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COMPARATIVE STUDY OF CONVENTIONAL AND MICROWAVE INDUCED SYNTHESIS OF SELECTED HETEROCYCLIC MOLECULES

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ABSTRACT: Microwave induced organic reaction enhancement (MORE) is a simple, clean, fast, efficient & economical method for the synthesis of organic molecules and has emerged as a tool towards green chemistry. This technique can reduce the time of chemical reaction from hours to minutes. Conventional methods of synthetic reactions need longer heating time, elaborate and tedious apparatus set up which result in higher cost and environmental pollution. The reaction rate of microwave induced organic reaction increases 10-1000 times and the yield of the product increases by 10-30 % compared to that by the conventional methods. We synthesized selected heterocyclic molecules by both conventional and MORE methods. The comparative study of conventional V/S MORE methodologies was carried where MORE method was found more efficient over conventional classical methods.
KEYWORDS: Heterocyclic molecules, Conventional synthesis, Microwave enhancement.

INTRODUCTION

Microwave induced organic reactions have emerged as a new 'Lead' in organic synthesis. The microwave enhanced chemical reactions are gaining importance due to the advantages and environmentally friendly processes they offer, as compared to conventional reaction[(1,2)]. Conventional methods of organic synthesis usually need longer heating time, elaborate and tedious procedures which result in higher cost of process and the excessive use of solvents, reagents leads to environmental pollution. Pharmaceutical chemistry laboratories use large quantities of toxic chemicals and solvents to perform reactions exposing laboratory persons including students and environment to related hazards. Review of literature states that in a majority of cases, the cause for the observed rate increase is a purely thermal/kinetic effect.it is a result of the high reaction temperature that is quickly attained when irradiation of polar materials is done in a microwave field. The microwave energy reduces the heat-up and cool-down time for reactions.It uses 50% less power than electric furnaces of equivalent capacity.The probable mechanisms involved in microwave heating are as follows.

1.Dipolarization: In case of polar dielectric molecules such as water,methanol and ethanol, the molecules get aligned with the oscillating microwave field by the influence of microwave radiation.If this oscillating field is of high frequency,intermolecular interactions prevent any

molecular movement before the field has reversed. In the same way, low frequency radiation causes uniform polarization and as a result, there is no molecular motion.For intermediate frequencies such as microwave frequencies, the applied field is of such character that polar molecules are not quite in position to keep itself up with the changing polarity of the same field.This results in random motion.As a result, heating through molecular collision takes place.

2. Ohmic heating: For materials to get conducted, the conductivity species,ions, electrons, etc, get movement through the material.This occurs under the influence of applied electric (microwave) field.This causes polarization.The induced currents cause heating through electric (ohmic) resistance.

3.Interfacial polarization: This type of polari zation occurs in composites of insulating materials and conducting materials.An example of this kind is metallic particles dispersed in dielectric (insulating) silicone matrices.When microwave field is applied to the composite, the surfaces of the metallic particles become polarized.Since the surface of the metallic particle is in contact with the dielectric matrix,this results in reduction of the polarization of particles. As a result,polarization of the particles does not occur instantaneously (10^{-18}s in a 2.4 GHz field).It remains behind the polarity of the applied field.This procedure is seen for the dielectric heating regime.It causes dissipation of the applied field and results in heating.[3,4]

In our laboratory, as part of our project, we have synthesized selective heterocyclic molecules using microwave induced methods [5,6,7]. The Micro wave technique was performed in domestic microwave oven (SUNFLAME) for synthesizing selective heterocyclic molecules. Similarly, the conventional synthesis of same were performed and compared with microwave induced synthesis method. It was found that the reaction time was comparatively less from hr to min and the % yield were found to be higher when compared to conventional method. During our synthetic studies, it was observed that the conventional method of synthesising selected heterocyclic molecules such as phenytoin, Acridone, Coumalic acid, Benzimidazole, N-phenyl-phthalimide and 2,3-diphenyl Quinoxaline required a reaction time of 2-15 hours while the yields were always poor (<50%) therefore it was felt worth while to study these reactions under microwave-induced technique with the aim of decreasing the reaction time and increasing the yield. The experiment like determination of saponification value, degradation of atropine, analysis of loss on drying could be performed within minutes[8,9] with the help of microwave assisted technique and are being used for routine practical classes. Each time the products were isolated, the % yield and quality of the products was compared with the one obtained by conventional method. Each reaction was repeated at least three times (different time intervals) and the products by studying their melting point and percentage yield the comparative results were tabulated in the Table No:1.

MATERIALS AND METHODS

All the chemicals used were obtained from S.D.Fine Chem .ltd,Mumbai,Qualigens Fine Chemicals,Mumbai,Himedia laboratories Pvt.Ltd,Mumbai and CDH (P) Ltd,Delhi. Heating was done in a domestic microwave oven (SUNFLAME).Melting points were determined in open capillaries using (SUNBIM) melting point apparatus expressed in °C and are uncorrected.

GENERAL PROCEDURE:

i) Phenytoin[10]:

Method A (Conventional):

A mixture of 5.3 gm of benzyl,3gm of urea,15 ml of 30% aqueous sodium hydroxide and 25 ml of ethanol was taken in a 100 ml round bottomed flask.The reflux condensation was carried out for 2 hours. Then,the mixture was cooled to room temperature and the solution was poured into 125 ml of water, mix thoroughly and allowed it to stand for 15 minutes. Then, the solution was filtered under suction and filtrate was made strongly acidic with concentrated hydrochloric acid, cooled in ice water, filtered and recrystallised from industrial spirit.

Method A'(Microwave):

A mixture of 5.3 gm of benzyl,3 gm of urea,15 ml of 30% aqueous sodium hydroxide and 25 ml of ethanol was taken in a beaker. The beaker was then placed in a domestic microwave oven (SUNFLAME) at 190 watts for 6 minutes. Then, the mixture was cooled to room temperature and the solution was poured into 125 ml of water, mix thoroughly and allowed it to stand for 15 minutes.

Then, the solution was filtered under suction and filtrate was made strongly acidic with concentrated hydrochloric acid,cooled in ice water, filtered and recrystallised from industrial spirit.

Acridone[11]:

Method –B (Conventional) :

A mixture of 4 gm of N-Phenyl anthranilic acid and 10 ml of concentrated sulphuric acid was taken in a conical flask and heated for 1.5 hours on a steam bath. Then the hot dark green solution was poured slowly and continuously into 200 ml of boiling water in 500 ml beaker allowing the acid to run down from the sides of the beaker to prevent spattering. Then the mixture was boiled for 5 minutes and filtered while hot. The crude product was washed with hot water and recrystallised from acetic acid using charcoal.

Method-B' (Microwave):

A mixture of 4 gm of N-Phenyl anthranilic acid and 10 ml of concentrated sulphuric acid was taken in a conical flask and the reaction mixture was kept in a domestic microwave oven at 250 watts for 4 minutes. Then the hot dark green solution was poured slowly and continuously into 200 ml of boiling water in 500 ml beaker allowing the acid to run down from the sides of the beaker to prevent spattering. Then the mixture was boiled for 5 minutes and filtered while hot. The crude product was washed with hot water and recrystallised from acetic acid using charcoal.

ii) Coumalic acid[12]:

Method –C (Conventional):

25 ml of sulphuric acid was added to 20 gms of finely powdered malic acid which was taken in a 2 litre round bottomed flask. Three 15 ml portions of fuming sulphuric acid (25% So_3) was added at intervals of 45 minutes. A slight exothermic reaction occurred with the steady evolution of gas. Then the mixture was swirled frequently to obviate excessive foaming and when the evolution of gas had slackened, the reaction mixture was heated on a water bath for 2 hours. Then the mixture was cooled and poured into 80 gms of ice with stirring. The mixture was then kept aside in a refrigerator for 24 hours, filtered the crude coumalic acid and washed with small portions of ice water. The crude product was recrystallised from methanol.

Method-C' (Microwave):

A mixture of 2 gms of malic acid with 4 ml of concentrated sulphuric acid was added with 3 portions of 1.5 ml of fuming sulphuric acid with 45 minutes time interval . Then the beaker was placed in a domestic microwave oven at 250 watts for 4 minutes. Then, adequate amount of ice was added and kept in the refrigerator for about 24 hours. The product was filtered and recrystallised from methanol.

iii) Benzimidazole[13]:

Method-D (Conventional):

In a 250 ml round bottomed flask fitted with a condenser, a mixture of 27 gm of O-Phenylene diamine and 17.5 gm (16 ml) of 90% formic acid was refluxed thermally at 100°C for 2 hours. The reaction mixture was cooled and 10% sodium hydroxide solution was added slowly, then the crude product was washed with ice cold water, dissolved in 400 ml of boiling water for recrystallization, filtered and dried at 100°C.

Method D' (Microwave):

In a conical flask a mixture of 27 gm of O-Phenylene diamine and 17.5 gm(16 ml) of 90% formic acid was taken. Then the conical flask was placed in a domestic microwave oven at 100 watts for 6 minutes. The reaction mixture was cooled and 10% sodium hydroxide solution was added slowly, then the crude product was washed with ice cold water, dissolved in 400 ml of boiling water for recrystallization, filtered and dried at 100°C.

iv) N-Phenyl Phthalimide[14]:

Method-E (Conventional):

A mixture of 1 gm of aniline and 1 gm of phthalic anhydride was dissolved in 10 ml of glacial acetic acid. The solution was transferred into 100 ml round bottomed flask and refluxed for 1 hour. Then, the crude product was separated, filtered and recrystallised from ethanol.

Method-E'(Microwave):

A mixture of 1 ml of aniline and 1 gm of phthalic anhydride was dissolved in 10 ml of glacial acetic acid contained in a 25 ml beaker and placed in a domestic microwave oven at 250 watts for 4 minutes. Then, the crude product was separated, filtered and recrystallised from ethanol.

v) 2,3-Diphenyl Quinoxaline[15]:

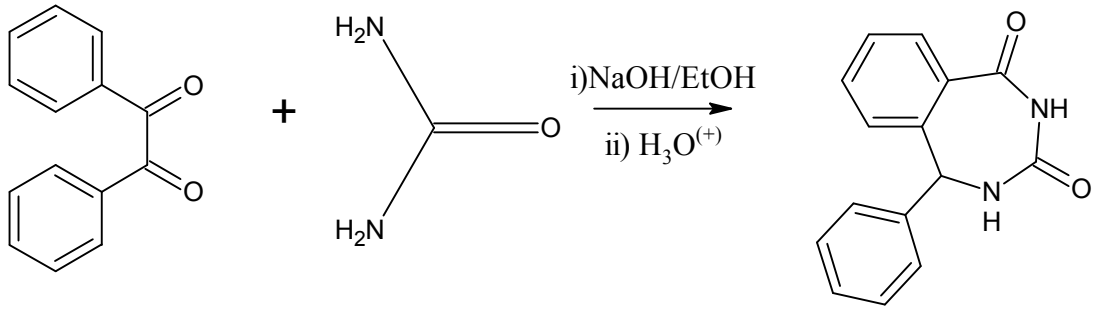
Method-F (Conventional):

1.26 gm of benzil was dissolved in 8 ml of warm rectified spirit and transferred into 100 ml round bottomed flask containing 1.08 gm of O-Phenylene diamine dissolved in 8 ml of rectified spirit. The mixture was refluxed for 1 hour on a boiling water bath. Then, water was added until slight cloudiness persists. The crude product was filtered and recrystallised from rectified spirit.

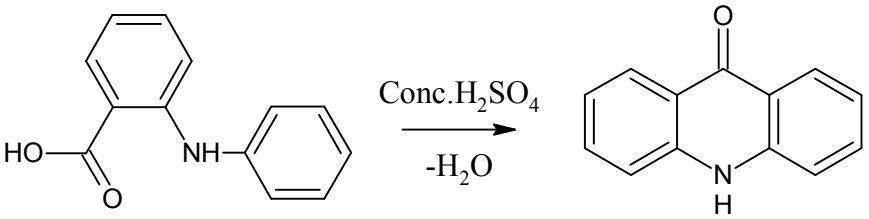
Method-F' (Microwave):

1.26 gm of benzil was dissolved in 8 ml of warm rectified spirit and transferred into 100 ml beaker containing 1.08 gm of O-Phenylene diamine dissolved in 8 ml of rectified spirit. The beaker was placed in a domestic microwave oven at 250 watts for 4 minutes. Then water was added until slight cloudiness persists. The crude product was filtered and recrystallised from rectified spirit.

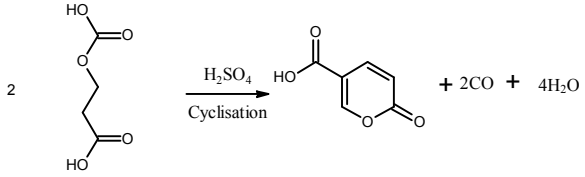
Reactions:



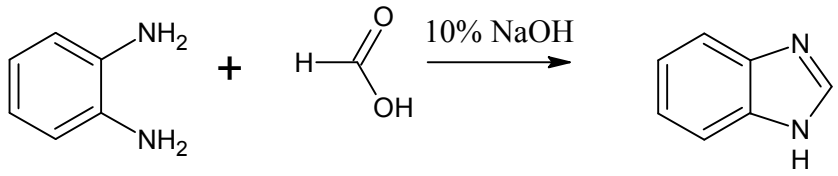
Benzil **Urea** **Phenytoin**



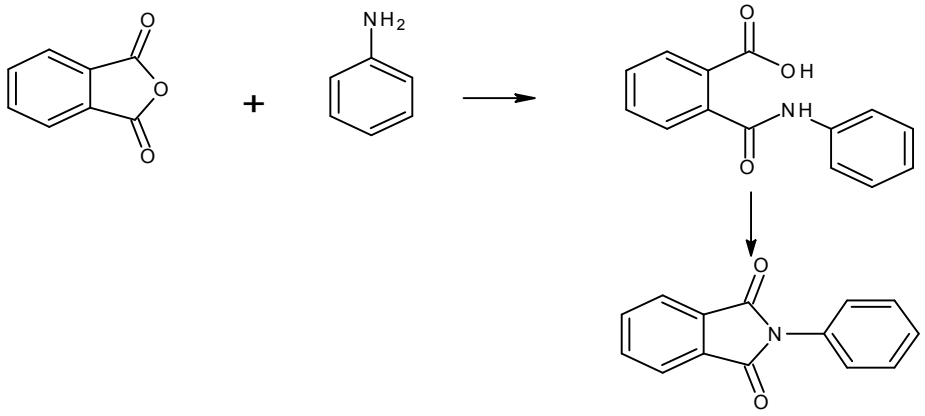
N-Phenyl anthranilic acid **Acridone**



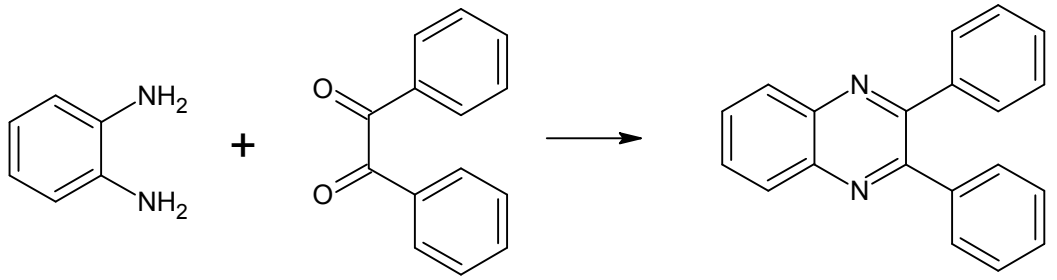
Malic acid **Coumalic acid**



O-Phenylene Diamine **Formic acid** **Benzimidazole**



Phthalic anhydride **Aniline** **N-Phenyl phthalimide**



O-Phenylene Diamine **Benzil** **2,3-Diphenyl Quinoxaline**

RESULTS AND DISCUSSION

The microwave heating effectively reduced the reaction time from 2-15 hours to a few minutes (2-8 minutes).By using microwave radiation for heating, all the six compounds were prepared in yields that were appreciably higher than the conventional methods (Table-1).

Highest yield improvement was observed for all the six compounds(a-f) when compared with conventional method. From the results,it was observed that the melting point and reaction time for the six compounds such as Phenytoin (295-297°C, 6 minutes), Acridone(296-298°C,4 minutes),Coumalic acid(206-208°C,4 minutes), Benzimidazole(170-172°C,6 minutes),N-Phenyl phthalimide(190-202°C,4 minutes) and 2,3-Diphenyl quinoxaline(111-113°C,4 minutes) were much better when compared to the conventional method .

CONCLUSION

From the above result, it would be concluded that the microwave assisted method is a efficient,fast,simple and environment friendly method for the synthesis of a large number of organic heterocyclic molecules. In addition the yield is also increased. Hence it is a viable and feasible method for performing the synthesis of drug, intermediates and chemicals.

Table-1: Physical data of heterocyclic molecules (a-f) and comparative study of conventional vs microwave method

COMPOUND	MP(° C)	CONVENTIONAL METHOD		MP(°C)	MICROWAVE METHOD	
		Time (hours)	% yield		Time (minutes)	% yield
a	294-299	2-2.5	75	295-297	6	80
b	295-300	1.5-2	70	296-298	4	85
c	206-208	2-2.5	62	206-208	4	80
d	168-173	2-2.5	85	170-172	6	94
e	185-205	1-1.5	80	190-202	4	92
f	110-114	1-1.5	75	111-113	4	85

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