PROJECT REPORT

On

"MICROWAVE ASSISTED SYNTHESIS OF HETEROCYCLIC COMPOUNDS"

Submitted by

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In partial fulfillment for the award of the BSc Degree in Chemistry

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B.Sc. CHEMISTRY PROJECT REPORT

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This is to certify that the project "**MICROWAVE ASSISTED SYNTHESIS OF HETEROCYCLIC COMPOUNDS**" is the work done by **NIRANJANA MANOJ, CATHERINE DIONA PEREIRA, APARNA ANTONY.**

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Staff-member in charge

Submitted to the Examination of Bachelor's Degree in Chemistry

Date:……

Examiners:…….

DECLARATION

I hereby declare that the project work entitled "**MICROWAVE ASSISTED SYNTHESIS OF HETEROCYCLIC COMPOUNDS** " submitted to Department of Chemistry, St. Teresa's College (Autonomous) affiliated to Mahatma Gandhi University, Kottayam, is a record of an original work done by me under the guidance of Dr. Elizabeth Kuruvilla, Department of Chemistry, St. Teresa's College (Autonomous), Ernakulam and this project work is submitted in the partial fulfillment of the requirements for the award of the degree of Bachelor of Science in Chemistry.

NIRANJANA MANOJ
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Chapter 1

Introduction

Synthesis of new chemical entities is major bottleneck in drug discovery. Conventional methods for various chemical synthesis is very well documented and practiced. In 1855, Robert Bunsen invented the burner which acts as energy source for heating a reaction vessel, this was later superseded by oil bath or hot plate. Microwave Assisted Organic Synthesis (MAOS), which has developed in recent years, has been considered superior to traditional heating.[1]

Microwave assisted organic synthesis (MAOS) has emerged as a new "lead" in organic synthesis. The technique offers simple, clean, fast, efficient, and economic for the synthesis of a large number of organic molecules. In the recent year microwave assisted organic reaction has emerged as new tool in organic synthesis. Important advantage of this technology include highly accelerated rate of the reaction, reduction in reaction time with an improvement in the yield and quality of the product. The technique is now considered as an important approach toward green chemistry, because this technique is more environmentally friendly.[2] This

technology is still under-used in the laboratory and has the potential to have a large impact on the fields of screening, combinatorial chemistry, medicinal chemistry and drug development. Conventional method of organic synthesis usually need longer heating time, tedious apparatus setup, which result in higher cost of process and the excessive use of solvents/ reagents lead to environmental pollution.

1.1 Microwave in organic Synthesis

Microwave have been used to speed up chemical reactions in the laboratories which led scientists to investigate the mechanism of microwave dielectric heating and to identify the advantages of the technique for chemical synthesis. During recent years, microwaves have been extensively used for carrying out chemical reactions and have become a useful non-conventional energy source for performing organic synthesis.This is supported by a great number of publications in recent years, particularly in 2003, related to the application of microwaves as a consequence of a great availability of dedicated and reliable microwave instrumentation.[3] The first recorded application of microwave energy in organic synthesis is the aqueous emulsion polymerization of butyl acrylate, acrylic acid and methacrylic acid using pulsed electromagnetic radiation.[4]

1.2 Effects Of Solvents

In the case of the microwave-assisted reactions using (organic) solvents, the reactants are usually dissolved in the solvent, which often couples effectively with microwaves and thus acts as the energy transfer medium.[5] Every solvent and reagent will absorb microwave energy differently. They each have a different degree of polarity within the molecule, and therefore, will be affected either more or less by the changing microwave field. A solvent that is more polar, for example, will have a stronger dipole to cause more rotational movement in an effort to align with the changing field. A compound that is less polar, however, will not be as disturbed by the changes of the field and, therefore, will not absorb as much microwave energy. Unfortunately, the polarity of the solvent is not the only factor in determining the true absorbance of microwave energy, but it does provide a good frame of reference. Most organic solvents can be broken into three different categories: low, medium, or high absorber, as shown in table 1. The low absorbers are generally hydrocarbons while the high absorbers are more polar compounds, such as most alcohols.

Absorbance level	**Solvents**
High	DMSO, EtOH, MeOH, Propanols, Nitobenzen, Formic Acid, Ethylene Glycol
Medium	Water, DMF, NMP, Butanol, Acetonitrile, HMPA, Methyl Ethyl Ketone, Acetone, Nitromethane, Dichlorobenzene, 1,2-Dichloroethane, Acetic Acid, trifluoroacetic Acid,
Low	Chloroform, DCM, Carbon tetrachloride, 1,4-Dioxane, Ethyl Acetate, Pyridine, Triethyamine, Toluene, Benzene, Chlorobenzene, Pentane, Nexane and other hydrocarbons

Table 1: Different categories of solvents used in microwave assisted synthesis.

1.3 Microwave frequency

Microwave heating refers the use of electromagnetic waves ranges from 0.01 m to 1 m wave length of certain frequency to generate heat in the material. These microwaves lie in the region of the electromagnetic spectrum between millimeter wave and radio wave i.e. between I.R and radio wave. They are defined as those waves with wavelengths between 0.01 metre to 1 meter, corresponding to frequency of 30 GHz to 0.3 GHz.

1.4 Benefits Of Microwave Assisted Synthesis

Microwaves can accelerate the rate of reaction, provide better yields and higher purity, uniform and selective heating with lower energy usage, achieve greater reproducibility of reactions and help in developing convenient and cleaner synthetic routes. The main advantages of microwave assisted organic synthesis are[6]:

1.4.1 Faster reaction: Based on experimental data it has been found that microwave-enhanced chemical reaction rates can be faster than those of conventional heating methods by as much as 1,000-fold. The microwave can use higher temperatures than conventional heating system, and consequently the reactions are completed in few minutes instead of hours, for instance, synthesis of fluorescein, which usually takes about 10 hours by conventional heating methods, can be conducted in only 35 minutes by means of microwave heating.

1.4.2 Better yield and higher purity: Less formation of side products are observed using microwave irradiation, and the product is recovered in higher yield. Consequently, also the purification step is faster and easier. For example, microwave synthesis of aspirin results in an increase in the yield of the reaction, from 85 % to 97 %.

1.4.3 Energy saving: Heating by means of microwave radiation is a highly efficient process and results in significant energy saving. This is primarily because microwaves heat up just the sample and not the apparatus, and therefore energy consumption is less.

Uniform and selective heating: In conventional heating, the walls of the oil bath get heated first, and then the solvent. As a result of this distributed heating in an oil bath, there is always a temperature difference between the walls and the solvent. In the case of microwave heating, only the solvent and the solute particles are excited, which results in uniform heating of the solvent. Selective heating is based on the principle that different materials respond differently to microwaves. Some materials are transparent whereas others absorb microwaves.

1.4.4 Green synthesis: Reactions conducted using microwaves Are cleaner and more eco-friendly than conventional heating methods. Microwaves heat the compounds directly; therefore, usage of solvents in the chemical reaction can be reduced or eliminated. Synthesis without solvent, in which reagents are absorbed on mineral support, has a great potential as it offers an eco-friendly green protocol in synthesis. The use of microwaves has also reduced the amount of purification required for the end products of chemical reactions involving toxic-reagents.

An area where MAOS can play an important role is in chemical and pharmaceutical industries. These industries have to deal with constraints related to the environmental aspects and saving energy. An alternative to overcome such problems in organic synthesis is the use of microwave (MW) irradiation as a source of energy.

Acridines are a well known group of compounds with a wide variety of biological properties[7]: DNA intercalating agents, anticarcinogenic, bactericidal, antimalarial, insecticides and antifungic.

Numerous research groups have focused on the synthesis of new compounds that possess cytotoxic activity, among which acridine/acridone compounds play an important role. Acridine/acridone analogs are known anticancer drugs and cytotoxic agents, and they represent a very interesting class, displaying other forms of bioactivity. They are used as biological fluorescent probes, anti-bacterial drugs, e.g., **1**–**6** [8], anti-protozoal drugs, e.g., **7**–**12**[9], anti-malarial agents, e.g., **13**[10], and anti-HIV drugs, e.g., **14**[11] (Figure 1).

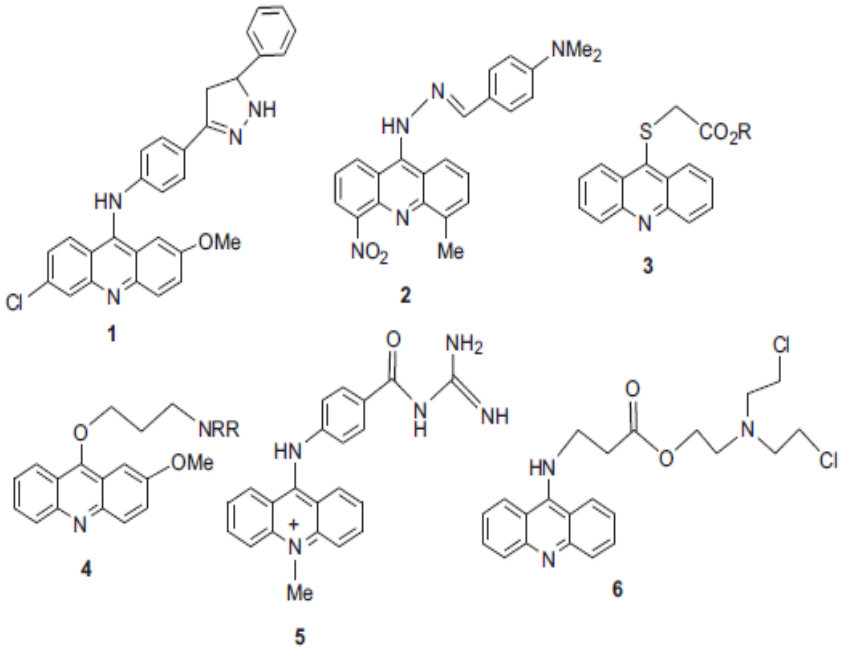


Figure 1: Structures of few biologically active acridine derivatives.

The utility of acridines as chemotherapeutics is due to their chemical and biological stability and their capability of effective binding to DNA or RNA[12], resulting in the disorder of the biological functions in living cells. The mechanism of their intercalation into DNA is based on _-stacking interaction with base pairs of double-stranded nucleic acids. The heterocyclic,

polyaromatic flat structure of acridine fits effectively into the gap between two chains of polynucleotides, and the intercalation of the acridine moiety disturbs their crucial role in cell division. The ability of acridines to

intercalate into DNAis necessary for their antitumor activity. The strength and kinetics of binding acridine to DNA have a crucial impact on the activity of this type of anticancer agent.

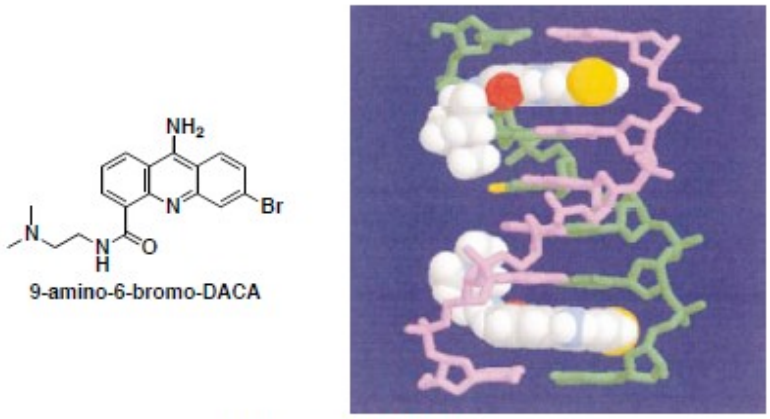


Figure 2: Complex of an acridine derivative with DNA

There are several approaches to their synthesis. Bernthsen reaction is one of the classical methods. It is mainly the heating of diphenylamine in the presence of zinc chloride and a carboxylic acid, temperature of reaction is 200-280 ºC and reaction times are several hours. But usually the yields are low. In order to avoid the long reaction times and high temperatures, microwave assisted synthesis of acridines were tried by different groups.[13] An example is shown in Figure 3.

A one step reaction of dimedone with aniline or *p*-chloroaniline in formic acid to give the 10- aryl-decahydroacridine

derivatives required heating at 150 ºC for 23 hours. This cyclocondensation can be conveniently achieved within 12 minutes using a solvent-free condition under MW irradiation.

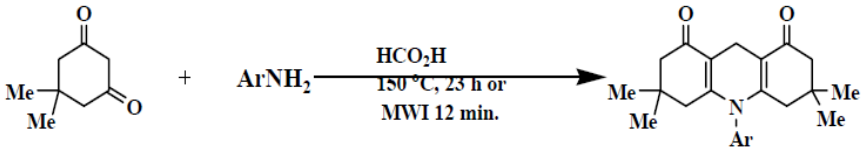


Figure 3: Microwave assisted synthesis of 10- aryl-decahydroacridine derivative.

Our objective was to develop new microwave assisted synthetic protocol for the synthesis of 9-substituted acridine derivatives. The methylation of the nitrogen of the acridine ring makes them water soluble and thus useful in studying its interaction with biomolecules in aqueous media. Furthermore they are reported to have high fluorescence quantum yields which makes them suitable for biosensing applications.

The conventional Berthsen procedure requires high reaction temperatures, which leads to charring of the reaction mixture reducing the yields. We have used microwave to carry out the synthesis of a series of 9-substituted acridine derivatives.

Chapter 2

Materials and Methods

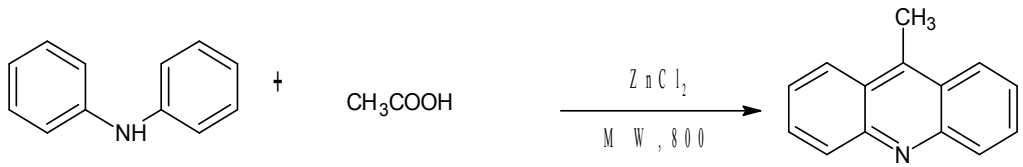
2.1 Introduction

Anhydrous zinc chloride, diphenylamine, benzoic acid, concentrated sulphuric acid, acetic acid, sodium bicarbonate, chloroform, sodium chloride and sodium sulphate used was from Nice Chemicals. Microwave assisted reactions were carried out in Qpro-M microwave synthesizer. Formation of the compounds was routinely checked by TLC on silica gel-G plates and spots were located by iodine. Column chromatography was carried out using 60 mesh size Silica Gel.

2.1.1 Synthesis of 9-methylacridine

1.69 g, 0.01 mmol of diphenylamine , 0.60 g, 0.01mmol acetic acid and 6.80 g, 0.05 mmol of zinc chloride was mixed well and ground in mortar. It was immediately transferred in to a conical flask and kept in microwave oven. The microwave irradiation was operated in 10 seconds cycle for 4-5 times. The crude reaction mixture was dissolved in chloroform. It was washed with sodium bicarbonate solution. The chloroform layer was then separated. Anhydrous sodium sulphite was added and filtered. The

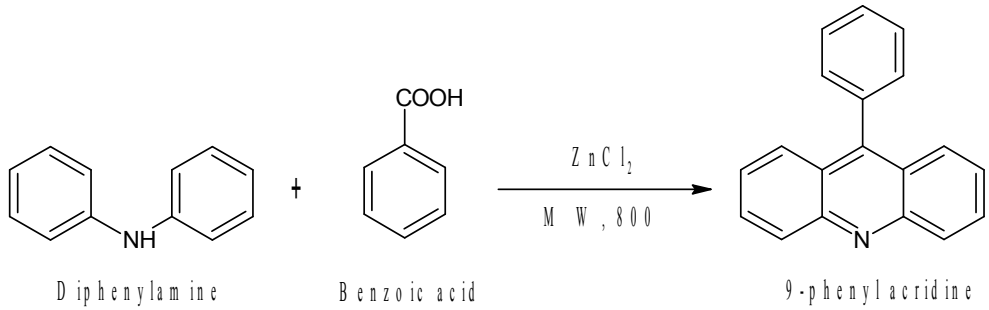
chloroform extract was then evaporated to dryness. It was then dissolved in minimum chloroform and then loaded on silica gel (60 mesh) and column chromatography was done with chloroform as solvent. The product (R_f= 0.79 , Solvent- Chloroform) was separated and evaporated to dryness. Yield: 85 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.46 (m, 5H, Ar-H), 7.59–7.64 (m, H, Ar-H), 7.71 (d, 2H, Ar-H), 7.76–7.80 (m, 2H, Ar-H), 8.28 (d, 2H, Ar-H) ^{13}C NMR: δ 125.2, 125.6, 126.9, 128.4, 128.5, 129.7, 130.0, 130.5, 135.9, 147.1, 148.7 ppm.



2.2.2 Synthesis of 9-phenylacridine

1.69 g, 0.01 mmol of diphenylamine, 1.22 g, 0.01 mmol benzoic acid and 6.80 g, 0.05 mmol of zinc chloride was mixed well and ground in mortar. It was immediately transferred in to a conical flask and kept in microwave oven. The microwave irradiation was operated in 10 seconds cycle for 4-5 times. The crude reaction mixture was dissolved in chloroform. It was washed with sodium bicarbonate solution. The chloroform layer was then separated. Anhydrous sodium sulphite was added and filtered. The

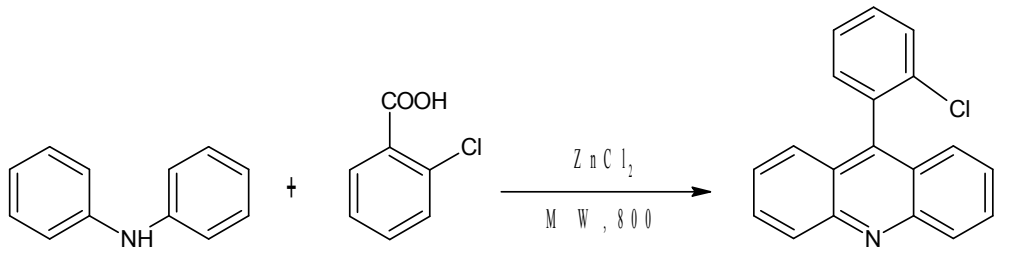
chloroform extract was then evaporated to dryness. It was then dissolved in minimum chloroform and then loaded on silica gel (60 mesh) and column chromatography was done with chloroform as solvent. The product (R_f=0.4545, Solvent - chloroform) was separated and evaporated to dryness. Yield of the product = 90% . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.46 (m, 5H, Ar-H), 7.59–7.64 (m, H, Ar-H), 7.71 (d, 2H, Ar-H), 7.76–7.80 (m, 2H, Ar-H), 8.28 (d, 2H, Ar-H) ^{13}C NMR: δ 125.2, 125.6, 126.9, 128.4, 128.5, 129.7, 130.0, 130.5, 135.9, 147.1, 148.7 ppm.



2.2.3 Synthesis of 9-(2-chlorophenyl)acridine

1.69 g, 0.01 mmol of diphenylamine, 1.56 g, 0.01 mmol ortho-chlorobenzoic acid and 6.80 g, 0.05 mmol of zinc chloride was mixed well and ground in mortar. It was immediately transferred in to a conical flask and kept in microwave oven. The microwave irradiation was operated in 10 seconds cycle for 4-5 times. The crude reaction mixture was dissolved in chloroform. It was washed with sodium bicarbonate

solution. The chloroform layer was then separated. Anhydrous sodium sulphite was added and filtered. The chloroform extract was then evaporated to dryness. It was then dissolved in minimum chloroform and then loaded on silica gel (60 mesh) and column chromatography was done with chloroform as solvent. The product (R_f= 0.40 , Solvent- Chloroform) was separated and evaporated to dryness. Yield of the product = 73%.



Diphenylamine ortho-chlorobenzoic acid 9-(2-chlorophenyl)acridine

Chapter 3

Results and Discussion

The microwave assisted synthesis of different substituted acridine derivatives were carried out. The 9-methyl acridine was synthesised by mixing diphenylamine and acetic acid in 1:1 ratio and heating in the microwave in the presence of excess anhydrous zinc chloride. Inorder to synthesise the 9-phenyl acridine and 9-(2-chlorophenyl)acridine, the diphenylamine was treated with benzoic acid and 2-chlorobenzoic acid respectively. The reaction was monitored using thin layer chromatography. The product was obtained in 4-5 minutes. The Bernthsen procedure for the synthesis of acridines usually involves heating upto 280 ^{0}C for more than 24 h. The yields obtained were around 40-50 %. The microwave synthesis reduces the reaction time significantly with quantitative yields. However, it was observed that increasing the reaction time results in the charring of the reaction mixture. The reaction mechanism is shown in figure 4.

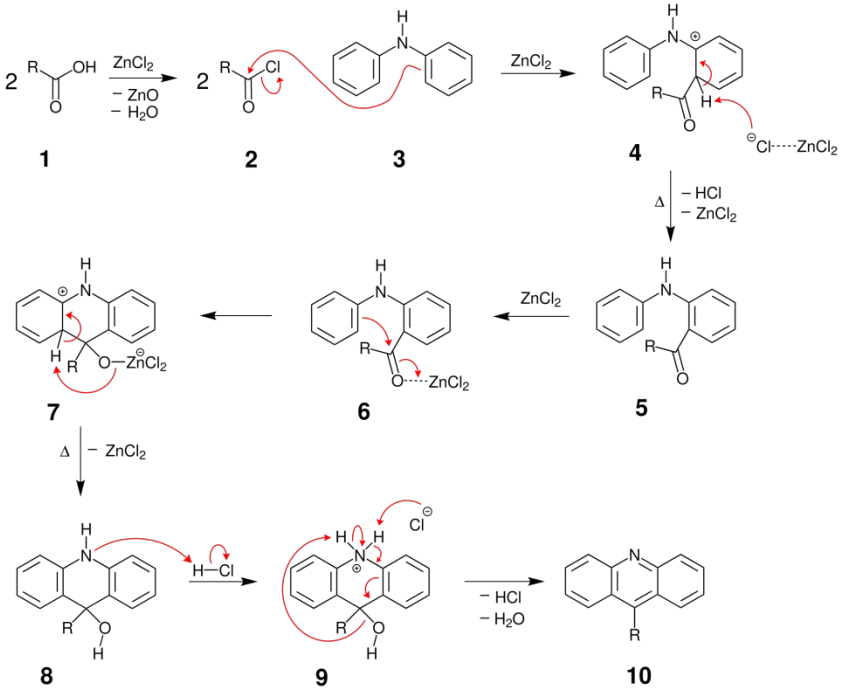


Figure 4: Reaction mechanism

The acridine derivatives obtained were purified using column chromatography with chloroform and hexane mixture as eluant. The purified derivatives were characterised using ^{1}H and ^{13}C NMR and by IR spectroscopy. The proton NMR showed the characteristic peaks for the aromatic protons of the acridine ring. The IR showed a characteristic band at 1673 cm^{-1} indicating the presence of C=N bond.

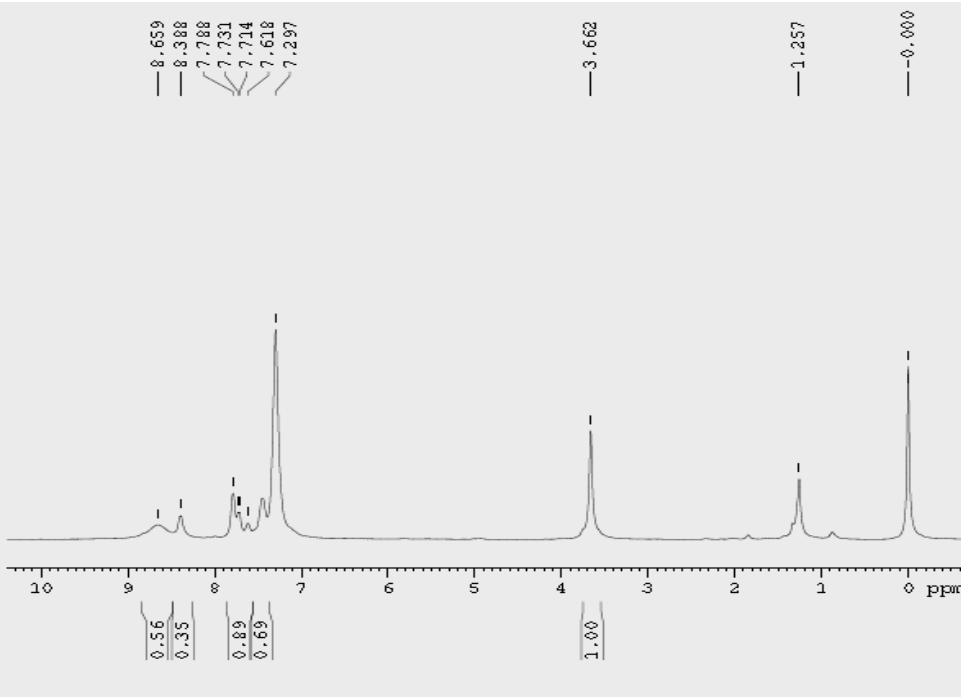


Figure 5. ^{1}H NMR spectrum of 9-methyl acridine (solvent $CDCl_3$)

Figure 5 shows the proton NMR of 9-methyl acridine. The spectrum shows a singlet at δ 3.6 ppm which corresponds to the three protons of the methyl group. The aromatic protons of the acridine ring appear as multiplets between δ 7.61 – 8.38 ppm. Similarly the other acridine derivatives also exhibited the characteristic peaks.

Chapter 4

Conclusions

In conclusion, we have demonstrated the microwave assisted synthesis of heterocyclic compounds such as acridines. The quantitative yields obtained under significantly short reaction times prove the advantage of this technique. The synthesis of acridine as well as other heterocyclic compounds with potential pharmaceutical applications can be carried out using the microwave assisted synthesis.

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