MICROWAVE ASSISTED PYRAZOLE DERIVATIVE SYNTHESIS

A Dissertation

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Affiliated to

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By

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Binay Kumar Dash

Guide certificate

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This is to certify that the dissertation entitled **"MICROWAVE ASSISTED PYRAZOLE DERIVATIVE SYNTHESIS"** submitted by Binay Kumar Dash to the Department of Chemistry, National Institute of Technology, Rourkela for the degree of Master of Science in Chemistry is based on the result obtain in the bonafide project work carried out by him under my guidance and supervision .

I further certify that to the best of my knowledge Binay Kumar Dash bears a good moral character.

N.I.T,Rourkela **Dr. N. Panda**

Date:

Introduction:

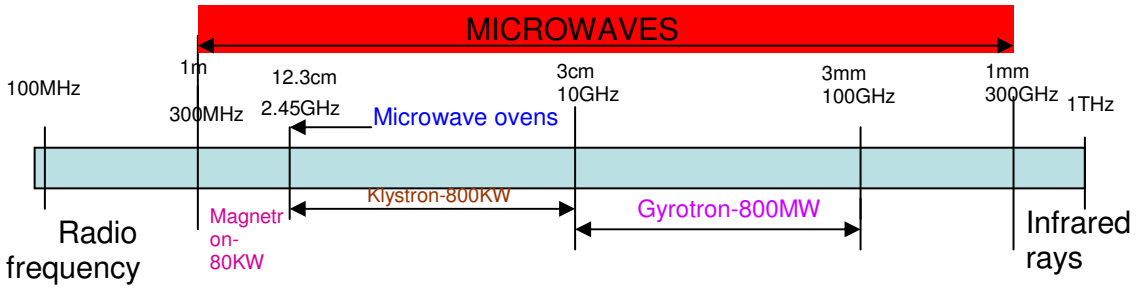
In the past few decades, many significant advances in organic chemistry, such as the novel synthetic reagents and methods, as well as the advent of an array of analytical apparatus and techniques, have made the organic synthesis more dynamic and effective than ever before. However, the practical aspects for carrying out laboratory-scale reactions have changed little during this period. Especially when heating is necessary, oil baths and heating jackets are the main equipment used. These traditional heating techniques are slow and time-consuming, and sometimes can lead to overheating and decomposition of the substrate and product. To this end, microwaves have been employed in organic chemistry to reduce the reaction times from hours to minutes, to increase yields and selectivity[1].

Although microwave technology has been used in inorganic chemistry since 1970s, Giguere[2] and Gedye[3] first implemented it to accelerate the organic reactions in 1986. The slow development of the technique in organic synthesis was principally attributed to the lack of controllability and reproducibility due to using poorly designed domestic microwave ovens as reactors. Safety is another consideration since explosions have been reported[3]. However, with the availability of commercial microwave equipment intended for organic synthesis and the development of the solvent-free techniques, microwave assisted organic chemistry has experienced exponential growth since the mid-1990s.

Here we studied the syntheses of pyrazoles derivative with the help of microwave oven. As we know Pyrazole and its derivates are shown to possess important biological and pharmaceutical activities[4,5] such as antimicrobial[6], antiviral[7], antitumor[8] ,anti-inflammatory[9] ,antifungal[10],and antidepressant[11] activities. They are also useful intermediates for many industrial products[12,13].A lot of synthesis of pyrazoles have been developed[11]. However, these syntheses are usually carried out in organic solvents. Recently, solventless organic reactions such as Michael additions[14], Aldol condensations[15], Claisen condensation[16], Stobbe condensation[17], and Thorpe reactions[18] have been studied. Compared with the reactions in the organic solvents, solventless reactions are often rapid, regio or chemo selective, occur in high yields and have environmental and economic advantages[14].For these reasons, we studied syntheses of pyrazole derivatives by the solventless reaction of 1,3-dicarbonyl compounds with hydrazines in silica-G with the help of microwave oven.

Microwave Region:

In the electromagnetic spectrum, microwave region is located between infrared radiation and radio frequencies and corresponding to wave length of 1cm to 1m (frequencies of 30 GHz to 300 MHz respectively). Domestic and industrial microwave heaters operates at 12.2 cm (2450 MHz) or 33.3cm (900MHz, so that there is no interference).



Microwave Oven:

Heating effect of water is very strong at 20GHz but the domestic ovens operate at a much lower frequency, 2.45GHz. The reason for this is that it is necessary to heat food efficiently throughout its interior. If the frequency is optimal for maximum heating rate, the microwaves are absorbed in the outer region of the food, and penetrate only a short distance. At 2.45 GHz the microwaves penetrate into depth of 1 – 3/2, makes the water molecules vibrate at the rate of two billion times per sec and the food is heated up.

A microwave oven consists of a high power source, a wave guide feed and the oven cavity.The source is generally a magnetron in which the microwaves are generated. A magnetron is a thermionic diode having an anode and a directly heated cathode. As the cathode is heated, electrons are released and are attracted towards the anode. The anode is made up of an even number of small cavities, each of which acts as a turned circuit. The gap across of each cavity behaves as a capacitance.

A very strong magnetic field is induced axially through the anode assembly, and has the effect of bending the path of the electrons as they travel from the cathode to the anode. As the defected electrons pass through the cavity gaps, they induce a small charge into the turned circuit, resulting in the oscillation of the cavity. Alternate cavities are linked by two small wire straps which ensure the correct phase relationship. This process of oscillation continues until the oscillation has achieved a sufficiently high amplitude. It is taken off the anode via an antenna. Of the 1200W of electric line power used by the magnetron, around 600W is converted into electro magnetic energy. The remainder is converted into heat that must be dissipated through air and water cooling.

MECHANISM OF MICROWAVE HEATING:

A material can be heated by applying energy to it in the form of high frequency electromagnetic waves due to the ability of electric field to exert a force on charged particles. If the Particle present in the substance can move freely through it, a current has been induced. However, if the charge carrier bound to certain regions they will move until a counter force balanced them and the net result is a dielectric polarisation. Both conduction and dielectric polarization are sources of microwave heating.

The source of microwave dielectric heating lies in the ability of an electric field to polarize charges in a material and the inability of this polarization to follow rapid reversal of an electric field.

The total polarisation is the sum of a number of individual components.

$$\alpha_t = \alpha_e + \alpha_a + \alpha_d + \alpha_I$$

α_e - the electronic polarization arises from the realignment.

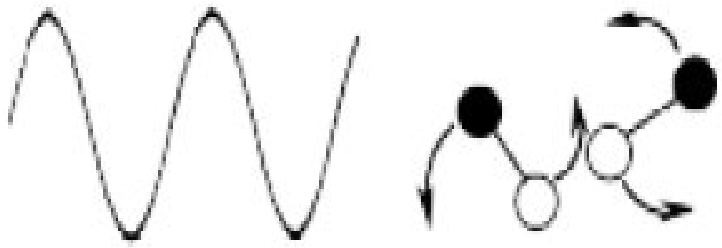
α_a - the atomic polarisation results from the relative displacement of nuclei due to the unequal distribution of charge with in the molecule.

α_d – the dipole polarisation , resulting from the orientation of permanent dipoles by the electric field.

α_I – the interfacial polarisation

they experience The major factor is dipole polarization. It is due to the dipole moment which in turn results from the differing electronegativities. A low frequencies, the time taken by the electric field to change direction is longer than the response time of dipoles and the dielectric polarisation keeps in phase with the electric field. The field provides energy necessary to make the molecules rotate into alignment. Some of the energy is transferred to the random motion each time dipole is knocked out of alignment and then realigned. The transfer of energy is so small, that the temperature hardly rises. If the electric field oscillates rapidly, it changes direction faster than the response time of the dipoles. Since the dipoles do not rotate, no energy is absorbed and the material does not heat up.

In the microwave range of frequencies, the time in which the field changes is about the same as the response time of the dipoles. They rotate because of the torques, but resulting polarization lags the changes of the electric field. When the field is at a maximum strength, polarization may still be low. It keeps rising as the field weakens. The lags indicate that the material absorbs energy from the field and is heated.



Dipolar molecules which try to align with oscillating electric field.

Microwave reactors in organic synthesis

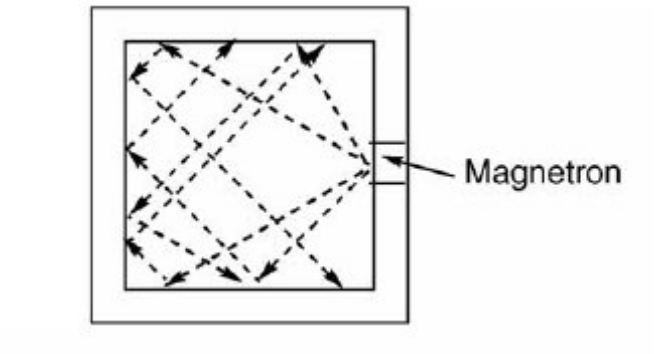
There are two types of reactors used for microwave assisted organic synthesis:

(1)Multimode Reactors

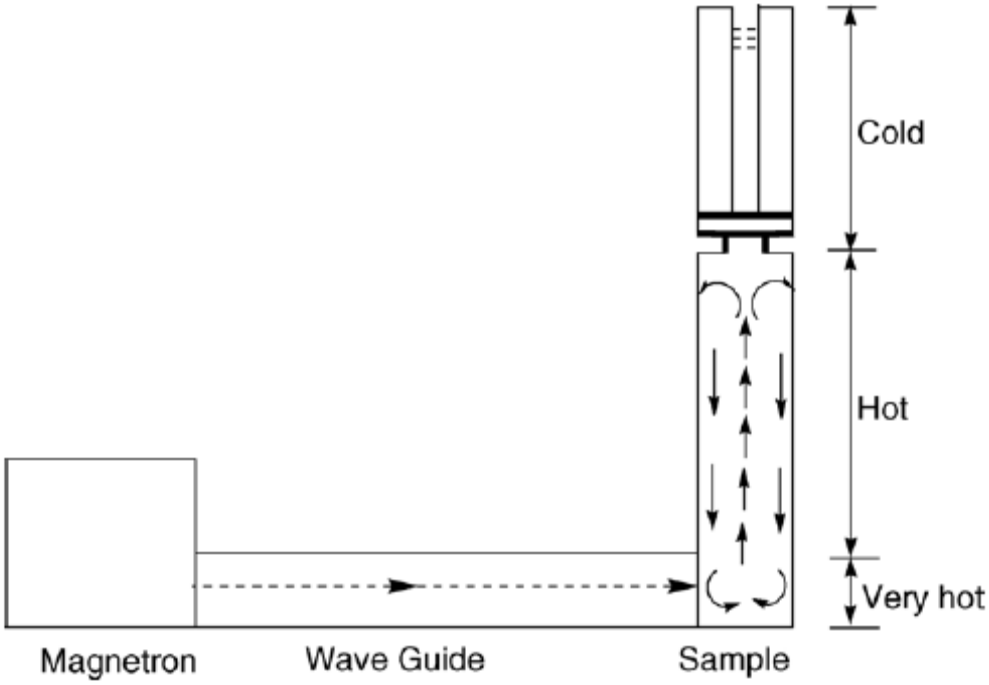
(2)Monomode Reactors

Domestic microwave ovens as multimode reactors are the most common instruments used in organic synthesis since they are comparatively inexpensive and readily available. Using domestic microwave cavity has done a lot of satisfying organic synthesis. However, the multimode reactors provide a field pattern with areas of high and low field strength, commonly referred to as “hot and cold spots.” This non-uniformity of the field leads to the heating efficiency varying drastically between different positions of the sample. In addition, domestic microwave ovens lack the ability to monitor and control temperature. All of these characteristics can lead to poor experimental reproducibility.

In order to carry out more accurately and safely organic reactions, microwave domestic ovens can be simply modified by piercing a hole on the top of cavity. This allows the introduction of tube (acting as a air cooler) surrounded by a water cooler to maintain reactions under solvent reflux, or under inert atmosphere or allowing the addition of compounds in multisteps procedures.



Multimode reactors



Monomode reactors

The single mode cavity, as the name implies, allows only a single mode to enter the cavity by waveguide. A properly designed monomode reactor can prevent the formation of “hot and cold” spots. This advantage is very important in organic synthesis since the actual heating pattern can be controlled. Therefore, higher reproducibility and predictability are achieved. In addition, higher power levels can be obtained in single mode systems. Nowadays, more sophisticated monomode reactors are available, such as the CSIRO continuous microwave reactor and the CSIRO microwave batch

reactor. These reactors allow temperature control via changing power and temperature monitoring with preinstalled digital thermometers. Moreover, some ovens even interface with Computers for reaction monitoring.

Reaction Medium:

In microwave-induced organic reaction, the reactions are carried out in solvent medium or on solid support in which no solvent is used.

Reactions in solvent medium, the choice of solvent is most important. The solvent used must have a dipole moment so as to absorb microwaves and a boiling point at least 20-30° higher than the desired reaction temperature.

An excellent energy transfer medium for many types of reactions in a domestic microwave oven is N,N-dimethyl formamide(DMF), a good solvent with high boiling point (160°C) and higher dielectric constant($\in$=36.7) . The solvent can retain water formed in a reaction, thus obviating the need for a water separator. The temperature can be raised to about 140°C without noticeable vapourization.

SOLVENT	**BOILING POINT**	**DIELECTIRIC CONSTANT (∈)**
Formamide	216°C	111
Methanol	65°C	32.7
Ethanol	78°C	24.6
Cholrobenzene	132°C	5.6

Hydrocarbon solvents such as hexane **(∈ =1.9)**, benzene **(∈ =2.3)**, toluene **(∈ =2.4)** etc, because of less dipole moment, are unsuitable as they absorb microwave radiations poorly. But the addition of small amounts of alcohol or water to these solvents can lead to dramatic coupling effects. Hence, a 1:4 ethanol: toluene mixture can be heated to boiling in few minutes in a standard microwave oven.

In solid reactions, the reaction is to perform on a solid state support (no solvent) which couples effectively with microwaves, examples of such solid supports are: phyllosilicates (M^{n+}– montomorillonite), silica and alumina.

Advantages:

The rapid heating capacity of the microwave leads to a considerable saving in dissolution or reaction time. Further, the use of microwave acceleration eliminated the need for heating baths and reaction flask and reflux condensers with ground glass joints. The smaller volume of solvent required contributed to a saving in cost and diminished the waste disposal problem.

Limitations:

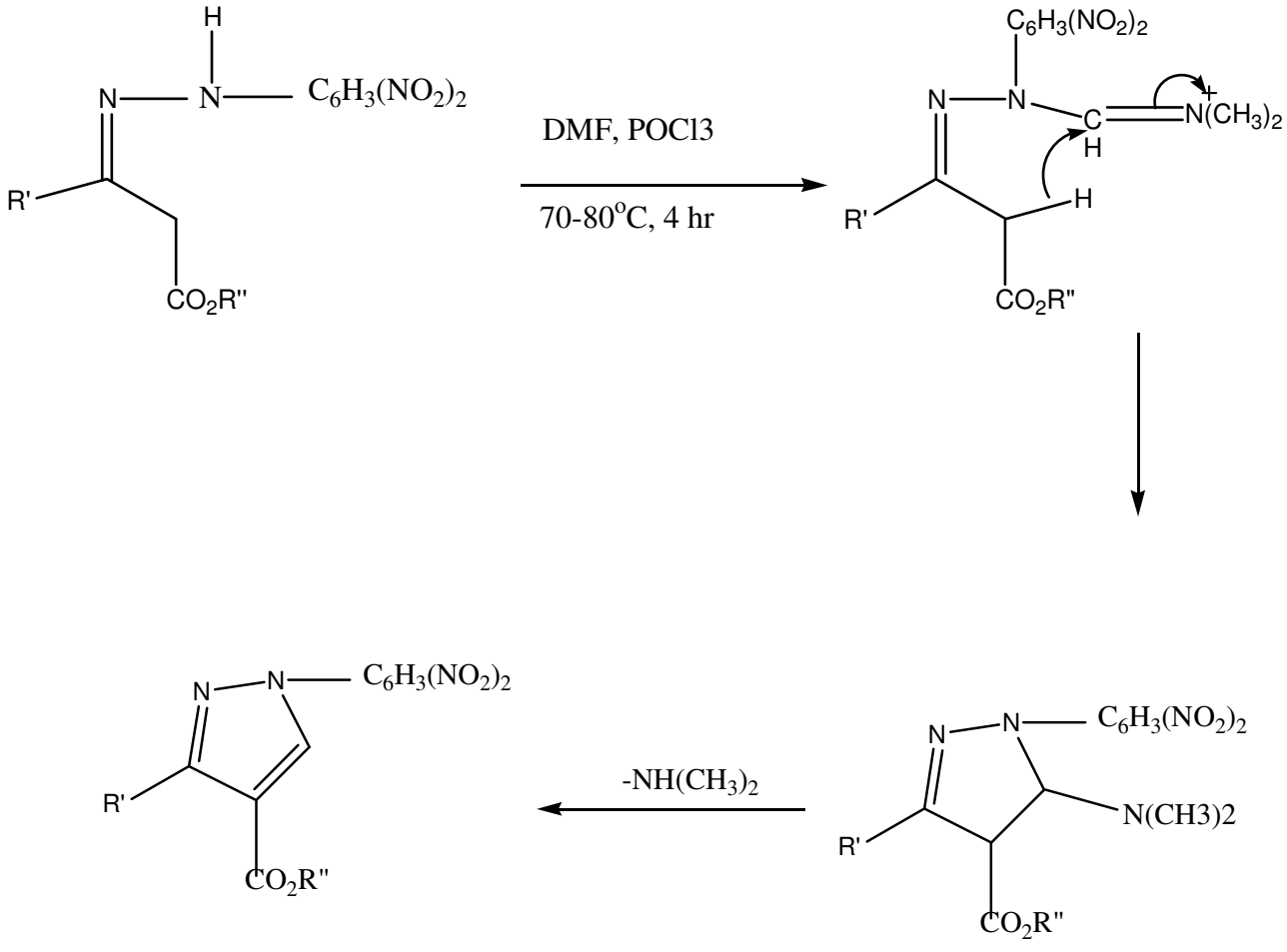
These procedures are strongly limited by the presence of solvents which reach their boiling points with in very sort time (1min) of exposure to microwaves. Consequently, high pressures are developed, thus leading to damage to vessels material or microwave oven itself and occasionally lead to explosions.

Precautions:

Long heating times and reactions using a large volume of reactants should be avoided because these conditions generate very high pressure in the vessel in some reactions. If the volume of the reaction mixture is kept between10 and 15% of the volume of the containers, the pressure will not exceed safe limits. To ensure a safe experiment, heating time of more than 5 min. at a power of 560 Watts should be avoided. Higher power levels should be avoided regardless of the heating times or the volume of the container.

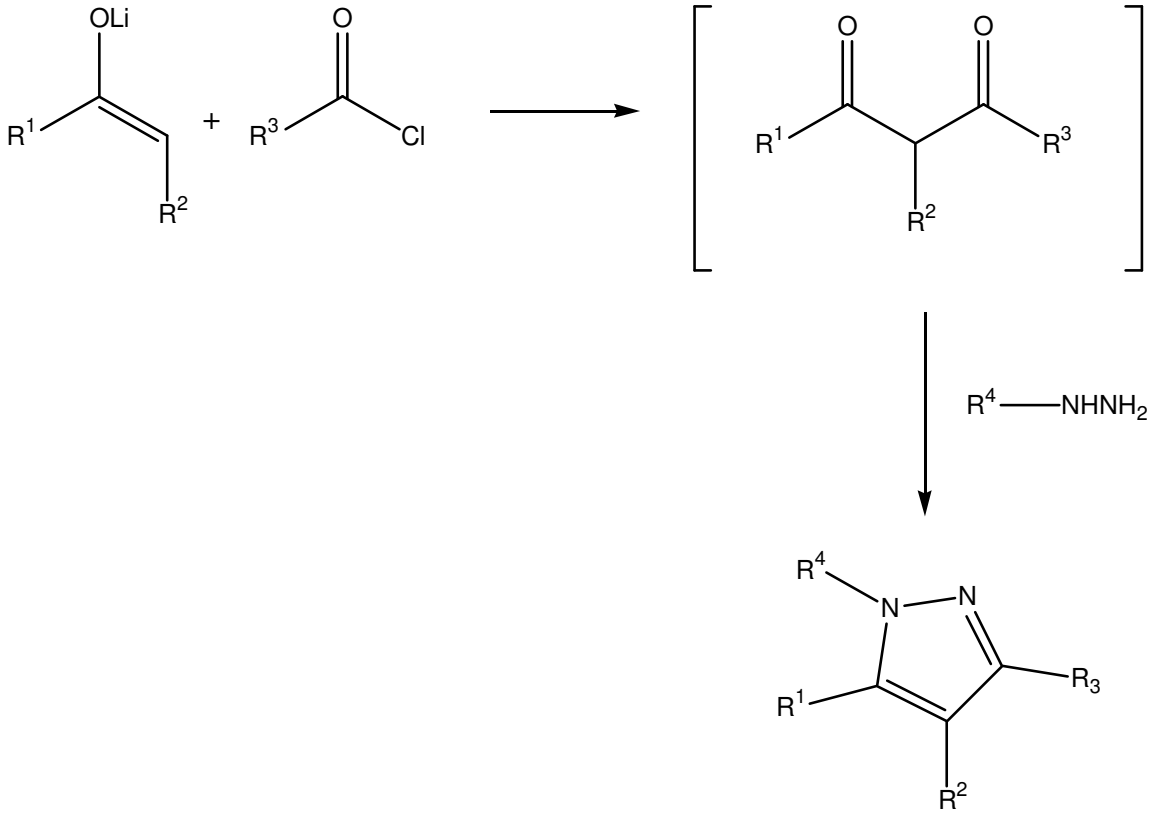
Review Work:

1. Hydrazones and semihydrazones of ketones yield pyrazoles upon treatment with vilsmeier reagent. 1H-pyrazole-4-carboxylate were synthesized according to the reported procedures from 2,4 Dinitro phenyl Hydrazones of β-keto esters upon treatment with DMF/ $POCl_3$.The ester group remains unaffected under the reaction condition and adds to the excellent yield of the pyrazole by increasing the acidity of active methylene proton. No further formylation takes place even with excess of reagent.

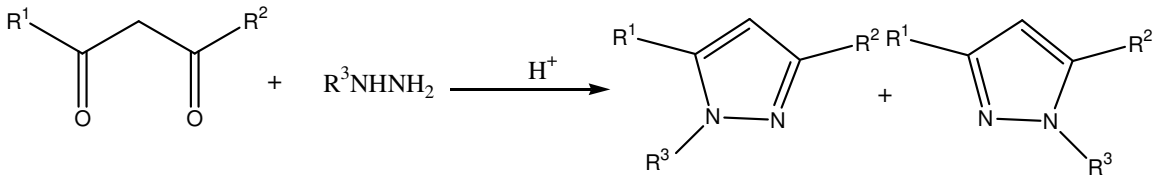


2. Pyrazole derivatives has been derived from 1,3-Diketones which was synthesized directly from ketones and acid chlorides and were then converted in situ into pyrazoles by the addition of hydrazine[19]. This

method is extremely fast, general and chemo selective, allowing for the syntheses of previously inaccessible pyrazoles and synthetically demanding pyrazole- containing fused ring



3. Solvent less reaction of 1,3-dicarbonyl compound with hydrazines[20] .



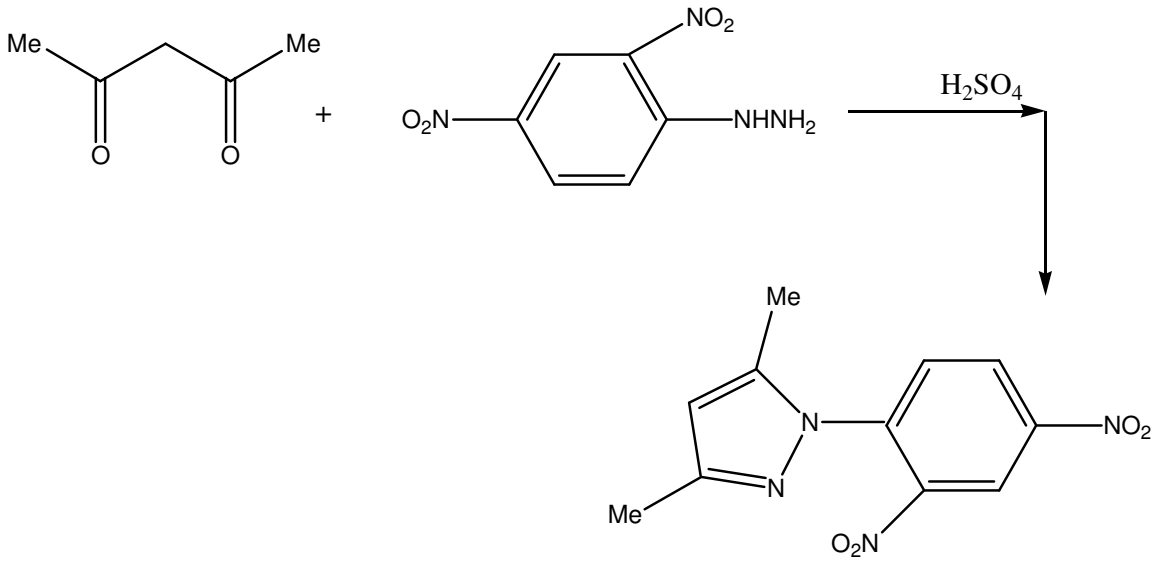
Application:

Microwave assisted syntheses of pyrazoles derivatives:

Experiment I

Reaction of acetyl acetone and 2,4-Dinitro phenyl hydrazine.

The method described is the dry condensation of acetyl acetone with 2,4-Dinitro phenyl hydrazine under microwave.



Procedure:

1 ml of acetyl acetone and 1.97gm of 2,4-Dinitro phenyl hydrazine was added in a mortar and mixed well.1-2 drops of conc. H_2SO_4 was added into the mortar in mixing conditions and mixed well. The mixture was then mixed with 3gms of silica-G. The resulting solid was irradiated with microwave for 2mins. After cooling, the solid was extracted with 10ml dichloro methane. The solvent was evaporated under rotatory evaporator and

the residue was washed with 10ml Diethyl ether. Dissolve the residue in 10ml ethyl acetate then purified through column chromatography and hence pure compound can be recrystallized under rotatory evaporator.

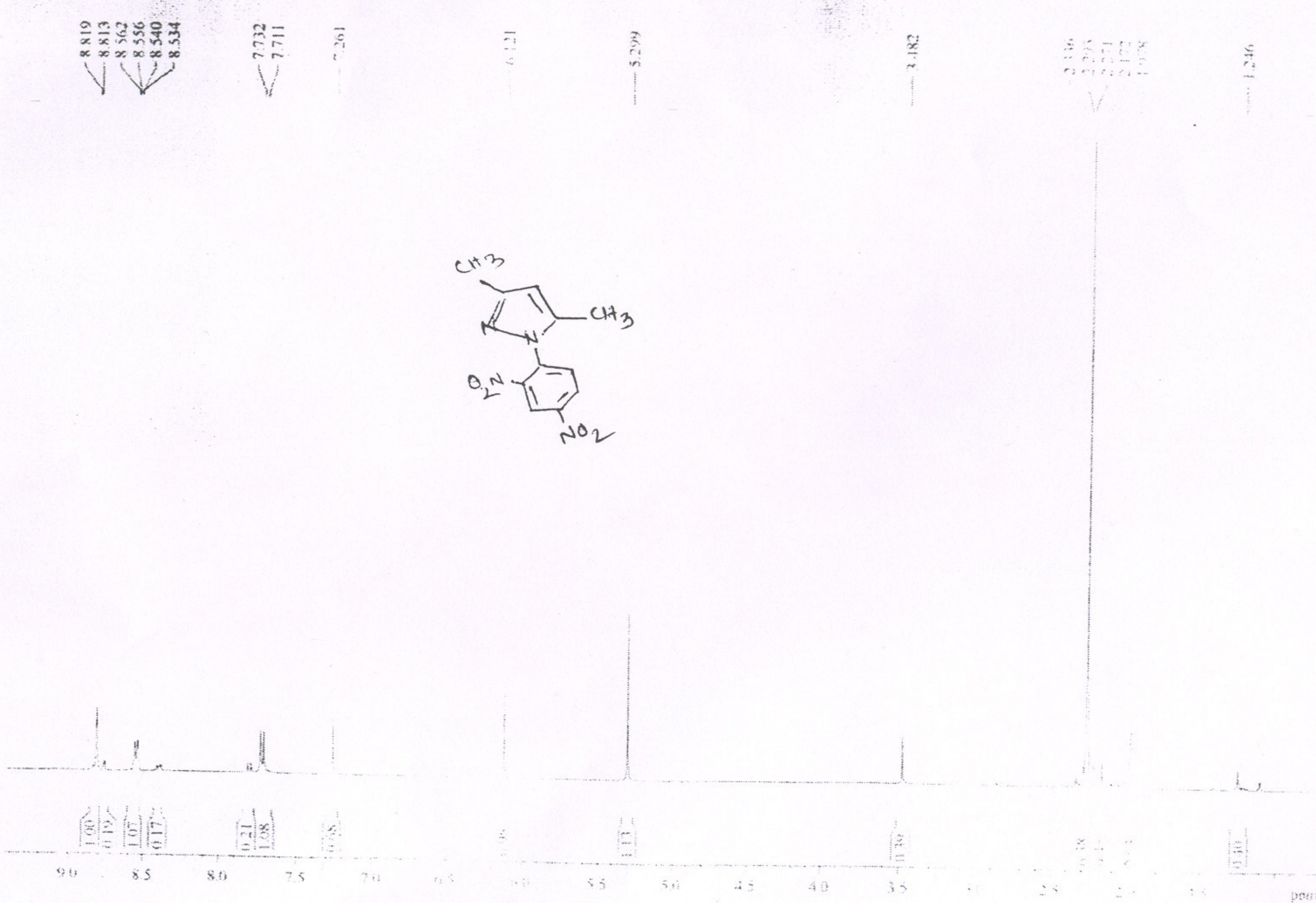
Yield:

84% pure product was obtained with little impurities having melting point 110^0c.

Analytical Data:

NMR sheet is provided for the resulting product.

PP / SAS / 150


8.819
8.813
8.562
8.556
8.540
8.534
7.732
7.711
7.261
5.299
3.182
1.246
CH3
CH3
O2N
NO2
N
1.00
0.19
1.07
0.17
0.21
1.08
1.13
0.30
9.0
8.5
8.0
7.5
7.0
5.5
5.0
4.5
4.0
3.5
ppm

Experiment II

Reaction of acetyl acetone and phenyl hydrazine.

The method described is the dry condensation of acetyl acetone with phenyl hydrazine under microwave.

Procedure:

1.02 ml of acetyl acetone and 0.98ml of phenyl hydrazine was added in a mortar and mixed well.1-2 drops of conc. H_2SO_4 was added into the mortar in mixing conditions and mixed well. The mixture was then mixed with 3gms of silica-G. The resulting solid was irradiated with microwave for 2mins. After cooling, the solid was extracted with 10ml dichloro methane. The solvent was evaporated under rotatory evaporator and the residue was washed with 10ml Diethyl ether. Dissolve the residue in 10ml ethyl acetate then purified through column chromatography and hence pure compound can be recrystallized under rotatory evaporator.

Yield:

Didn't get any desired product.

Analytical Data:

Didn't get any data related to desired product.

Experiment III

Reaction of Benzoyl acetone and 2,4 Dinitro phenyl hydrazine.

The method described is the dry condensation of Benzoyl acetone with 2,4-Dinitro phenyl hydrazine under microwave.

Procedure:

1gm of benzoyl acetone and 1.22gm of 2,4-Dinitro phenyl hydrazine was added in a mortar and mixed well.1-2 drops of conc. H_2SO_4 was added into the mortar in mixing conditions and mixed well. The mixture was then mixed with 3gms of silica-G. The resulting solid was irradiated with microwave for 2mins. After cooling, the solid was extracted with 10ml dichloro methane. The solvent was evaporated under rotatory evaporator and the residue was washed with 10ml Diethyl ether. Dissolve the residue in 10ml ethyl acetate then purified through column chromatography and hence pure compound can be recrystallized under rotatory evaporator.

Yield:

Didn't get any desired product.

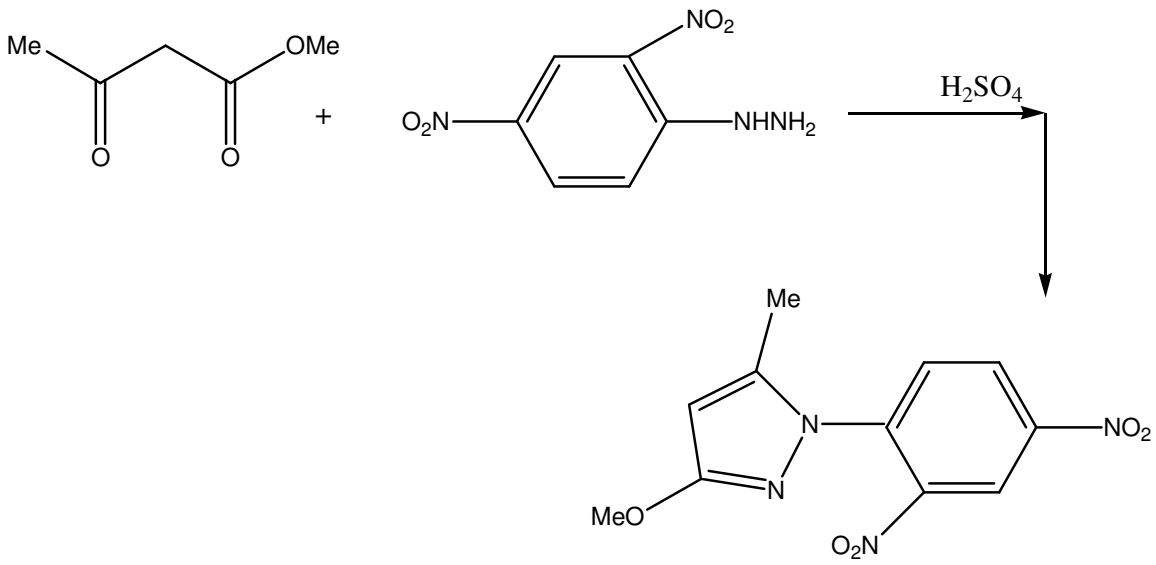
Analytical Data:

Didn't get any data related to desired product.

Experiment IV

Reaction of Methyl aceto acetate and 2,4 Dinitro phenyl hydrazine.

The method described is the dry condensation of Methyl acetoacetate with 2,4-Dinitro phenyl hydrazine under microwave.



Procedure:

1ml of Methyl acetoacetate and 1.gm of 2,4-Dinitro phenyl hydrazine was added in a mortar and mixed well.1-2 drops of conc. H_2SO_4 was added into the mortar in mixing conditions and mixed well. The mixture was then mixed with 3gms of silica-G. The resulting solid was irradiated with microwave for 2mins. After cooling, the solid was extracted with 10ml dichloro methane. The solvent was evaporated under rotatory evaporator and the residue was washed with 10ml Diethyl ether. Dissolve the residue in 10ml ethyl acetate then purified through column chromatography and hence pure compound can be recrystallized under rotatory evaporator.

Yield:

74% pure product was obtained with little impurities having melting point 117^0c.

Analytical Data:

NMR sheet is provided for the resulting product.

ppm
0.5
1.0
1.5
2.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
1.06
1.00
3.10
2.40
3.30
2.80
1.61
1.00

Conclusion:

This eco-friendly solvent-free approach using microwave irradiation opens numerous possibilities for conducting rapid heterocyclic synthesis using a variety of supported reagents on mineral oxides and phase transfer catalysis conditions. The use of multimode oven, monomode reactor and conventional glass apparatus, demonstrates the numerous practical applications in laboratory scale experiments. Furthermore, there are different advantages of these solvent-free protocols as "*Green Chemistry*" since they provide absence of solvent thereby preventing pollution in organic synthesis. The absence of solvent clearly reduces the reaction time and generally improves the yields. In fact it is noticeable that in several cases thermal effects play a determinant part in the rates and in the chemio and regio- or stereo selective heterocyclic synthesis. Additionally, there are many heterocyclic reactions with great potential for automated medicinal and combinatorial chemistry which traditionally have been performed with long reaction times that might be dramatically accelerated by solvent-free microwave irradiation. Today, new therapeutic hetero-macromolecular targets are increasingly being identified as drug targets. The lead generation and lead optimization processes must be accelerated. Traditional methods of organic heterocyclic synthesis are simply too slow to satisfy the future demand for compounds. Microwave assisted solvent-free chemistry is a technique that has the power to accelerate the generation of organic molecules.

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