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THESIS ACCEPTANCE LETTER

The thesis titled **"Synthesis of Heterocyclic Compounds from Hydrazine and its derivatives using Microwave (MW) irradiation"** Submitted by Md. Mahbubul Islam Talukder, Roll No.: 040203103-F, Registration No.: 0402018, Session: April, 2007 has been accepted as satisfactory in partial fulfillment of the requirement for the Degree of Master of Philosophy (M. Phil) on December 27, 2007.

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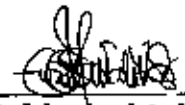

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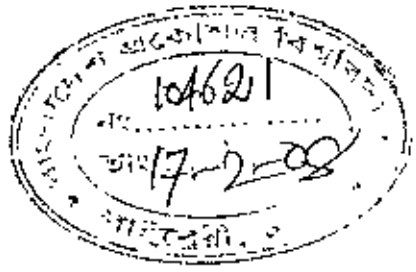
Contents

Spectrum

Graph



Chapter One

Introduction

1.1. Background of Microwave:

Once, chemists might have spent days sweating over a Bunsen burner, pleading with a reactive brew to release its product, but with the arrival of combinatorial chemistry, those heady days are long gone, and vast arrays of molecules are generated in a trice, even with compound libraries coming into sharper focus, the rate-determining step, especially in the pharmaceutical industry, remains the seed at which usable quantities of materials can be synthesized. Microwave irradiation is becoming an increasing popular method of heating samples in the Laboratory. It offers a clean, cheap and convenient method of heating which often results in higher yields and shorter reaction times. Despite this popularity, and an increasing amount of literature on the subject, microwaves remain an area of mystery and magic for many people. The purpose of this part is to provide useful details concerning the application of microwaves in chemical reaction. The pioneers of the application of microwaves into more canonic synthesis thought that it could produce similar effects in assisting the reactions carried out in research Laboratories. In most cases it was proved that reactions were saving a great deal of time[1]. Regardless of the mechanism of action of microwaves on the chemical systems, this part will deal with a few points that seem in a peculiar way to characterize the use of microwaves in carrying out chemical reactions and this technique that is set to revolutionize synthesis has moved to the fore front of chemical research: microwave assisted organic synthesis (MAOS)[2-5]. While fire is now rarely used in synthetic chemistry, it was not until Bunsen invented the burner that the energy from this heat source could be applied to a reaction vessel in a focused manner. The Bunsen burner was later superseded by the isomantle, oil bath or hot plate as a source of applying heat to a chemical reaction. Microwave chemistry has been around for decades. In the 1960s, Physical chemists used domestic microwave ovens to give their reaction systems a temperature kick and microwave-generated polymers were all in the range in 1967. By the early 1980s several chemists were bringing domestic ovens in the laboratory, and in the mid-1960s groups led by Richard Gedye (Laurentian University, Sudbury, ON), Goerge Majetich (University of Georgia,

Atlanta), Raymond Giguere (Mercer University, Atlanta, GA), Rajender Varma (Sam Houston state University, Huntsvile, TX), and others have found that microwaves can accelerate, boost the yield, and initiate otherwise impossible reactions. To date ~1500 microwave chemistry papers have been published. However, since the late 1990s, the number of publications related to MAOS has increased dramatically to a point where in a few years; most chemists will probably use quick bursts of microwave energy to heat and drive chemical reactions[5, 6]. But as Pino Pilotti of Personal Chemistry (Upsala, Sweden) points out, many would-be microwaves were put off by spurious results. "There is no way one can get reproducible results using a normal domestic microwave oven, because you can get interferences between the microwaves" he explains. "Parts of the plate are heated very much, others at the temperature you are hopping for, while other regions are not heated at all. The occasional excellent results were task force by the explosions and lack of reproducibility" Most reaction rates are accelerated by increasing temperature that is based on the well-known 'rule of thumb' that for every 10°C increase in temperature, the rate is approximately doubled. The maximum temperature of a reaction is usually the boiling point of the solvent. But in a closed microwave vessel, the temperature of the mixture can be raised further, so, the reaction rate increases accordingly.

As of 2007, many of the top pharmaceutical, agrochemical and biotechnology companies are already using MAOS as a forefront methodology for library synthesis and lead optimization as they realize the ability of the enabling technology to speed chemical reactions. Not only microwaves are sometimes able to reduce chemical reaction times from hours to minutes, but they are also known to reduce side reactions, increase yields and improve reproducibility. Almost all type of organic reaction requiring heating or thermal condition can be performed using microwave radiation. Microwave dielectric heating is dependent on the ability of a solvent or matrix to absorb microwave energy and to convert it into heat [5, 6]. The matrix absorbs the radiation by two mechanism: dipole polarization and conduction.

When irradiated with microwave frequencies, the ions or dipole of the sample align in the applied electric field. As the applied field oscilates, the dipole or ion field attempts to realign itself with the alternating electric field and, in the process, energy is lost in from of heat through molecular friction and dielectric loss. A mount of heat generated by this process is directly related to the ability of the matrix to align itself with the frequency of the applied field. If the dipole doses not

have time to realign, or reorients too quickly with the applied field, no heating occurs. The allocated microwave frequency of 2.45 GHz used in all commercial systems lies between these two extremes and gives the molecular dipole time to align in the field, but not to follow the alternating field precisely. Microwave irradiation produces efficient internal heating (*in situ* heating), resulting in even heating throughout the sample, as compared with the wall heat transfer that occurs when an oil bath is applied as an energy source. Consequently, the tendency for the initiation of boiling is reduced, and superheating above the boiling point of the solvent is possible even at atmospheric pressure. Superheating can be generated rapidly in closed microwave-transparent vessels to temperatures as high as 100°C above the normal boiling point of a particular solvent.

It is this combination of rapid microwave heating and sealed vessel technology that is responsible for most of the observed rate enhancements seen in MOAS. It is possible, however, that macroscopic or microscopic hotpots resulting from selective heating of specific reagents or catalysts can develop, leading to even faster conversions and the realization of chemistries that cannot be conducted by conventional heating, the current trend clearly is to use dedicated instruments for chemical synthesis[6-8]. Most of today's commercially available microwave reactors feature build-in magnetic stirrers, direct temperature control of the reaction mixture with the aid of fibre optic probes of infrared sensors and software that enables online temperature/pressure control by regulation of microwave output power. As of 2006, suppliers of microwave instrumentation for organic synthesis have also moved towards combinatorial/high-throughput platforms, addressing the needs of the drug discovery industry[9].

The bottleneck of parallel synthesis is typically optimization of reaction conditions to afford the desired products in suitable yields and purities. Since many reaction sequences require a heating step for extended time periods, these optimization are often difficult and time-consuming. Microwave-assisted heating has been shown to be an invaluable optimization method since it reduces reaction times dramatically, typically from days or hours to minutes or seconds[7]. Many reaction parameters can be evaluated in a few days to optimize the desired rapidly using the new technology, either in a parallel or sequential mode. Several large pharmaceutical companies have reported dramatic productivity increases in switching from

conventional synthesis to MAOS[10-15] although the initial investment costs are considerable; the dramatically increased efficiency of the microwave approach allows a return of investment in a short time pan.

1.2. Diverse reaction:

With these machines becoming more common to industry and academia, the number of microwave reaction is growing. This not only allows them to generate interesting products and to demonstrate that it is possible to use microwave heating to interconvert alcohols and alkenes, but it also allows them to avoid volatile organic solvents and acid catalysts, adding to microwaving's green credentials. Controlling the stereochemical outcome of a drug synthesis is crucial because many materials either have hazardous isomers or are less effective medicines as isomeric mixtures. Microwave – assisted organic synthesis works in two ways:

(a) Microwave syntheses in Liquid Media and

(b) Microwave syntheses in Solid media

1.2.1 Microwave Syntheses in Liquid Media:

General Remarks: Any dipolar solvent with relatively low molecular weight will tend to display a capacity for heating under microwave irradiation. Many solvents are not only heated but display a capacity for superheating. This has been investigated by a number of authors[16], and a model proposed for the behavior based on the mechanism of nucleate bubble formation which is required for boiling.[16] Superheating, which may result in boiling points being raised by up to 20°C above their conventional value under microwave irradiation, is widely believed to be responsible for the rate and yield increases which accompany many liquid phase reactions.

1.2.2 Microwave syntheses in Solids Media:

General Remarks: In addition to the physical changes indeed in ceramic materials, the microwave dielectric losses of many solid compounds may be used to provide sufficient heat to drive chemical changes.

1.3 Microwave Heating:

A chemist seems that microwave ovens are 'tuned' so that water molecules absorb microwaves into rotational energy levels, and this causes molecular motion, and thus heating. This common misunderstanding comes from in failure to realize that while water has quantized rotational energy levels in the microwave region, in

the liquid phase, the quantization rotational level is, for all practical purpose, non-existent. The easiest way to visualize the mechanism of microwave heating is to picture a microwave for what it is a high frequency oscillating electric and magnetic field. Anything that may be electrically or magnetically polarized by this 'oscillating' field will be affected to some extent. Two principal heating methods exist:-dipolar polarization and conductive heating[17].

Microwave energy is therefore similar to that transported by infrared or visible or ultraviolet waves and all follow the same laws. The frequencies of microwaves range from 300 MHz to 30 GHz (1-0.01 cm wavelength). 2.45 GHz (12.3 cm wavelength) is a frequency allotted by an international Commission for domestic or industrial ovens[18]. Microwaves represent a non ionizing radiation, which influences molecular motions such as ion migration or dipole rotation, but not alternating the molecular structure. In 2.45 GHz microwaves the oscillation of the electric field of the radiation occurs 4.9×10^9 times per second; the time scales in which the field changes is about the same as the response time (relaxation time) of permanent dipoles present in most organic and inorganic molecules[19]. This fact represents a fundamental characteristic for an efficient interaction between the electromagnetic field of microwaves and a chemical system. The absorption of microwaves causes a very rapid change of temperature of reagents, solvents, and products containing salt. Moreover in the case of solutions containing salt or strong acids and bases the energy can also be dissipated through ionic conduction, causing heating or overheating of the solvent (together with a possible increase of the pressure, when the reaction is carried out in close vessels).

1.4.1 Dipolar polarization:

For a molecule in a polar liquid such as water (methanol, ethanol, THF, etc), there are intermolecular forces which give molecule in motion some inertia. Under a very high frequency electric field, the polar molecule will attempt to follow the field, but intermolecular inertia stops any significant motion before the field has received, and no net motion results. If the frequency of field oscillation is very low, then the molecules will be polarized uniformly and no random motion results. In the intermediate case, the frequency of the field will be such that the molecules will be almost, but no quite, able to keep in phase with the field polarity. In the case, the random motion resulting as molecules jostle to attempt in vain to follow the field is

the heating we observe in the sample. It is interesting to note that whilst the efficiency of microwave absorbance varies noticeably with frequency for any liquid, the frequency of a domestic microwave oven (2.45 GHz) is not selected so that it is at the maximum absorbency for water (something like 10GHz).

1.4.2 Interfacial polarization:

This mechanism is important for systems comprised of conducting inclusions in a second, non-conducting material. An example would be a dispersion of metal particles in, say, sulpher is microwave transparent and metals reflect microwaves yet, curiously, the combination forms an extremely good microwave absorbing material (So good, in fact, that interfacial polarization effects are reputed to be the basis of 'stealth' radar absorbent materials). Interfacial polarization is an effect which is very difficult to treat in a simple manner, and is most easily viewed as a combination of the conduction and dipolar polarization effects. For a (non-superconducting) metal, there will always be a very thin surface layer in which some of the incident microwaves are attenuated, and in which induced currents will give rise to heating. For a bulk metal this heating effect is so small as to be irrelevant, but in powders this surface layer makes up a large proportion of the material. However, the polarization induced in the metal is also subject to the properties of the surrounding medium – in simple terms, it induces a 'drag' on the polarization of the metallic inclusions – making it less effective than it might otherwise be. Under these circumstances, the polarization of the metallic particles does not take place instantaneously, but lags behind the induced field, as for the polar molecule in the dipolar polarization mechanism. Hence, the frequency dependence of the sample's heating properties is similar to that of the dipolar polarization mechanism, despite being due to a conduction mechanism.

1.5.1 Conductive heating:

If we irradiate an electrical conductor or semiconductor with microwave energy, any mobile charge carriers (electron, ion etc) move relatively easily through the material under the influence of the electric field. These induced currents heat the sample, owing to electrical resistance. If the sample is a metallic conductor, most of the microwave energy is reflected with relatively little energy penetrating beyond a few microns into the surface. However, colossal surface voltages may still be induced,

and these are responsible for the dramatic electrical discharges that are observed when a metal is placed in a microwave oven.

Conductive heating can be demonstrated in a domestic microwave oven by using materials such as copper oxide or carbon. One should be aware, however, that these materials become very hot, very quickly, and that the electrical potentials induced in the materials can sometimes lead to dramatic (but otherwise harmless) electrical discharge. Alternatively, if pure water is heated in a microwave oven where the polarization of a dilute salt solution is heated. In the latter case, both dipolar polarization and conductive mechanisms contribute to the heating effect.

1.5.2 Conduction Mechanisms:

For a very good conductor, complete polarization may be achieved in approximately 10^{-18} second, indicating that under the influence of a 2.45 GHz microwave, the conducting electrons move precisely in phase with the field. Thus, if one takes pure water and heats it in a microwave oven, where the polarization mechanism dominates, we find that the heating rate is significantly less then when one takes the same volume of water and add salt. In the latter case, both mechanisms occur, and contribute to the heating effect.

1.5.3 Dielectric heating:

Microwave heating arises from the ability of some liquids and solids to transform the absorbed electromagnetic energy into heat: the heating effect originates from the microwave electric field which forces dipoles to rotate and ions to migrate and form a slower response of dipoles and ions follow the rapid reversal of the electric field. The ability of a material to increase its temperature under microwave at a given frequency and temperature is referred to the dissipation factor, defined as $\tan \Delta = \epsilon''/\epsilon'$, where ϵ'' is the dielectric loss factor, related to the efficiency of a medium to convert microwave energy into heat, while ϵ' is the dielectric constant and measures the ability of a molecule to be polarized by an electric field. In the case of water, ϵ' is relatively high at low frequency but rapidly drops to zero above 30 GHz, while ϵ'' shows a parabolic profile reaching a maximum at around 20 GHz. The frequency of 2.45 GHz, chosen for practical purposes, represents a compromise both to minimize the drop of the dielectric constant with the increasing frequency and to maximize the penetration depth of the radiation: in short, to maximize the heating

rate of an absorbing mass of water[20,21]. This choice has also a historical valency, since it is related to the previous domestic application of microwaves toward water either in defrosting or cooking food. This frequency can be successfully applied also to heat short-chain aliphatic alcohols[22].

1.6 Waves in a square box:

Unfortunately, microwaves can not be treated in quite the same way as a heating mantle, because of their long wavelength (12.2 cm for a domestic oven). In any microwave oven, the microwaves are retained by the metal walls and there is interference of the waves as they are reflected off the sides of the oven. At some points the waves add together to give high intensity standing waves anti and at other points they cancel out (nodes). You can demonstrate this by using a microwave oven that has had its turntable removed. Place a large plate of evenly spaced marshmallows in the microwave and heat for *ca* 30s. Several of the marshmallows triple in size and are too hot to touch, while some remain at room temperature and are unaltered in size. Alternatively, use a piece of filter paper wetted with cobalt chloride solution. This compound is pink when surrounded by water molecules and blue when they are moved, *e.g.* by heating, and the cobalt chloride paper is dried out much more rapidly at the antinodes than at the nodes.

Although it is possible to modify a domestic oven for chemical syntheses, the wave nature of microwaves means that highly reproducible work requires slightly more sophisticated microwave applicators. In a well-designed system, energy can be imparted directly and efficiently into the reaction components, with little energy lost through reflections or through heating the reaction vessel.

1.6.1 The Microwave Oven:

The heart of the oven is the magnetron an oscillator that converts high voltage pulse into a pulse of microwave power. The microwave enters a waveguide, whose reflective walls allow the transmission of the radiation from the magnetron into the cavity. The cavity is a sort of box and is the part of the oven where microwaves interact with the chemical system. A microwave oven is constructed to deliver a preset frequency (2.45 GHz in most cases) and power: a control unit regulates the power value introduced into microwave system is 600-700 watts: in 6 min irradiation. approximately 43000 cal are delivered into the cavity.

Under microwave irradiation two main problems arise: the uniformity of the absorption and the reflection of the waves. The microwave energy travels on a beam: escaping from the guide the wave is deviated by the circulator (this works similar to a round about) into the cavity, the cavity walls reflect the beam, until it hits the sample and is absorbed. To increase the probability of interaction between the sample and the wave, to maximize absorption, the sample is put on rotating glass disk. To absorb the excess microwaves a beaker of water is placed inside the cavity, which acts as a dummy load. This way the magnetron (and also the operator) is protected from the reflected power.

To carry out chemical reaction the cavity of domestic microwave ovens can easily be modified: a hole in the top often accommodates a reflux condenser for working at room pressure. Otherwise it is common to work in beakers with high walls, toped only by a watch glass or in flasks with a funnel placed in the neck. Since glass practically does not absorb microwaves, the upper part of the glass container, not in contact with solvents, remains cool during irradiation and acts as condenser for the vapors [23].

1.6.2 The Behavior of the solvent:

Together with the ability to dissolve reagents and products, a solvent under microwave can play a more active role. The acceleration of a chemical reaction under microwaves depends on the dielectric properties of the solvent. Solvents are able to directly absorb microwave increase the reaction rate of the dissolved reagents. Solvent, such as hydrocarbons, that cannot absorb microwaves themselves, can be indirectly heated under microwaves, only when in the presence of materials able to interact with the radiation. Polar solvents of low molecular weight and high dielectric constant irradiated by microwaves increase their temperature very rapidly, reaching boiling point in a short time. In this class of solvents the rate of a given reaction is more enhanced. Typical solvents widely employed in microwave chemistry are water, methanol, ethanol, and acetone. Dimethyl formamide is also used as useful solvent for operating under microwaves. It is completely miscible with water, is a good solvent for polar and less polar solutes, has a high boiling point, allowing the use of open vessels in carrying out chemical reactions.

A phenomenon frequently observed when microwaves are applied to chemical processes is the overheating of the solvent. In the presence of microwaves, common solvents are found to boil at higher temperatures: for water the difference is about 5°C, 19°C for methanol, up to 36°C was the difference measured for tetrahydrofuran and acetonitrile. These differences were explained with the different mode of energy supply. The transfer of heat from an electrical bath to the solution inside the vessel ('traditional heating'), is affected by the imperfections of the glass surface, which activate the boiling. Driven by this activation the solvent boils at a lower temperature and, according to this view, the boiling temperatures, as they are reported for most solvents, could be underestimated. This activation is absent in the presence of microwaves: the radiation reaches the bulk of the solvent directly and the transfer of energy is no longer mediated by the vessel surface. Many authors suggested that the boiling temperature measured in this way should be 'true', reflecting real intermolecular interactions existing inside the liquid phase [23].

This phenomenon was suggested as responsible for the higher reaction rates observed under microwaves in most cases. In fact, since each 10°C temperature increase causes the reaction rate to double, it can easily be understood how chemical reactions can be speeded up in the presence of microwaves.

If overheating may be observed in open vessels, in closed vessels this phenomenon can lead to an increase of the pressure of the system. Especially with low boiling solvents and in the presence of large volumes in low-capacity vessels, there is a risk of explosion. The rapid increase of temperature under microwaves can cause a quick increase of the internal pressure, which can be potentially dangerous in the absence of a safety apparatus. The development of high pressures and the necessity to use specialized Teflon vessels represent major limitations of microwaves in chemical systems [24].

An obvious solution to these problems is to operate in open vessels at room pressure, avoiding closed reactors. An additional suggestion could be the use of limited amounts of solvent, just enough to prepare a slurry reacting mixture: the dissolution of the solid and title achievement of a homogeneous system occurs at the reaction temperature.

1.6.3 Materials and Microwaves:

An important problem in microwave application to chemical reactions is related to the nature of the solid material present in different modes inside the system crossed by the radiation. These can be part of the chemical system: solvent, reagents, products and catalysts: or be part of the apparatus and oven.

Materials can be divided into three broad categories: materials which reflect microwaves; materials which are crossed by the microwaves, without being absorbed; materials which absorb the radiation and are therefore, able to start the heating or to activate a chemical reaction. Many materials are practically transparent (quartz) and can be penetrated by the radiation; some others materials, such as metals, reflect the radiation: other materials, such as dielectrics, interact with microwaves to different extents[25]. Chemical reactors must be transparent to microwaves and are made of Teflon or poly (ethylene); glass is also a suitable material, especially for high temperature reactions, but it is not completely transparent to microwaves.

A particular problem in this context is the measurement of the temperature, which cannot be obtained nsing conventional instruments, such as mercury thermometers or metal thermocouples. The temperatures can be measured by thermal indicators or indirectly by the melting of suitable: glass fiber thermocouples are suggested.

Mechanical stirrers, made of Teflon and glass, are preferred to a magnetic bar. In most cases, however, stirring is not necessary to homogenize the distribution of heat, since microwaves can reach the bulk of even a slurry mass directly [26].

Materials that absorb microwaves can display different rates of heating, according to their composition and the dimension of their particles, when solids [25]. The inclusion of such materials in the form of powder or fibers within the mass of polymer can improve microwave absorption and locally raise tile, temperature, thus increasing the hardening or improving the compaction of polymeric materials, indirectly acting as an adhesive.

1.6.4 The type of chemical reactions:

The effect of microwaves on chemical reactions is generally evaluated by comparing the time needed to obtain a given yield of the final products with respect to traditional heating. In most examples reported in the literature[27-29] the amount of reagents employed in these tests ranges from a few milligrams to a few grams. The reaction vessel is simply kept in the oven for a preset time, following most of the details described above.

One of the most interesting problems that mater technology should solve is the possibility of scaling-up the processes under microwaves. For this purpose flux reactors have been suggested. The reagents pass into the oven continuously through a serpentine at such a rate that each portion of the mass absorbs a fixed amount of microwave energy. Power levels can be modulated through the microwave Output: at a fixed power of the oven for varying times; or for a fixed time by varying patterns of on-off cycles [30].

Reactions which benefit more from the presence of microwaves are obviously those which have low rates under traditional conditions[31-33]. The reactions examined represent a large variety, ranging from hydrolysis of nitriles, amides and esters, to the formation of esters and ethers oxidation and hydrogenations; rearrangements and polymerizations, etc [34-35].

The Dials-Alder reaction represents a good model to study the effect of microwaves [9]; the carbonyl group, besides being important in driving the reaction, acts as a antenna towards the radiation. The reaction is rapid when the starting diene is electron-rich and the dienophile is electron-poor; when dienophiles lack of activating groups the reactions requires a high temperature (> 300°C). The reaction between antracene and maleic anhydride is a classical example of this[36].

Esters and nitriles are hydrolyzed very slowly either in basic or acidic medium under traditional conditions. Hydrolysis of these compounds offers a typical example of application of microwaves. A positive role is played in this case by the presence of strong acids or bases that increase the heating rate under microwave irradiation.

Etherification is a reaction largely studied under microwaves. The rate of etherification of benzoic acid was found to be increased under microwaves and the increase is a function of the length of the hydrocarbon chain of the alcohol. It must be pointed out that the boiling point of the alcohol also increases: higher

temperatures of the reaction can therefore also be used in the traditional method: as a consequence in this case the comparison between the two techniques is no longer homogeneous [34].

In the case of the Williamson reaction to form ethers between alkoxydes and alkyl chlorides the ratio between substitution and elimination did not change [34].

On the contrary in the case of the sulphonation of naphtalene, the substitution in position 2 preferentially occurs under microwaves at temperature higher than 130°C; while under traditional heating the filial product contains almost equimolar of 1 and 2 naphtalene-sulfonic acids at temperature lower than 130°C[37].

Polymer chemistry will probably benefit greatly from the application of microwaves: in fact the presence of polar groups in the starting materials particularly favours the absorption of microwaves, allowing rapid and controlled synthesis, hardening and curing of the final products[38]. In these systems, different modes of energy supply can drive a reaction differently: e.g. in the case of epoxy resins, short impulses favour self-polymerization, whereas longer impulses of microwaves allow the reaction with amines.

The use of solid materials for the so-called dry-chemistry or without solvent appears very interesting and represents a new frontier for chemistry under microwaves [39-40].

Moreover the experimental conditions adopted in these cases simplify the chemical system, due to the absence of solvent and the problems related to it, such as loss for evaporation or pressure increase in closed vessels. According to this methodology the reagents are dispersed on the surface of an inorganic and insoluble support, such as silica gel, alumina, commercial bentonite and other oxides or silicates. Kept thus in close proximity on a large surface, the reagents are irradiated by microwaves in the absence of solvents and the reaction is very efficiently driven. At the end of the reaction the final products can simply be washed by a solvent and processed as usual. An acetylenic alcohol adsorbed on montmorillonite undergoes 92% rearrangement under microwaves, while, under conventional heating at the same temperature and for the same time, gives only a trace of the final product[41-42].

In some cases the yield of the reaction is affected by the nature of the inorganic support. The influence of microwaves was demonstrated when the

pinacol/pinacolone rearrangement takes place in the presence of a charged phyllosilicate: moreover the conversion yield clearly depends on the nature of the inter layer cation of the solid support.

In addition to the benefit of saving solvents, a salient feature of this methodology is the selectivity of some reactions, such as those concerning protection and deprotection of functional groups. A neat selectivity was found in deacetylation of alkyl and aryl esters or among the different positions in the steroid nucleus of a bile acid methyl ester: in this last case, the different options are obtained simply by regulating the time of irradiation of the substrate dispersed on alumina[43].

Using clayfen, i.e. clay-iron (III) nitrate in the solid state, alcohols are readily oxidized in high yields to the corresponding carbonyl compounds. Sulphides can be oxidized to sulphoxides or to sulphones using sodium periodate on silica gel: under microwaves selectivity can be obtained by simply changing the ratio between reagents to oxidant. Another example of' reaction carded on a solid support is the condensation between 1-bromooctane and potassium acetate. These reactants do not display any property to absorb microwaves. On the contrary potassium acetate dispersed on alumina reaches 300°C in 3 min under microwaves: this specific activation makes the reaction rapid; in this respect silica was found less efficient.

A very interesting field for the application of microwaves is the synthesis of radiopharmaceuticals or labeled drugs, especially when very short half-life positron emitters are employed. With isotopes such as 122°C, (3.6 min), 11°C (20 min), 18°C(110 min) the gain of even a few minutes in the reaction time could be of extreme importance for the final activity. The reactions of common radioisotopes are also improved in the presence of microwaves: reaction times as well as exposure to the radioactive emissions and the risks of possible coritaminations are reduced[44 -45].

1.7 Microwaves in the laboratory

For microwaves to be used as a practical heating method in the laboratory, or in industry, there have to be good reasons for choosing them over existing technology. Studies over the past decade have uncovered several reasons why microwave heating can be advantageous.

1.7.1 Superheating

Consider heating water in a round-bottomed flask by a heating mantle. Heat is slowly transferred from the glass to the core by convection, and boiling occurs when bubbles of vapors form at a nucleation site, a particle or a surface. Because we are heating from the outside, if the core of the water may be as much as 5°C cooler than the edge, even at the boiling point.

Microwaves, on the other hand, heat the water directly and almost uniformly. Under these conditions, the core is hotter than the outside because of surface cooling (often incorrectly expressed as heating from the inside-out), so that when the nucleation sites in the glass are hot enough to allow boiling, the core is some 5°C hotter. Thus by using microwaves, we can raise the effective boiling point of water by as much as 5°C, an effect known as superheating. (The reason why people are scolded as they add coffee to a cup of microwave-heated milk is that the against of coffee provide nucleation sites on which bubbles form explosively)

Solvents such as tetrahydrofuran or acetonitrile (enthanitrile) exhibit superheating levels of up to 40°C. From a chemical perspective this is important. If we consider that, for an average reaction, a 10°C rise doubles the reaction rate, and then simply using microwaves to heat a reaction can speed it up appreciably.

1.7.2 Selective heating

An important attribute of microwave heating is the ability to put energy directly into the reaction components, or to heat selectively one reaction component. Consider, for example, the direct synthesis of metal sulphides and selenides. To synthesize these materials, which are used as energy storage devices and as semiconductors, takes several days by conventional methods. The former involves mixing sulphur and the metal, both in powder form, and heating them in a sealed tube. The problem is that sulphur vaporizes as it warms up, and if the temperature gets too high or rises too quickly, the pressure of the sulphur vapor will blow the tube a part. To avoid this, the mixture is heated slowly and cautiously, even though this means it may take a week or more for the ingredients to combine and form the metal sulphide. Microwaves, on the other hand, may be used to heat the mixture rapidly, and without fear of an explosion, because microwaves heat only the metal and not the sulphur. Sulphur vapor recondenses in the cool parts of the tube before flowing

back to the hot metal. Instead of taking days, the reaction is complete in 15 minutes. This is also a visually stunning reaction because the microwaves stimulate a plasma glow in the shulphur vapor.

1.7.3 Green Advantages

While microwaves are both financially and energetically expensive to produce, the efficiency with which they can be used makes them an attractive 'green' alternative to other forms of heating. Moreover, in recent years there has been a drive within the chemical industry to reduce both the production of waste products and the use of solvents. Waste products equate with wasted resources, and solvents can be toxic, flammable, and expensive to dispose off Microwave chemistry provides a cleaner alternative, this time by exploiting the ability of microwaves to heat the reactants directly. Using only a minimum amount of solvent, the reactants are absorbed into a sponge-like support material (clays, aluminas, zeolites etc.). The reactants are then heated directly with microwaves to generate the products, which are then extracted, again with a minimum amount of solvent. Because microwave heating is essentially uniform throughout the material, there is no time lost waiting for thermal conduction to heat the sample and consequently, reaction times are often measured in minutes or even seconds.

A 'green' approach has been adopted by Chris Strauss, at the Commonwealth Scientific and Industrial Research Organization (CSIRO) in Australia. Strauss and his team carry out organic reactions in supercritical water - water at high pressures and elevated temperatures - instead of organic solvents. Under these conditions, the properties of water change markedly from those that we encounter under ambient conditions, and it acts as an excellent organic solvent. The advantage is that the solvent is non-flammable, and when the reaction is completed, the waste solvent may be disposed of down the laboratory drains.

The microwave chemistry is more than an academic interest has been demonstrated recently by the Dow Chemical Company in the US, faced with tighter regulation of emission from an existing down or cleaning it up. By switching to a 60kW microwave-based process, the plant has reduced its production of waste and unwanted by products, with increasing productivity and reducing energy costs.

1.8 Application of Microwave oven in organic chemistry:

The popularity of microwave hearting for organic synthesis has increased to the extent that it now forms the basis of a number of commercial systems, and has even made its way into undergraduate laboratory courses. Microwave ovens provide a clean and cheap alternative to conventional oil baths. Most conveniently, reactions may be run at atmospheric pressure in reflux systems in ovens which have been modified to accept an appropriate condenser. As previously discussed, dipolar solvents are essential in microwave heating, and it is often necessary to adapt solvent systems in synthetic reactions to accommodate these substituting solvent systems for microwave synthesis. It is often the case that higher boiling point solvents are used. By doing this, it has been possible to enhance the efficiency of a number of syntheses.

1.9 Productivity Increase:

The bottleneck of parallel synthesis is typically optimization of reaction conditions to afford the desired products in suitable yields and purities. Since many reaction sequences require a heating step for extended time periods, these optimizations are often difficult and time consuming.

Microwave-assisted heating has been shown to be an invaluable optimization method since it reduces reaction time dramatically, typically from days or hours to minutes or seconds. Many reaction parameters can be evaluated in a few days to optimize the desire chemistry. Compound library can then be synthesized rapidly using the new technology, either in a parallel or sequential mode.

Several large pharmaceutical companies have reported dramatic productivity increases in switching from conventional synthesis to MAOS. Although the initial investment costs are considerable, the dramatically increased efficiency of the microwave approach allows a return of investment in a short time span. This has prompted several pharmaceutical companies to install multiple microwave reactors in their R&D laboratories, in some cases even eliminating oil baths and heating mantles from their laboratories.

The success stories of MAOS in the drug discovery process are manifold and have been documented in several recent article involving target and lead discovery, lead optimization and drug development. With the most recent advance in reactor technologies such as continuous flow microwave systems, even process chemists are

now taking MAOS seriously. Chemistry applications have ranged from conventional solution phase synthesis to protocols involving polymer-supported reagents or scavengers, in addition to solid or fluorous phase techniques. Most recently, microwaves have also been used to speed up biochemical processes such as polymerase chain reaction or enzyme-mediated protein mapping. Therefore, the full scope and potential of this technology may not yet have been realized.

1.10 Obstacles to acceptance of the technology:

Given the advantages of microwave synthesis, it might be thought surprising that not everybody is using it. One of the possible reasons for this could be mental inertia, as the use of this new technology requires a change in the chemist's mindset, abandoning the traditional favorite's tools of the trade such as heating mantle, oil baths or hot plates.

Another factor that is certainly holding the field back is prices. The cheapest of the new generation of microwave reactors currently sells for about US$20,000, which is beyond the buying power of many laboratories. More elaborate systems geared towards the drug discovery industry that have integrated automation and liquid handing capabilities, database and electronic laboratory functionalities or an added scale-up option involving continuous flow cells are considerably more expensive. Despite this fact, it is clear that microwave synthesis is an enabling technology for every academic and industrial laboratory. They will truly become the Bunsen burner of the 21st century. The time for microwave synthesis certainly has arrived.

1.11 Preface of a Microwave Oven:

A microwave oven, or microwave[46], is a kitchen appliance employing microwave radiation primarily to cook or heat food. Microwave ovens have revolutionized cooking since their use became widespread in the 1970s.

1. History
2. Descriptions
3. Efficiency
4. Safety and controversy
    - 4.1 Acute dangers
    - 4.2 Controversial hazards
    - 4.3. Radiation

1.11.1 History

Cooking food with microwaves was discovered by Percy Spencer while building magnetrons for radar sets at Raytheon. He was working on active radar set when he noticed a strange sensation, and saw that a peanut candy bar he had in his pocket started to melt. Although he was not the first to notice this phenomenon, as the holder of 120 patents, Spencer was no stranger to discovery and experiment, and realized what was happening. The first food to be deliberately cooked with microwaves was popcorn, and the second was an egg (which exploded in the face of one of the experimenters).

In 1946 Raytheon patented the microwave cooking process and in 1947, the company built the first microwave oven, the Radarange. It was almost 6 feet (1.8 m) tall and weighed 750 pounds (340 kg). It was water-cooled and produced 3000 watts, about three times the amount of radiation produced by microwave ovens today. An early commercial model introduced in 1954 generated 1600 watts. In 1965 Raytheon acquired Amana, which introduced the first popular home model

In the 1960s, Litton bought Studebaker's Franklin Manufacturing assets, which had been manufacturing magnetrons and building and selling microwave ovens similar to the Radarange. Litton then developed a new configuration of the microwave, the short, wide shape that is now common. The magnetron feed was also unique. This resulted in an oven that could survive a no-load condition indefinitely.

1.11.2 Description

A microwave oven consists of:

1. A magnetron.
2. A magnetron control circuit (usually with a microcontroller),
3. A waveguide, and
4. A cooking chamber

A microwave oven works by passing microwave radiation, usually at a frequency of 2450 MHz (a wavelength of 12.24 cm), through the food. Water, fat, and sugar molecules in the food absorb energy from the microwave beam in a process called dielectric heating. Most molecules are electric dipoles, meaning that they have a positive charge at one end and a negative charge at the other, and therefore vibrate as they try to align themselves with the alternating electric field induced by the microwave beam. This molecular movement creates heat. Microwave heating is most

efficient on liquid water, and much less so on fats, sugars, and frozen water. Microwave heating is sometimes incorrectly explained as resonance of water molecules, which only occurs at much higher frequencies, in the tens of gigahertz.
Most microwave ovens allow the user to choose between several power levels, including one or more defrosting levels. In most ovens, however, there is no change in the intensity of the microwave radiation; instead, the magnetron is turned on and off in cycles of several seconds at a time. This can actually be observed when micro waving airy foods like Krembos: it blows up during heating phases, while it deflates when the magnetron is turned off.

The cooking chamber itself is a Faraday cage enclosure to prevent the microwaves escaping into the surroundings. The oven door is usually a glass panel for easy viewing, but has a layer of conductive mesh to maintain the shielding. Since the mesh width is much less than the wavelength of 12 cm, the microwave radiation can not pass through the door, while visible light (with a much shorter wavelength) can.

Professional chefs generally find microwave ovens to be of limited usefulness. On the unlike the people who are lacking in free time, or not comfortable with their skills. A variant of the conventional microwave is the convection microwave. A convection microwave is a combination of a standard microwave and a convection oven.

1.11.3 Efficiency

A microwave oven does not convert all electrical energy into microwaves. A typical consumer microwave oven consumes 1100 W but delivers only 700 W of microwave power. The remaining 400 W are dissipated as heat by components of the oven. The main source of energy loss is the magnetron tube, which is much less than 100% efficient at generating microwave output from the power source. Lesser amounts of power are consumed by the oven lamp, AC power transformer losses, magnetron cooling fan, food turntable motor and control circuits. This waste heat does not end up in the food but is mostly expelled from the cooling vents on the oven and heats the air in the kitchen.

Of the microwave power that the oven generates, about 77% is typically used to heat, compared with 10% to 60% in conventional ovens. (Data collected by boiling water in microwave and measuring temperature change).

1.11.4 Safety and controversy; Acute dangers:

Liquids, when heated in a microwave oven in a container with a smooth surface, can superheat; that is, reach temperatures that are a few degrees celsius above their normal boiling point without actually boiling. The boiling process can start explosively when the liquid is disturbed, such as when the operator grabs hold of the container to take it out of the oven, which can result in severe burns.

Tin foil, aluminium foil, ceramics decorated with metal, and products containing other metals can cause sparks when they are used in a microwave. Micro waving small, smooth, solid metal objects without pointed ends (for example, a spoon) can sometimes be safe, and usually does not produce sparking (putting a spoon into a liquid also helps prevent superheating). Forks, however, will readily produce sparks when placed in the microwave. This is because while it acts as an antenna, absorbing microwave radiation just like other metal objects such as the spoon, the pointed ends of the fork will act to concentrate the electric field formed at the tips. This has the effect of exceeding the dielectric breakdown gradient of air, about 3 megavolts per meter (3×10^6V/m), causing sparks to form. This effect is directly analogous to the effect of St. Elmo's fire.

The formation of sparks on sharp metal objects may be prevented by placing the utensil in some food or liquid while in the microwave, as this has the effect of preferentially conductively dissipating the charge before the electric fields can build to the point where they exceed the breakdown value of air. Any time dielectric breakdown occurs in air, some ozone and nitrogen oxides are formed, both of which are toxic. Finally, as mentioned previously, any metal or conductive object placed into the microwave will act as an antenna, and its electrons will thus be thrashed back and forth through the object (a high frequency alternating current) causing some ohmic heating to occur. The extent of this heating effect will vary depending on the size, shape and conductivity of the object.

1.11.5 A microwave oven with a metal shelf

Several microwave fires have been noted where Chinese takeout boxes with a metal handle are micro waved, and also where "homemade" microwave popcorn bags have been sealed using a metal staple, which is then heated and sets fire to the bag. This type of accident can pose a dangerous situation because of the extremely flammable mixture of popcorn and oil in the bag. Thus, it is good practice to remove any metal utensils or metal containing objects from a microwave oven before operating it, as the behavior of these objects when immersed in a strong microwave radiation field is unpredictable.

It is a common myth that metallic kitchen equipment, like kitchen forks and knives, can somehow repel the microwaves back into the magnetron and cause it to catch fire. This is highly unlikely.

1.11.6 Controversial hazards; Radiation:

Microwave ovens produced after 1971 must meet the Food and Drug Administration safety requirements for radiation leakage; less than 5 mW/cm^2 at approximately two inches from the surface of the oven. This is far below the exposure level that is currently considered to be harmful to human health. The radiation produced by a microwave oven is non-ionizing. As such, it does not have the same cancer risks associated with ionizing radiation such as X-rays and ultraviolet light.

1.11.7 Home Microwave Oven Suitable

The discussion on the use of microwave units specially designed for synthesis use, which are often quite expensive, becomes rather heated at times. Unmodified home microwave units are suitable in some cases. However, simple modifications (for example, a reflux condenser) can heighten the safety factor. High-pressure chemistry should only be carried out in special reactors with a microwave oven specifically designed for this purpose. A further point in favor of using the more expensive apparatus is the question of reproducibility, since only these specialized machines can achieve good field homogeneity and in some cases can even be directed on the reaction vessel.

1.12 Microwave chemistry

Microwave chemistry is the science of applying microwave irradiation to chemical reactions[47-49]. Microwaves act as high frequency electric fields and will

generally heat anything with a mobile electric charge. Polar solvents are heated as their component molecules are forced to rotate with the field and lose energy in collisions. Semi conducting and conducting samples heat when ions or electrons within them form an electric current and energy is lost due to the electrical resistance of the material. Heating a reaction or chemical reactor by microwave radiation (as seen in a domestic microwave oven) has a number of advantages over conventional heating;

1. The heat is formed directly and rapidly in the sample.
2. Energy is not wasted in heating furnaces or oil baths.
3. The entire volume of the reactor can be heated (virtually) uniformly.
4. Selected volumes of the sample (including microscopic regions) can be selectively heated.

Conventional heating usually involves the use of a furnace or oil bath that heats the walls of the reactor by convection or conduction. The core of the sample takes much longer to achieve the target temperature (Particularly when heating a large sample of ceramic bricks, for example, Rapid and homogeneous heating has the following benefits:

1. Reaction rate acceleration
2. Milder reaction conditions
3. Higher chemical yield
4. Lower energy usage

Some of these effects are derived from superheating or hot spots, well known effects in micro waving. Selective heating is particularly important in the microwave heating of supported metal catalysts. A specific application in synthetic chemistry is in the microwave heating of a binary system comprising a polar solvent and a polar solvent obtain different temperatures. Applied in a phase transfer reaction a water phase reaches a temperature of 100°C while a chloroform phase would retain a temperature of 50°C. Microwave chemistry is particularly effective in dry media reactions.

1.13 Microwave Synthesis

It has long been known that molecules undergo excitation with electromagnetic radiation. This effect is utilized in household microwave ovens to heat up food. However, chemists have only been using microwaves as a reaction

methodology for a few years. Some of the first examples gave amazing results, which led to a flood of interest in this novel technique.

The water molecule is the target for microwave ovens in the home; like any other molecule with a dipole, it absorbs microwave radiation. Microwave radiation is converted into heat with high efficiency, so that "superheating" (external link) becomes possible at ambient pressure. Enormous accelerations in reaction time can be achieved, if superheating is performed in closed vessels under high pressure; a reaction that takes several hours under conventional conditions can be completed over the course of minutes.

1.13.1 Thermal vs. Non- thermal Effects

Excitation with microwave radiation results in the molecules aligning their dipoles within the external field. Strong agitation, provided by the reorientation of molecules, in phase with the electrical field excitation, causes an intense internal heating. The question of whether a non-thermal process is operating can be answered simply by comparing the reaction rates between the cases where the reaction is carried out under irradiation versus under conventional heating. In fact, non-thermal effect has been found in the majority of reactions, and the acceleration is attributed to superheating alone. It is clear, though, that non-thermal effects do play a role in some reactions.

1.13.2 Microwave effect

The phrase microwave effect is a term that is applied to a range of observations in microwave chemistry. There are two general classes of microwave effects:

1. Specific microwave effects.
2. Non-thermal microwave effects.

A recent review has proposed this definition[47] and examples of microwave effects in organic chemistry have been summarized[48].

Specific microwave effects are those effects that cannot be (easily) emulated through conventional heating methods. Examples include: (i) selective heating of specific reaction components, (ii) rapid heating rates and temperature gradients, (iii) the elimination of wall effects, and (iv) the superheating of solvents. Microwave-

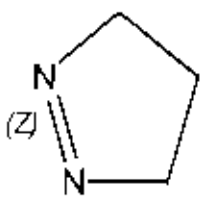
specific effects tend not to be controversial and invoke "conventional" explanations (i.e. kinetic effects) for the observed effects.

1.13.3 Non-thermal microwave effect

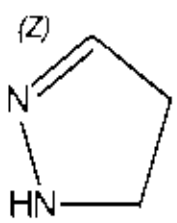
Non-thermal microwave effects have been in order to explain unusual observations in microwave chemistry. As the name suggests, the effects are supposed not to require the transfer of microwave energy into thermal energy. Instead, the microwave energy itself directly couples to energy modes within the molecule or lattice. Non-thermal effects in liquids are almost certainly non-existent[47-48], as the time for energy redistribution between molecules in a liquid is much less than the period of a microwave oscillation. A recent review has illustrated this in application to organic chemistry, though clearly supports the existence of non-thermal effects [3]. It has been shown that such non-thermal effects exist in the reaction of O + HCl(DCl) → OH(OD) + Cl in the gas phase and the authors suggest that some mechanisms may also be present in the condensed phase[50]. Non-thermal effects in solids are still part of an ongoing debate. It is likely that, through focusing of electric fields at particle interfaces, microwaves cause plasma formation and enhance diffusion in solids via second-order effects[50-52]. As a result, they may enhance solid-state sintering processes. Debates are still raging (January 2006) about non-thermal effects of microwaves that have been reported in solid-state phase transitions[53].

2.1 Preface of Pyrazoles & Pyrazolines:

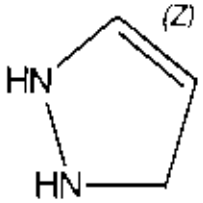
Pyrazolines are five member heterocyclic compounds containing 2 adjacent nitrogen atoms and they are aliphatic in character possessing a double bond in the ring. According to the position of the double bond, there are three types of pyrazolines.



1-pyrazoline



2-pyrazoline



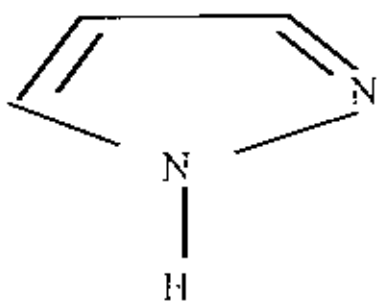
3-pyrazoline

1-Pyrazoline are unstable and in many cases these compounds irreversibly isomerizes to 2-Pyrazolines[54]. These are also not very important from the practical point of view.

3-Pyrazolines are due to the absence of effective practical importance.

2-Pyrazolines are of the greatest theoretical and practical importance. 1- and 3- aryl substituted 2-pyrazolines exhibit interesting reactivities and spectral properties due to the presence of extended conjugated system.

A second double bond in the ring produced Pyrazoles which are aromatic heterocyclic compounds and are also important as such. There have been some notable advances in recent years in the chemistry of pyrazole types of heterocycles. These are reflected in the monograph[54] on pyrazoles, pyrazolines and related compounds.



P y r a z o l e

From the literature it is seen that the development of pyrazoline chemistry paralleled that of pyrazoles. Because of the close structnral relationship, it has become a practice to treat the pyrazolines as a chemical sub-unit of the pyrazoles. That is why: it is the objective of the present review to treat them collectively. For the sake of convenience details about pyrazoles are avoided.

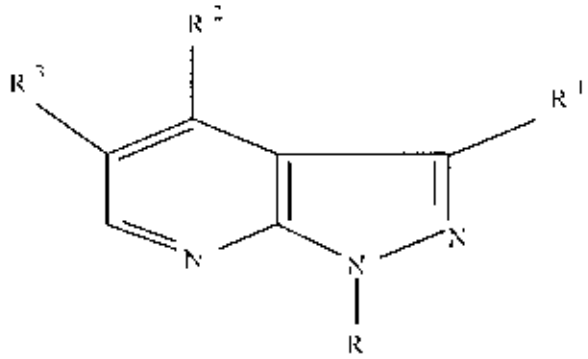
2.2 Importance of Pyrazolines and Pyrazoles.

2-Pyrazolienes and pyrazoles have a wide spectrum of utility in every sphere of human life. In practical field, some of the compounds have been used as medicine, where as other may be cited to demonstrate their outstanding industrial importance.

2.2.1 Physiological Applications

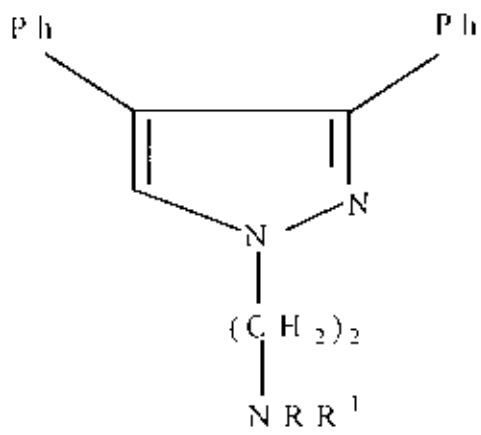
Many pyrazoline and pyrazole derivatives have been extensively used as physiologically active substances. Certain β-dialkylamioethyl and β-piperidinoethyl-1, 5-diaryl-2- pyrazolines have been found[55,56] to be useful as relatively nontoxic local

anaesthetics. Sulfonyl urea derivatives of pyrazole have been found[57] to show antidiabetic activity. Some pyridino derivatives for example, pyrazolo (3. 4-b) pyridine derivatives (I) act[58] on the central nervous system to produce tranquilizing and anticonvulsant effect.



R, R^1 = alkyl, cycloalkyl phenyl
R^2 = H, alkyl, phenyl
R^3 = alkyl, phenyl, alkoxy
(I)

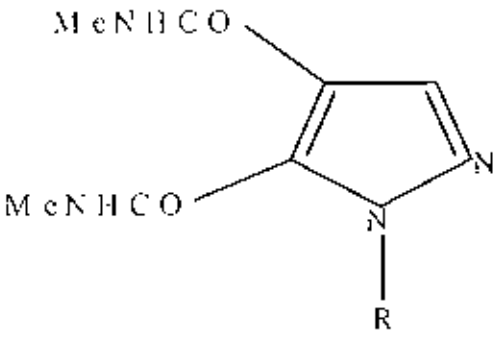
Certain pyrazole and pyrazoline e.g., 3,4-diphenyl-1H-pyrazole-1-propanamine (II) and its derivatives have been found to show antidepressant[59] activity.



R = H R^1 = H, Me
R = R^1 = Me, Et
(II)

Several 1-substituted-4-amino pyrazole derivatives have been largely used as antipyretic[60] agents. On the other hand some other derivatives have anti-inflammatory[61] activity.

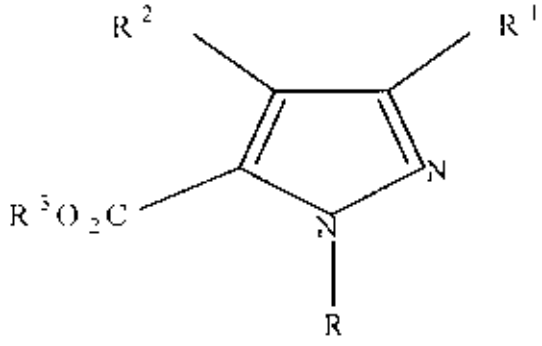
Pyrazole dicarboxylic acid derivatives (III) have excellent antimnestic[62] activity. Some 3-amino pyrazoles have been found to be very much effective against allergy and also show virucidal[62] activity in mice and human being.



R = Me, Et, Pr and CH_2:CHCH$_2$

(III)

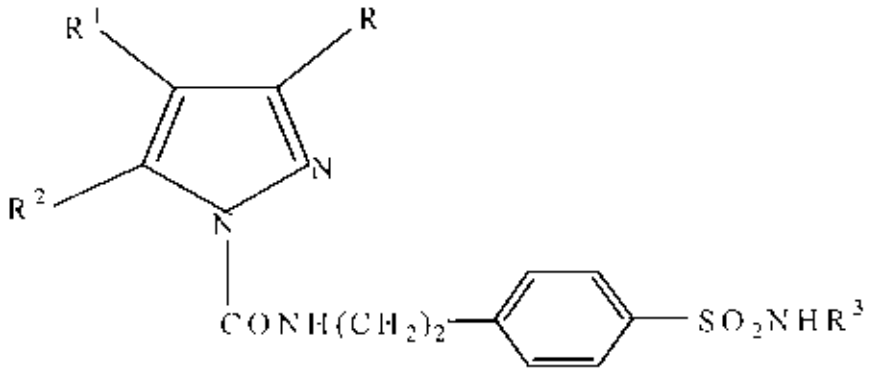
Several 5-coarboxylic acid derivatives (IV) are effective as antigout[63] agents and a number of other derivatives have been widely used as antihallation[64] agents. Azolylmethy11 amine derivatives of pyrazoles have shown microbiocidal[65] activity. 1-pyrazole carboxylic acid derivative (V) showed



R = H, Me
R^1 = Pyridyl, thienyl, Ph
R^2 = H, alkyl, Halo
R^3 = H, alkyl

(IV)

Significant hypoglycemic activity, Preliminary clinical studies on adult human diabetics indicated this compound to be a most satisfactory, potent, oral hypoglycemic agents[66].

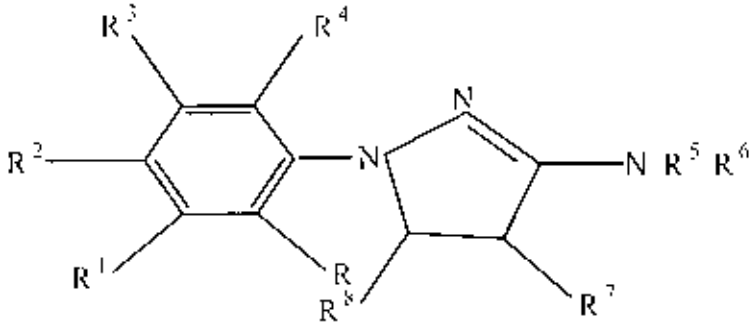


R, R^1, R^2 = H, Me, Et

R^3 = Cyclohexyl carbonyl

(V)

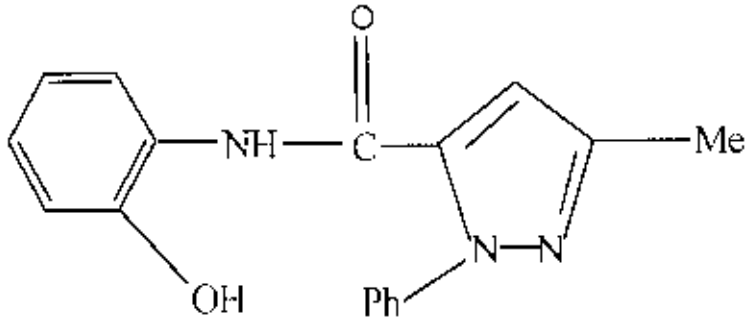
A large number of amino pyrazoles and pyrazolines exhibited antispasmodic, amebecidal and antithrombotic[67] activity. Several other amino derivaties e.g. 1-aryl-3-amino-2-pyrazoline (VI) and its derivaties have been found to show archidonic[68] activities and show excellent promise in chemotherapy and revolutionized the whole field of medicine.



R, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 = H, alkyl

(VI)

Several 1-phenyl-5-salicyloylimino pyrazoles e.g., N (1-phenyl-3-methyl pyrazole-5-ayl) salicylamide (VII) can be used as analgesic[69].

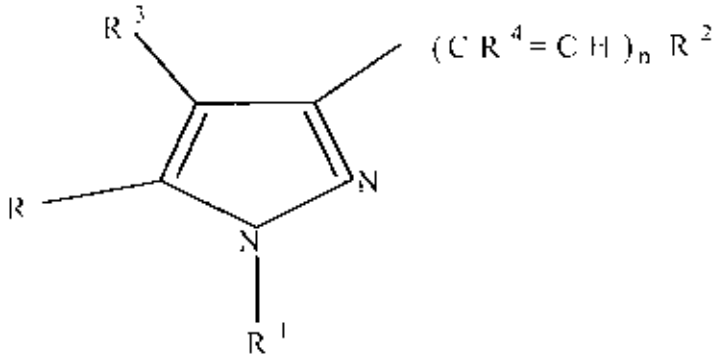


(VII)

Besides these, a number of chemists, biochemists pharmacologists, bacteriologists and innumerable industrial scientists have clearly demonstrated the tremendous applications of pyrazole and pyrazoline derivaties in various fields.

2.2.2 Industrial Applications

Pyrazole and 2-pyrazoline derivaties e.g., (VIII) have been extensively used as fluorescent brighteners and electro photographic materials[70].



R = p-MeO-C_6H_4-
R^1 = Ph
R^2 = p-Me_2N-C_6H_4-
R^3 = Me
R^4 = H
n = 1

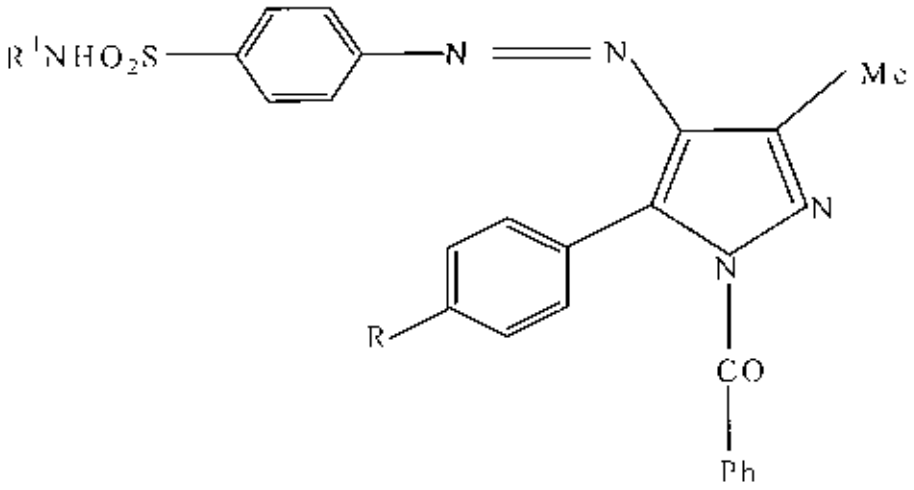
(VIII)

Several 2-pyrazoline derivatives can be used as whitening agent, electro photographic charge transport agents[71], corrosion inhibitor[72], and bleaching agents for textiles[73]. 1, 3, 5-triaryl-2-pyrazolines have been shown to be effective scintillation solutes[74-75]. These types of compounds have a light producing ability and show a small degree of self quenching[54].

Certain pyrazoline derivatives have been used as lubricating oil antioxidants[76], and others have been used as antioxidants for natural rubber[77]. Potential high volume uses for fluorescent pyrazolines are as water soluble bleaches[78-79].

1, 3-dichloroacetyl-5 methyl-2-pyrazolines and pyrazoles are employed to some extent in the control of mites, spiders and other insects of that type but their chief use is as fungicides[80,81]. Several 1- and 4-benzoyl pyrazoles, for example,

1-benzoyl-3-methyl-5-aryl-4 (N-substituted p-sulfamyl benzone azo) pyrazole (IX) and its derivatives exhibited effective bactericidal activity[82-83].

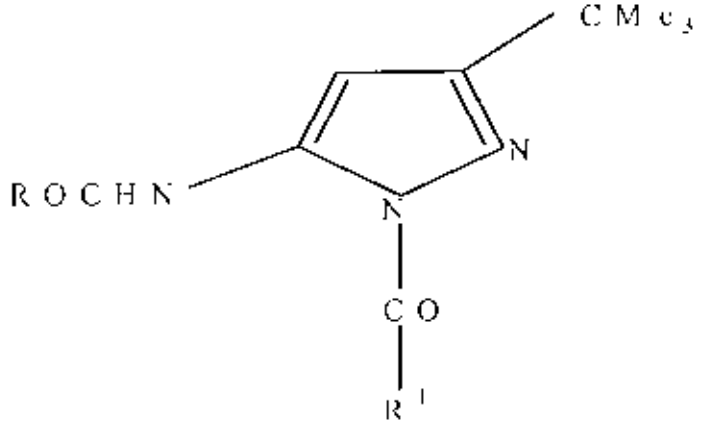


R = Cl, Br. Me. Et

R¹ = H, AC

(IX)

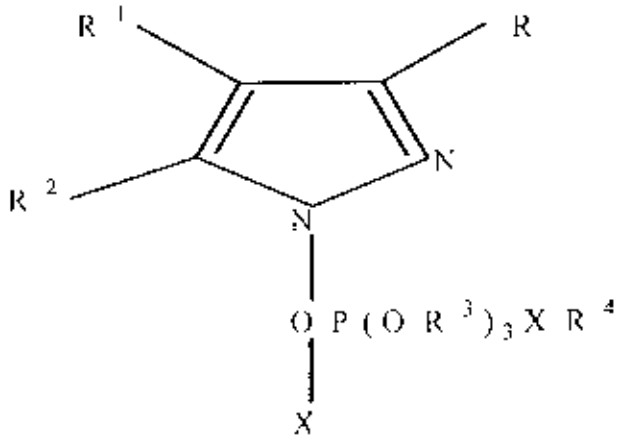
Some other derivatives of pyrazolines and pyrazoles have largely been used as insecticides[84], and various amino derivatives have been successfully used as herbicides[85].



R, R¹ = alkoxy, allyloxy

(X)

1-Acetyl-3-fluoroaryl-5-pheynyl/furyl-4H-4. 5-pyrazolines can be used as antifertility agents[86]. Halogenated-1-hydroxy pyrazoles (XI) can be used as effective pesticides. These classes of compounds are also very powerful insecticides and acaricides[87], which kill mites and ticks and are used in USA largely on the southern cotton, vegetables and citrus corps.

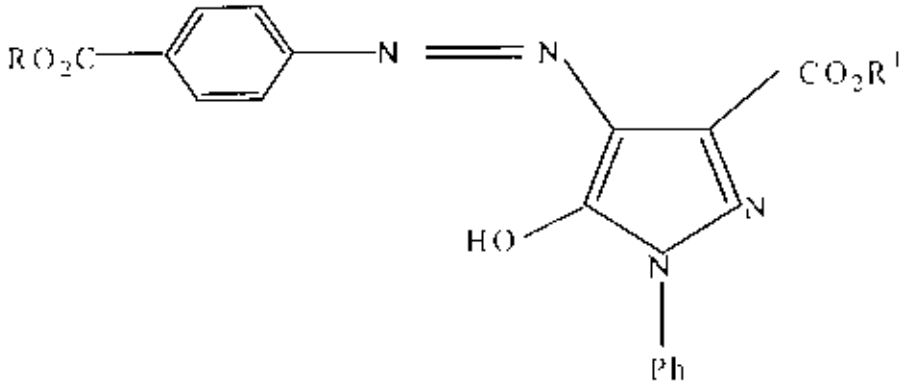


R , R^1, R^2 = H , alkyl

X = halogen

(X I)

A number of azopyrazoles and pyrazolines e.g. (XII) are extensively used as pigments[88]. These classes of compounds can also be used as various types of dyes and coloring materials. These compounds are used as disperse dye.



R = $PhOCH_2CH_2$

R^1 = CH_3

(XII)

These dyes have excellent light fastness and relatively better wash fastness than usual disperse dyes. These compounds can also be used to dye polyester fibers[89], and for printing of various other textile[90]. These can also be used as dye for jet printing inks[91,92], and in dishwashing detergents containing bleaches with colour stability. Some of these dyes can be used water based jet printing inks and others can be used as food dye[93].

Other industrial use includes catalyst for curing of acrylic adhesives[94], and as coating for corrosion-resistance and paintability[95].

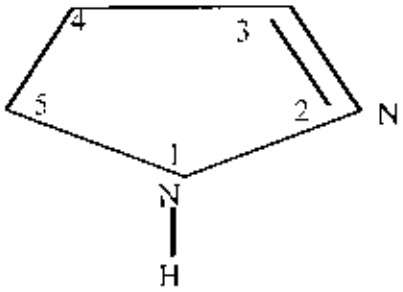
Beside these, many other industrial importance of pyrazoline and pyrazole derivative has been demonstrated.

2.3 Structure and Physical Properties of Pyrazolines and Pyrazoles.

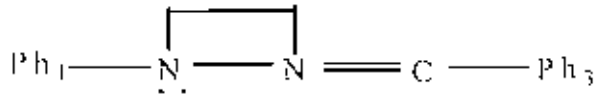
2.3.1 Structure and Physical Properties.

2-pyrazoline itself is a liquid, b. p. 144°C. It is yellowish in color and has characteristic sweet smell.

The ring system is not planer. N-1, N-2 and C-3 are in one plane where as C-4 and C-5 is in another plane. The behaviors of these compounds are consistent with the presence of extended conjugation as in the case of 1, 3-diaryl derivatives. Substitution in 1- and 3-positions dramatically changes the properties of the systems by further extending conjugation. Therefore, the chromophoric system is responsible

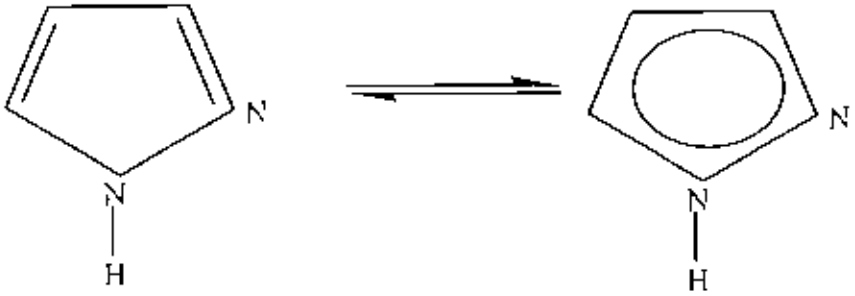


for all types of properties of 2-pyrazolines. Aryl substituted 2-pyrazolines are luminescent compounds due to the presence of the chromophoric system.



Pyrazole itself is a highly crystalline, colourless solid, melts at 70°C and boils at 187-188oC. It is soluble in water but almost insoluble in petroleum ether. It has a peculiarly penetrating sweetish smell unlike most amines.

The pyrazole ring, like other nitrogen containing heterocycles, can be represented as.



The pyrazole ring is present in two different environments in the crystal and average molecular dimensions from the X-ray data have been calculated[96]. The C-C bond in the ring is shorter than the normal benzoid bond (1.395A°). The resonance energy (29.3 kcal/mole), calculated from the heat of combustion data is however lower than that of benzene (36 kcal/mole). The chemical reactions of pyrazoles are consistent with the presence of a great deal of aromatic character. By substitution reaction the geometry of pyrazolines is distorted but that of pyrazoles is not. So pyrazole is an ideal system for many chemical and spectroscopic investigations.

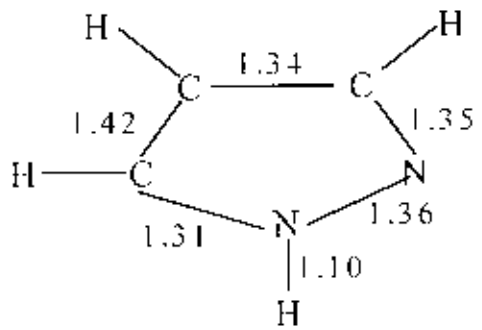


Fig. 1: Mean bond leangth (A^0) in pyrazole

Table 1: Boiling point and pKa values of nitrogen heterocyclic compounds

Compound	Boiling point °C at 760 mm.	Basic pKa	Acidic pKa
Pyridine	115	5.6	-
Pyrrole	130-131	-9.8	17.5
2-Pyrazoline	144	-	-
Pyrazole	187	2.5	14
1-Methl pyrazole	127	2.1	-

The boiling point of pyrazole (187°C) is much higher compared to pyridine (115°C) and 2-pyrazoline (144°C) due to hydrogen bonding.

The solubilities of pyrazole at 25°C in water, benzene, and cyclohexane (expressed as gm/100 gm of solvent) are 130, 18 and 3[97]. In general, however an increase in molecular weight lowers the solubility in water and raises that in benzene. Refractive indices of alkylpyrazoles lie in the range 1.46 - 1.48 and specific gravities lie between 0.89-1.02[98].

2.3.2. Spectral Properties

The advent of ultraviolet and infrared spectroscopy has made determination of pyrazoline and pyrazole structures a relatively simple matter due to very characteristic absorption patterns of these compounds.

Simple 2-pyrazolines show a maximum at 240-244 nm.[99] which is significantly affected by substitution at 1-or 3-position due to extended conjugation. When the 1-position of pyrazoline is substituted by a benzene ring a second maximum appears at about 280 nm[100] besides the original maximum. This new maximum is generally substitution stable but shifts to 354 mm on introduction of a second benzene ring at position 3[101]. Addition of a third benzene ring at position 5 of the pyrazoline ring causes not alternation in the established spectral pattern[102]. In contrast to the relatively stable 354 nm band, the maximum in the 240 mm region of 1, 3, 5- triaryl-2- pyrazoline is very sensitive to changes in substitution on any of the attached systems.

The spectra of several 3-carbalkoxy-2-pyrazolines with no substitution at position 1 have also been recorded[103]. These compounds showed a maximum at 292-296 mm. The spectrum of methyl-2-pyrazoline-3-carboxylate showed a hypsochromic shift to 288 nm in hydrochloric acid solution[104].

3- pyrazolines which has a benzene ring in conjugation with the double bond shows[54] a strong maximum at about 229 nm and a weaker one tat 288 nm.

The ultraviolet absorption spectra of pyrazoles have been well-studied. Unsubstituted pyrazoles show[105] an absorption maximum at 211 nm. Alkyl pyrazoles show selective absorption with a maximum in the region 210- 225 nm. The small bathochromic effect of alkyl substituents as a rule does not exceed 2-3 nm. The maxima for al aryl pyrazoles lies between 250-280 nm. The introduction of such chromophoric group as $-NO_2$. -COR, -CHO, -COOEt into alkyl pyrazoles results in a bathochromic shift of the order of 25-40 nm[106].

A large number of infra-red spectra of pyrazolines and pyrazoles are available in the literature and in commercial collections. As these data have been accumulated, various workers have sought for "Group frequency" correlations, relating the appearance of absorption bands at particular frequencies with the presence in the

molecule of given structural units. A number of useful assignments have been obtained in this way.

The N-H stretching and carbon-nitrogen double bond stretching absorptions are important in the i.e. spectra of pyrazolines and pyrazoles. Most of the remaining group frequencies are of little value. The N-N absorption is weak i.e., but strong and easily detected in the Raman spectra.

The infra-red spectra of 2-pyrazolines with an unsubstituted 1-position show[107] an N-H stretching frequency as a sharp, easily recognized band in the range 3400-3485 cm^{-1}. In most non polar solvents, the intensity is high but in polar solvents where hydrogen bonding is possible, the absorption band is broad. Pyrazolines with no aromatic substituent at position 3 show[108] a strong C=N band at 1564-1570 cm^{-1}. In 1, 3, 5-triaryl-2-pyrazolines a single intense band due to both C=N and aromatic ring frequencies is observed 1580-1600 cm^{-1} and is indicative of considerable interaction[102] between the two π-systems. A similar combination has been observed in the case of 3, 3'-bis-1-phenyl-2 – pyrazoline[109].

Infra-red spectra of pyrazoles in the crystalline form and in concentrated solution show an absorption band corresponding to the N-H group in the region, 3100-3500 cm^{-1}, the breadth of the band suggesting association[110]. An intense band at 1592 cm^{-1} is attributed to C=N and weak bands at 1552 cm^{-1} and 1658 cm to C=C[111].

Nuclear magnetic resonance spectra of pyrazolines and pyrazoles are considerably of more value. These have quite characteristic features and structural assignments are easily done from the chemical shifts and integrated intensities. Analysis is facilitated by the absence of any strong coupling. 1,3,5-Triaryl-3-pyrazolines show characteristic signals, a multiplet at 3.22 ppm for methylene protons at position 4 and a doublet at 5.25 ppm for methine proton at position 5[112].

For unsubstituted pyrazole in D2O C-H resonance appears as two peaks, the larger, being a doublet at about 7.30 ppm is assigned to the 3-proton while the smaller peak, a triplet at 6.0 ppm, is assigned to the protons at position 4[113].

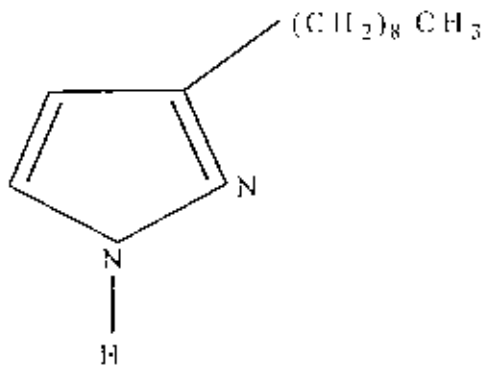
2.4 Sources of Pyrazolines and Pyrazoles

Pyrazoline itself or compounds containing pyrazoline ring are not available in nature. These are purely synthetic compounds. On the other hand, compounds containing pyrazole ring are widely distributed in nature.

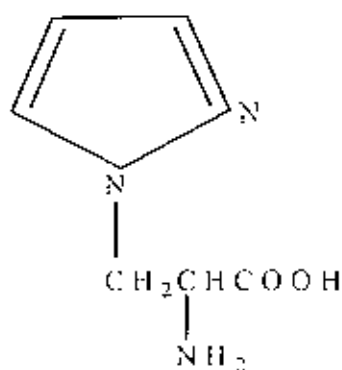
Until 1954, the pyrazole ring was believed to be unknown in nature. In 1954, however, the first natural pyrazole derivative was isolated by Kosuge and Okeda[111].

These authors isolated 3-n-nonylpyrazole (XVII) from Houttuynia cordate (a plant of the "piperacae" family from tropical Asia) and observed its antimicrobial activity.

A pyrazolic amino acid, levo-β- (1-pyrazolyl) alanine (XVIII), has been isolated[115] from watermelon seeds. These were the only naturally occurring pyrazole derivatives at that time and it was interesting to compare their rarity with the isomeric imidazole ring. Other sources of pyrazole derivatives have been reported recently.



(XVII)



(XVIII)

2.5 Syntheses of Pyrazolines and Pyrazoles.

2.5.1 Syntheses of Pyrazolines

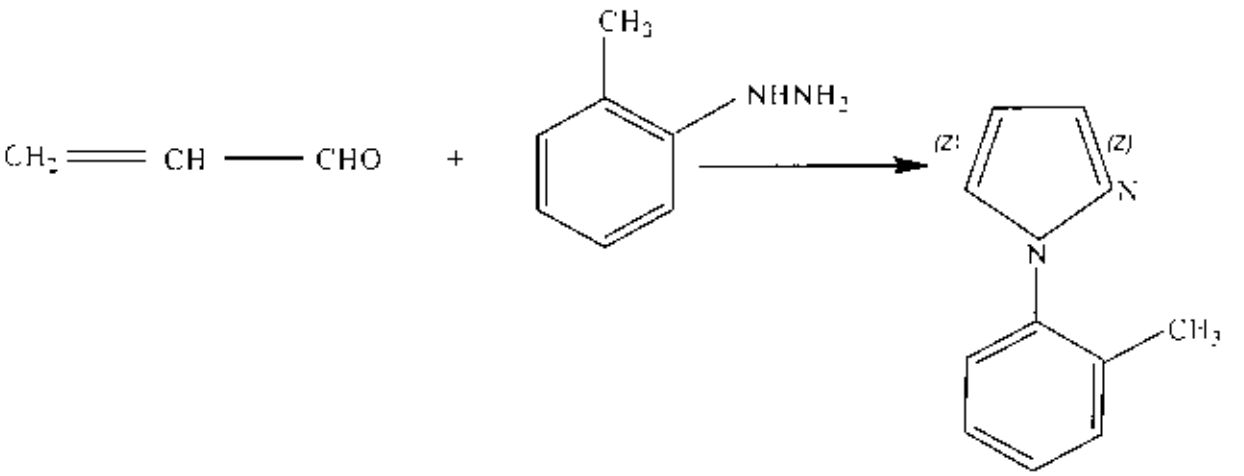
Synthetic approaches to the pyrazolines have generally been based on a limited number of reaction types. The most obvious route that of pyrazole reduction has not been widely applied and is only of historical interest. This is because the pyrazoline ring can be generated directly and in many instances, with no alternative by product. The dehydrogenation of pyrazolidines has also been used to a limited extent. This reaction has assumed importance only in fused ring systems.

The initial report of pyrazoline synthesis occurred in 1885 when Knorr and Blank[116] described the slow reduction of 1,3-diphenyl-5-methyl pyrazole with sodium in and when it reacted with nitrous acid in heated hydrochloric acid, a blue green colour was produced. The nitrous acid reaction was later used as the basis for the "Knorr pyrazoline test" which has been used diagonstically. Pyrazoline itself was first

synthesized by Curtius and wirshing[117], who obtained it in less than 50% yield from the spontaneous reaction of acrolein and hydrazine.

2.5.1.1 Aryl hydrazine based syntheses.

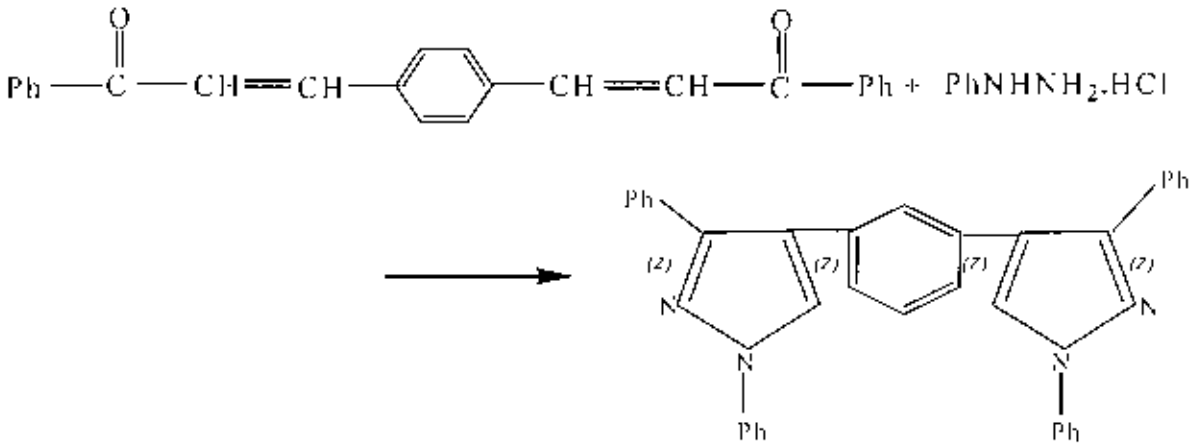
In 1887 fisher and Knovenagel[118] reported that phenyl -hydrazine and acrolein reaction to yield 20-22% of a compound, melting at 51-52°C and boiling at 273-74°C with no decomposition (Scheme 1). This substance was classed as pyrazoline because of a positive Knorr reaction.



Scheme 1

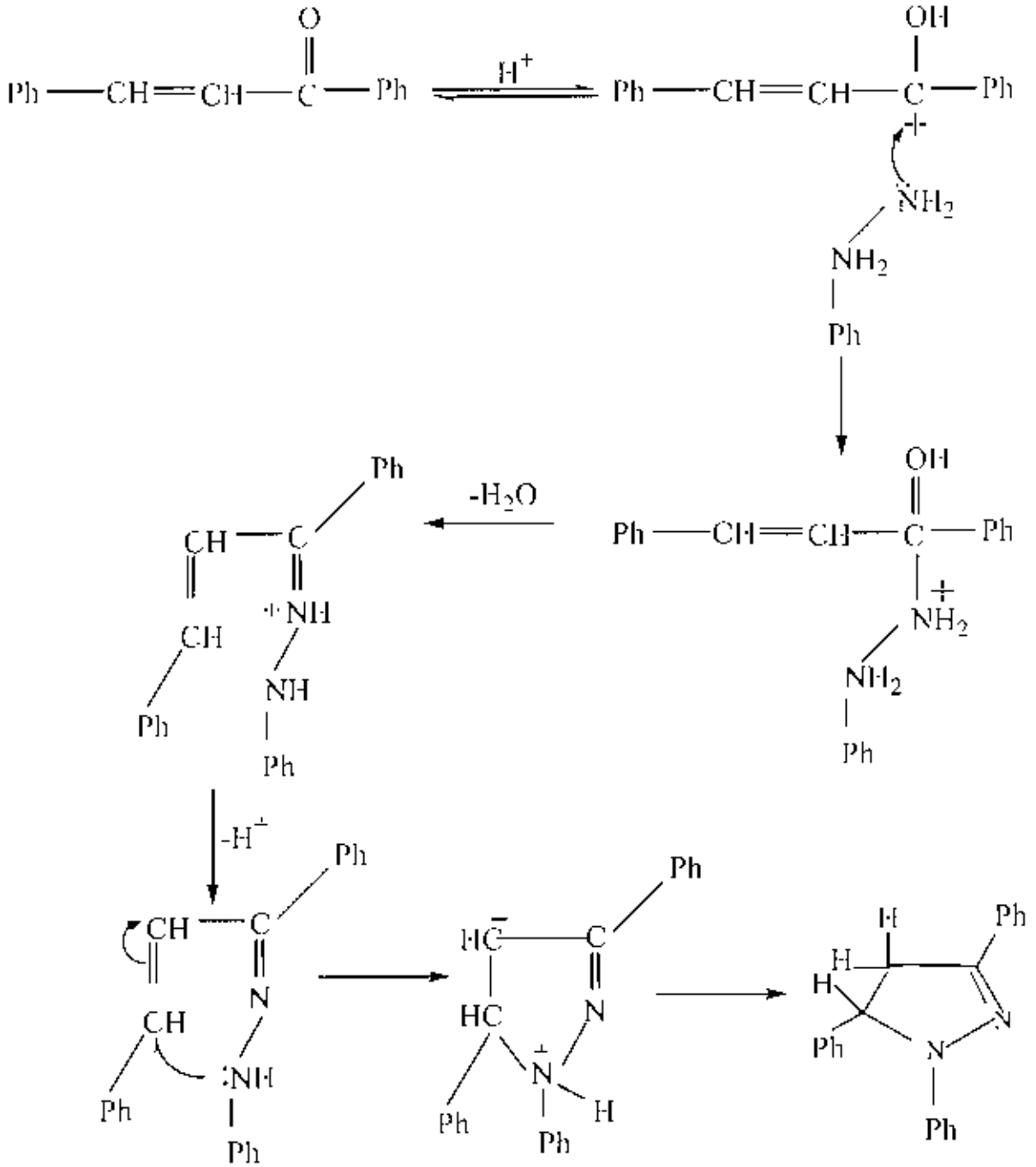
2.5.1.1.1 Condensation of hydrazines with αβ-unsaturated carbonyl compounds.

Aromatic hydrazines condense with αβ-unsaturated carbonyl compounds to yield pyrazolines under a wide variety of experimental conditions, such as reaction in methanol, ethanol, and diethyl ether at room and elevated temperatures[119]. The reaction has also been carried out in sulphuric acid[120] and, refluxing benzene and xylense[121]. Pyrazolines with thienyl, thiazolyl and furlyl substitutents have also been obtained by using shorter reaction times, and at slightly elevated temperature with glacial acetic acid as solvent. Dichalcones reacted with phenylhydrazine in acidic condition to produce dipyrazoline[122] (Scheme 2)



Scheme 2

It has been reported[54] that ketones with terminal unsaturation react with great ease to produce pyrazolines without catalytic assistance. The ease of this reaction appears to be due to the favorable steric arrangement of the intermediate hydrazones. It may be mentioned here that the reaction path has also been fairly well established. Isomeric Ketones lead to the same pyrazolines due to the favorable arrangement of intermediate hydrazones[123]. (scheme 3)

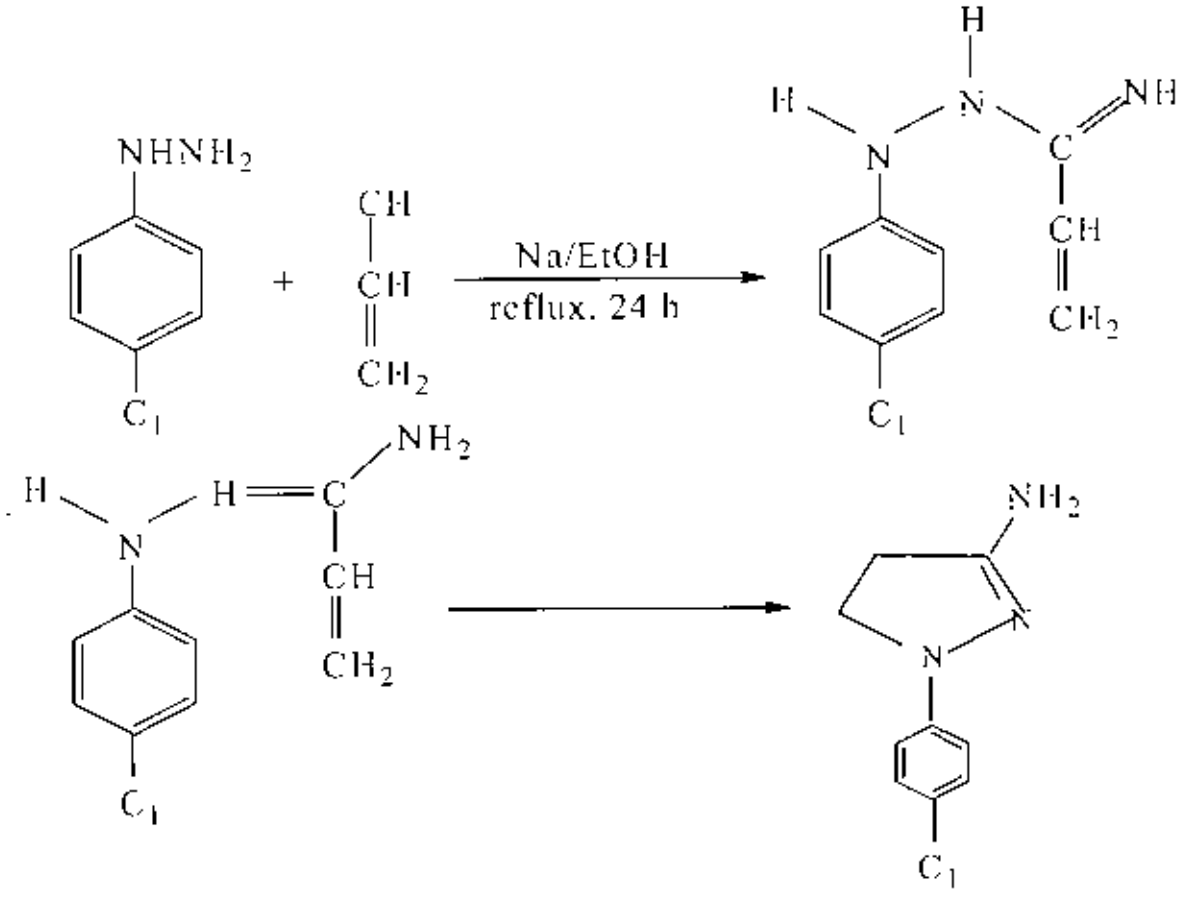


Scheme 3

It is necessary to add that aldehydes with terminal unsaturation do not undergo hydrazine cyclization leading to pyrazoline formation with any great facility, such as acrolein yields sizeable quantities of hydrazone before conversion to 1-phenyl-2-pyrazoline[125]. Even there are reports that ketones behave similarly[124].

2.5.1.1.2 Addition of Hydrazines to αβ-Unsaturated Nitriles

An interesting variation of the reaction between unsaturated compounds and arylhydrazines is the synthesis of 1-aryl-3-amino-2-pyrazolines from αβ- unsaturated nitriles[126] (Scheme 4). This reaction has been carried out with sodium in ethanol and required extended reaction time.



Scheme 4

2.5.1.1.3 Condensation of Hydrazines with β-Substituted Ketones

Various types of β-substituted ketones have also served as pyrazoline precursors as a variation of the basic reaction. These include Mannich bases of many varieties, e.g., β-bromo-[127], β-chloro-[128], β-hydroxy ketones[129] and β- seleno ethers[130]. The reaction has been carried out in acetic acid at reflux or elevated temperatures alone or in combination with hydrochloric acid. Both 2N sulphuric acid and 3% sodium hydroxide have also been used[131]. This reaction has been carried out for 60 h at 100°C[132]. Quantitative yields of 1,3,5-triaryl-2-pyrazolines were obtained from phenyl hydrazine and 1,3-diphenyl-3-bromo-propene-3-one[133].

2.5.1.1.4 Condensation of Hydrazines with Oxiranes and Aziridine

Small ring compounds such as substituted aziridines and oxiranes react readily with phenylhydrazine to form 1-phenyl-4-hydroxy or 4-alkylamino-2-pyrazoline, usually with additional 3,5- substitution[54].

2.5.1.2 Aliphatic Hydrazine Based Syntheses

2.5.1.2.1 Condensation with Aβ-Unsaturated Carbonyl Compounds

Condition for the reaction of hydrazine and its aliphatic derivative with αβ-unsaturated carbonyl compounds are as varied as those using arylhydrazines. These reactions are generally less vigorous and the reaction times are shorter. Ethanol has been used extensively as the solvent either as such or in the presence of sodium acetate[134] at temperature ranging from ambient to reflux[135], and using reaction times between 5 min and 24 h. Methanol has also been used as solvent in the same way. The reaction has also been performed under acidic or basic conditions in aqueous media usually at room temperature but occasionally under cooling or at reflux[136].

2.5.1.2.2 Condensation with β- Substituted Ketones and β-Epoxy Ketones

Formation of phyrazolines from hydrazines or simple aliphatic hydrazines and β-substituted ketones has not been carried out frequently. In those cases studied, either neutral or basic conditions prevail and reaction time varied greatly. Mannich bases have been used[137] occasionally. The Mannich base derived from acetylcyclopropane and dimethyl amine did not form a pyrazoline but the related vinyl cyclopropylketone did[138].

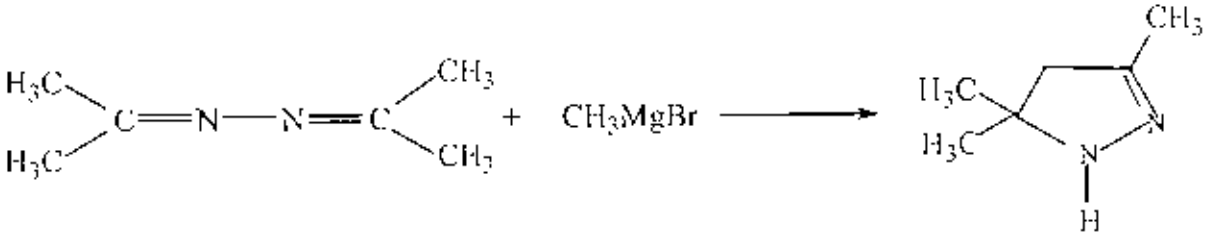
2.5.1.2.3 Addition to Aβ-Unsaturated Nitriles

Nitriles with αβ-unsaturation react with hydrazine in a manner similar to phenylhydrazine to produce 1H-3-amino-2-pyrazolines. Alkoxide catalysis, anhydrous media and extended reaction times are used[54].

2.5.1.3 Cyclization Based Syntheses

Several ketazine have undergone acid catalyzed rearrangement to produce pyrazolines. This reaction first described by Curtius and Fosterling[139], is an unusual example of intramolecular addition. Typical catalyst for the reactions are maleic and

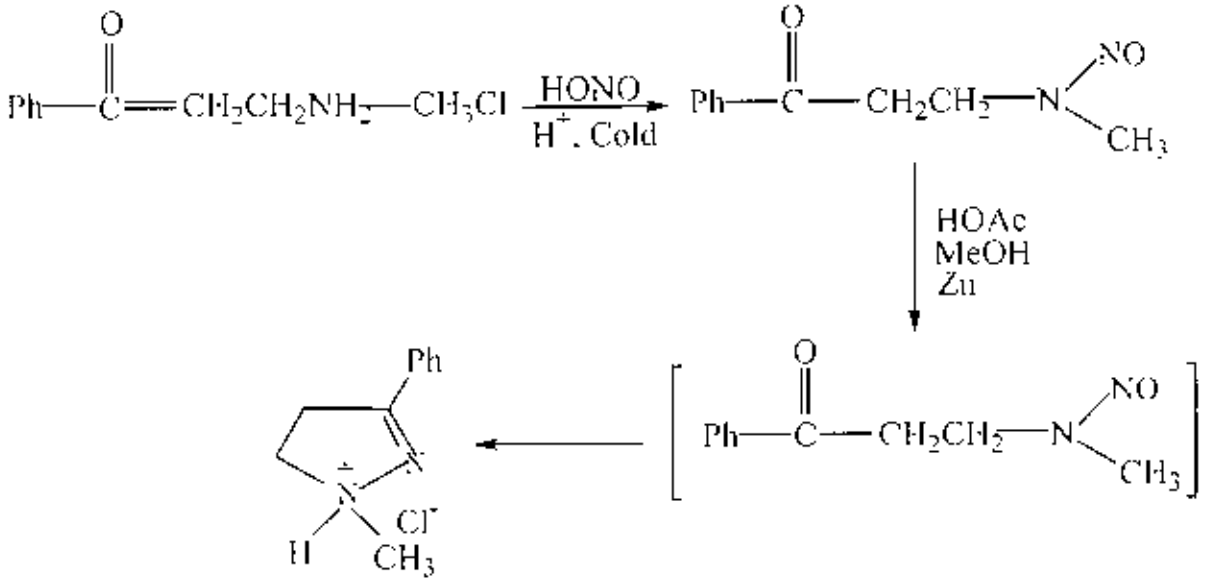
thiocyanic acids[140], and stannic chlorides[141]. It has also been found that acetone azines cyclized when reacted with methylmagnesium bromide (Scheme 5)



Scheme 5

2.5.1.4 Misellaneous Hydrazine Based Syntheses

It is known from the preceding discussion that the common 2-pyrazoline synthesis involves condensation of carbonyl compounds with a hydrazine derivative and that this is followed by either addition to a carbon-carbon double bond or reaction with a substituent to the carbonyl group. Pyrazolines have also been formed by a formal reversal of this sequence[142] (scheme 6)

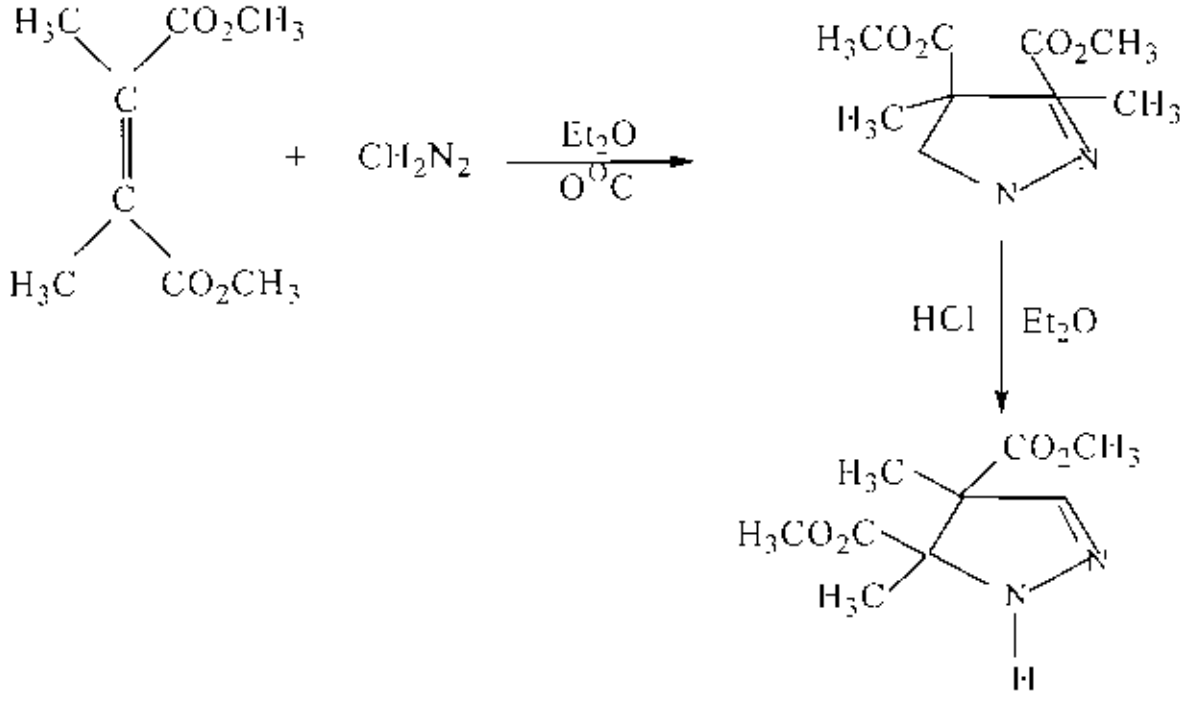


Scheme - 6

2.5.1.5 Aliphatic Diazocompound Based Syntheses

Diazomethane reacts with dimethyl formate producing quantitative yields of 4, 5-dicarbomethoxy-2-pyrazoline[143]. Highly reactive and unstable idazoalkanes like diazomethane, ethane, propane and cyclobutane are quite volatile and in pyrazoline syntheses are invariably reacted with unsaturated compounds at temperatures ranging from ambient to 4°C[144]. Reaction times vary greatly, depending to some extent upon the nucleophilic structure, and range from instantaneous to several days. Ethyl ether is the most common solvent but methylene chloride, chloroform,

tetrahydrofuran and ether-benzene mixture have also been used[145]. Compounds of greater stability and lower volatility than diazomethane and its congeners, e.g. phenyldiazomethane, diphenyldiazomethane, the diazoesters and amides and diazoacetones react at higher temperatures, generally between ambient and 115°C. Ethyl diazoacetate has been reported to react so vigorously with diethyl fumerate that cooling is required to control that reaction. Phenyl diazomethane also react at low temperatures with both diethyl fumerate and maleate[146]. The reaction time varies widely and various solvents have been used such as alcohol, methanol-sulphuric acid mixture, methanol-ethylether mixture and petroleum ether[147]. (Scheme 7)



Scheme 7

From this reaction it is concluded that 1-pyrazolines are general intermediates and are stable, only when they cannot rearrange into conjugated isomers.

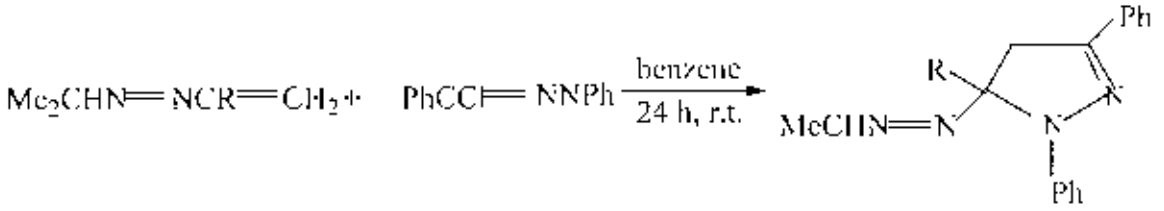
Recent method for the preparation of pyrazoline involves the reaction of diazomethane with acylamino cinnamates[148]. In this reaction diazomethane reacted with methyl-2 –acetimido or benzimido cinnamates to give 2-pyrazolines.

2.5.1.6 Miscellaneous Pyrazoline Syntheses.

Among other pyrazoline syntheses the most important one had been by pyrazole reduction. Addition of hydrogen to a single double bond is easily effected. The reduction is catalyzed by palladium on barium sulphate at 18°C. At higher temperatures further reduction ensues[149]. The sodium-ethanol couple has also been used[150,151], but in many instances reductive cleavage occurred.

Recently, reaction of 1-phenyl-3-methyl-5-amino pyrazole with salicylic acid to produce 1-phenyl-5-salicyloylimino pyrazolines has been reported[70]. Aryl diazonium salts reacted under highly alkaline conditions with 3-acetylbutyrolactone yielding 1-aryl-3-arylazo-2-pyrazolines in low yields[54].

A most recent method of pyrazoline syntheses involves the reaction of αβ-unsaturated azo compounds with diphenyl nitrile amine[152]. The reaction has been carried out in benzene for 24 h at room temperature with 97% yield (Scheme 8)



Scheme 8

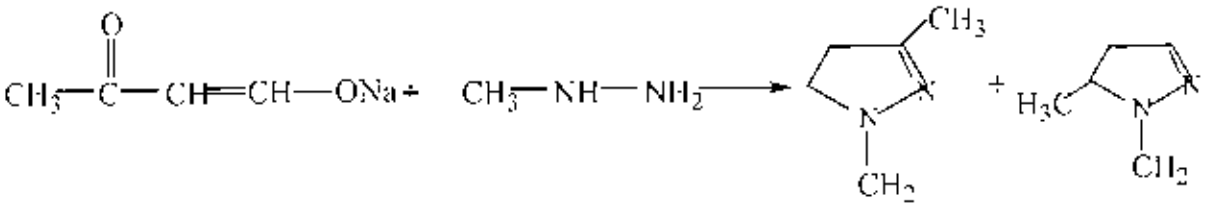
2.5.2 Syntheses of Pyrazoles

The parent pyrazole was obtained for the first time by Buchner[153] in 1889 on heating pyrazole 3, 4, 5-tricarboxylic acid at 230-240°C. By similar procedure pyrazole was prepared from pyrazole 3, 5-dicarboxylic acid and from its silver salt. Pyrazole also was formed from pyrazole - 3 and 4 - carboxylic acid and also from 3, 4,-dicarboxylic acid.

2.5.2.1 Synthesis of Pyrazole Derivatives from β-Dicarbonyl Compounds and their Functional Derivatives.

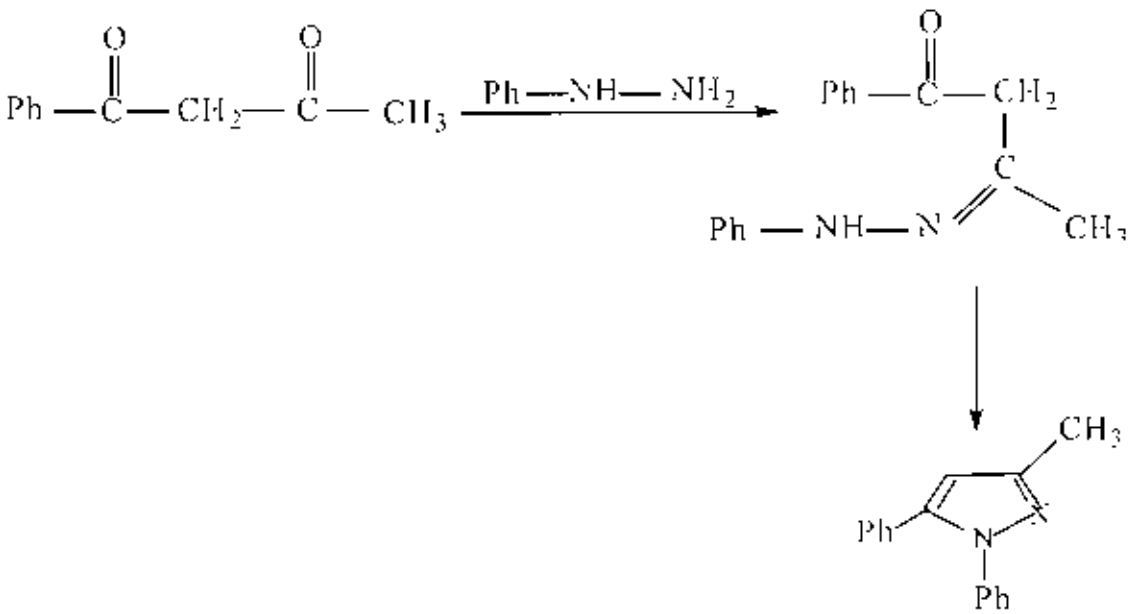
The synthesis of pyrazole from β-dicarbonyl compounds and hydrazines is the most widely used and general method for pyrazole synthesis. The reaction of methylhydrazine with sodium salt of formyl acetone produced a mixture of two isomeric pyrazoles[154] (Scheme 9). Both the, dimethyl-pyrazoles were liquid at room

temperature (b.p. 136°C & 150°C) but they could easily be identify from their different boiling and from the melting points of their picrates (137 and 170°C).



Scheme 9

Benzoyl acetone reacts with phenylhydrazine to give a monophenyl hydrazone, which on heating or treatment with acid or with hydrogen chlorides in pyridine produces[155] 3-methyl-1, 5-diphenyl pyrazole (Scheme 10)



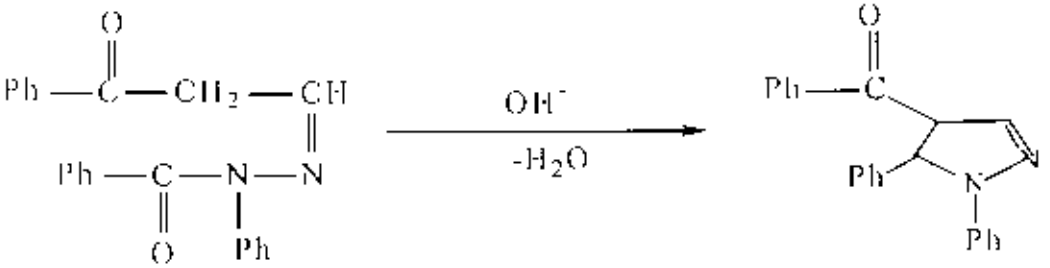
Scheme 10

2.5.2.2 Syntheses from Acetylenic Carbonyl Compounds.

The synthesis of pyrazole from acetylenic carbonyl compounds has not been widely employed because the starting materials are not readily available. When hydrazine itself is employed in this reaction pyrazoles are produced directly. When a substituted hydrazine is employed, the two isomeric pyrazoles[156] are obtained. The reaction between methylhydrazine and phenylpropioaldehyde produced a single product, 1-methyl-5-phenyl pyrazole.

2.5.2.3. Syntheses by Ring Closure

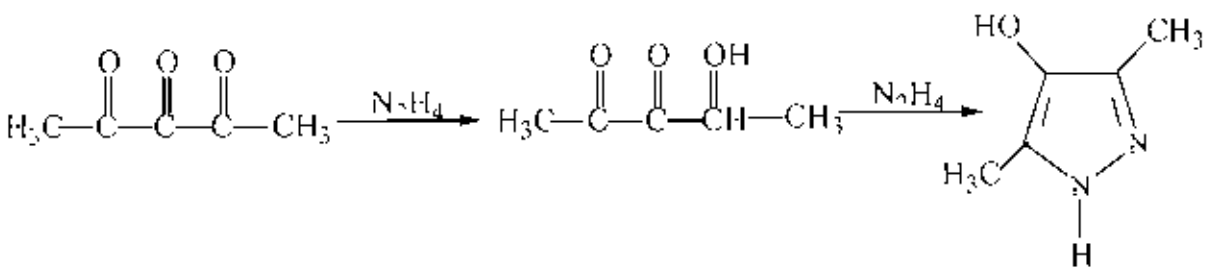
The syntheses of pyrazoles from acylhydrazones of β-dicarbonyl compounds is of interest that it involves the ring closure between carbon atoms 4 and 5 of the pyrazole ring. Thus the reaction of 1-aroyl-1-phenyl hydrazones of benzoylacetaldehyde in the presence of alcoholic sodium hydroxide produced 4-benzoy1-1, 5-diphenyl pyrazole[57] (Scheme 11).



Scheme 11

2.5.2.4 Syntheses from 1, 2, 3-tricarbonyl Compounds

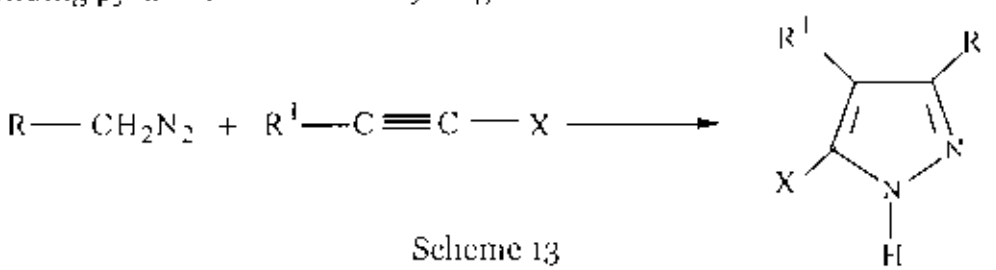
Compounds containing three adjoining carbonyl groups react with hydrazine to yield 4-hydroxy pyrazoles. Thus, pentane 2, 3, 4-trione produced 4-hydroxy- 3. 5 dimethyl pyrazole[54] (Scheme 12)



Scheme 12

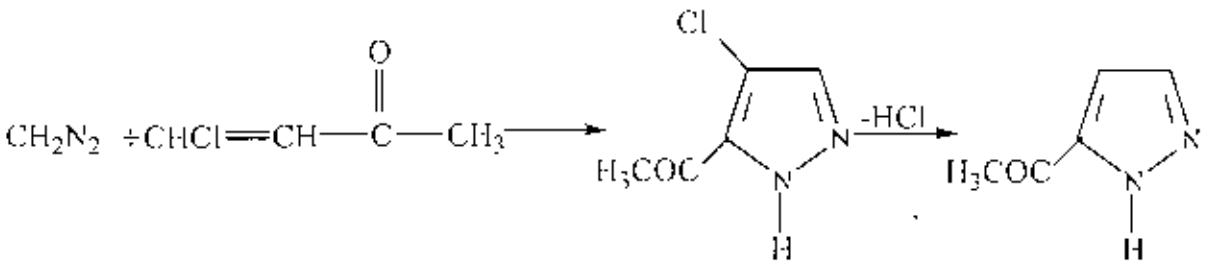
2.5.2.5 Syntheses from Aliphatic Diazo Compounds with Acetylene Derivative

Aliphatic diazo compounds react readily with acetylene derivatives to yield pyrazoles. The reaction has usually been carried out at room temperature in a convenient solvent. The most commonly used diazo compounds, are diazomethane and ethyl diazoacetate[54] (Scheme 13) compounds containing the -CH=C-Hal or the-CH=C-NO_2 groups also react with aliphatic diazo compounds to yield directly the corresponding pyrazole with loss of hydrogen halide or nitrous acid.



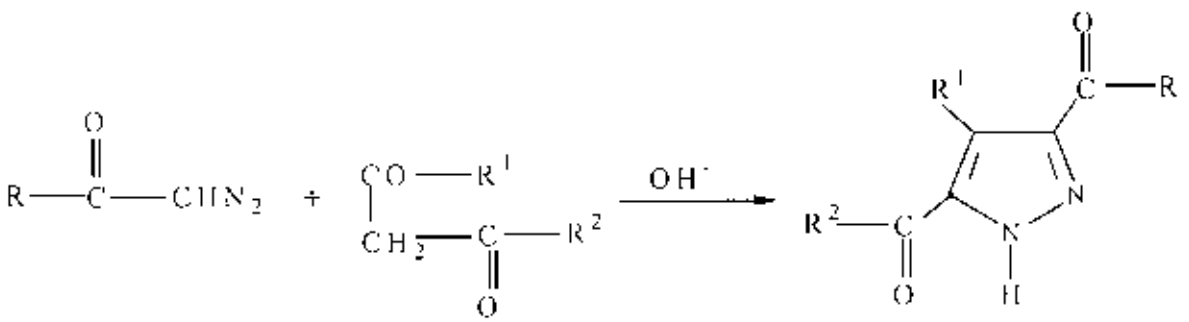
Scheme 13

The direction of addition of the diazo compound to the halo-vinyl compounds is determined by the group joined to the double bond (usually carbonyl or carboethoxyl) (Scheme 14)



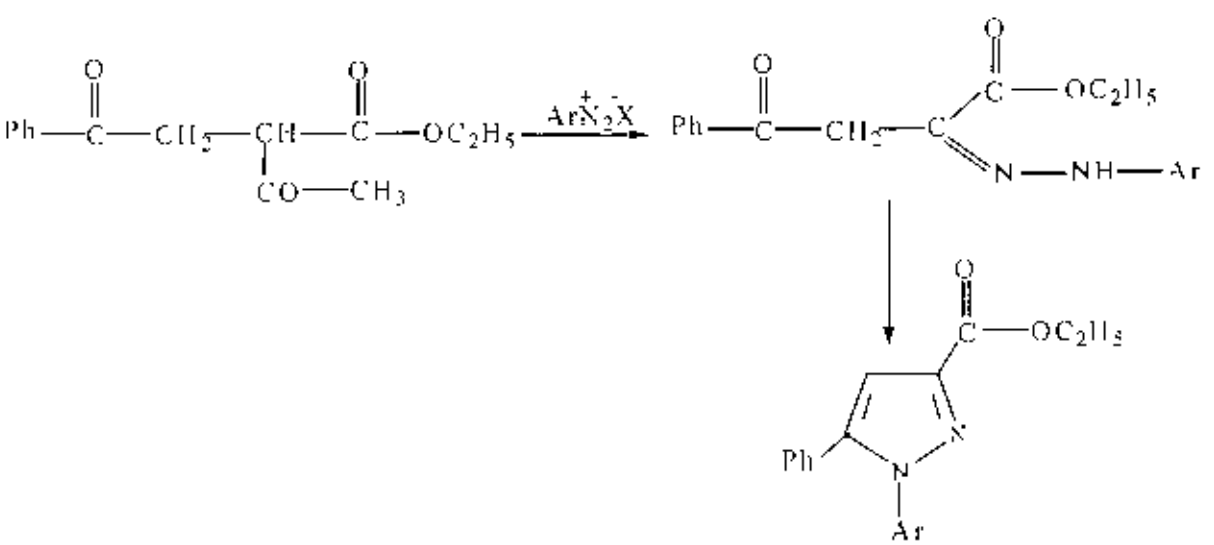
Scheme 14

Ethyl diazoacetate and diazoketone react with β-carbonyl compounds and with β-ketoesters in presence of dilute alkali to yield pyrazoles according to the following reaction[158] (Scheme 15)



Scheme 15

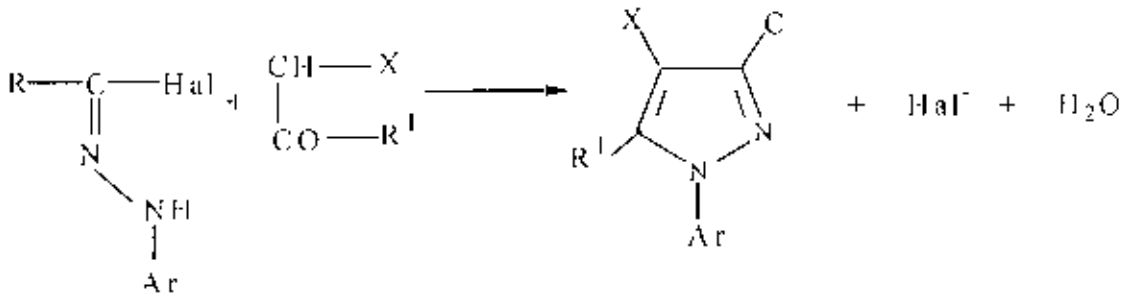
Hydrazone produced from aromatic diazo compounds and carbonyl compounds with an active β-hydrogen react with β-dicarbonyl derivatives (e.g., phenl acetoacetates) producing pyrazoles[159] (Scheme 16)



Scheme 16

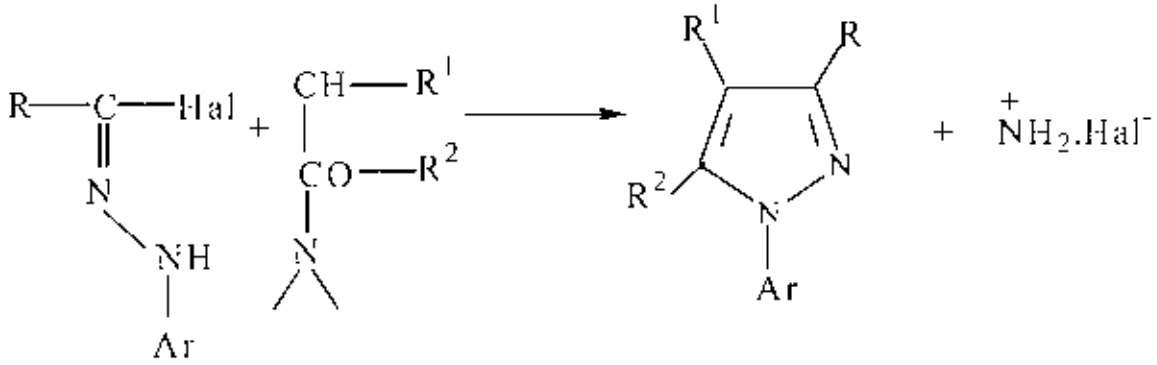
2.5.2.6 Syntheses from hydrozonic halides

One of the more general syntheses of the pyrazole ring utilizes the reaction of hydrazonic halides with activated methylene compounds in their salt form. Various substituted pyrazoles have been obtained[160] by this reaction (Scheme 17)



Scheme 17

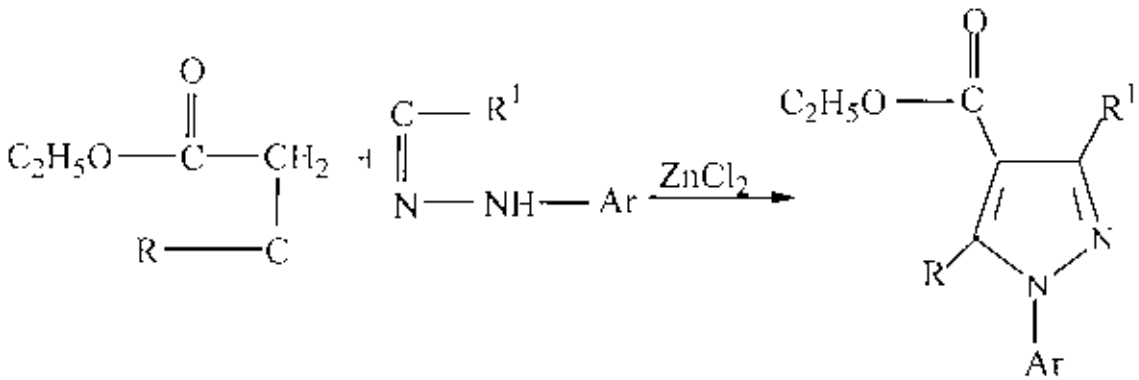
The use of enamines to give pyrazoles in syntehses with hydrozonic halides is also of value. The importance of the method is that it offers, generally in high yields, compounds (Such as 4-alkylpyrazoles) that are not easily obtained by other methods. Enamines from aliphatic, arylaliphatic, and alicyclic ketones and from aliphatic aldehydes react[54] with hydrazonic halides according to the general scheme show below (Scheme 18)



Scheme 18

2.5.2.7 Syntheses from aldehyde arylhydrazones of β- ketoesters.

Aryl hydrazones of aliphantic and aromatic aldehydes condense with β-ketoesters in presence of anhydrous zinc chloride at temperatures ranging from 120°C to 140°C to yield the esters of pyrazole-4-carboxylic acids[161] (Scheme 19). The intermediate steps in this reaction are not known and the nature of the oxidation step has not been clarified.



Scheme 19

2.5.2.8 Syntheses from epoxides and from ethylene imine derivatives.

Epoxides of αβ-unsaturated ketones react with hydrazine and phenyl hydrazine yielding pyrazoles[162]. From the reaction with hydrazine it has been possible sometime to obtain 4-hydroxy pyrazolines, which are converted later into pyrazoles on treatment with acetic acid or with alcoholic alkalies. With phenylhydrazine, 1-phenyl pyrazoles are directly obtained[54].

2.5.2.9 Synthese from pyrazolines by oxidation or other reactions.

Conversion of pyrazolines to pyrazoles can be accomplished in several different ways. These include oxidation, dehydrogenation and elimination reactions. A variety of oxidizing agents have been used to convert pyrazolines[193] to pyrazoles. Among the oxidizing agents, those frequently used are bromine in chloroform, lead tetracetate in acetic acid, potassium permanganate, nitric acid, chromic acid and manganese dioxide have been used[54].

3.1 Preface of Hydrazine & its derivatives:

In the past century, hydrazine[164], an important intermediate in the synthesis of countless chemicals with N-N bonds, has grown into a major industrial commodity with a wide range of uses. It is used as a fuel in rocket propulsion, as a boiler feed water deoxygenating agent, and in the manufacture of foamed plastics, pharmaceuticals, and biodegradable pesticides and herbicides, to name just a few uses. Since the first edition of *Hydrazine and Its Derivatives: Preparation, Properties, Applications* was published in 1984, there has been considerable development in this field and many new aspects of hydrazine chemistry and applications have evolved.

Hydrazine is a chemical compound with formula N_2H_4 used as a rocket fuel. Hydrazine is a liquid with weak basic properties similar to ammonia. Due to the alpha effect the nucleophilicity is much stronger than that of ammonia, which makes it more reactive. It can be made by oxidizing ammonia with sodium hypochlorite (the Raschig process). It is a monopropellant rocket fuel.

Hydrazine derivatives 1,1-dimethylhydrazine and 1,2-dimethylhydrazine, in which two of the hydrogen atoms are substituted with methyl groups, are also described as **hydrazines**. 1,1-Dimethylhydrazine is used to make hypergolic (self-igniting) bipropellant rocket fuels.

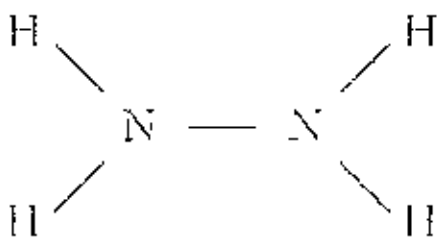
3.2 Health effects

Breathing hydrazines may cause coughing and irritation of the throat and lungs, tremors, or seizures. Breathing hydrazines for long periods may cause liver and kidney damage, as well as serious effects on reproductive organs. Eating or drinking small amounts of hydrazines may cause nausea, vomiting, uncontrolled shaking, inflammation of the nerves, drowsiness, or coma. Hydrazine is found in chewing tobacco and cigarettes. Tumors have been seen in many organs of animals that were exposed to hydrazines by ingestion or breathing, but most tumors have been found in the lungs, blood vessels, or colon. 1,2-Dimethylhydrazine has caused colon cancer in laboratory animals following a single exposure. The Department of Health and Human Services (DHHS) has determined that hydrazine and 1,1-dimethylhydrazine are known carcinogens. The International Agency for Research on Cancer (IARC) has determined that hydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine are possible human carcinogens. The Environmental Protection Agency (EPA) has determined that hydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine[165] are probable human carcinogens. The American Conference of Governmental Industrial Hygienists (ACGIH) currently lists hydrazine and 1,1-dimethylhydrazine as suspected carcinogens, but has recently recommended that the listing of hydrazine be changed to that of animal carcinogen, not likely to cause cancer to people under normal exposure conditions. The False Morel contains the chemical gyromitrin, which is metabolized into monomethyl hydrazine inside the body. Consequently, the toxic effects of this mushroom are the same as with hydrazine poisoning.

3.3 Use

Hydrazine (anhydrous or as the hydrate) has numerous commercial uses. The principal current use for hydrazine is as an intermediate in the production of agricultural chemicals such as maleic hydrazide. It is also used as an intermediate in the manufacture of chemical blowing agents which are used in the production of plastics such as vinyl flooring and automotive foam cushioning, as a corrosion inhibitor and water treatment agent, as a rocket propellant, and, to a lesser extent, as a reducing agent, in nuclear fuel reprocessing, as a polymerization catalyst, as a scavenger for gases, and several other uses. It has also been used as a medication for sickle cell disease and cancer. From the late 1950s through the 1960s the primary use of hydrazine was as a rocket propellant. In 1964, 73% of the hydrazine consumed in the United States was used for this purpose. By 1982, other commercial uses dominated the market; 40% of the hydrazine consumed was used in agricultural chemicals, about 33% for blowing agents, 15% as a corrosion inhibitor in boiler water and only 5% aerospace propellant[66] (Budavari et al. 1989; Fajen and McCammon 1988; HSDB 1995; Schmidt 1988; WHO 1987).1,1-Dimethylhydrazine is used mainly as a component of jet and rocket fuels. Other uses include an adsorbent for acid gases, a stabilizer for plant growth regulators, an intermediate for organic chemical synthesis, and in photography. 1,2-Dimethylhydrazine is used only as a research chemical and has no known commercial uses (ACGIH 1991a; Budavari et al. 1989; HSDB 1995).

3.4 Properties



The structure formula of Hydrazine

3.5 Disposal

General	
Name	Hydrazine
Chemical formula	N_2H_4
Appearance	Colourless liquid
Physical	
Formula weight	32.0 amu
Melting point	274 K (1 °C)
Boiling point	387 K (114 °C)
Density	1.01g/ml
Solubility	very soluble
Thermochemistry	
$\Delta_f H^o_{gas}$	95.35 kJ/mol
$\Delta_f H^o_{liquid}$	50.63 kJ/mol
$\Delta_f H^o_{solid}$	37.63 kJ/mol
$S^o_{gas, 1\ bar}$	238.66 J/mol·K
$S^o_{liquid, 1\ bar}$	121.52 J/mol·K
Safety	
Ingestion	Extremely Toxic, possibly carcinogenic
Inhalation	Very dangerous—extremely destructive to the upper respiratory tract
Skin	Can cause severe burns, can be absorbed into bloodstream
Eyes	Can cause permanent damage
More info	Hazardous Chemical Database
LD50	as low as 25mg/kg

Hydrazine, 1,1-dimethylhydrazine, 1,2-dimethylhydrazine, and wastes containing these chemicals are classified as hazardous wastes by EPA. Generators of waste containing these contaminants must conform to EPA regulations for treatment, storage, and disposal. Liquid injection or fluidized bed incineration

methods are acceptable disposal methods for these wastes. Oxidation of spills of hydrazine fuels with sodium or calcium hypochlorite or hydrogen peroxide prior to disposal has been recommended. However, incomplete reaction of 1,1-dimethylhydrazine with hypochlorite leads to formation of several by-products, including carcinogenic N-nitrosoalkylamines. Ozonation of wastewater containing hydrazine fuels has been shown to reduce concentrations of the fuels, their associated impurities, and oxidation products to environmentally acceptable levels. Biodegradation is also an acceptable treatment for wastewaters containing hydrazine wastes (Brubaker 1988; EPA 1991a; HSDB 1995; Jody et al. 1988; WHO 1987). According to the TRI, about 106,000 pounds of hydrazine and 3,000 pounds of 1,1-dimethylhydrazine were transferred to landfills and/or treatment/disposal facilities in 1993 (see Section 5.2) (TRI93 1995).Of this quantity, about 1,400 pounds of hydrazine were discharged to publicly owned treatment works.

4.1 Aim of the present work

It has been already well understood from the previous chapter that the aromatic derivatives of 2-pyrazoline are extensively used as fluorescent brighteners electrographic materials, whitening agents, herbicides, fungicides pesticides and other biologically active ingredients. On the other hand, these compounds are synthesized by: condensation of αβ-unsaturated aldehydes or ketones with hydrazines and some other alternative methods of synthesis of 2-pyrazoline derivatives have been recently reported. It is seen from the literature that the chemical modification of the 2-pyrazoline ring systems has not been done to an appreciable extent. It was planned to develop newer and more convenient methods for the derivatization of the pyrazolines ring system to produce newer compounds which may be more important both physiologically and industrially. Accordingly we planned to:

1. Synthesize αβ-unsaturated ketones, precursors for the synthesis of aromatic derivatives of pyrazolines under MW irradiation.
2. Synthesize pyrazolines by the reaction of αβ-unsaturated ketones with various hydrazine hydrochlorides under MW irradiation.
3. Compare Microwave Assisted Organic Synthesis (MAOS) with conventional method of synthesis with special interest to look in to the reaction time, yield and environment friendleness of MAOS.
4. Determine the structures of all the starting materials as well as the final products by chemical and spectroscopic methods.
5. Show the effective use of domestic MW oven.

****

Chapter Two

Experimental

5.1 General Experimental methods and Techniques

The general techniques and equipment that have been adopted and used during this research work are briefly described bellow:

5.1.1 Reagents and Solvents

The reagents and solvents were purified and dried before use. Some were used as such from the bottle. The reagents and solvents were of the analytical reagent grade bought either from E. Merck or BDH.

Acetophenone, acetone, benzene, n-hexane, petroleum ether, ethyl acetate, ethyl acetoacetate, chloroform, absolute alcohol (Methanol, Ethanol). isopropanol, etc. were distilled before use.

5.1.2 Purification

a) Benzaldehyde

Reagent grade benzaldehyde was treated with potassium carbonate and filtered. The filtrate was distilled with a quick-fit apparatus and colourless fraction distilling at 170-180°C was collected.

b) Methanol

Reagent grade methanol was dried over anhydrous sodium sulphate before distillation. The fraction distilling at 63-64°C was collected in a quick-fit flask.

c) Ethanol

Commercially available absolute alcohol was dried and purified by literature methode[91]. It was distilled and the fraction distilling at 77-78°C was collected and stored in a well-stoppered bottle.

d) Diethyl ether

Commercial grade of diethyl ether was dried over sodium wire in a reagent bottle and left overnight before use.

e) Petroleum ether

The petrol (motor fuel) collected from local petrol pump was distilled and the fractions between 40-60°C and60-80°C were collected separately.

f) Ethyl acetate

The commercial grade of ethyl acetate was distilled and the fraction at 77°C was collected.

g) Anisaldehyde

Commercial grade anisaldehyde was distilled and the colorless fraction distilling at 248-249°C was collected and stored in well-stoppered bottle.

5.1.3 Separation of reaction Mixtures

The reaction mixtures were separated by the following methods:

Solvent extraction (Using Separating Funnel)

Separation by extraction method involved the transfer of a substance from one material phase in to a second phase. Solvent extraction method was employed either for the isolation of dissolved substances from solutions, or from solid mixtures or for the removal of undesired soluble impurities from mixtures. Common extraction solvents were diethyl ether, benzene, chloroform and petroleum ether. The success of the separation was dependent upon the solubility of the substance to be extracted in that solvent and upon the ease with which the solvent could be removed from the solute. Diethyl ether, owing to its powerful solvent properties and its boiling point (35°C), was the most used one during this work. Water, concentrated hydrochloric acid and ammonia were also used for this work.

Gravity Filtration (Using Fluted Filter paper)

Gravity filtration was commonly used for the collection of a solid material that was insoluble in the liquid with which it was associated.

Suction Filtration (Using Buchner Funnel)

This method was employed for the collection of a solid that has crystallized from a solvent. Effective operation of the suction filtration technique depends on the extent of pressure reduction within the filter flask.

5.1.4 Drying of Products

The products were dried in oven and in air after separation and purification.

5.1.5 Determination of Melting Points

In general, a sharp melting point is one of the most characteristic properties of a pure organic compound. The melting points were determined by Gallen camp apparatuses.

5.1.6 Chromatographic Technique: Thin Layer Chromatography (TLC)

Thin layer plates (7.5 × 2.5 cm) were prepared by drawing a 0.2 mm film from a suspension of silica gel (G60, E- Merck) in chloroform (2:1 w/v) over thoroughly cleaned glass plates. The plates were dried at room temperature for 24h. In the present work recoated aluminium sheets (0.2 mm; E. Merck) were mainly used for thin layer chromatographic analysis.

The sample solutions were applied with glass capillaries at about 1 cm from the bottom of the plates. The spotted plates were then immersed vertically in a chromatographic tank containing the solvent in such away that the spotted mark of the sample remained above the solvent. The plates were developed with ascending technique and finally the plates were removed when the solvent front reached about 1.5 cm from the top of the plates. The plates were allowed to dry and

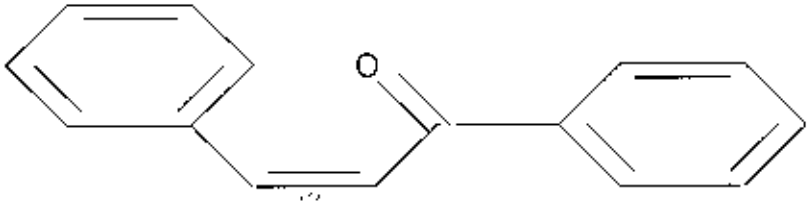
It is the best and modern separation technique. Different component in a sample can be differentiated and qualitatively determined simultaneously by this technique. In chromatography, two immiscible phases are brought on to contract wherein one phase is stationary and the other is mobile. The sample mixture introduced into the mobile phase undergoes a series of interactions with stationary and phase. Interaction exploits differences in the physical and chemical properties of the component under the influence of the mobile phase through the column containing stationary phase. Separation depends on the order of increasing interaction with the stationary phase. The least retarded components elute first and strongly interacted component elute last.

5.2 Preparation of Ketones

5.2.1 Preparation of Benzylideneacetophenone 1

Acetophenone (1.20 ml, 0.01 mole) and Benzaldehyde (1.06 ml, mole) were dissolved in methanol (13.5 ml, 0.42 mole) in two separate conical flasks. The two solutions were mixed quickly and to it freshly prepared sodium hydroxide solution (10%, 0.68 ml, 0.017 mole) was added drop wise. The reaction was carried out in a special microwave assisted glass ware. The mixture was put on the microwave oven in the flask along with a beaker of ice. The microwave was set at 600 Watt and started. The reaction turned yellow in colour after 15 seconds irradiation and appeared cloudy. But after some seconds it formed a clear solution. The reaction mixture was irradiated for few more minutes and the reaction was monitored by TLC. TLC finding showed that an irradiation of about 5 minutes completed the reaction with the colour turning yellowish orange and the appearance of precipitate was observed. The reaction flask was then removed from the microwave oven and was allowed to stand overnight in refrigerator for complete precipitation.

The precipitates were filtered under suction on a Buchner funnel, washed with cold water to remove completely any remaining alkali and dried under vacuum.The crude product was recrystallised several times from methanol to give pure benzylideneacetophenone **1** ,(2.20 g, 97.35%), melting point 55-56°C (Lit[167]. 56°C)



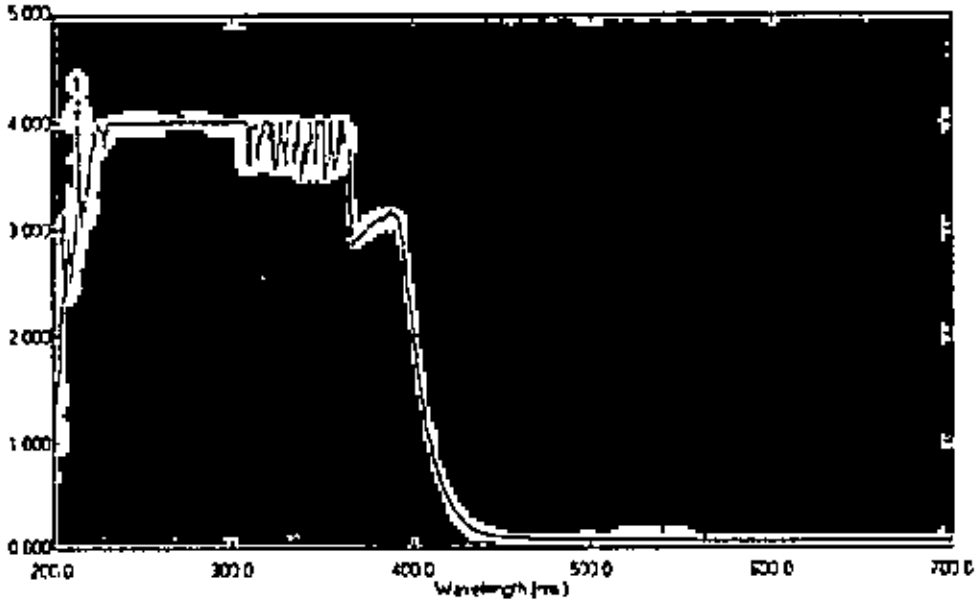
Benzylideneacetophenone

The UV **(Fig. 1)** spectrum of the compound 1 had absorption band 214.50 nm due to $\pi \longrightarrow \pi^*$ transition of the C=C-C=O system.

The IR **(Fig. 2)** spectrum (nujul) of the compound 1 had absorption band at 1670 (C=C Stretching), 1610 (-C=O stretching), 1595 (Aromatic hydrocarbon C=C stretching) and 760 (C-H deformation) cm^{-1}.

The ^1H NMR **(Fig. 3)** spectrum ($CDCl_3$) of the compound 1 had signals at δ (ppm): 7.42 (m, 10H, aromatic), 7.32 (d, 2H, ethylene, Z).

The ^{13}C NMR (Fig. 4, 5) spectrum of the compound 1 had signals at δ (ppm): 188 (carbonyl carbon), 144 (ethylene), 132 (Ar C), 130 (Ar C), 128 (Ar CH), 125 (Ar CH), 122 (ethylene carbon).



File Name: NZ001

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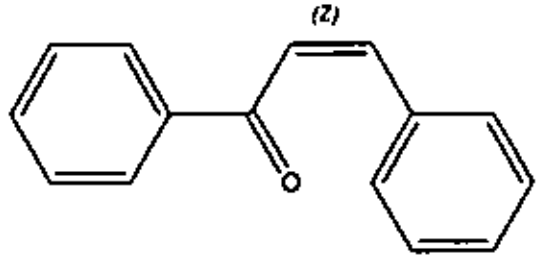
Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.5

No.	Wavelength (nm.)	Abs.
1	214.50	3.9999



Benzylideneacetophenone

Figure: 1

Figure: 2

Figure: 3

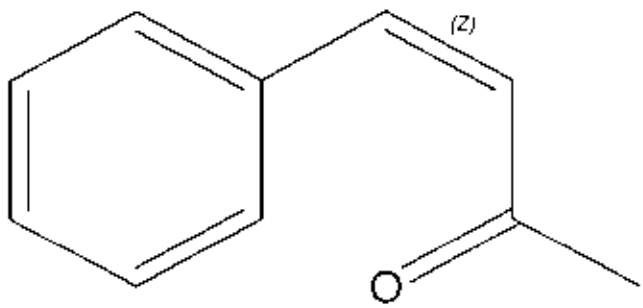
Figure: 4

Figure: 5

5.2.2 Preparation of Benzylideneacetone 2

Aqueous sodium hydroxide solution (10% 0.8ml, 0.02 mole) was added drop wise to a mixture of acetone (1.2 ml, 0.02 mole), Benzaldehyde (2.1 ml, 0.0198 mole) and methanol (6.41 ml, 0.2). The reaction was carried out in a special microwave assisted glass ware. The mixture appeared cloudy first then after some times formed light yellow solution. Then the mixture was put in the Microwave oven with one separate beaker of ice. The microwave was set at 600 Wt and the reaction was started. The colour changed yellowish after 30 seconds of the irradiation after 1 minute the solution became dark yellow. The reaction was monitored by TLC. In the end precipitate started to appear in the reaction fask. The reaction mixture was allowed to stand overnight in refrigerator for complete precipitation.

The mixture was filtered under suction on a Buchner funnel, washed with cold water to remove completely any remaining alkali and dried under vaccum. The crude product was crystallised several times from methanol to give pure benzylideneacetone 2 , (3.25 g, 98.5%), melting point 42-43°C (Lit[168] 42°C).

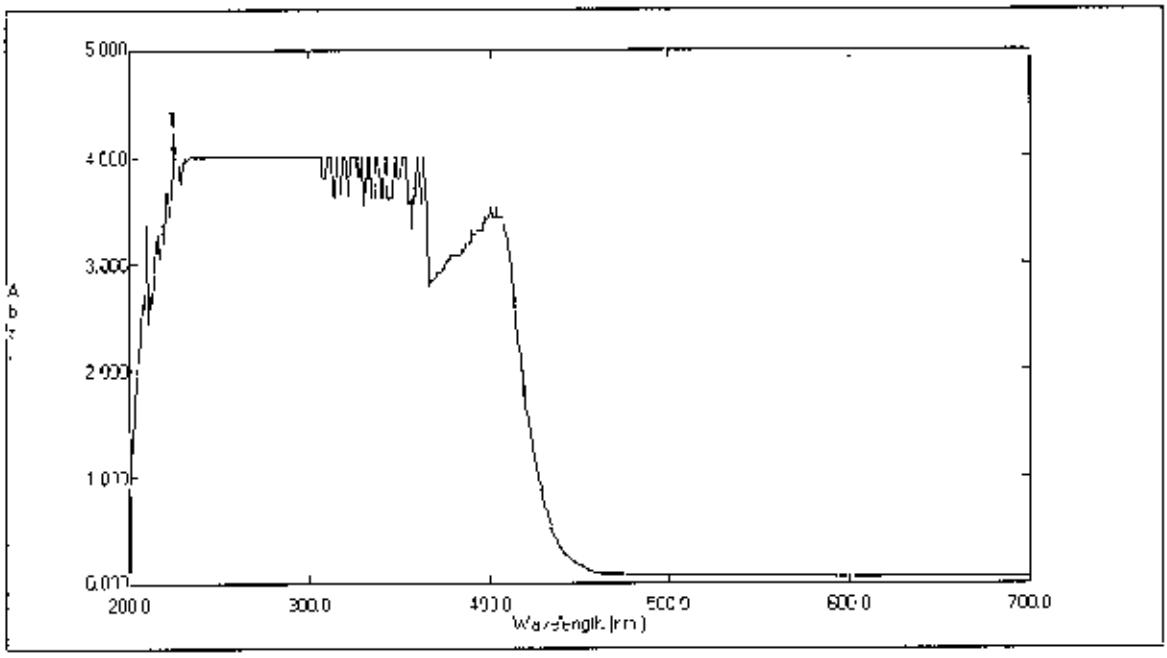


Benzylideneacetone

The UV **(Fig. 6)** spectrum of the compound 2 had absorption band at λ_{max} 225 nm due to $\pi \longrightarrow \pi^*$ transition of the C=C-C=O system.

The IR **(Fig. 7)** spectrum (nujol) of the compound 2 had absorption band at ν_{max}(nujol)1600 (C=O stretching). 1590 (aromatic hydrocarbon C=C stretching), 1460 (C-H bending CH_2), 1375 (C-H deforming in CH_3) and 765 (C-H deforming out of the plane) cm^{-1}.

The ^1H NMR **(Fig. 8)** spectrum ($CDCl_3$) of the compound 2 had signals at δ (ppm): 7.18 (m,5H, aromatic), 6.29 (d, 1H, ethylene, Z) 5.9 (d, 1H, ethylene, Z), and 1.57 (s, 3H, methyl).



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Data Original

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Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.5

No.	Wavelength (nm.)	Abs.
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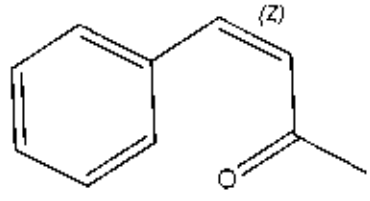


Benzylideneacetone

Figure: 6

Wavelength μm
3
4
5
6
7
8
9
10
11
12
13
14
15
16
100
90
80
70
60
50
40
30
20
10
0
Benzylideneacetone
3800
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
625
Wavenumber

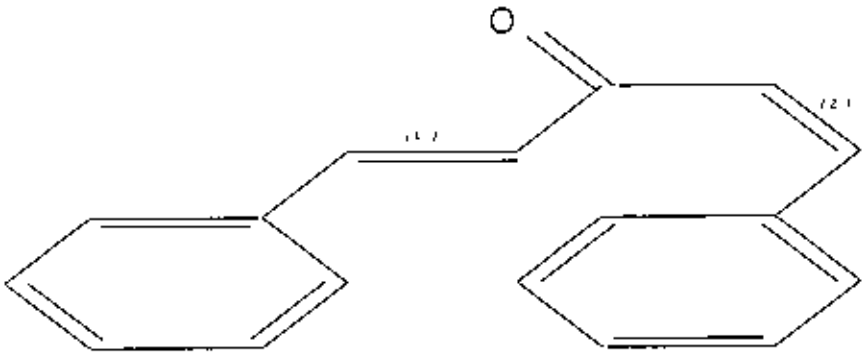
Figure: 7

Figure: 8

5.2.3 Preparation of Dibenzylideneacetone 3

The mixture of acetone (0.6 ml, 0.01 mole), benzaldehyde (1.7 ml, 0.016 mole) and methanol (5.9 ml, 0.18 mole) was added drop wise in an aqueous solution of sodium hydroxide (10%, 0.4 ml, 0.01 mole). The mixture appeared cloudy first but after some times it changed to a clear solution. The mixture was then put on the microwave oven and a separate beaker of ice was put. After setting the microwave at 600 Wt, the reaction started gradually with 15 seconds duration. The mixture turned to yellow color after 30 seconds and TLC was taken. After 60 seconds completion of the reaction was seen by TLC. Precipitation in the resulting solution started and the flask was allowed to stand overnight in refrigerator for complete precipitation.

The mixture was filtered under suction on a Buchner funnel, washed with cold water to remove completely any remaining alkali and dried under vaccum pump. The crude product was recrystallised several times from methanol to give pure dibenzylideneacetone **3** , (2.2 g, 95.65%), melting point 110-112°C (Lit.[169] 112°C).



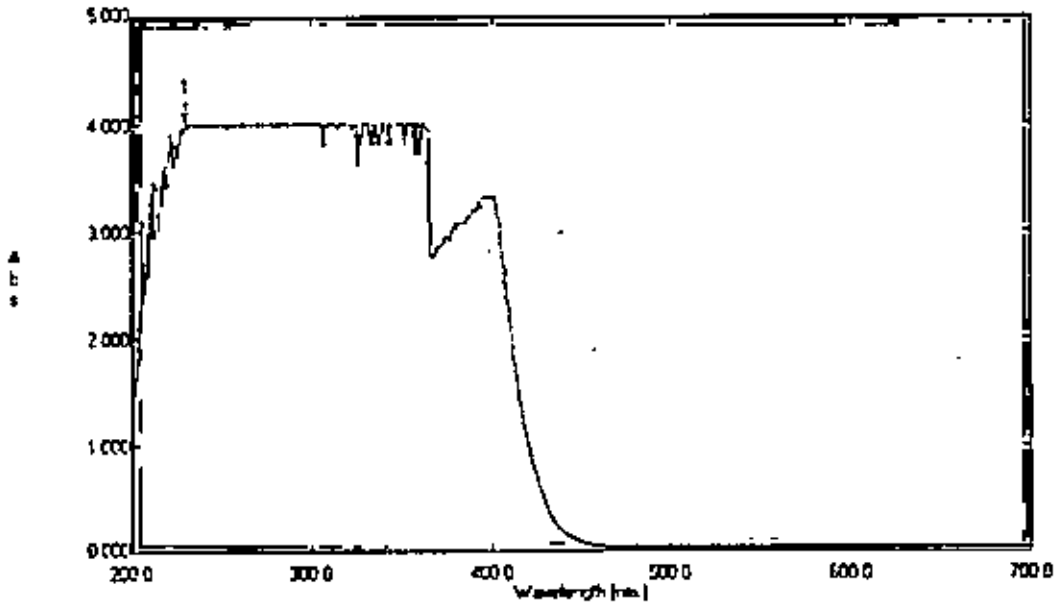
Dibenzylideneacetone

The UV **(Fig. 09)** spectrum of the compound 3 had absorption band at λ_{max} 230 nm due to $\pi \longrightarrow \pi^*$ transition of the C=C-C=O system.

The IR **(Fig. 10)** spectrum (nujol) of the compound 3 had absorption band at ν_{max} 1662 (C=C stretching), 1600 (C=O stretching), 1590 (Aromatic hydrocarbon C=C stretching), and 770 (C-H deformation out of plane) cm^{-1}.

The ^1H NMR **(Fig. 11)** spectrum ($CDCl_3$) of the compound 3 had had a multiplet at δ (ppm): 7.28 (m, 10H, Aromatic), 7.5 (d 2H, ethylene, E), 6.67 (d, 2H, ethylene, Z).

The ^{13}C NMR (Fig. 12) spectrum ($CDCl_3$) of the compound 3 had δ (ppm): 188.9 (carbonyl carbon), 143 (ethylene carbon), 134 (ethylene carbon), 130 (Ar-C-ethylene), 125 (Ar CH).



File Name: NZ003

Created: 11:45 05/08/06
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.5

Nn.	Wavelength (nm.)	Abs.
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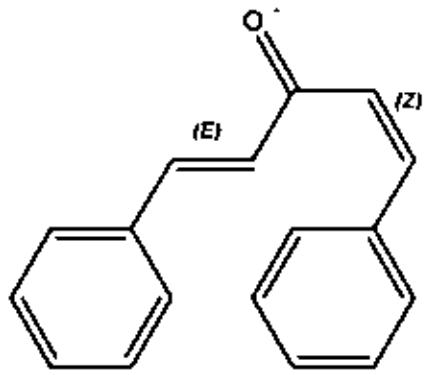


Dibenzylideneacetone

Figure: 09

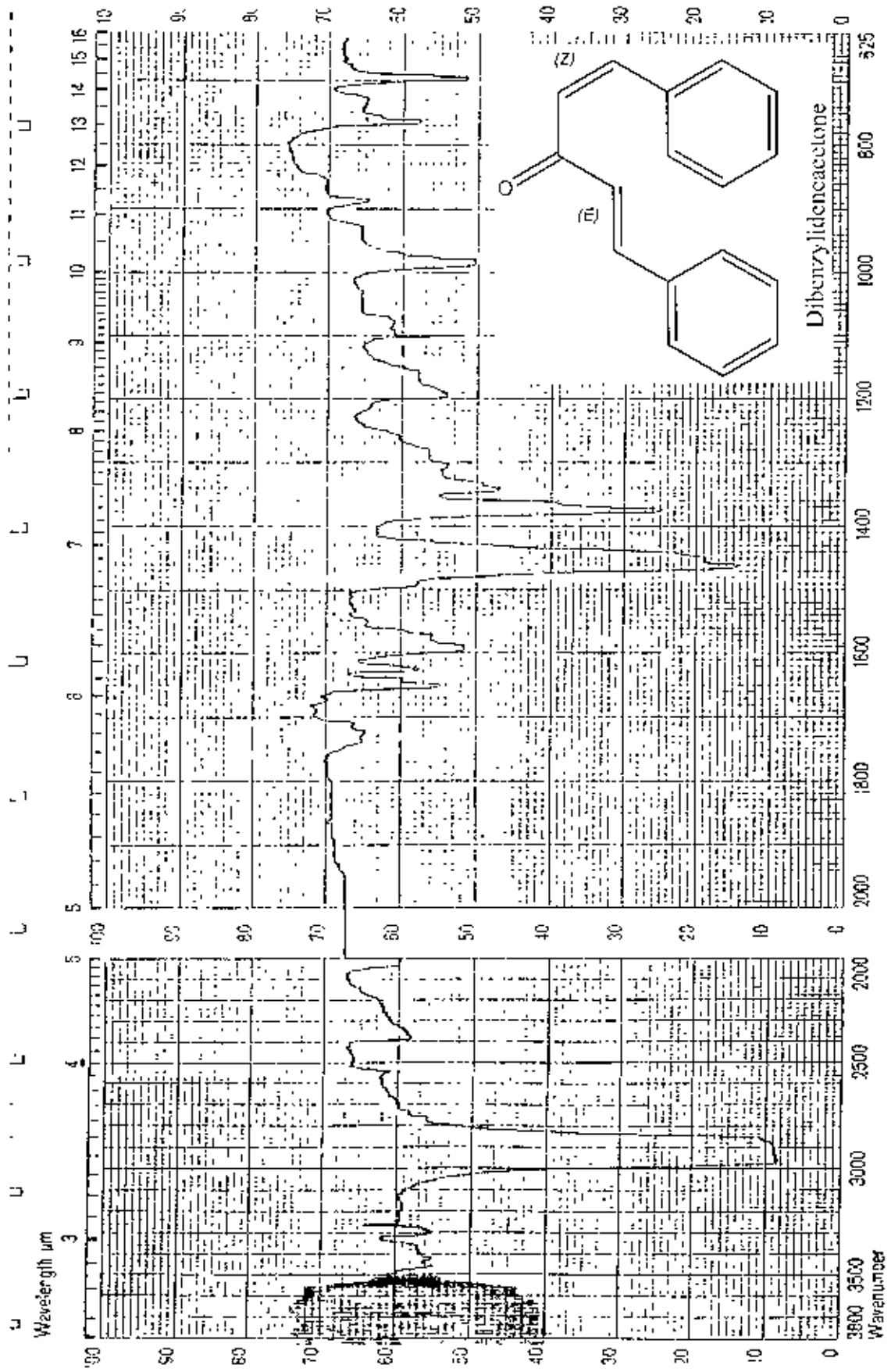


Figure: 10

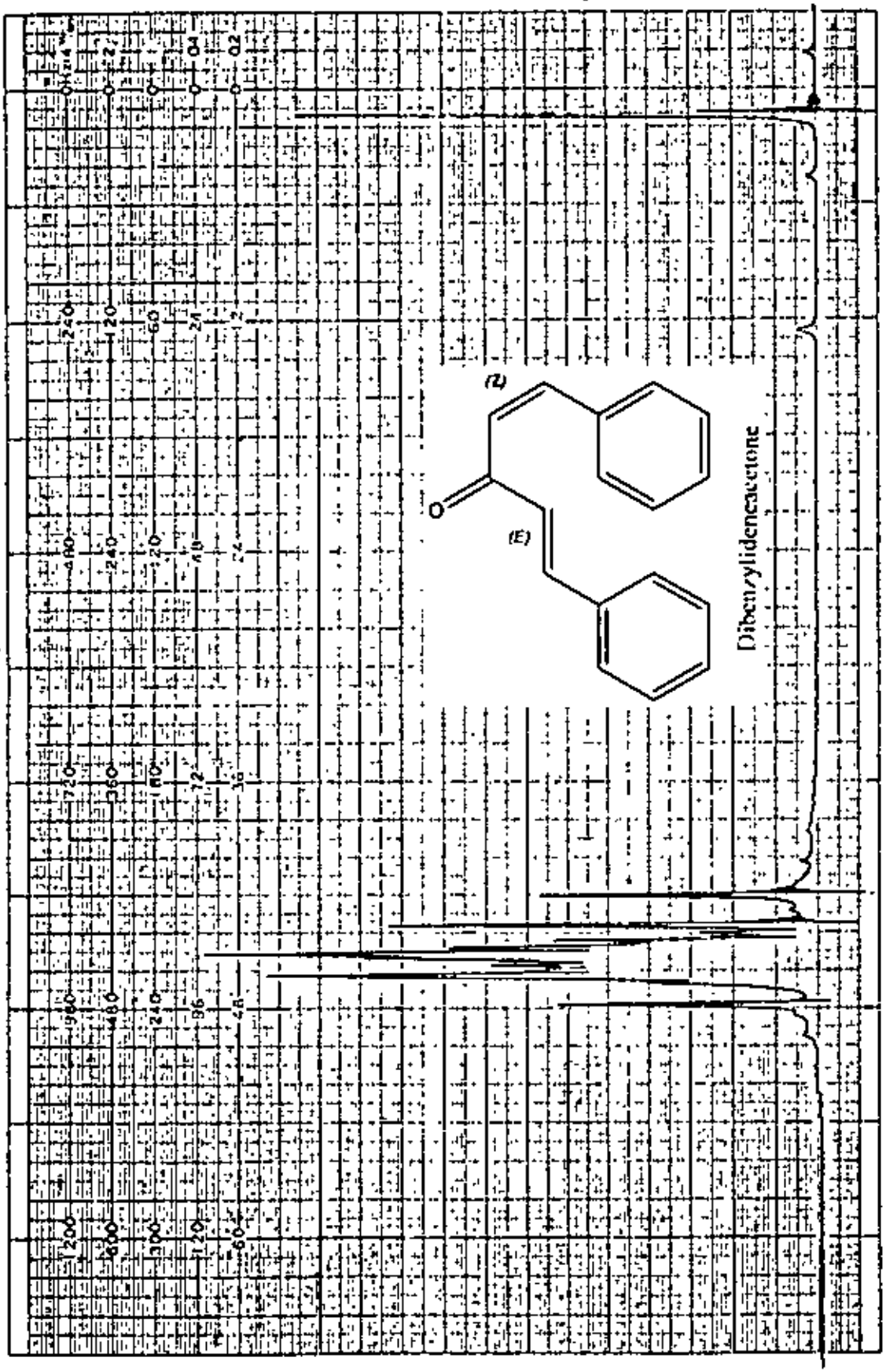


Figure: 11

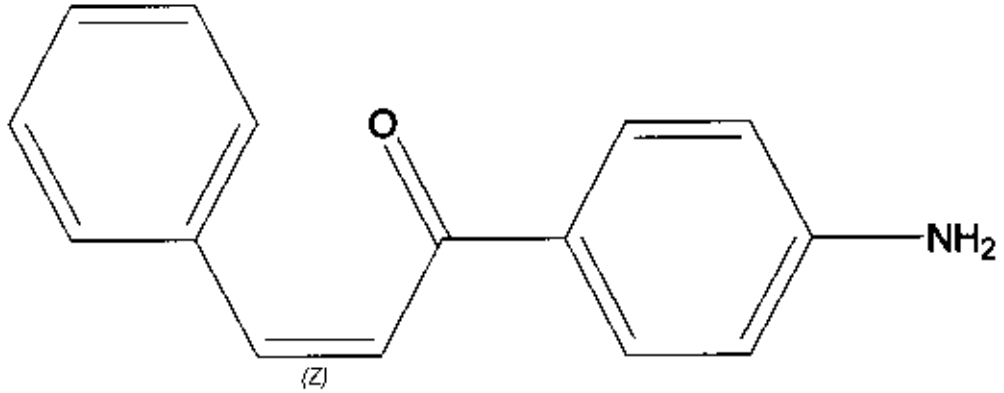
Figure: 12

5.2.4 Preparation of Benzylidene-p-aminoacetophenone 4

p-Aminoacetophenone (1.352 g, 0.01 mole) and benzaldehyde (1.06 ml, 0.01 mole) were dissolved in methanol (13.5 ml, 0.42 mole) in two separate conical flasks. The two solutions were allowed to mix quickly and then freshly prepared sodium hydroxide solution (10%, 0.68 ml, 0.017 mole) was added drop wise to it. The reaction was carried out in a special microwave assisted glass ware. Then the mixture was kept on the Microwave oven with a separate beaker of ice. The microwave was set at 600 Wt and the reaction was started in15 seconds duration. The colour of the mixture turned yellow within15 seconds.

Irradiation was continued for 4 minutes in total with intervals for monitoring the reaction by TLC. TLC when the reaction was complete as shown in TLC, The appearance of precipitate was observed in the reaction mixture and the flask was allowed to stand overnight in refrigerator for complete precipitation.

The mixture was filtered under suction on a Buchner funnel, washed with cold water to remove completely any remaining alkali and dried under vacuum pump. The crude product was crystallized several times from methanol to give pure benzylidene-p-aminoacetophenone 4 , (2.320 g, 96.19%), melting point 165-166°C.



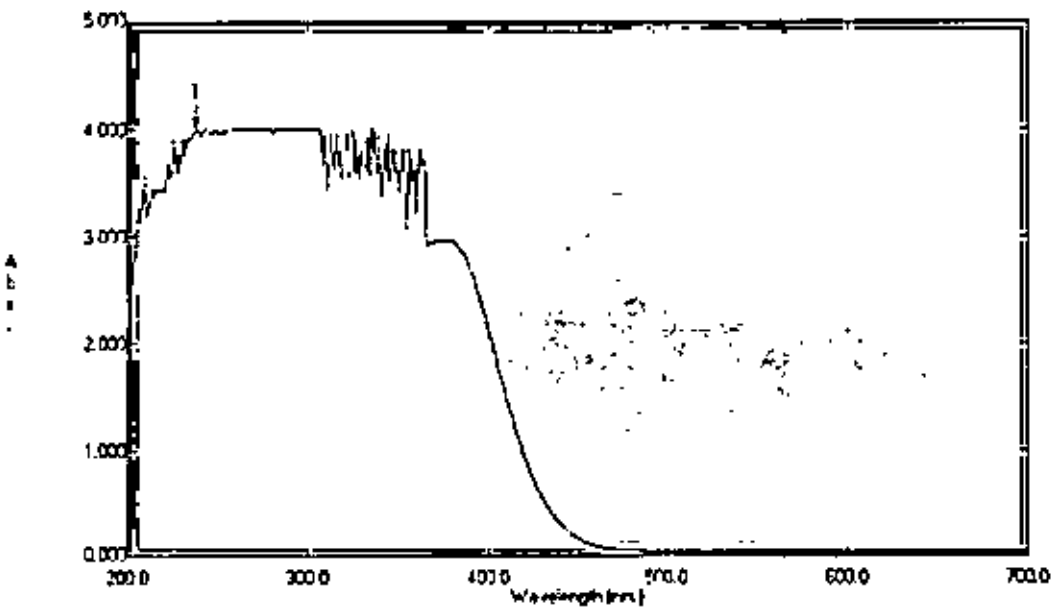
Benzylidene-p-aminoacetophenone

The UV **(Fig. 13)** spectrum of the compound 4 had absorption band at λ_{max} 237 nm due to $\pi \longrightarrow \pi^*$ transition of the C=C-C=O system.

The IR **(Fig. 14)** spectrum (KBr) of the compound 4 had absorption band at ν_{max} 3352 (-N-H stretching, hydrogen bonded), 1652 (C=O stretching), 1595 (aromatic hydrocarbon C=C stretching), 1523 (>N-H often too weak to be noticed) cm^{-1}.

The ^1H NMR (Fig. 15, 16) spectrums ($CDCl_3$) of the compound 4 had signals at δ (ppm): 7.88-7.78 (m, 5H, aromatic), 7.70 (d, 1H, ethylene, Z), 7.58 (d, 1H, ethylene, Z), 7.52-7.46 (m, 5H, benzene-NH_2), 3.35 (s, 2H, aromatic C-NH).

The ^{13}C NMR (Fig. 17, 18) spectrum of the compound 4 had signals at δ (ppm): 171.6 (carbonyl carbon), 151.09 (ethylene carbon, Z), 143.16 (ethylene carbon-CO, Z), 131 (Ar-C-NH_2), 130 (Ar-CH), 128 (Ar C), 126 (Ar CH), 122-112 (Ar CH).



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Measuring Mode: Abs.
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Slit Width: 2.0
Sampling Interval: 0.5

No.	Wavelength (nm.)	Abs.
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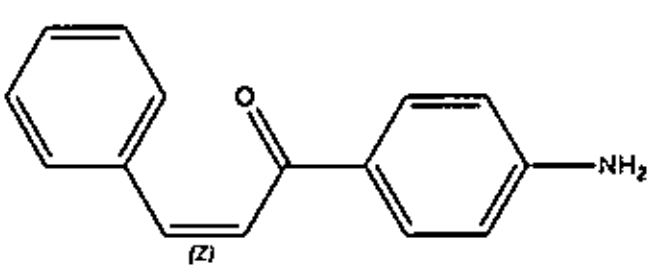


Benzylidene-p-aminoacetophenone

Figure: 13

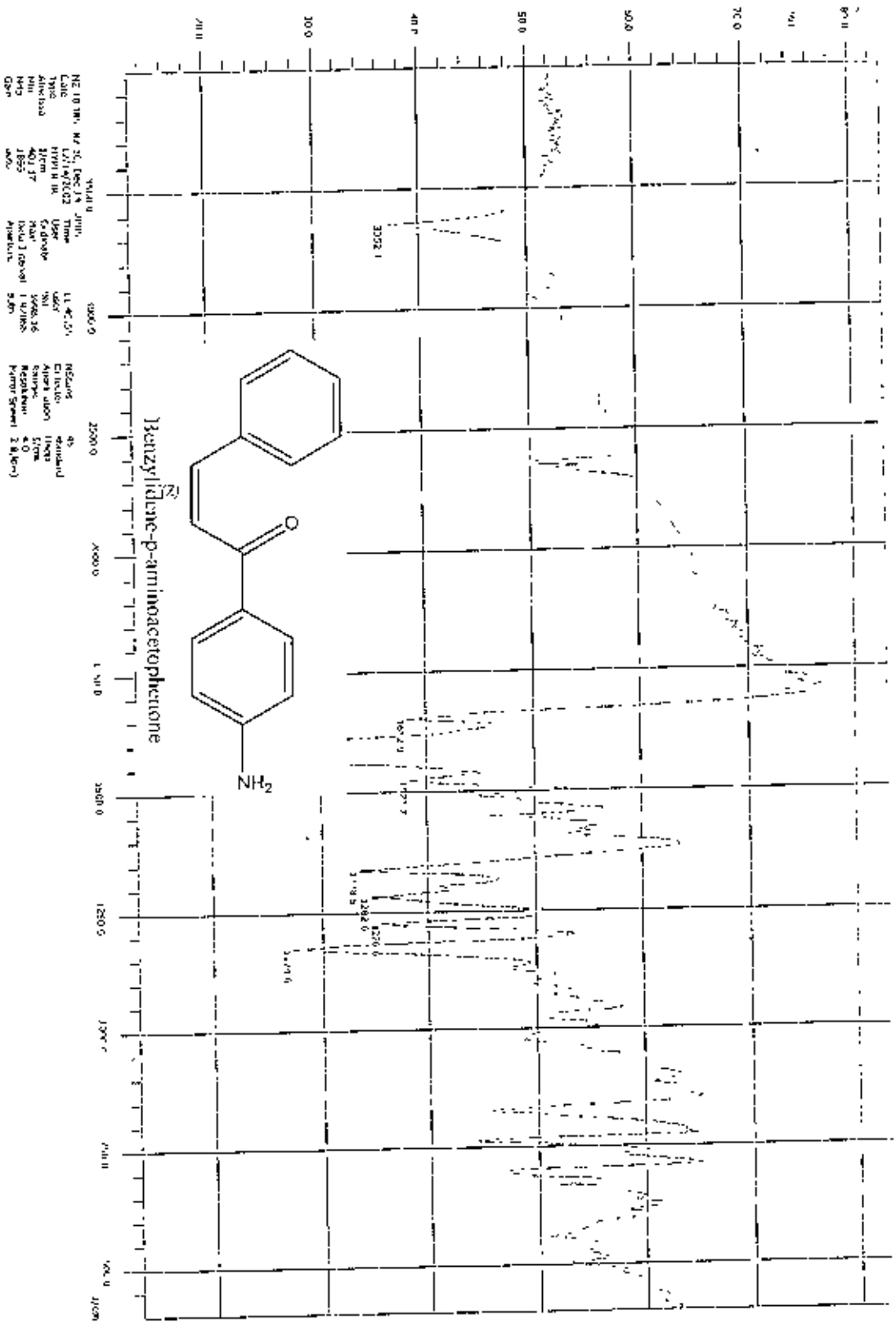


Figure: 14

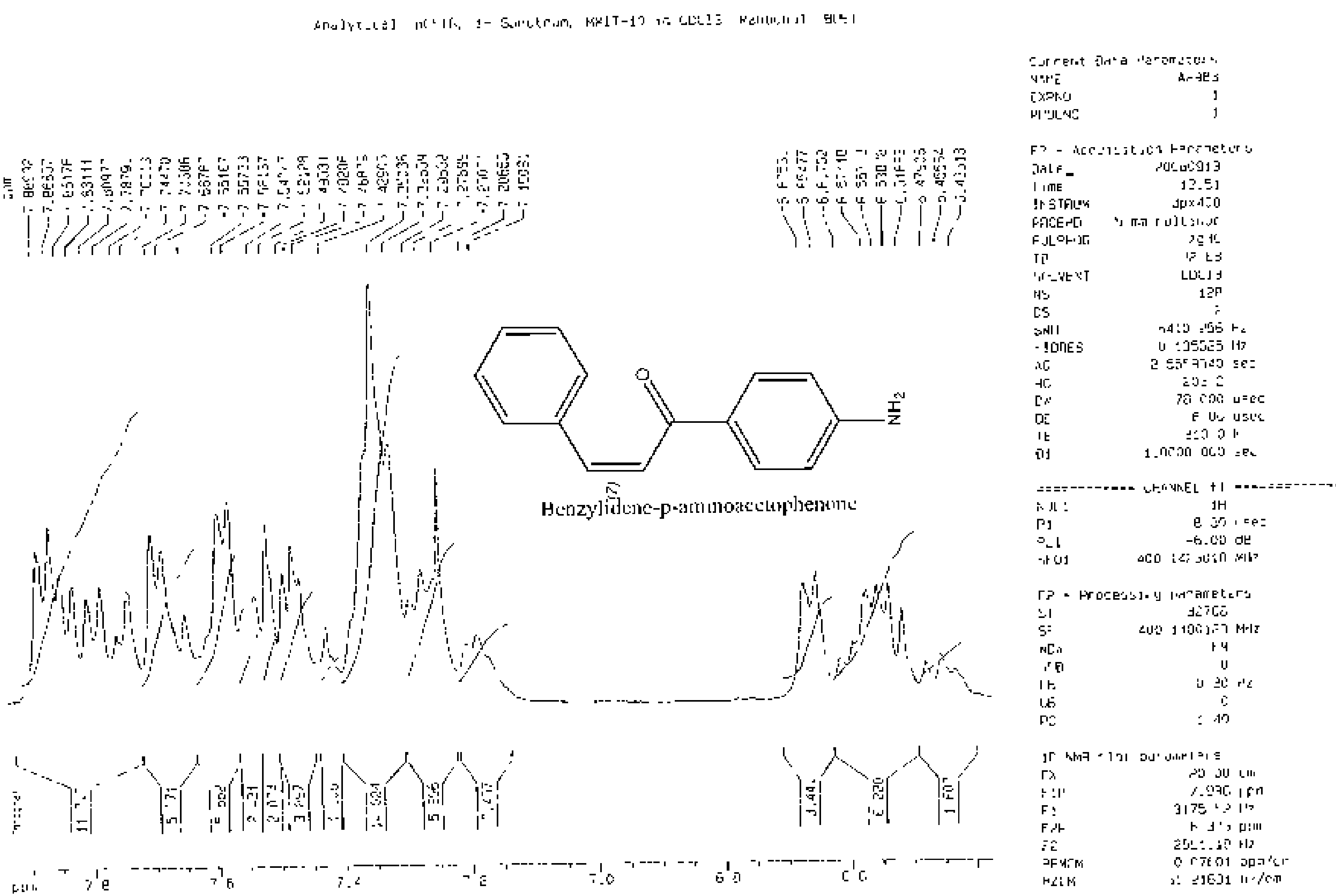

Benzylidene-p-aminoacetophenone
NH_2
Current Data Parameters
F2 - Acquisition Parameters
F2 - Processing parameters
1D NMR plot parameters
CHANNEL f1

Figure: 15

Figure: 16

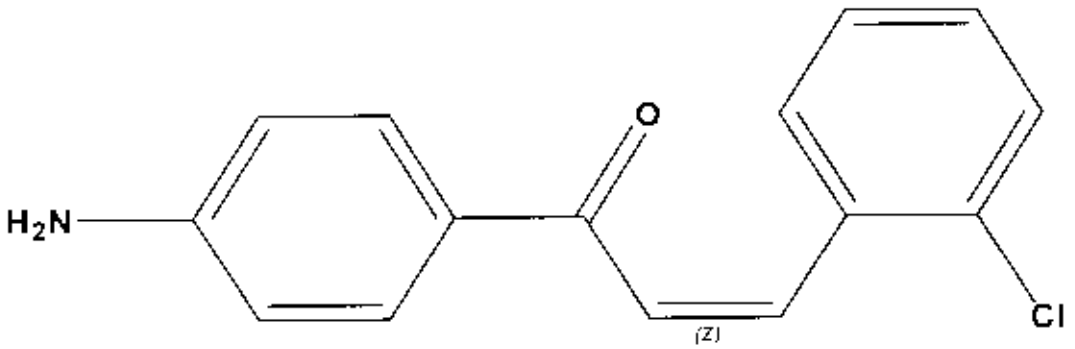
Figure: 17

Figure: 18

5.2.5 Preparation of o-Chlorobenzylidene-p-aminoacetophenone 5

p-Amino Acetophenone (1.352 g, 0.01 mole) and o-Chloro Benzaldehyde (1.41 ml, 0.01 mole) were dissolved in methanol (13.5 ml, 0.42 mole) in two separate conical flasks. The two solutions were mixed quickly in a special microwave assisted glass ware. Then freshly prepared sodium hydroxide solution (10%, 0.68 ml, 0.017 mole) was added drop wise to it. Then it was kept in the Microwave oven with a separate beaker of ice. When NaOH solution had been added drop wise, the mixture became dark brawn colored solution. The microwave was set at 600 Watt and run for to 2:00 minutes and at on interval of 30 seconds TLC was taken The resulting solution then started to precipitate and was allowed to stand overnight in refrigerator for complete precipitation.

The mixture was filtered under suction on a Buchner funnel, washed with cold water to remove completely any remaining alkali and dried under vacuum pump. The crude product was crystallized several times from methanol to give pure o-Chlorobenzylidene-p-aminoacetophenone 5, (2.76 g, 99.9%), melting point 170-171°C.

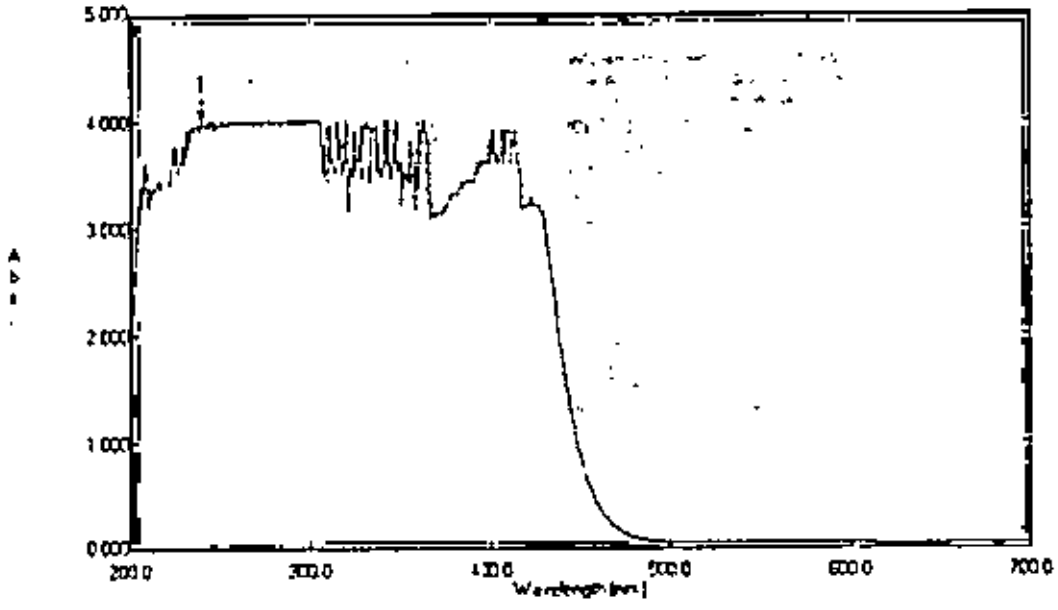


o-Chlorobenzylidene-p-aminoacetophenone

The UV **(Fig. 19)** spectrum of the compound 5 had absorption band at λmax 239 nm due to $\pi \longrightarrow \pi^*$ transition of the C=C-C=O system.

The IR **(Fig. 20)** spectrum (KBr) of the compound 5 had absorption band at ν_{max} 3388 (N-H stretching hydrogen bonded), 1600 (C=O stretching), 1595 (aromatic hydrocarbon C=C stretching), 1492 (ethylene C=C stretching), 1271 (C-N stretching), and 756 (C-Cl stretching) cm^{-1}.

The ^1H NMR **(Fig. 21)** spectrums ($CDCl_3$) of the compound 5 had signals at δ (ppm): 7.92-7.78 (m, 4H, benzene-NH_2), 7.50 (d, 1H, ethylene, Z), 7.43 (d, 1H, ethylene, Z), 7.39-7.31 (m, 4H, benzene-Cl), 4.19 (s, 2H, aromatic c-NH_2).



File Name: NZ014

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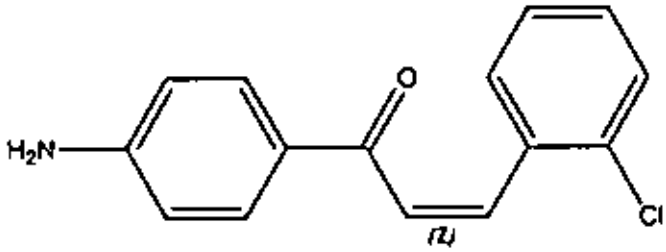
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.5

No.	Wavelength (nm.)	Abs.
1	239.50	3.9999



o-chlorobenzylidene-p-aminoacetophenone

Figure: 19

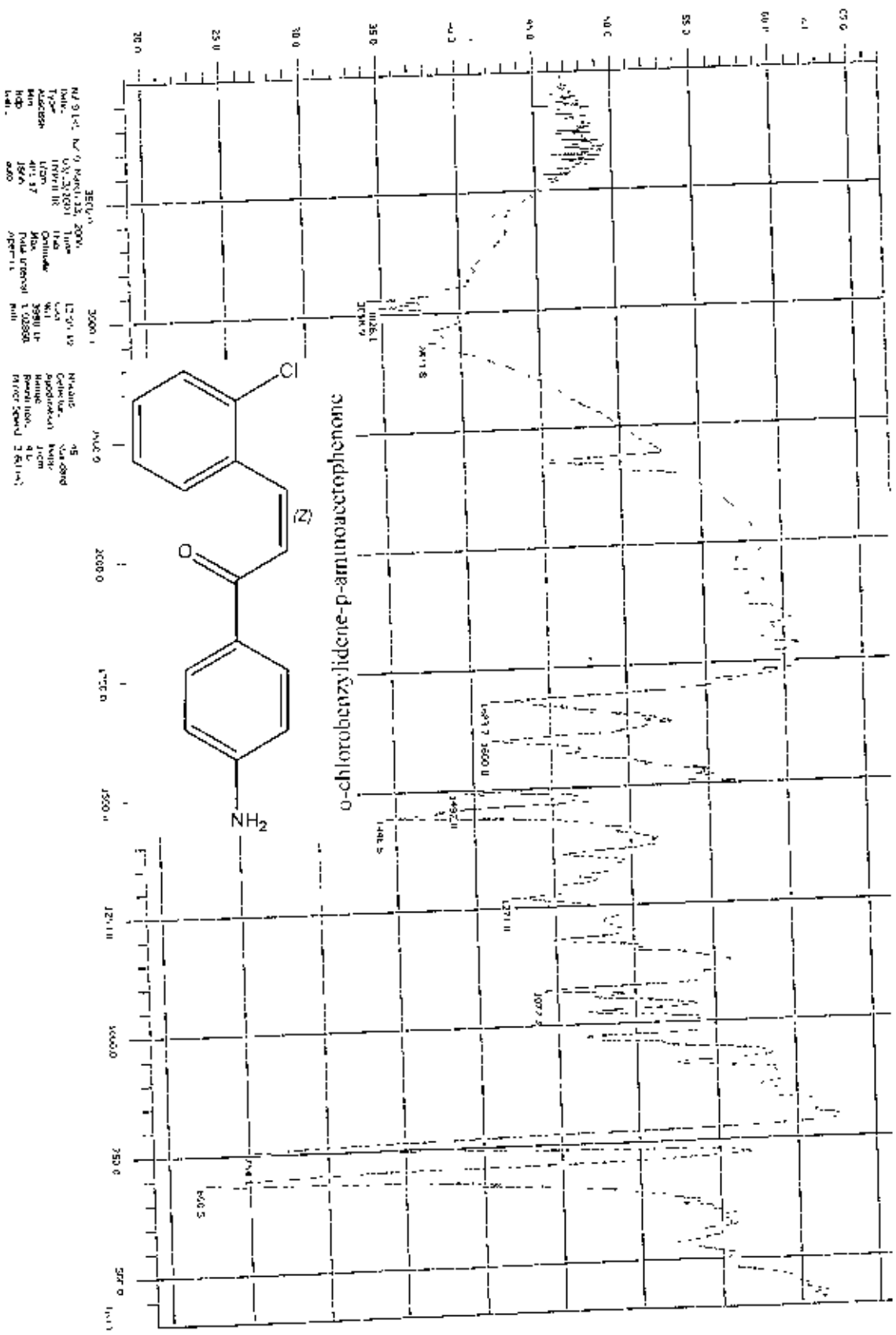


Figure: 20

o-chlorobenzylidene-p-aminoacetophenone
NH2
O
Cl
Integral

Figure: 21

5.3 Preparation of Pyrazolines

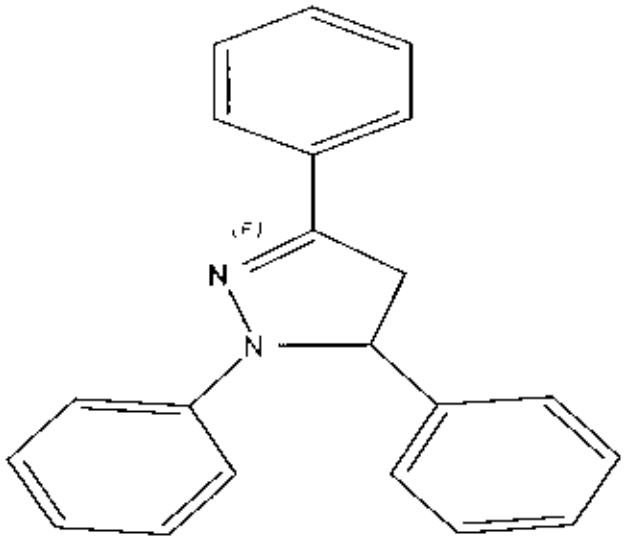
5.3.1 1,3,5-Triphenyl-2-pyrazoline 6

Benzylideneacetophenone (2.081 g, 0.01 mole) and phenylhydrazine hydrochloride (1.446 g, 0.01 mole) were taken in a 50 ml ground joint flask to which isopropanol (12.99 ml, 0.22 mole) was added. The reaction was carried out in a special microwave assisted glass ware. Then the mixture was taken on the Microwave oven and one beaker of ice was also put. The microwave was set at 600 Wt and the reaction was started gradually in 15 seconds duration. The progress of the reaction was followed by TLC (methanol : chloroform 3 : 2). On the starting of the reaction in micro wave the color of the reaction mixture initially appeared as light yellow and gradually heating turned the solution to orange colour then to deep brown at the end of 1:00 minute.

Heating was continued for more 1:00 minute on MW at 600 Wt. The solution color became more deep brown and the reaction was followed by TLC. After 3:00 minutes, the reaction was found to be complete as shown by TLC.

The resulting solution then started to precipitate and was allowed to stand overnight in refrigerator for complete precipitation..

Light yellowish crystals were filtered under suction on a Buchner funnel and dried under vacuum pump. The crude product was recrystallized form methanol to give pure 1, 3, 5-Triphenyl-2-pyrazoline 6 (3.491 g, 98.99%), melting point, 135-136°C (Lit.[170] 136°C). The compound was homogeneous (R_f 0.67) on TLC (methanol : chloroform 3 : 2).



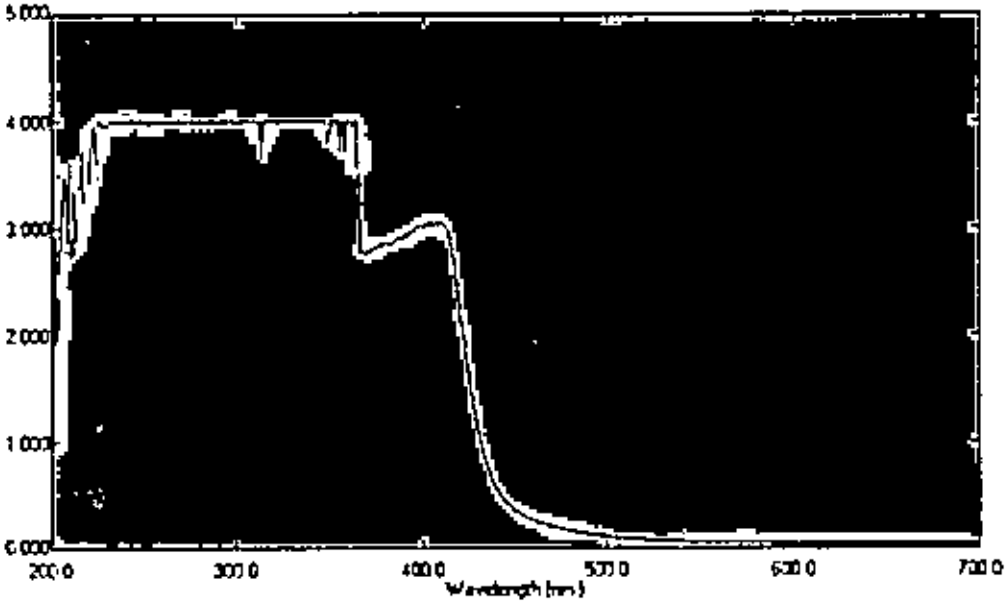
1,3,5-Triphenyl-2-pyrazoline

The UV **(Fig. 22)** spectrum of the compound 6 showed absorption maxima λ_{max} at 356 and 242 nm due to $\pi \rightarrow \pi^*$ transition.

The IR **(Fig. 23)** spectrum (nujol) of the compound 6 had absorption bands at ν_{max} 1590 (aromatic hydrocarbon C=C stretching and 750 (5 adjacent aromatic C-H) cm^{-1}.

The ^1H NMR **(Fig. 24)** spectrum ($CDCl_3$) of the compound 6 had signals at δ (ppm): 7.18 (m, 15H, aromatic), 5.21 (dd, 1H, methine, CH) and 3.40 (m, 2H, methylene, CH_2).

The ^{13}C NMR **(Fig. 25, 26)** spectrum ($CDCl_3$) of the compound 6 had signals at δ (ppm): 144.2 (imine carbon), 130 (Ar C), 129 (Ar C), 128.08 (Ar CH), 126 (Ar C), 119 (Ar CH), 113 (Ar CH), 42.2 (ethylene carbon, CH_2).



File Name: NZ004

Created: 11:48 05/08/06
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.5

No.	Wavelength (nm.)	Abs.
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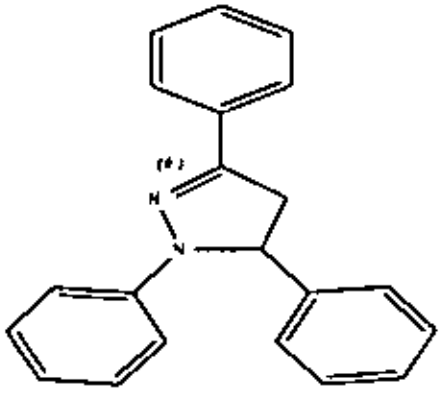
2	242	3.999



1,3,5-triphenyl-2-pyrazoline

Figure: 22

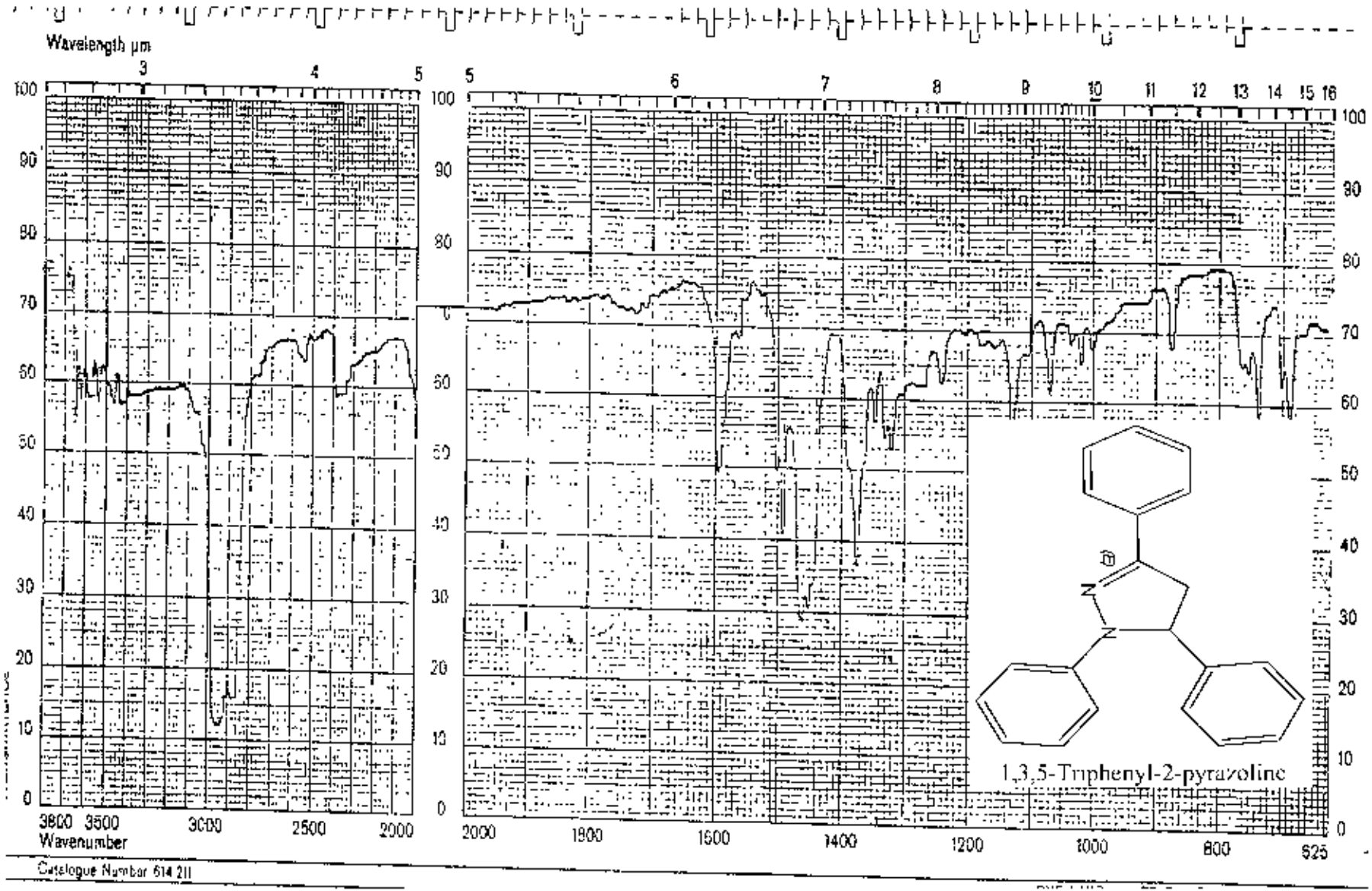

Wavelength µm
3
4
5
6
7
8
9
10
11
12
13
14
15
16
100
90
80
70
60
50
40
30
20
10
0
3800
3500
3000
2500
2000
Wavenumber
2000
1800
1600
1400
1200
1000
800
625
1,3,5-Triphenyl-2-pyrazoline
N
N
Catalogue Number 614 211

Figure: 23

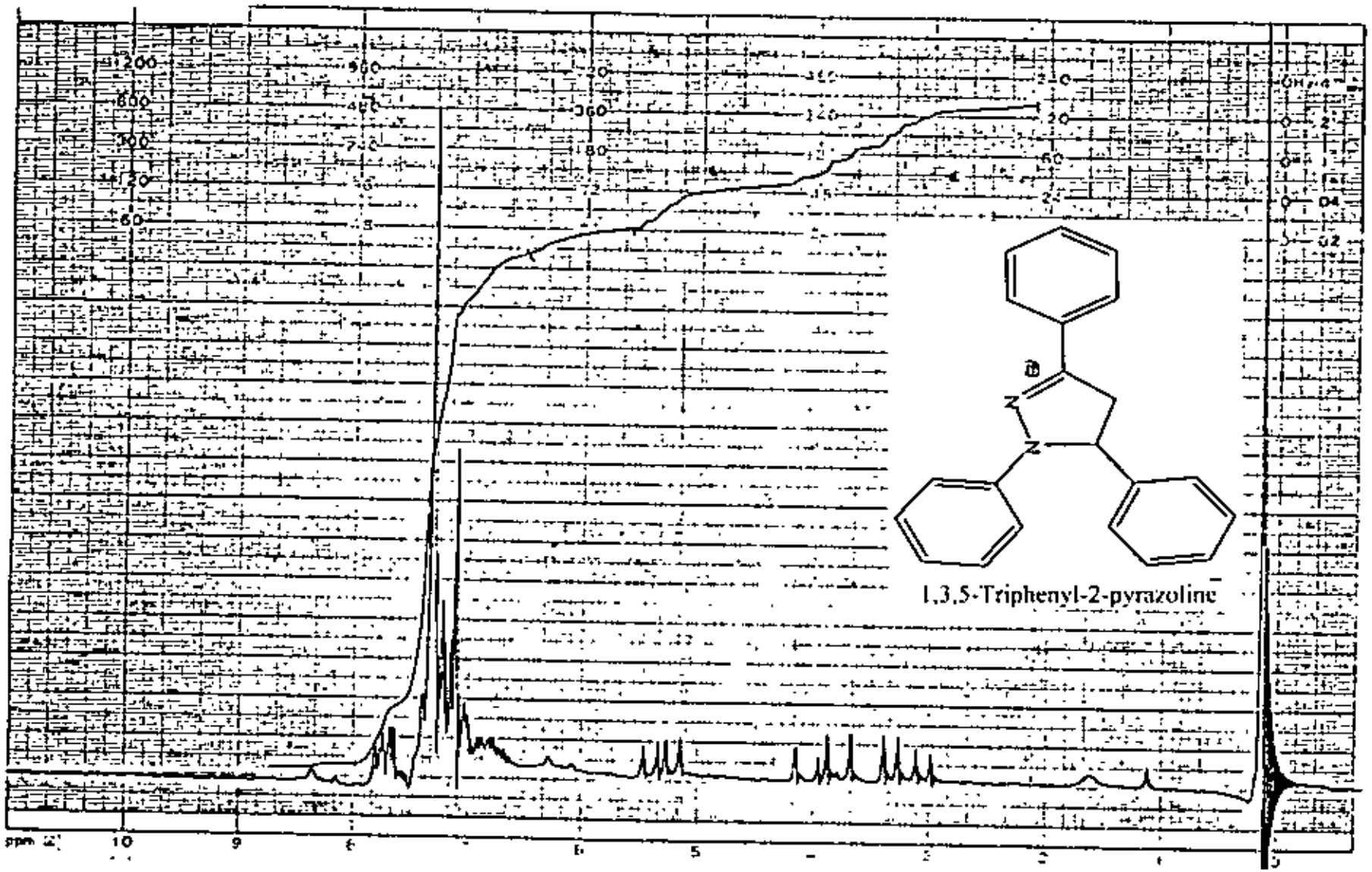


Figure: 24

Figure: 25

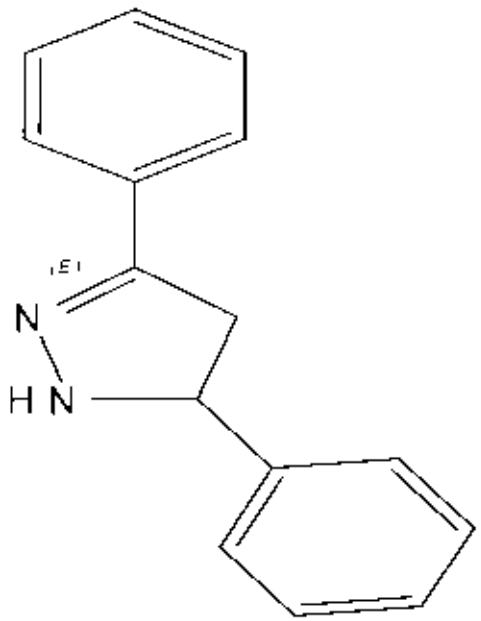
Figure: 26

5.3.2 3, 5-diphenyl-2-pyrazoline 7

Benzylideneacetophenone (2.081 g, 0.01 mole) and hydrazine hydrochloride (0.69 ml, 0.01 mole) were mixed in a special flask where isopropanol (12.99 ml, 0.22 mole) was added. The flask of the mixture was put on the Microwave oven and a beaker of ice was kept beside it. Microwave was set at 600 Wt for 15 seconds duration The progress of the reaction was followed by TLC (methanol : chloroform 3 : 2).

The reaction mixture was heated on MW at 450 Watt for about 1 minute. The solution color did not change. Irradiation was continued for 2.5 minutes. The resulting solution then started to from precipitate and was allowed to stand overnight in refrigerator for complete precipitation. Precipitate from fridge is white in colour but soon became brownish.

White crystals were filtered under suction on a Buchner funnel and dried under vaccuum pump. The crude product was recrystallized form methanol to give pure 3, 5-diphenyl-2-pyrazoline 7 (2.51 g, 90.58%), melting point, 162-163°C (Lit.[7] 163°C). The compound was homogeneous (R_f 0.66) on TLC (methanol : chloroform 3 : 2).



3, 5-diphenyl-2-pyrazoline

The IR **(Fig. 27)** spectrum (KBr) of the compound 7 had absorption bands at ν_{max} 3328.9 (N-H stretching), 1651 (m, N-H deformation) 1579 (aromatic hydrocarbon C=C stretching), 1519 (N-H deformation, w), 1357 C-H deformation) and 1278 .7 (C-N stretching) cm^{-1}.

The ^1H NMR **(Fig. 28, 29, 30)** spectrum ($CDCl_3$) of the compound 7 had signals at δ (ppm): 7.95 (s, 1H, NH), 7.18 (m, 10H, aromatic), 4.6-5 ppm (dd, 1H, CH) and 3.40 ppm (m, 2H, CH_2).

The ^{13}C NMR **(Fig. 31, 32)** spectrum of the compound 7 had signals at δ (ppm): 153 (imine carbon), 148 (Ar C), 128 .4 (Ar CH), 133 (Ar C), 128.5 (Ar CH), 42.9 (methine, CH carbon) and 31 (ethylene carbon, CH_2).

Figure: 27

Figure: 28

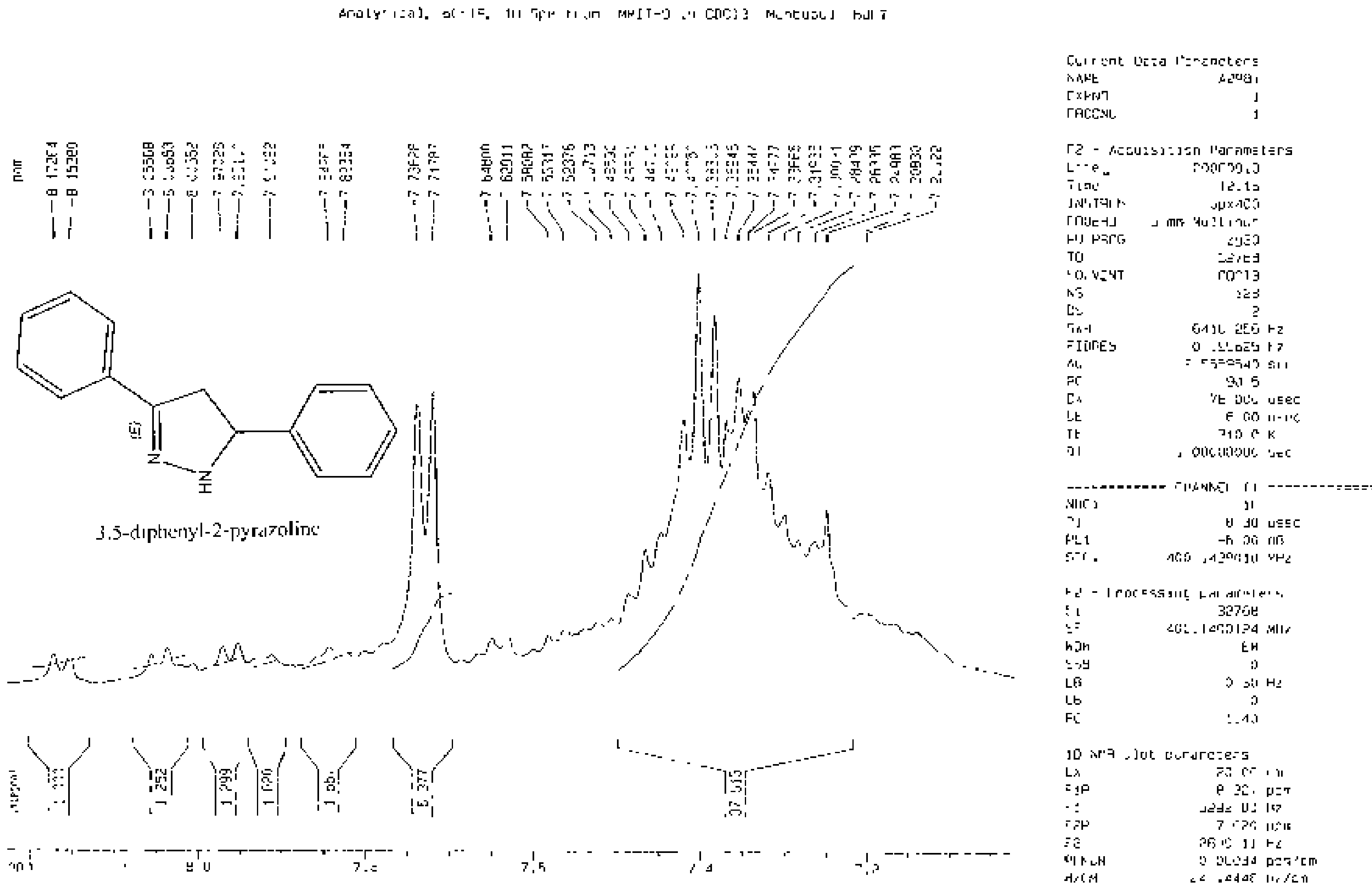

3,5-diphenyl-2-pyrazoline
HN
N
(E)
Current Data Parameters
F2 - Acquisition Parameters
CHANNEL f1
F2 - Processing parameters
1D NMR plot parameters
ppm

Figure: 29

Figure: 30

Figure: 31

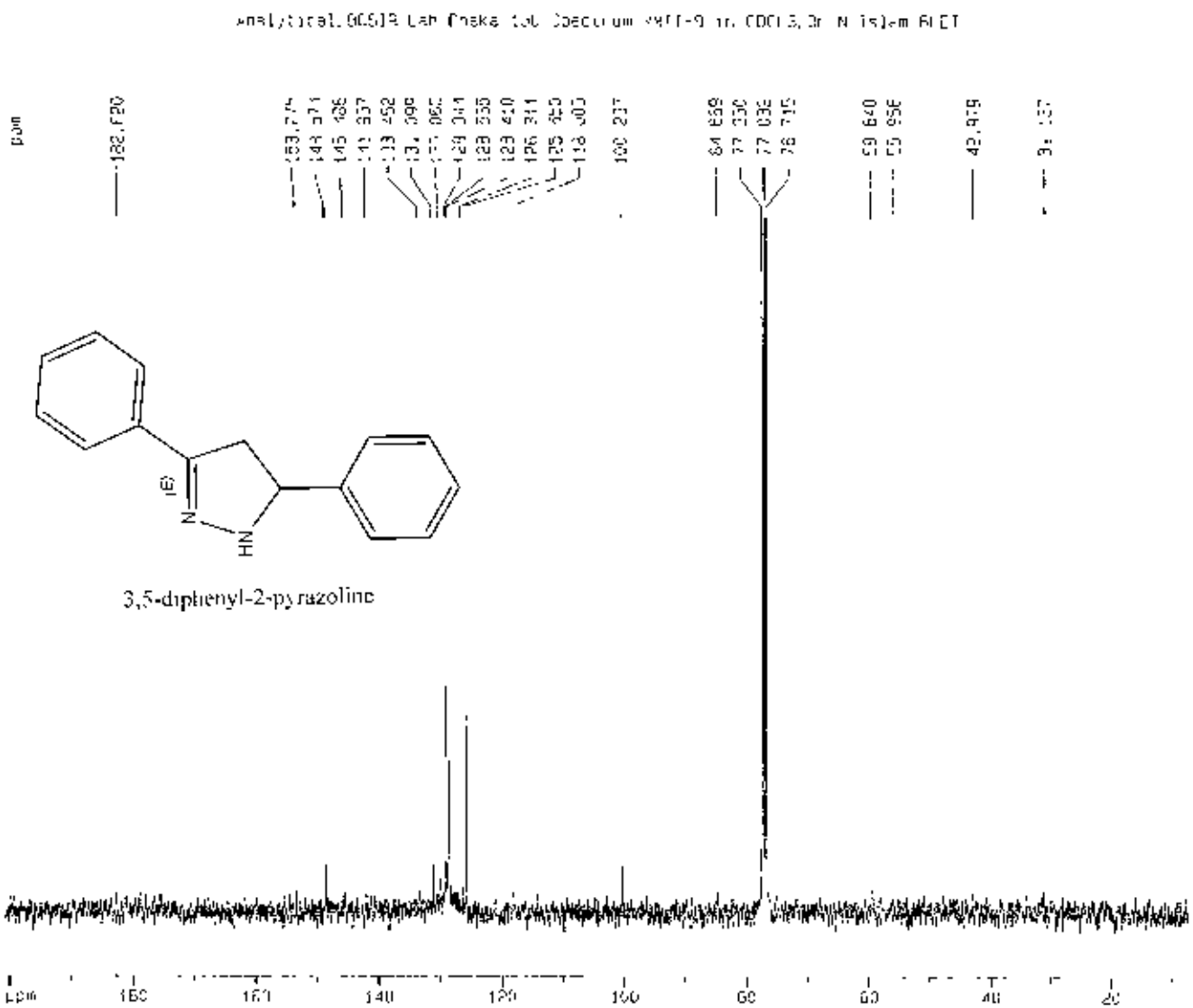

Analytical 060918 Lab Osaka lab Spectrum exp11-9 in CDCl3,3r N 1s1em 61 ET
ppm
182.720
153.774
148.371
145.486
141.937
133.452
131.998
129.344
128.535
128.410
126.311
125.455
118.303
100.237
64.659
77.330
77.032
76.715
59.640
55.956
42.979
31.137
3,5-diphenyl-2-pyrazoline
(E)
N
HN
ppm
180
160
140
120
100
80
60
40
20

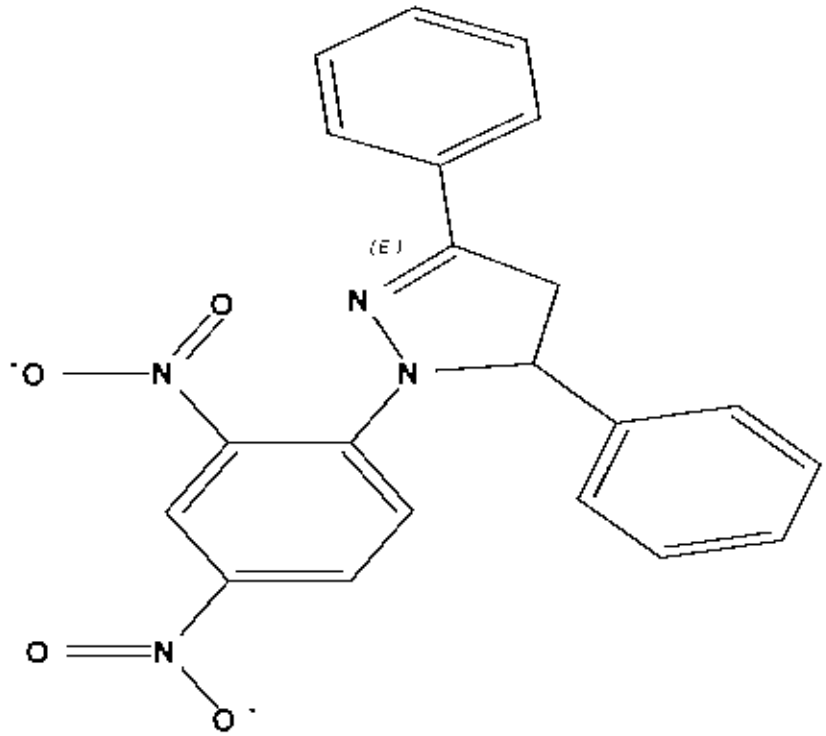
Figure: 32

5.3.3 1-(2, 4-dinitrophenyl)-3,5-diphenyl-2-pyrazoline **8**

Benzylideneacetophenone (2.081 g, 0.01 mole) and 2, 4-dinitro phenyl hydrazine (1.98 g, 0.01 mole) were taken in a flask. Isopropanol (12.99 ml, 0.22 mole) was also added in the flask. The mixture was put in the Microwave oven and one beaker of ice was also put. The microwave was set at 600 Wt and the irradiation was started. On the start of the reaction in microwave the color of the reaction mixture was initially light yellow and gradually getting heat it changed to orange and soon to deep brown within 30 seconds.

Then the reaction mixture again was irradiated on MW at 600 Wt for another 3.5 minutes. The reaction was monitored by TLC. In the end no colour change was found. The resulting solution then started to precipitate and was kept overnight in refrigerator for complete precipitation. Precipitate taken from the fridge was dark brown to light yellowish color.

Light yellowish crystals were filtered under suction on a Buchner funnel and dried under vacuum. The crude product was recrystallized form methanol to give pure 1-(2, 4-dinitrophenyl)-3,5-diphenyl-2-pyrazoline **8** (3.51 g, 98.90%), melting point, 142-143°C. The compound was homogeneous (R_f 0.70) on TLC (methanol : chloroform 3 : 2).



1-(2, 4-dinitrophenyl)-3,5-diphenyl-2-pyrazoline

The IR **(Fig. 33)** spectrum (KBr) of the compound 8 had absorption bands at ν_{max} 3421 (N-N stretching), 1610 (C-NO_2, N=O stretching), 1589 (aromatic hydrocarbon, C=C stretching), 1330 (C-H deformation), and 750 (C-H deformation out of plane) cm^{-1}.

The ^1H NMR **(fig. 34, 35)** spectrum ($CDCl_3$) of the compound 8 had signals at δ (ppm): 7.18 (m, 15H, aromatic), 6.5 (dd, 1H, methine, CH) and 3.40 (dd, 2H, methylene, CH_2).

The ^{13}C NMR **(Fig. 36, 37)** spectrum of the compound 8 had signals at δ (ppm): 168.7 (imine carbone), 144 (Ar C), 135 (Ar C-NO_2), 134 (Ar C-NO_2), 132 (Ar C-imine carbon), 129 (Ar CH), 128 (Ar CH), 122 (Ar CH) and 121 (Ar CH).

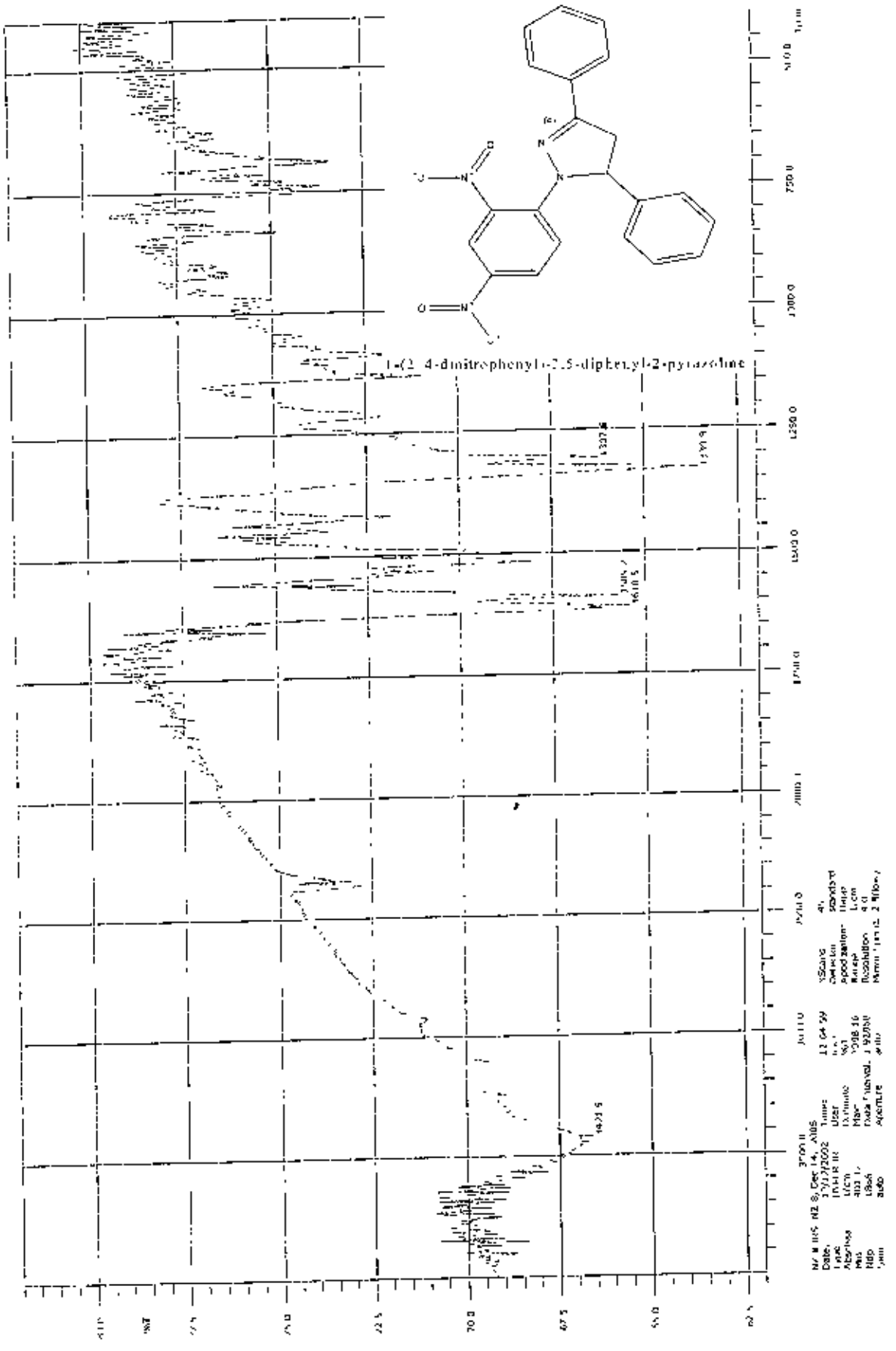


Figure: 33

Figure: 34

Figure: 35

Figure: 36

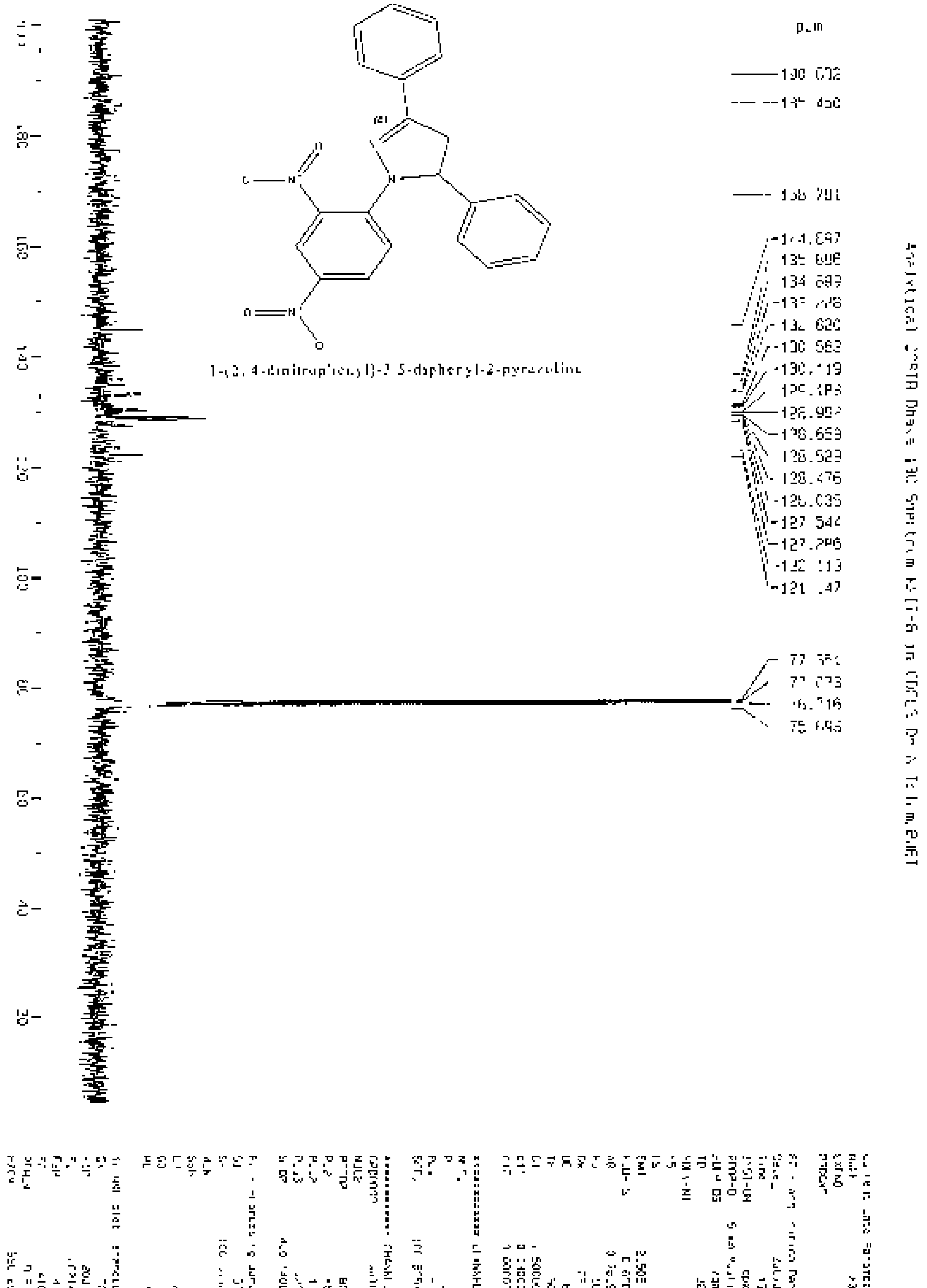


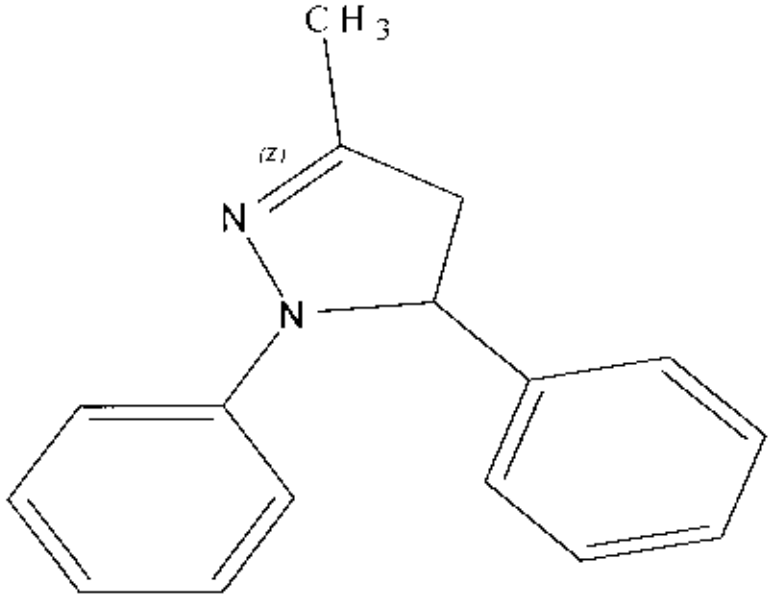
Figure: 37

5.3.4. 3-methyl-1, 5-diphenyl-2-pyrazoline 9

Benzylideneacetone (1.46 g, 0.01 mole) and phenylhydrazine hydrochloride (1.446 g, 0.01 mole) were taken in a 50 ml flask to which isopropanol (12.99 ml, 0.22 mole) was added. The reaction was carried out in a special microwave assisted glass ware. The mixture was kept in the Microwave oven and with another beaker of ice. The microwave was set at 600 Watt and the reaction was gradually started. The progress of the reaction was followed by TLC (methanol : chloroform 3 : 2). At the starting of the reaction in micro wave the color of the reaction mixture was initially light yellow and gradually getting heat it turned to orange. At the end of 2.5 minute it turned to deep brown.

To confirm that the reaction was over the solution was heated in Microwave oven for another 30 seconds but there was no change in color. The product from the reaction mixture solution started to precipitate and was put stand overnight in refrigerator for complete precipitation. Precipitate from the fridge was of dark brown to light yellowish color.

Light yellowish crystals were filtered under suction on a Buchner funnel and dried under vacuum pump. The crude product was recrystallized form methanol to give pure 3-methyl-1, 5-diphenyl-2-pyrazoline 9 (2.338 g, 97%), melting point, 115-116°C (Lit.[74] 114-115°C). The compound was homogeneous (R_f 0.71) on TLC (methanol : chloroform 3 : 2).



3-methyl-1, 5-diphenyl-2-pyrazoline

The IR **(Fig. 38)** spectrum (nujol) of the compound 9 had absorption bands at ν_{max} 1600 (C=N stretching in ring), 1590 (aromatic hydrocarbon C=C stretching), 1465 (C-N stretching), 1375 (C-H deformation in CH_3) and 750 (C-H deformation out of plane) cm^{-1}.

The ^1H NMR **(Fig. 39)** spectrum ($CDCl_3$) of the compound 9 had signals at δ (ppm): 7.18 (m, 10H, aromatic), 5.21 (dd, 1H, methine, CH), 3.40 (m, 2H, methylene, CH_2) and 2.35 (s, 3H, methane, CH_3).

The ^{13}C NMR **(Fig. 40, 41)** spectrum of the compound 9 had signals at δ (ppm): 144.8 (imine carbon), 138 (Ar C-N), 134 (Ar C-CH), 132 (Ar CH), 130 (Ar CH), 128 (Ar CH), 84.8 (CH) and 37 (CH_3).

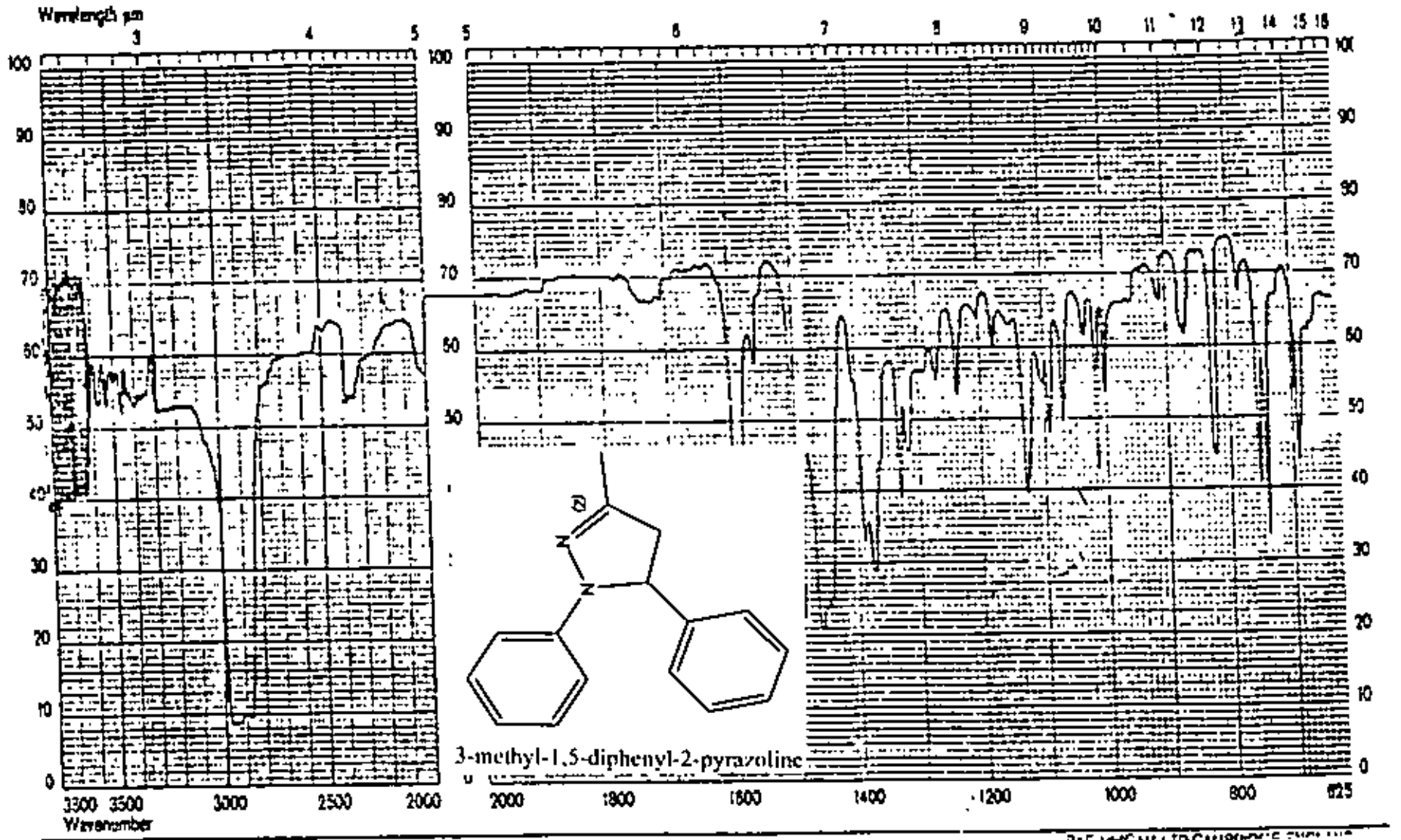

Wavelength µm
3
4
5
6
7
8
9
10
11
12
13
14
15
16
100
90
80
70
60
50
40
30
20
10
0
3300
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
625
Wavenumber
3-methyl-1,5-diphenyl-2-pyrazoline

Figure 3B

Figure: 39

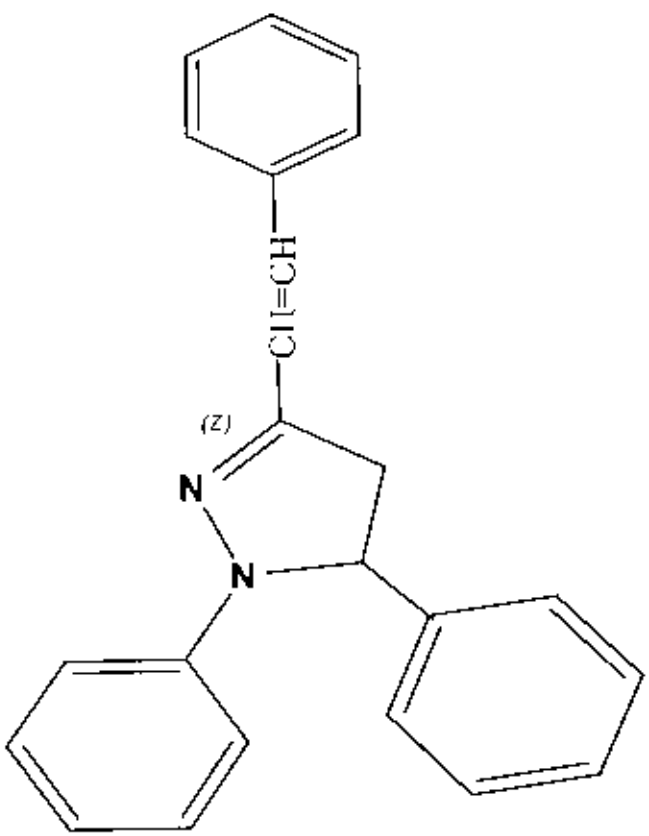
Figure: 40

Figure: 41

5.3.5 3-benzal-1,5-diphenyl-2-pyrazoline 10

A solution of dibenzylideneacetone (2.34 g, 0.01 mole) and phenyl hydrazine hydrochloride (1.446 g, 0.01 mole) were taken in a conical flask to which isopropanol (12.99 ml, 0.22 mole) was added. The mixture was kept in the microwave oven with a separate beaker of ice. The microwave was set at 600 watt and was switched on. The progress of the reaction was followed by TLC (methanol : chloroform 3 : 2).The irradiation was continued for about 4 minutes and at the end heating in Microwave oven another 30 seconds confirmed that the reaction was complete as there was no change in color.The resulting solution then started to precipitate and was allowed to stand overnight in refrigerator for complete precipitation. Precipitate from fridge was light yellowish color.

Light yellowish crystals were filtered under suction on a Buchner funnel and dried under vacuum pump. The crude product was recrystallized form methanol to give pure 3-benzal-1, 5-diphenyl-2-pyrazoline 10 (3.12 g, 95%), melting point, 151-152°C (Lit.[73] 152-153°C). The compound was homogeneous (R_f 0.70) on TLC (methanol : chloroform 3 : 2).



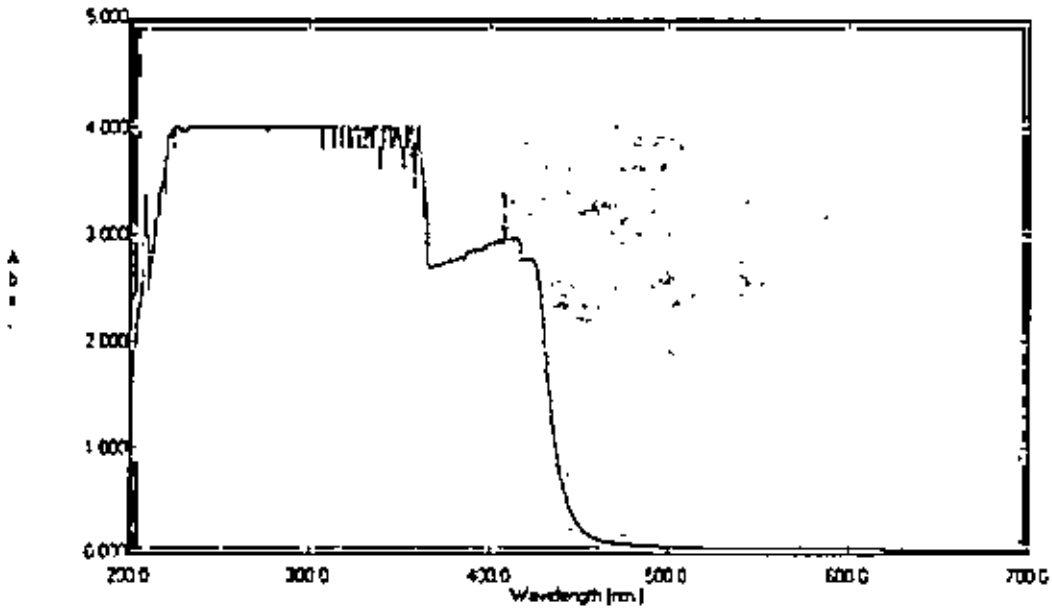
3-Benzal- 1,5-diphenyl-2-pyrazoline

The UV **(fig. 42)** spectrum of the compound 10 had absorption maxima λ_{max} at 408, 243 nm due to $\pi \rightarrow \pi^*$ transition.

The IR **(fig. 43)** spectrum (nujol) of the compound 10 had absorption bands at ν_{max} 1610 (C=C alkene stretching), 1600 (aromatic hydrocarbon C=C stretching) and 760 (C-H deformation out of plane) cm^{-1}.

The ^1H NMR **(Fig. 44)** spectrum ($CDCl_3$) of the compound 10 had signals at δ (ppm): 7.10 (m, 15H, aromatic), 7.3 (dd 2H, CH=CH), 5.21 (dd, 1H, methine, CH) and 3.32 (m, 2H, methylene, CH_2).

The ^{13}C NMR **(Fig. 45)** spectrum of the compound 10 had signals at δ (ppm): 143 (imine carbon), 130 (Ar C), 128 (Ar CH), 126 (Ar C), 119 (Ar CH), 54 (CH), 22 (CH_2) and 12 (CH=CH).



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Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.5

No.	Wavelength (nm.)	Abs.
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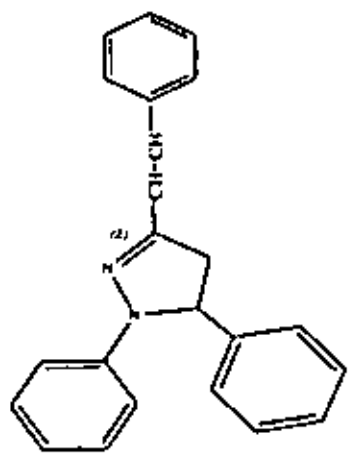
2	243.00	3.999



3-Benzal- 1,5-diphenyl-2-pyrazoline

Figure: 42

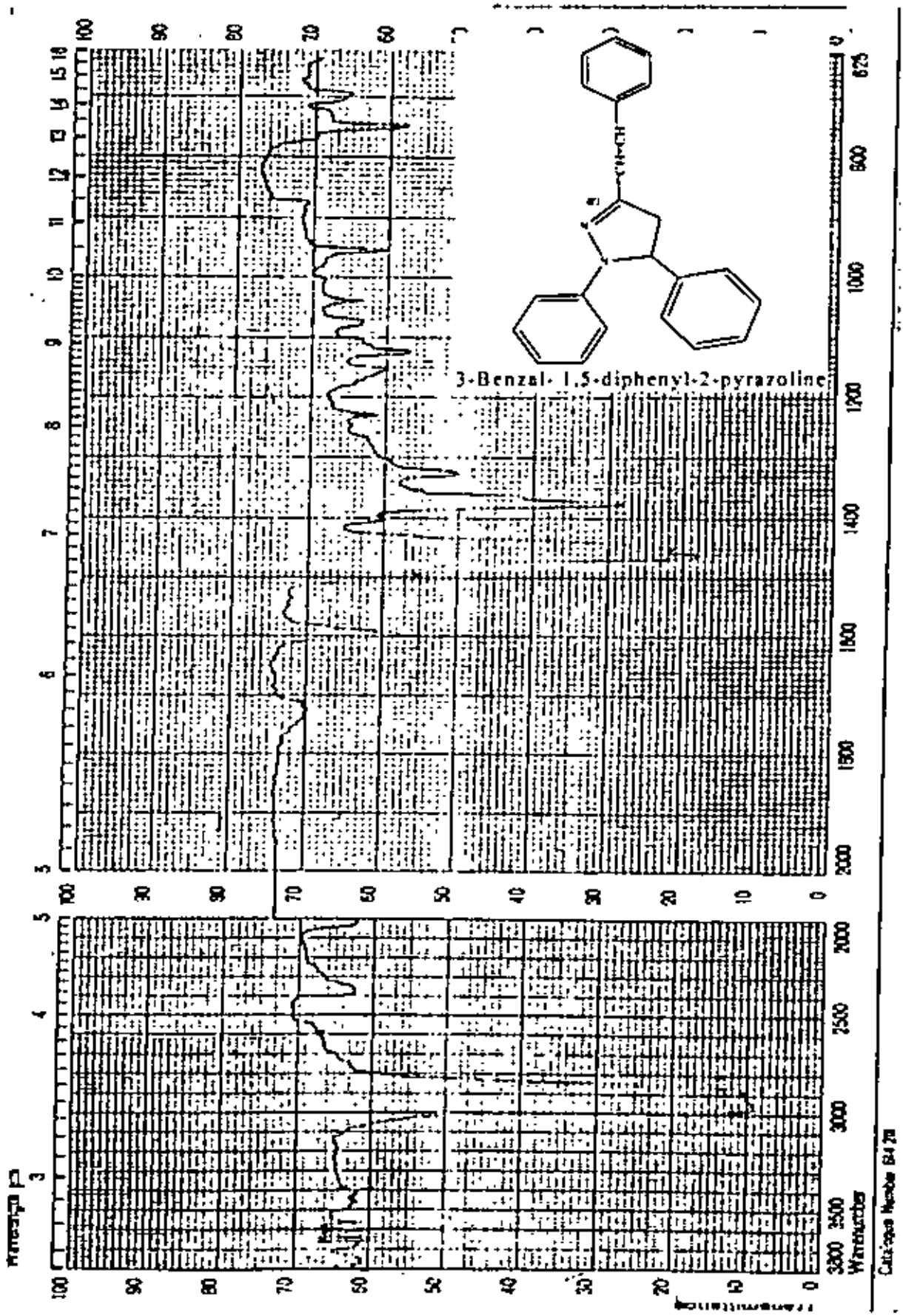


Figure: 43

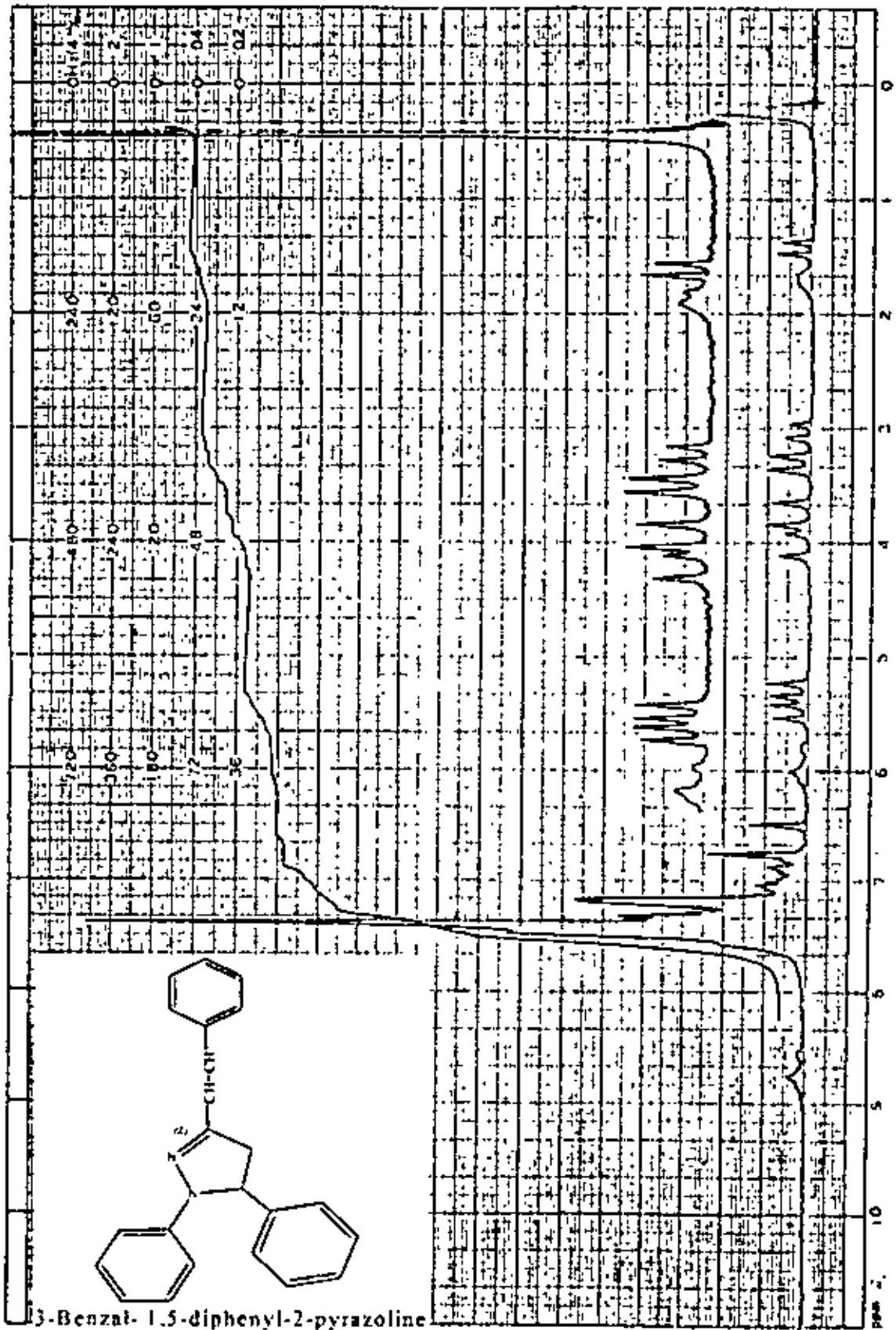


Figure: 44

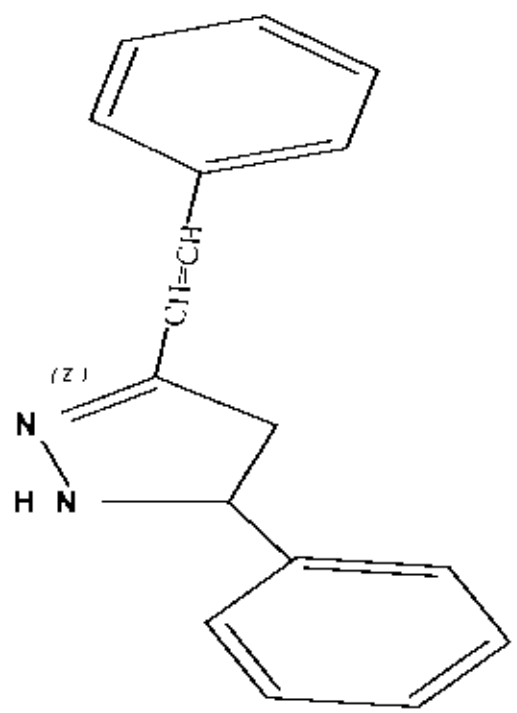
Figure: 45

5.3.6 3-benzal-5-phenyl-2-pyrazoline 11

A solution of dibenzylideneacetone (2.34 g, 0.01 mole) and hydrazine hydrochloride (0.69 ml, 0.01 mole) were taken in a 50 ml ground joint flask to which isopropanol (12.99 ml, 0.22 mole) was added. The reaction was carried out in a special microwave assisted glass ware. The mixture was put on the Microwave oven. Setting the microwave at 600 watt and the reaction was started gradually. The progress of the reaction was followed by TLC (methanol : chloroform 3 : 2). At the begining of the reaction in microwave the color of the reaction mixture was light yellow. It gradually turned greenish at the end of 1 minute.

The reaction mixture was again heated on MW at 600 Watt for 2.5 minute. Heating for more 30 seconds in Microwave oven ensured about completion of the reaction and color remained unchanged. The product started to precipitate and the reaction mixture was kept overnight in refrigerator. After complete precipitation it was taken out from the fridge which was light greenish yellow colored.

Light greenish yellow crystals were filtered under suction on a Buchner tunnel and dried under vacuum. The crude product was recrystallized form methanol to give pure 3-benzal-1, 5-diphenyl-2-pyrazoline 11 (3.02 g, 96%). melting point, 97-98°C (Lit.[174] 96-97°C). The compound was homogeneous (R_f 0.73) on TLC (methanol : chloroform 3 : 2).

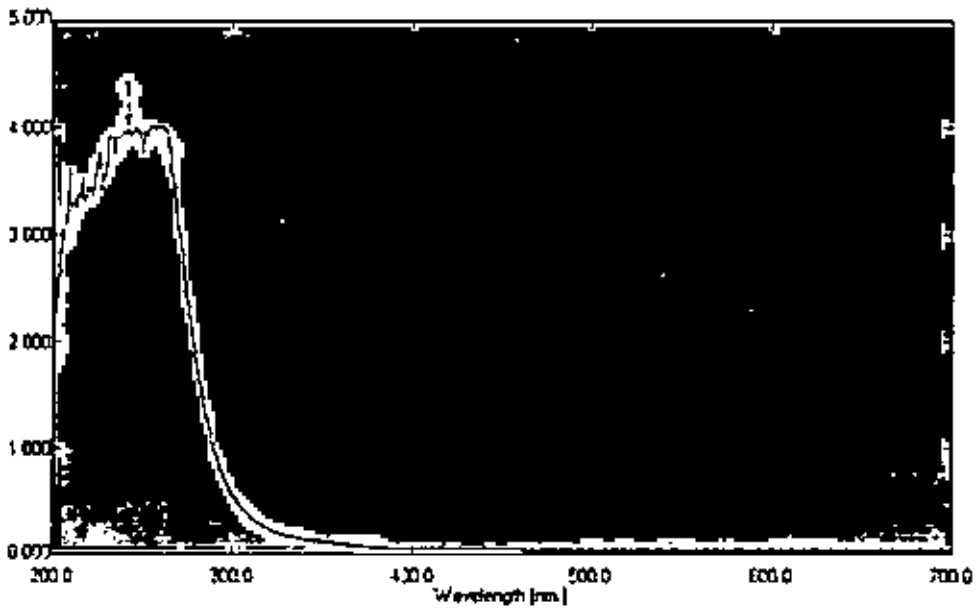


3-Benzal-5-phenyl-2-pyrazoline

The UV **(Fig. 46)** spectrum of the compound 11 had absorption maxima λ_{max} at 242 nm due to to $\pi \rightarrow \pi^*$ transition.

The IR **(Fig. 47)** spectrum (KBr) of the compound 11 had absorption bands at ν_{max} 2817 (C-H stretching), 1598 (aromatic hydrocarbon C=C stretching), 1498 (N-H stretching) and 1247 (alkene C=C stretching) cm^{-1}.

The ^1H NMR **(Fig. 48)** spectrum ($CDCl_3$) of the compound 11 had signals at δ (ppm): 8.6 (S, 1H, NH), 8.09 (dd, 2H, CH=CH), 7-7.9 (m, 10H, aromatic), 3.9-4 ppm (d, 1H, methine. CH), 2.0-3.0 (dd, 2H, methylene. CH_2)



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Slit Width: 2.0
Sampling Interval: 0.5

No.	Wavelength (nm.)	Abs.
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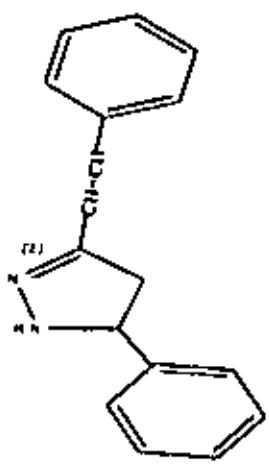
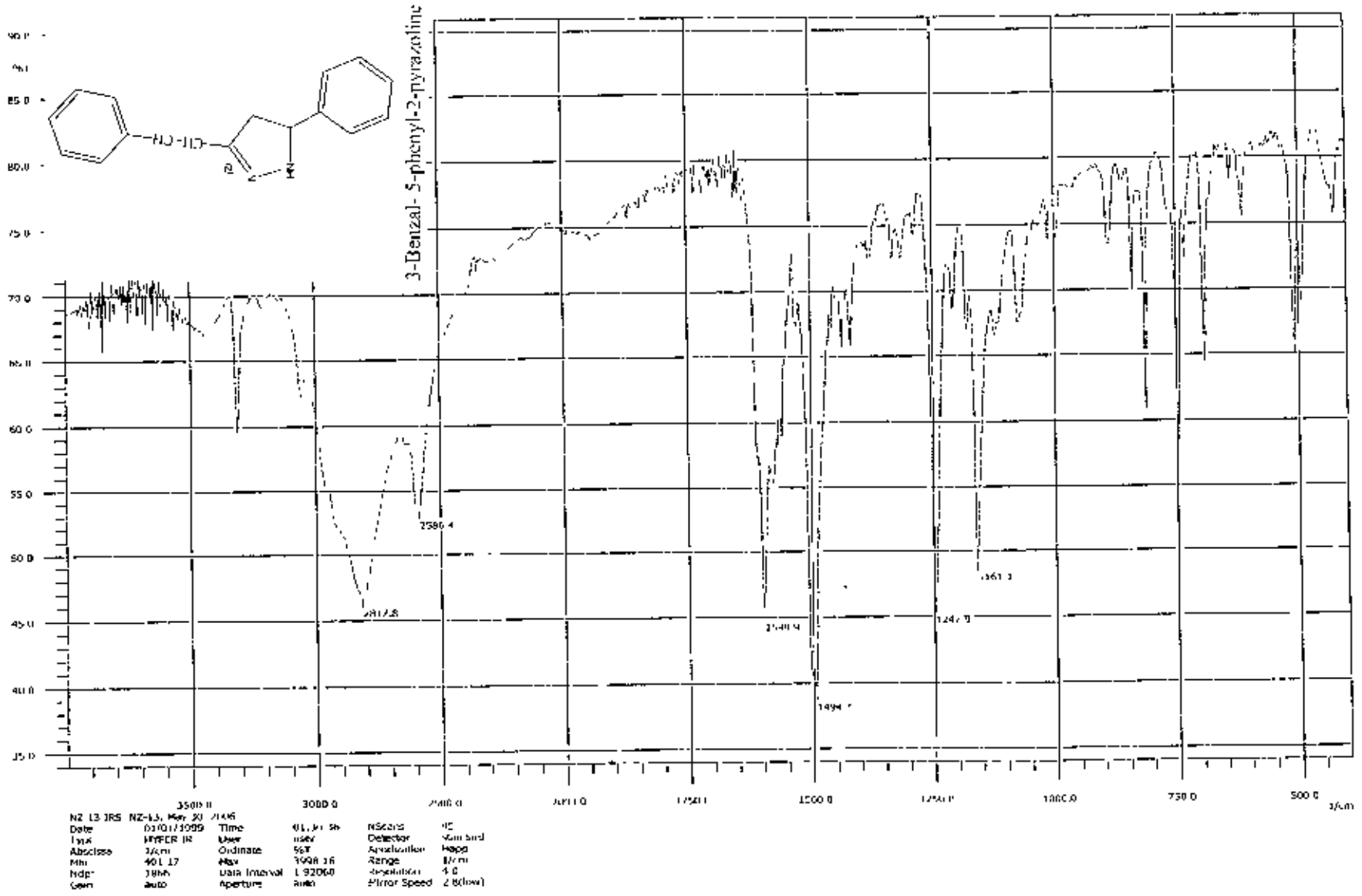


3-Benzal- 5-phenyl-2-pyrazoline

Figure: 46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2540.9
1498.7
1247.9
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2000.0
1500.0
1250.0
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750.0
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Ndp 1866
Gain auto
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User nsev
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Aperture auto
NScans 16
Detector Standard
Apodization Happ
Range 1/cm
Resolution 4.0
Mirror Speed 2.8(low)

Figure: 47

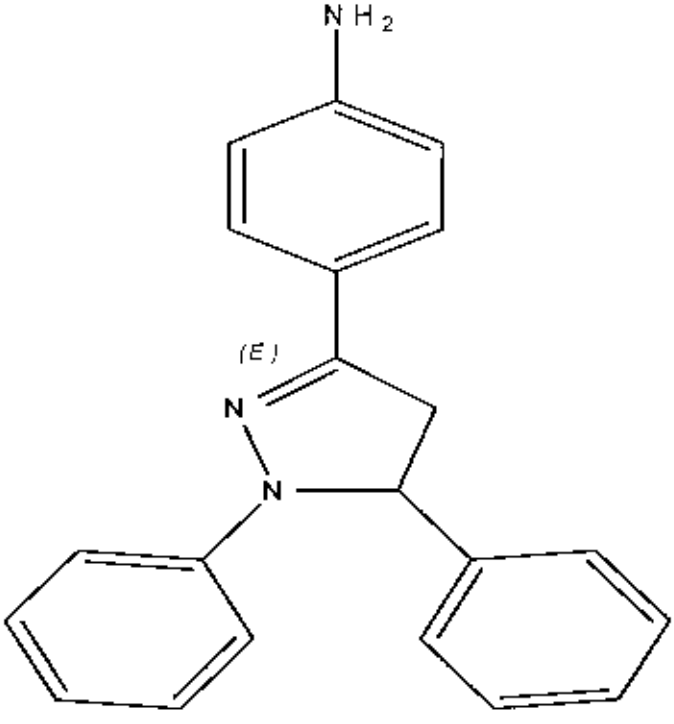
Figure: 48

5.3.7. 1,5-diphenyl-3(p-amino phenyl)-2-pyrazoline 12

A solution of Benzylidene-p-amino acetophenone (2.34 g, 0.01 mole) and phenyl hydrazine hydrochloride (1.446 g, 0.01 mole) were taken in a special microwave assisted glass ware to which isopropanol (12.99 ml, 0.22 mole) was added. The reaction was carried in a MW oven set at 600watt.The progress of the reaction was followed by TLC (methanol : chloroform 3 : 2). Light yellow colour was viewed at the start of the reaction in microwave and it gradually turned to greenish colored solution at the end of 1:00 minute when TLC was taken.

Then mixture was again heated on MW at 600 wt for 1.00 minute. The reaction color became more deep brown from green and reaction was monitored by TLC. The reaction mixture was irradiated for 4 minutes in total. The resulting solution then started to precipitate and was allowed to stand overnight in refrigerator for complete precipitation. Precipitate from the fridge was light reddish yellow color.

Light reddish yellow crystalline solution was filtered under suction on a Buchner funnel and dried under vacuum pump. The crude product was recrystallized form methanol to give pure 1, 5-diphenyl-3(p-amino phenyl)-2-pyrazoline 12 (3.10 g, 92%), melting point, 155-156°C. The compound was homogeneous (R_f 0.75) on TLC (methanol : chloroform 3 : 2).

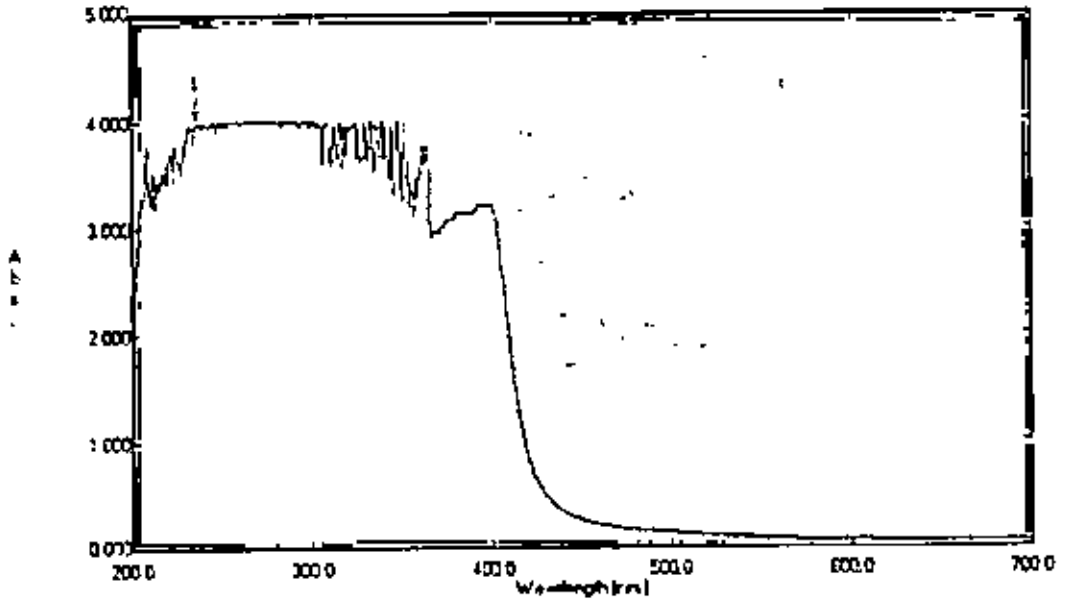


1,5-diphenyl-3(p-amino phenyl)-2-pyrazoline

The UV **(Fig. 49)** spectrum The of the compound 12 had absorption maxima λ_{max} at 336 nm due to to $\pi \rightarrow \pi^*$ transition.

The IR **(Fig. 50)** spectrum (KBr) of the compound 12 had absorption bands at ν_{max} 3390 (NH_2 value for solid state: broad; due to the presence of overtone band, etc), 1595 (aromatic hydrocarbon C=C stretching), 1550 (tertiary amides), 1398 (C-N stretching), 1332 (C-H deformation) and 746 (C-H deformation out of plane) cm^{-1}.

The ^1H NMR **(Fig. 51)** spectrum ($CDCl_3$) of the compound 12 had signals at δ (ppm): 7-8.3 (m, 14H, aromatic), 3.9 (s, 2H, aromatic, C-NH_2), 2.5 (dd, 1H, methine, CH) and 1.7 (m, 2H, methylene, CH_2).



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Sampling Interval: 0.5

No.	Wavelength (nm.)	Abs.
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Figure: 49

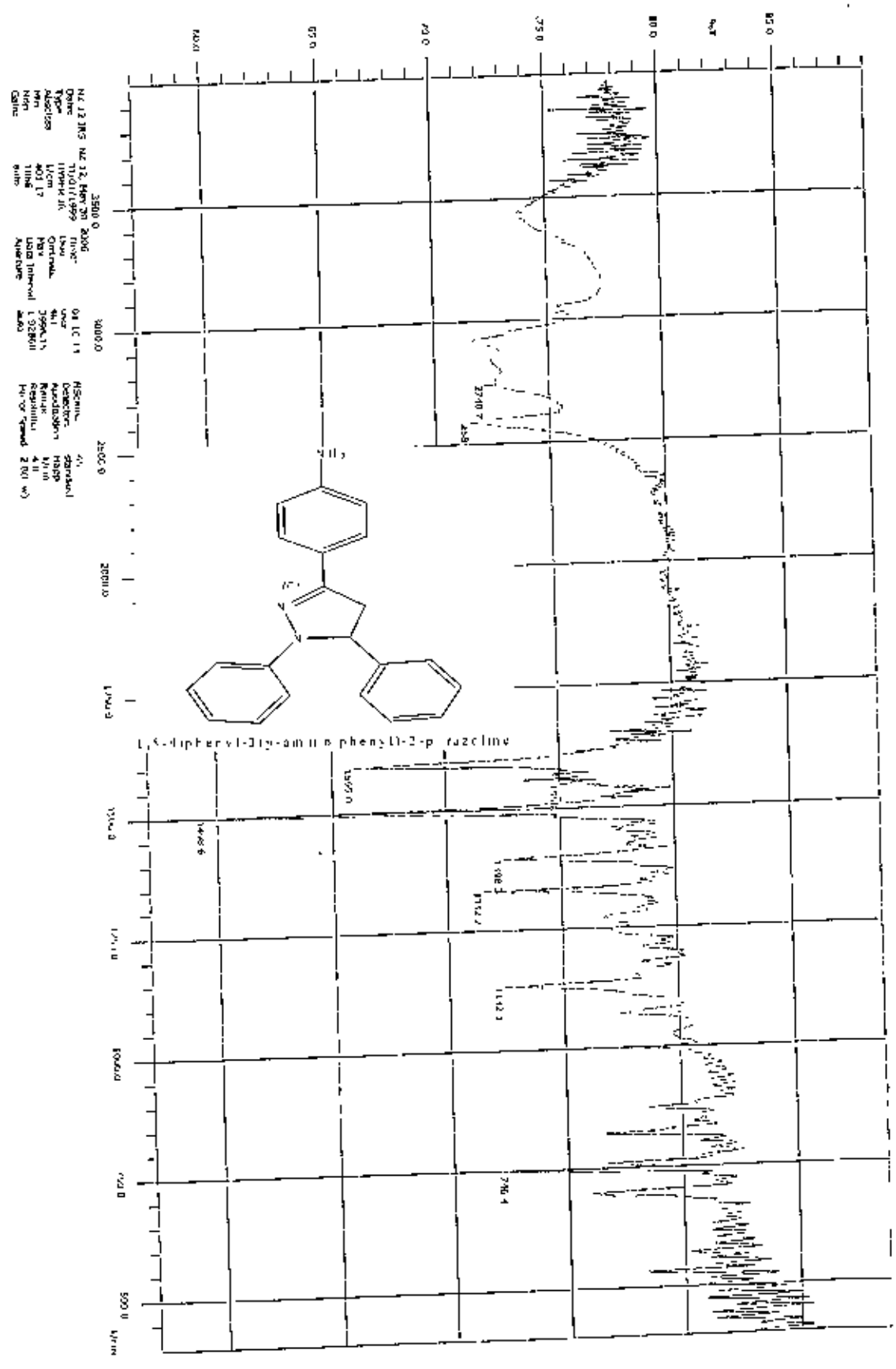


Figure: 50

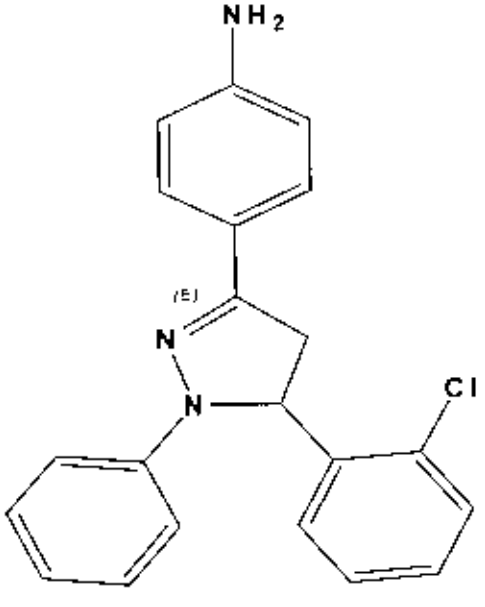
Figure: 51

5.3.8. 1-phenyl-5(o-chloro phenyl)-3(p-amino phenyl)-2-pyrazoline 13

The mixture of o-chlorobenzylidene-p-amino acetophenone (2.58 g, 0.01 mole) and phenyl hydrazine hydrochloride (1.446 g, 0.01 mole) were taken in a 50 ml ground joint flask to which isopropanol (12.99 ml, 0.22 mole) was added. The reaction was carrying out in a special microwave assisted glass ware which was put in the Micro oven with a separate beaker of ice. The microwave was set at 600 Watt and the reaction was started. The progress of the reaction was followed by TLC (methanol : chloroform 3 : 2). At the starting of the reaction in microwave the color of the mixture was initially light yellow and gradually turned to greenish solution at the end of 1 minute.

Then the reaction mixture was heated on MW at 600 Wt for another 1:30 minute. The color became deeper reddish-brown.TLC finding showed that the reaction was complete within another 2.5 minutes. At this point the product started to precipitate and was allowed to stand overnight in refrigerator for complete precipitation. Then it was taken out from the fridge and was light reddish black in color.

Light reddish black crystals were filtered under suction on a Buchner funnel and dried under. The crude product was recrystallized form methanol to give pure 1-phenyl-5(o-chloro phenyl)-3(p-amino phenyl)-2-pyrazoline **13** (3.20 g, 94%), melting point, 165-166°C. The compound was homogeneous (R_f 0.78) on TLC (methanol : chloroform 3 : 2).



1-phenyl-5(o-chloro phenyl)-3(p-amino phenyl)-2-pyrazoline

The IR **(Fig. 52)** spectrum (KBr) of the compound 13 had absorption bands at ν_{max} 3026-3058 (C-H stretching), 1602 (C=C stretching, alkene), 1492 (H-N stretching), 1452 (aromatic hydrocarbon, C=C stretching), 759 (H-Cl stretching) and 698 (C-H, aromatic out of plane band) cm^{-1}.

The ^1H NMR **(Fig. 53, 54)** spectrum ($CDCl_3$) of the compound 13 had signals at δ (ppm): 7.82-7.34 (m, 4H, benzylidenimin), 7.28-7.09 (m, 9H, aromatic), 3.94 (s, 2H, aromatic, C-NH_2), 2.99 (dd, 1H, methine, CH) and 1.27 (m, 2H, methylene, CH_2).

Figure: 52

Figure 53

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PROCNO 1

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FIDRES 0.195670 Hz
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RG 512
DW 78.000 usec
DE 6.00 usec
TE 310.0 K
D1 1.0000000 sec
======== CHANNEL f1 ========
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PL1 -0.00 dB
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F2P 7.565 ppm
F2 3029.30 Hz
PPMCM 0.06691 ppm/cm
HZCM 26.8235 Hz/cm

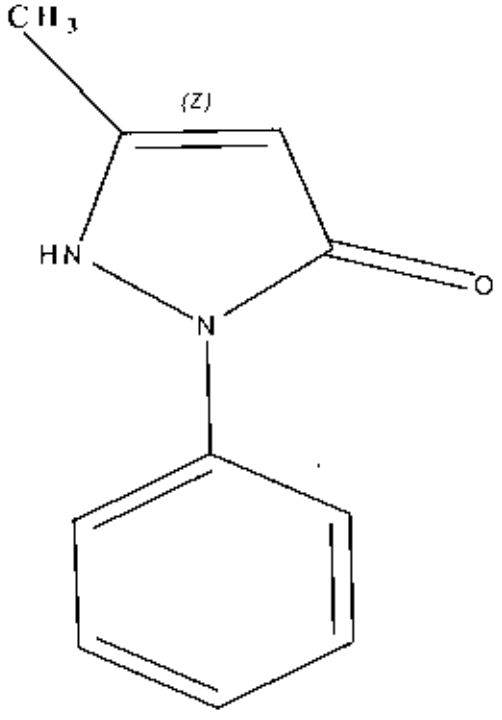
Figure: 54

5.3.9. 3-methyl-1-phenyl-5-pyrazolone 14

In a 50ml special microwave assisted glass ware 7.3 gm (0.05 mole) phenyl hydrazine hydrochloride, 9.3 g (0.1 mole) of solid sodium acetate and 6.4 ml (0.05 mole) of redistilled ethyl acetoacetate was placed with 10 ml of ethyl alcohol. Then 5 ml (0.05 mole) of 5% sodium carbonate solution was added. The mixture was put in the Microwave oven with a separate beaker of ice at 450 watt and the progress of the reaction was followed by TLC (methanol : chloroform 3 : 2). Initially the color of the reaction mixture in the microwave was light yellow and gradually formed dark yellowish at the end of 10 seconds. Irradiation was continued for one more minute with constant TLC monitoring.

Heating in Microwave oven for another 20 seconds showed no change in color and TLC finding indicated the completion of the reaction. The resulting solution then started to precipitate and was allowed to stand overnight in refrigerator for complete precipitation. The product from the fridge was deep brown colored.

Deep brown crystals were filtered under suction on a Buchner funnel and dried under vacuum. The crude product was recrystallized form methanol to give pure 3-methyl-1-phenyl-5-pyrazolone 14 (3.51 g, 95%), melting point, 128-129°C (Lit.[75] 127°C) The compound was homogeneous (R_f 0.81) on TLC (methanol : chloroform 3 : 2).



3-methyl-1-phenyl-5-pyrazolone

The IR **(Fig. 55)** spectrum (KBr) of the compound **14** had absorption bands at ν_{max} 3421.5 (N-N stretching secondary), 1624 (CO stretching), 1593 (aromatic hydrocarbon, C=C stretching), 1533 (N-H deformation, w), 1498 (N-H stretching) 1396 & 1355 (C-H deformation in CH_3), and 756 (C-H deformation out of plane) cm^{-1}.

The ^1H NMR **(Fig. 56, 57, 58)** spectrum ($CDCl_3$) of the compound **14** had signals at δ (ppm): 7.41-7.78 (m, 5H, aromatic), 2.19 (s, 1H, amine, NH), 2.15 (m, 1H, methine, CH) and 1.20 (d, 3H, methyl, CH_3).

The ^{13}C NMR **(Fig. 59)** spectrum of the compound **14** had signals at δ (ppm): 181.59 (Carbonyl carbon), 146.8 (Ar C), 128 (Ar CH), 118.9 (Ar CH), 112.4 (Ar CH), 61.3 (methylene, CH_2-N), 52.69 (methine, CH), 41.2 (methylene, CH-CH_2) and 18.6 (methyl, CH_3).

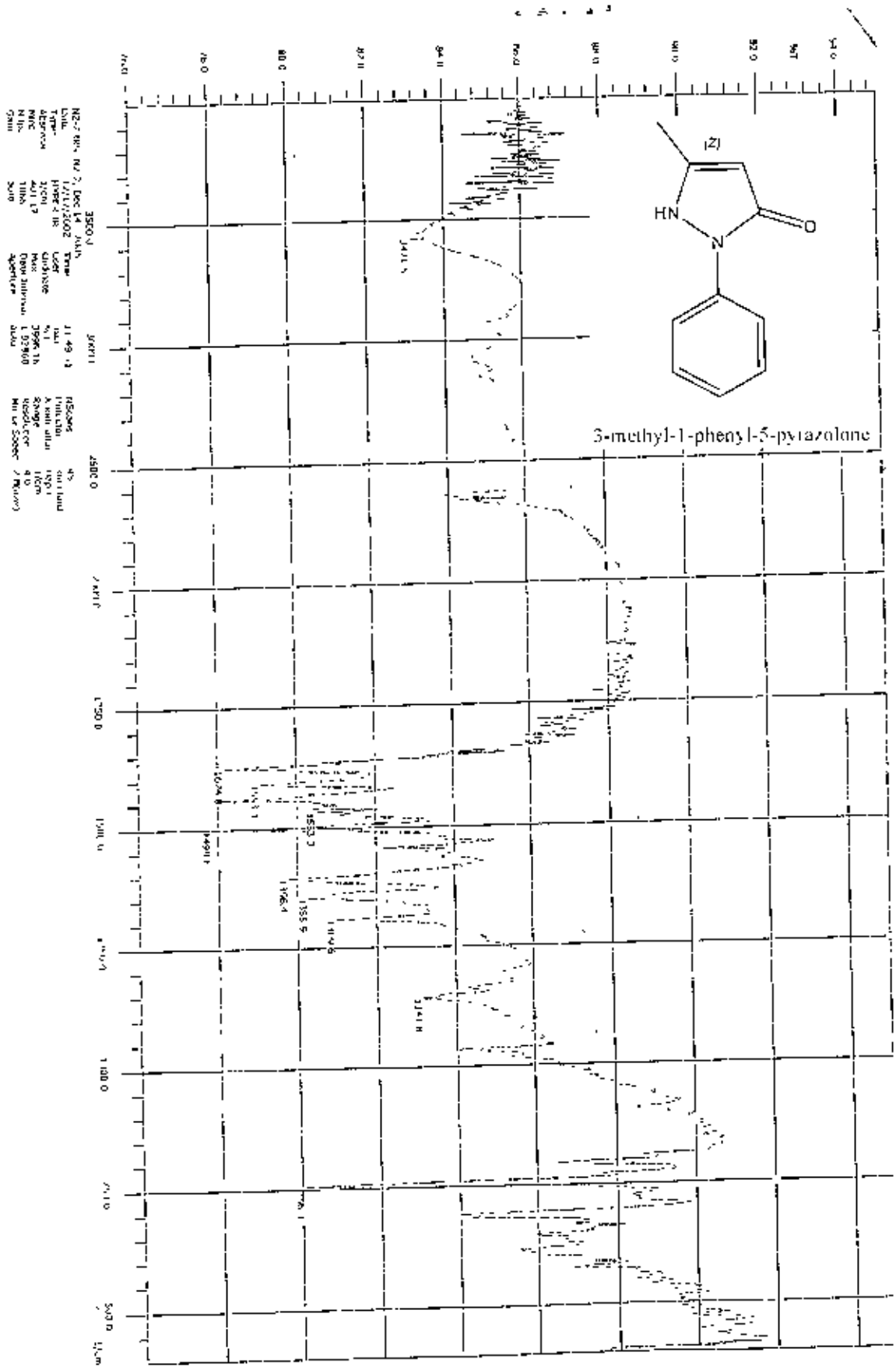


Figure: 55

Figure: 56

3-methyl-1-phenyl-5-pyrazolone
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N
O
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7.75570
7.41587
7.24973
7.12141

Figure: 57

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RG                 203.1
DW                 78.000 usec
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F1                 960.17 Hz
F2P                -0.516 ppm
F2                 -62.15 Hz
PPMCM              0.71429 ppm/cm
HZCM               285.74 Hz/cm
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Figure: 58

Figure: 59

Chapter Three

Result and discussion

Pyrazolines drew attention of researchers for the possibility of their use as organic dyes, used in pharmaceutical industry to alleviate inflammation, fever, pain, infections, and lesser extent as insecticides and herbicides. Keeping this objective in view some substituted pyrazolines were synthesized. Starting materials for these compounds were α,β-unsaturated ketones (benzylidenes).

α,β-unsaturated ketones (benzylidenes) (**1-5**) were prepared with the condensation of acetone, acetophenone and substituted acetophenone with benzadehydes and substituted benzadehydes. The reactions were carried out in methanol in presence of alkali under microwave (MW) irradiation.

The compounds **1-5** prepared under MW irradiation were in high yield, more than 90% on an average. The melting points (m. p.) of the synthesized compounds were in very good agreements with those of the compounds already prepared by conventional methods as reported earlier in literature.

The IR spectra of the compounds showed absorption bands at ν_{max} 3352-3388 for N-H stretching hydrogen bonded, 1660-1670 characteristic for C=O stretching, 1492-1460 for C-H stretching for CH_2, 1590-1610 cm^{-1} for C=C and aromatic skeletal stretching, 1375 for C-H deforming in CH_3, 1271 for C-N stretching and 756 for C-Cl stretching.

The ^{1}H-NMR spectra showed multiplet at around δ 7.3 ppm for aromatic protons, 6.69-7.5 for ethylene proton, 7.52-7.46 for benzene-NH_2. These data also agree with the earlier established spectral pattern of these compounds.

The ^{13}C-NMR spectra showed signals at around δ 190 ppm characteristic for C=O carbon, 144.2 for imine carbon, 151.09-143.16 for ethylene carbon and the signals between δ 128-132 ppm is characteristic for carbons of the aromatic ring.

The UV spectral data between λ_{max} 215-230 nm due to $\pi \rightarrow \pi^*$ transition of the C=C-C=O system is in consistent with these compounds.

Substituted pyrazolines (**6-13**) were prepared by condensing substituted α,β-unsatnrated ketones (benzylidenes) (**1-5**) with phenyl hydrazine hydrochloride, hydrazine hydrochloride, 2, 4-dinitrophenyl hydrazine in isopropanol under MW

irradiation. The yield of the obtained compounds was also high, above 90% on an average. Compound **(14)** was prepared by condensation of phenyl hydrazine hydrochloride with ethyl acetoacetate in sodium acetate. The structure of these compounds (**6-14**) was established from their spectral and melting point data as well. The melting points (m. p.) of the synthesized compounds **(6-11)** were in very good agreements with those of the compounds already prepared by conventional methods as reported earlier in literature. Compounds **(4, 5, 8, 12-13)** were new compounds and showed sharp melting points.

The IR spectra of the compounds **(6-14)** contain absorption bands ν_{max} (cm^{-1}) at 2740 to 3421 characteristic of N-N vibration of pyrazoline ring, two bands at 1593 and 1309 represent the symmetric and asymmetric vibration of –N-H group. 759 for H-Cl stretching. Absorption bands at around 1610 are characteristic of the presence of C=N and aromatic skeletal stretching.

The UV spectra of some the compounds **(10-14)** contain absorption bands at λ_{max} 236 nm to 408 nm and absorption coefficients of 2.9 to 3.9 characteristic respectively of different types of pyrazolines. The maximum at longer wavelength is due to the π-π^* conjugated system. The other absorption maximum is for heterocyclic ring with N-phenyl group.

The ^{1}H NMR spectrums of the compounds contain groups of signal of aromatic protons at δ 7.28 ppm for aromatic proton, 3.9 for benzene attached NH_2 proton, The spectra showed characteristic signals at 5.15- 5.21 (dd, 1H) for methine protons 3.32-3.40 ppm (m, 2H) for methylene protons and 1.98 for methyl proton.

The ^{13}C-NMR spectra of the compounds showed signals between δ 128-132 ppm are characteristic for carbons of the aromatic rings. Signals at δ 123 ppm and δ 142 ppm characteristic of different type's unsaturated carbon attached with carbonyl group and unsaturated carbon attached with phenyl group and carbon attached with one alpha nitrogen atom, 48-58.3 for methine carbon, 40-42.2 for methylene carbon and 19 -20 for methyl carbon.

Benzylidene preparation under microwave irradiation:

Entry	Different type of aldehydes and ketone	Product	Irradiation time [min.]	Power [W]	Temp. [°C]	Yield [%]
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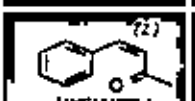
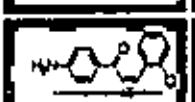
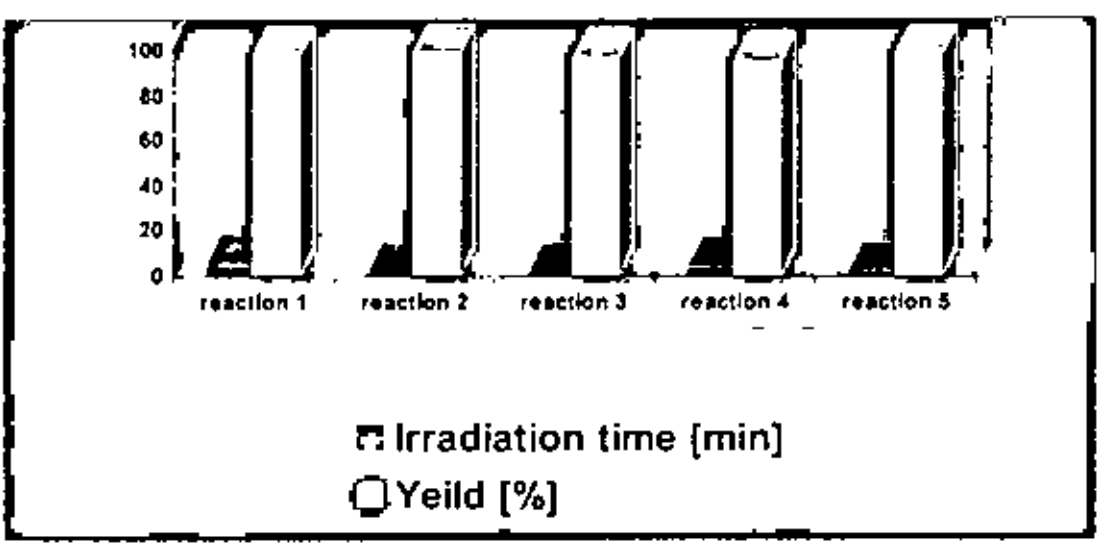
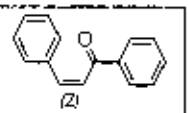
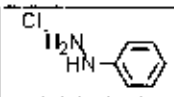
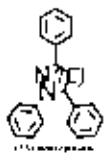
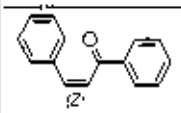
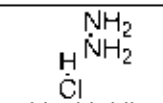
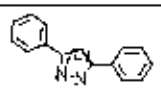
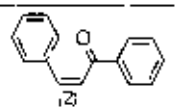
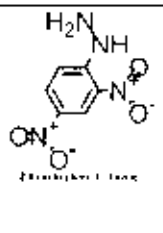
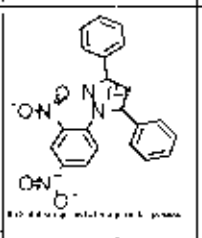
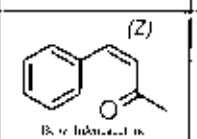
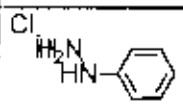
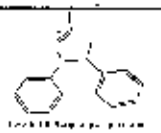
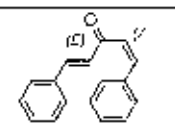
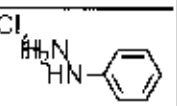
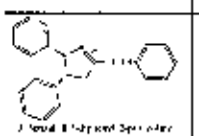
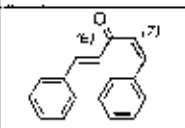
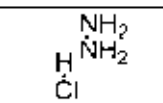
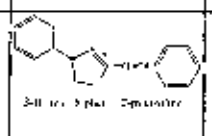
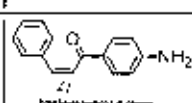
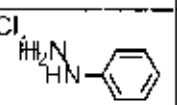
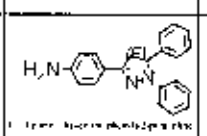
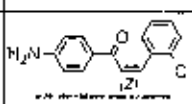
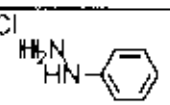
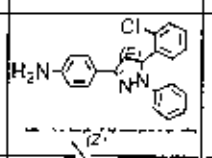
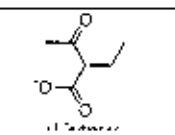
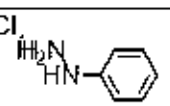
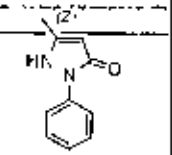
2			1.5	600	325	99
3			1.5	600	325	97
4			4	600	325	95
5			2	600	325	98

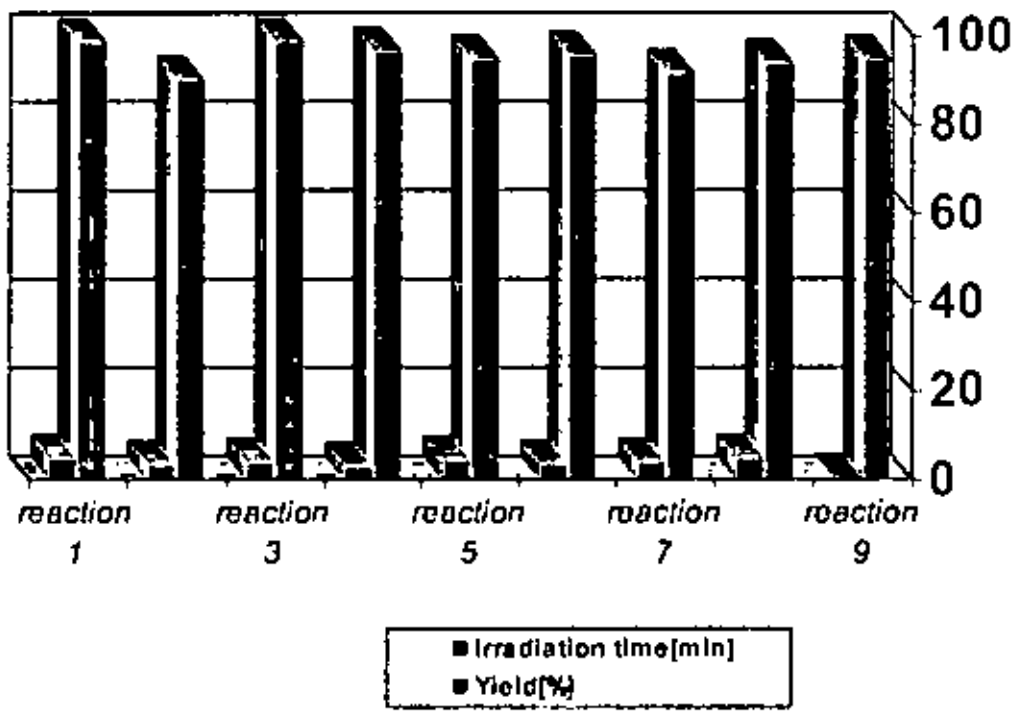
Benzylidene: The effect of Microwave synthesis Irradiation time [min] Vs Yield[%] plot:



Pyrazoline reactions under microwave irradiation with hydrazine and its derivatives:

Entry	Substrate		Product	Irradiation time [min]	Power [W]	Temp. [°C]	Yield [%]
1				5	600	325	98.99
2				3.5	600	325	90.58
3				4	450	300	98.99
4				3	450	300	97
5				4.5	450	300	95
6				3.5	600	325	96
7				4	600	325	92
8				5	600	325	94
9				0.5	450	325	95

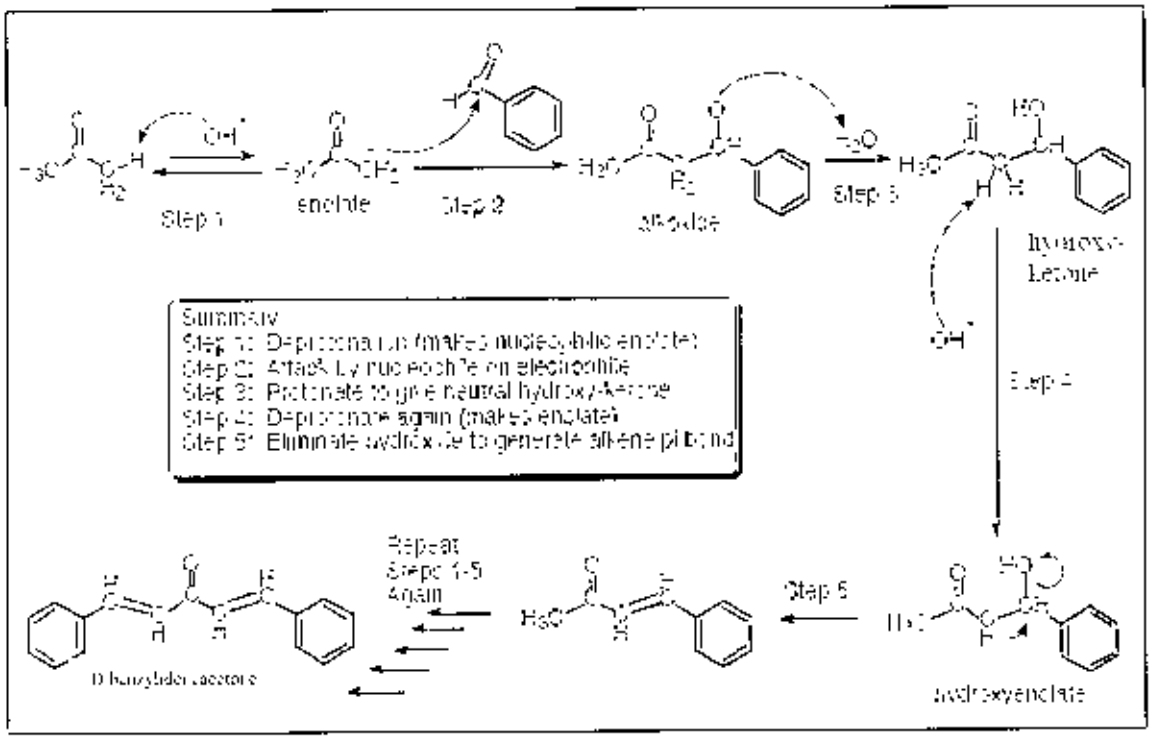
Pyrazoline: The effect of Microwave synthesis irradiation time [min] Vs Yield [%] plot



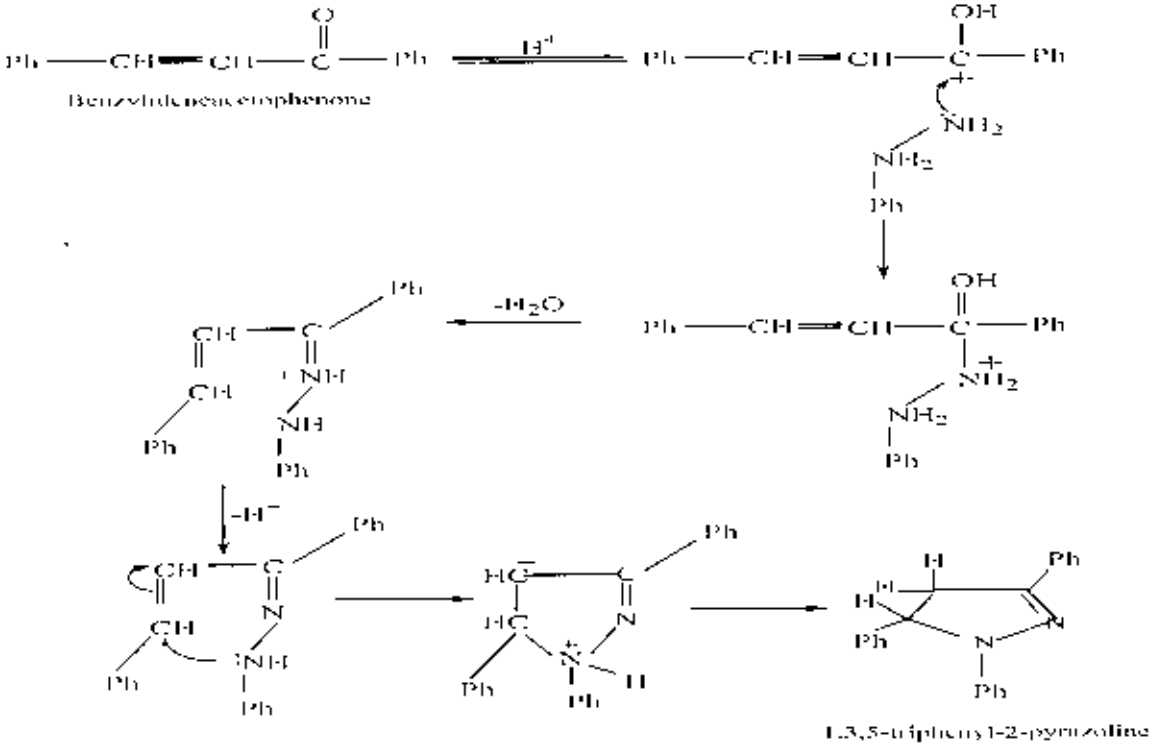
Chapter Four

Mechanism & Reaction

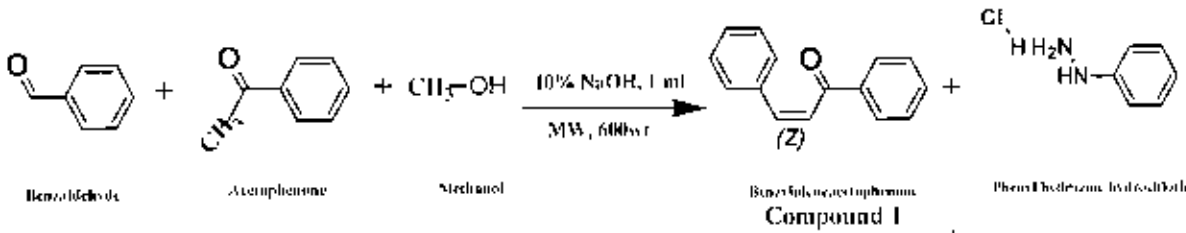
Mechanism (1): Benzaldehyde with acetone to dibenzylideneacetone



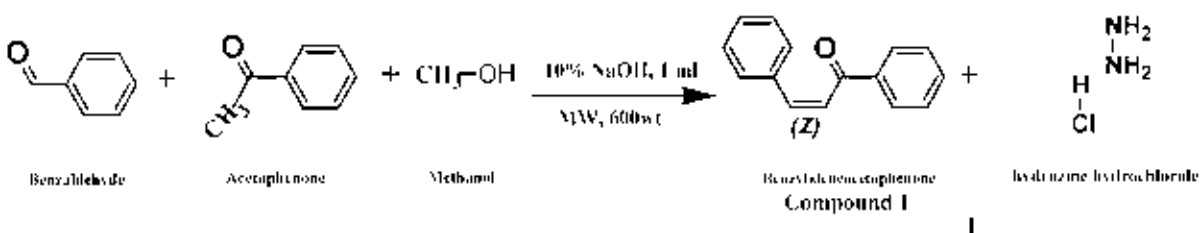
Mechanism (2): Benzylideneacetophenone to 1, 3, 5-triphenyl 2-pyrazoline



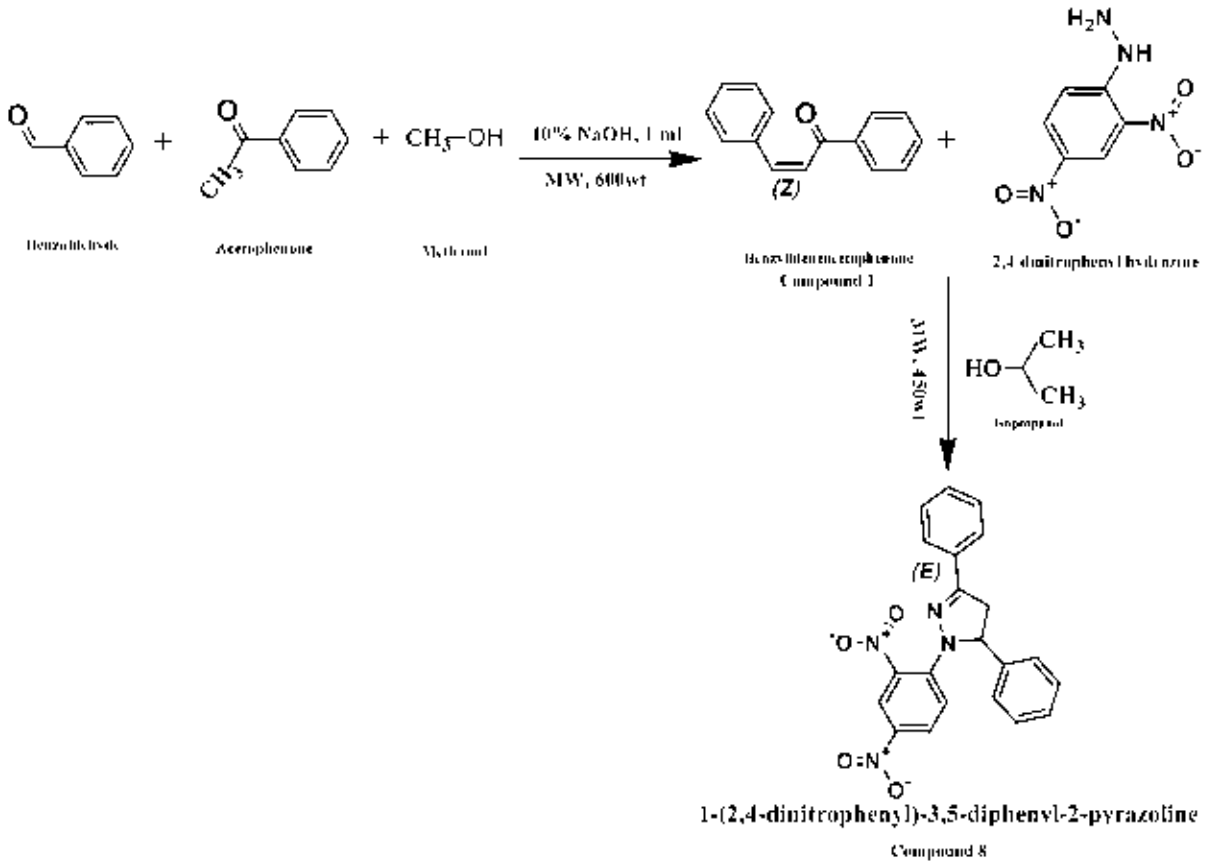
Reaction 1



Reaction 2

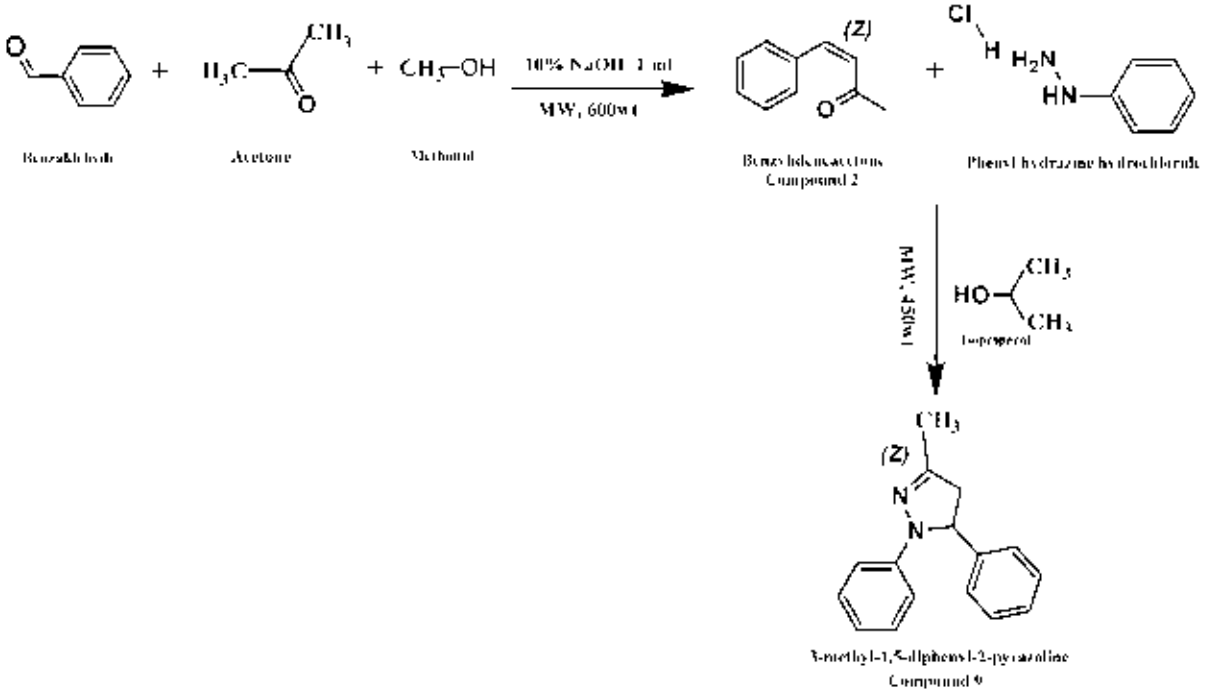


Reaction 3



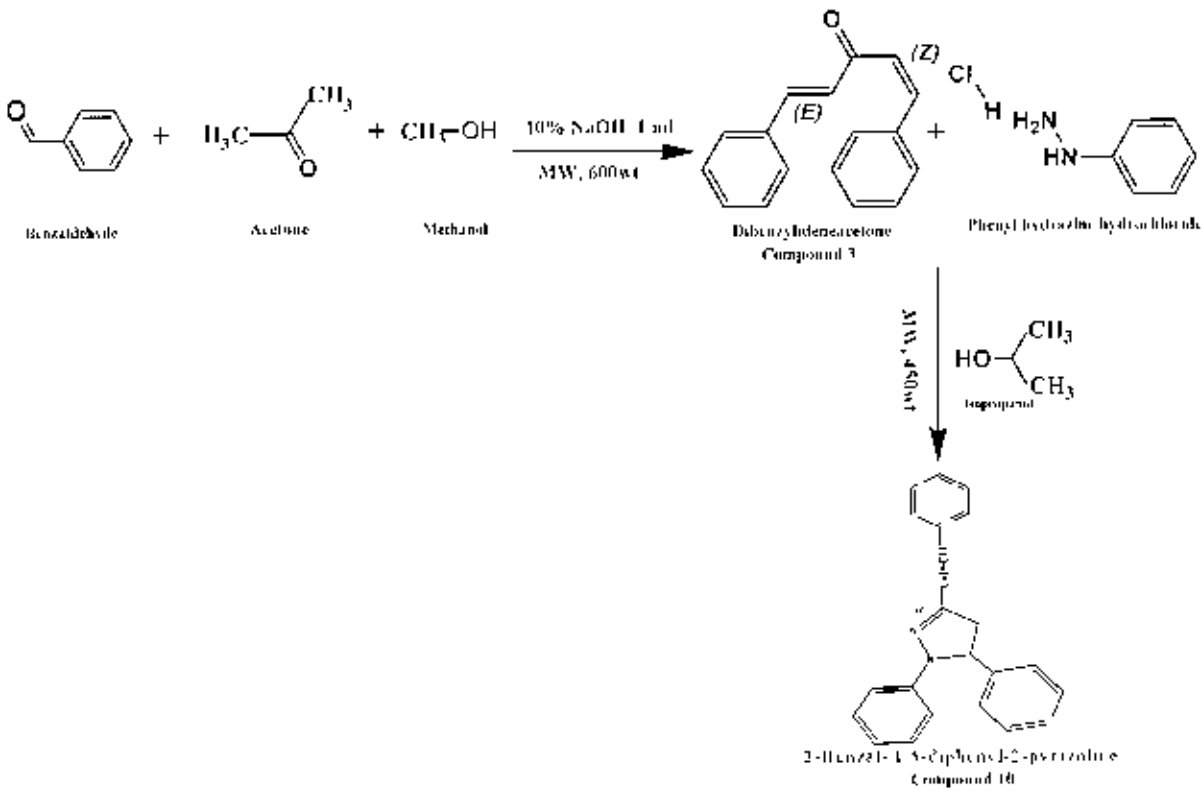
Compound 8

Reaction 4

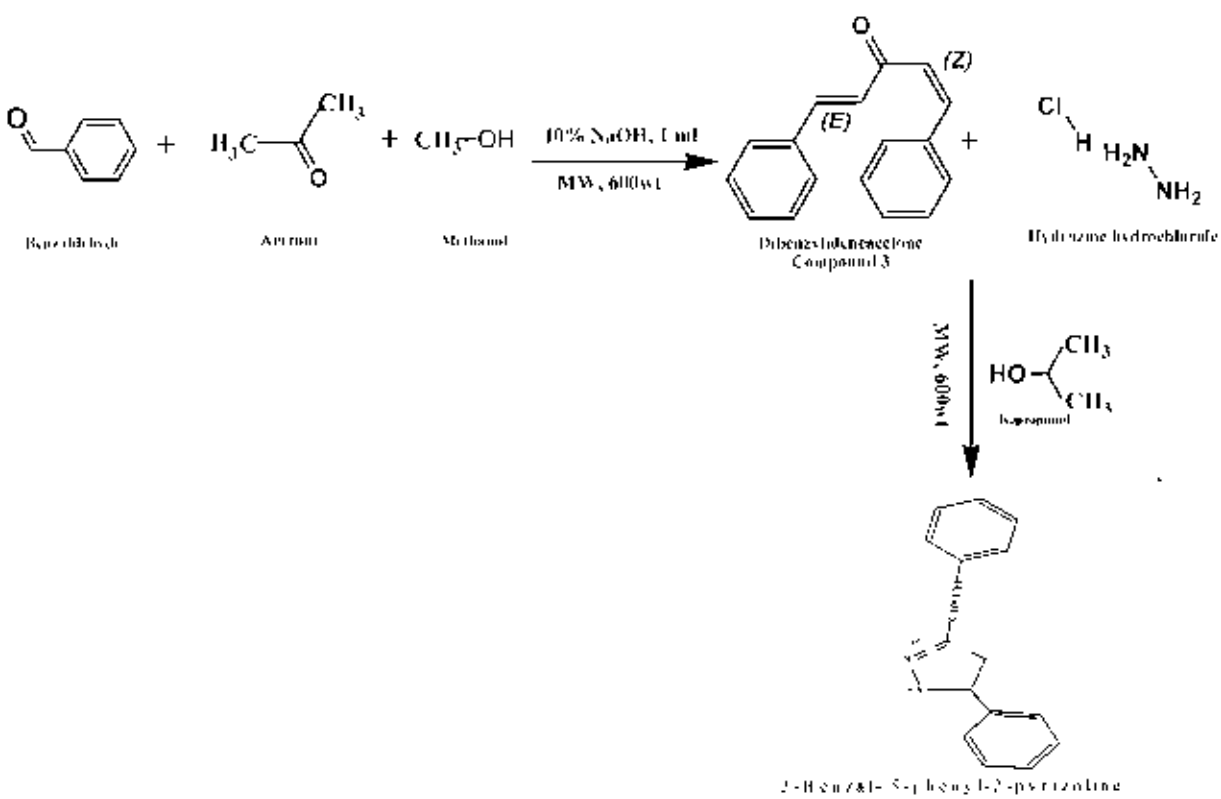


Compound 9

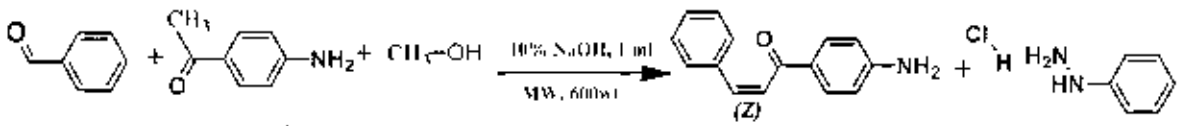
Reaction 5



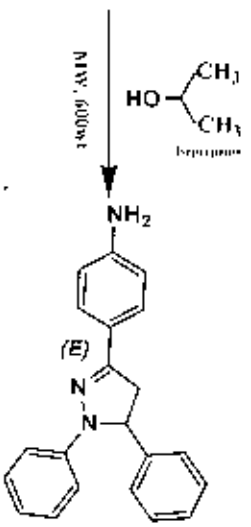
Reaction 6



Reaction 7



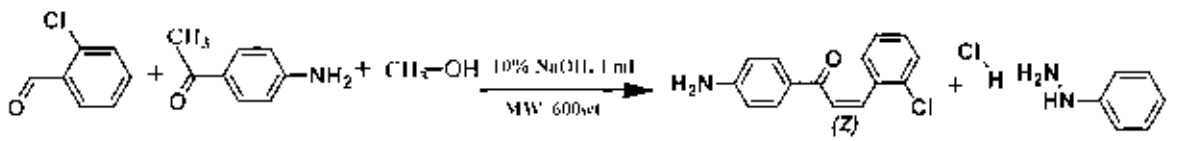
Benzaldehyde | p-aminoacetophenone | Methanol | Benzylidene-p-amino acetophenone (Compound 4) | Phenyl hydrazine hydrochloride



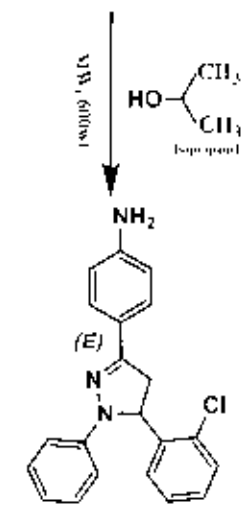
Isopropanol

1,3-diphenyl-5-p-amino phenyl-4,5-pyrazoline
Compound 12

Reaction 8



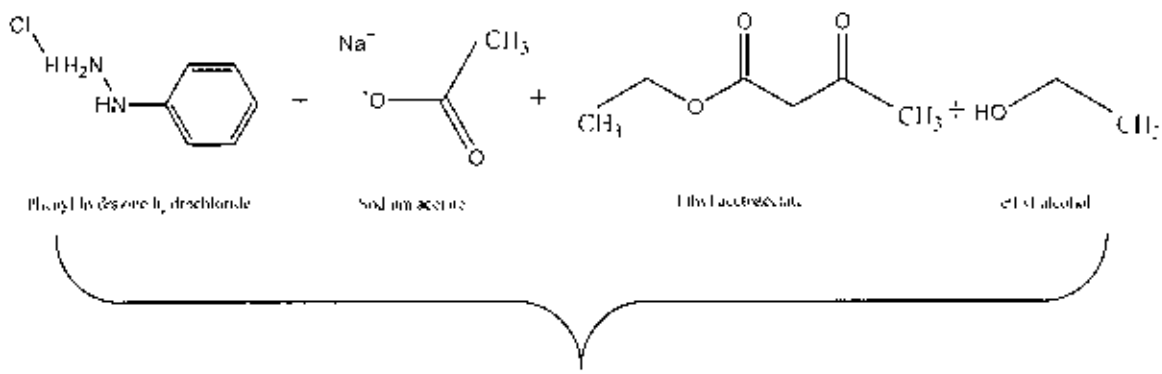
o-chlorobenzaldehyde | p-amino acetophenone | Methanol | o-chloro benzylidene-p-amino acetophenone (Compound 5) | phenyl hydrazine hydrochloride



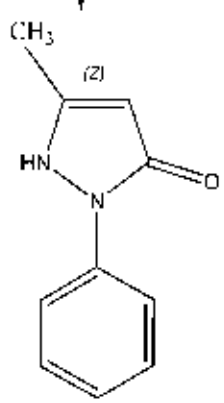
Isopropanol

1-phenyl-3-p-amino phenyl-5-(o-chloro phenyl)-2-pyrazoline
Compound 13

Reaction 9



Phenylhydrazine hydrochloride — Sodium acetate — Ethyl acetoacetate — Ethanol



3-methyl-1-phenyl-5-pyrazolone

Compound 11

Chapter Five

Conclusion

During this research an up to date literature survey was carried out on benzylidene and pyrazoline and their derivatives.

In the present work, five substituted α,β-unsaturated ketones (benzylidenes) and eight 2-pyrazolines derivatives and one 5-pyrazolines were synthesized. Out of fourteen final products, five (4, 5, 8, 12, 13, 14) are newly synthesized by us. Spectroscopic (IR, UV, ^{1}H NMR, & ^{13}C NMR) methods were applied for assigning the structures of the new and as well as old compounds.

Substituted benzylidenes **1** to **5** were synthesized by the condensation of substituted benzaldehyde and substituted ketones.

Substituted pyrazolines **6** to **13** were synthesized by the reaction of substituted benzylidene with different types of hydrazines.

When ethyl acetoacetate was warmed with an equivalent qnantity of phenyl hydrazine, the phenyl hydrazone was formed first; then latter it underwent ring formation to yield 3-methyl-1-phenyl-5-pyrazoline **14.**

All reactions were carried out in a *domestic microwave oven* with special fabricated glassware and optimum reaction conditions were determined. It was observed that the reactions were carried out in short time. The average yield of the products was much higher than the conventional method. Besides, low amount of chemicals were used making the synthesize environmental friendly. In other words, this modest thesis work was a part of 'Green Chemistry' too. It can be added that the efficient use of domestic MW oven was also shown in the work.

References

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