), 105.0 (*C*-5), 119.4 (*C*-3), 122.6 (*C*-7), 127.4 (*C*-2', 6'), 128.2 (*C*-4a), 128.9 (*C*-3', 5'), 129.2 (*C*-4'), 130.8 (*C*-8), 135.9 (*C*-4), 139.8 (*C*-1'), 144.6 (*C*-8a), 154.9 (*C*-2), 157.9 (*C*-6)

ν_{max} (neat): 3059, 2899, 1619, 1595, 1489, 1453, 1338 cm^{-1};

MS (m/z): 235 (M^+) (100), 220 (29), 192 (42)

Data consistent with literature.[170] [192]

2-(4-Methoxyphenyl)quinoline 145



Prepared by the procedure given for 2-phenylquinoline under solvent-free conventional heating conditions (3 hours) in the presence of silver-exchanged Montmorillonite K10 using aniline (137 µL, 1.50 mmol) and *trans*-*p*-methoxycinnamaldehyde (0.162 g, 1.00 mmol). Purified using column chromatography (20:1 hexane:ethyl acetate) to produce the title compound as a white solid: (0.141 g, 60%); (m.p. 120-122 ℃) (lit. 119-121 °C); R_f 0.43 (20:1 hexane:ethyl acetate);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.91 (3H, s), 7.06 (2H, d, *J* = 9.55 Hz), 7.52 (1H, t, *J* = 7.87 Hz), 7.74 (1H, t, *J* = 7.56 Hz), 7.82-7.87 (2H, m), 8.16-8.24 (4H, m)

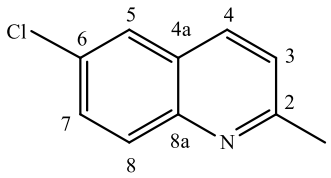
^{13}C NMR (400 MHz, $CDCl_3$) δ_C 55.4 (*C*-OCH_3), 114.4 (*C*-3', 5'), 118.7 (*C*-3), 126.3 (*C*-6), 126.9 (*C*-4a), 127.5 (*C*-5), 128.5 (*C*-2', 6'), 129.4 (*C*-8), 130.2 (*C*-7), 135.6 (*C*-1'), 137.7 (*C*-4), 147.0 (*C*-8a), 156.5 (*C*-2), 161.3 (*C*-4')

ν_{max} (neat): 3061, 2839, 1276, 1062, 1459 cm^{-1};

MS (m/z): 236 $(M+H)^+$ (56), 235 (100), 220 (73)

Data consistent with literature.[169]

6-Chloro-2-methylquinoline 146



Prepared by the procedure given for 2-phenylquinoline under solvent-free conventional heating conditions (3 hours) in the presence of silver-exchanged Montmorillonite K10 using *p*-Chloroaniline (0.191 g, 1.50 mmol) and crotanaldehyde (82.9 µL, 1.00 mmol). Purified using column chromatography (20:1 hexane:ethyl acetate) to produce the title compound as a yellow solid: (0.143 g, 80%) (m.p. 95-98 ℃) (lit. 94-98 °C); R_f 0.21 (20:1 hexane:ethyl acetate);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.76 (3H, s, *H*-2-CH_3), 7.32 (1H, d, *J* = 8.29 Hz, *H*-3), 7.61-7.64 (1H, m, *H*-7), 7.77 (1H, d, *J* = 8.78, *H*-8), 7.98 (1H, d, *J* = 3.87 Hz, *H*-5), 8.00 (1H, d, *J* = 8.87 Hz, *H*-4)

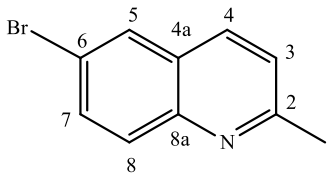
^{13}C NMR (400 MHz, $CDCl_3$) δ_C 25.08 (*C*-2-CH_3), 122.9 (*C*-3), 126.2 (*C*-6), 127.0 (*C*-4a), 129.9 (*C*-5), 130.5 (*C*-8), 131.6 (*C*-7), 135.6 (*C*-4), 145.7 (*C*-8a), 159.2 (*C*-2)

ν_{max} (neat): 3034, 2918, 1487, 1304, 831 cm^{-1};

MS (m/z): 178 (MH^+) (15), 177 (100).

Data consistent with literature.[171]

6-Bromo-2-methylquinoline 147



Prepared by the procedure given for 2-phenylquinoline under solvent-free conventional heating conditions (3 hours) in the presence of silver-exchanged Montmorillonite K10 using *p*-Bromoaniline (0.258 g, 1.50 mmol) and crotanaldehyde (82.9 µL, 1.00 mmol). Purified using column chromatography (20:1 hexane:ethyl acetate) to produce the title compound as a white solid: (0.181 g, 81%) (m.p. 103-105 ℃) (lit. 102-106 °C); R_f 0.33 (20:1 hexane:ethyl acetate);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.75 (3H, s, *H*-2-CH_3), 7.32 (1H, d, *J* = 8.29 Hz, *H*-3), 7.74-7.77 (1H, m, *H*-7), 7.92-7.99 (3H, m, *H*-8, 5, 4)

^{13}C NMR (400 MHz) δ_C 25.11 (*C*-2-CH_3), 119.6 (*C*-3), 122.9 (*C*-6), 127.6 (*C*-4a), 129.5 (*C*-5), 130.0 (*C*-8), 133.1 (*C*-7), 135.6 (*C*-4), 145.9 (*C*-8a), 159.4 (*C*-2)

ν_{max} (neat): 3070, 2914, 1226, 1334, 1487, 1276, 697 cm^{-1};

MS (m/z): 222 (MH^+) (13), 221 (100).[171]

Data consistent with literature.[171]

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APPENDIX