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Microwave Assisted Synthesis of Heterocycles- Green Chemistry Approaches

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Abstract : Green Chemistry is an approach to the synthesis, processing and use of chemicals that reduces risks to humans and the environment. The green chemistry involve use of techniques that contributions to achieve efficient, safe and clean conversions that are becoming general synthetic procedures. Present study focus on application of Microwave in synthesis of heterocycle compounds. The study shows that microwave assisted synthesis is one of the emerging tool with efficiency, time and cost effectiveness in organic synthesis. The compounds obtain in good yield as compared to the conventional method. Time required for synthesis is also reduced significantly by microwave irradiation. Compounds like Benzimidazole, Hanzsch dihydropyridine, coumarine and quinoxaline obtain in good yield with less time as compared to conventional synthesis.

Key Words: Microwave Assisted Synthesis, Green Chemistry, Benzimidazole, Hanzsch dihydropyridine, Biginelli Reaction.

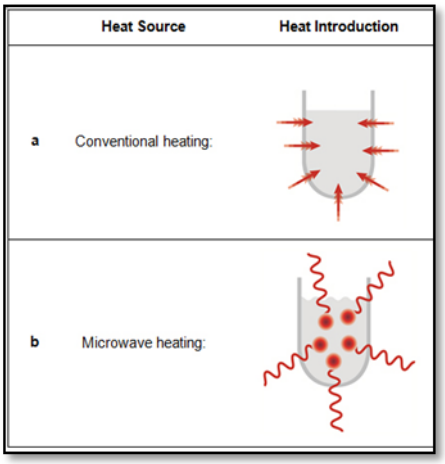
Introduction:[1,2,5]

The term Green Chemistry is defined as "The invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances". A robust, efficiency, and cost effective chemical process is required for acceptance in process chemistry. The synthetic schemes in green chemistry are designed in such a way that there is least pollution to the environment. Conventional methods for various chemical syntheses is very well documented and practiced. Microwave assisted organic synthesis has emerged as a new "lead" in organic synthesis. The technique offers simple, clean, fast, efficient, and economic conversion for the synthesis of a large number of organic molecules. In the recent year microwave assisted organic reaction has emerged as new tool in organic synthesis. Conventional method of organic synthesis usually need longer heating time, tedious apparatus setup, which result in higher cost of process and the excessive use of solvents/ reagents lead to environmental pollution. This growth of green chemistry holds significant potential for a reduction of the by product, a reduction in waste production and a lowering of the energy costs. Microwave heating refers the use of electromagnetic waves ranges from 0.01m to 1m wave length of certain frequency to generate heat in the material. They are defined as those waves with wavelengths between 0.01 metre to 1meter corresponding to frequency of 30GHz t 0.3GHz.

Principle of Microwave Heating:[2,3]

The basic principle behind the heating in microwave oven is due to the interaction of charged particle of the reaction material with electromagnetic wavelength of particular frequency. The phenomena of producing heat by electromagnetic irradiation are ether by collision or by conduction, some time by both.

Two basic principal mechanisms involve in the heating of material



1) Dipolar Polarization:

Dipolar polarisation is a process by which heat is generated in polar molecules. On exposure to an oscillating electromagnetic field of appropriate frequency, polar molecules try to follow the field and align themselves in phase with the field. Dipolar polarisation can generate heat by either one or both the following mechanisms:

1. Interaction between polar solvent molecules such as water, methanol and ethanol
2. Interaction between polar solute molecules such as ammonia and formic acid

2) Conduction mechanism:

The conduction mechanism generates heat through resistance to an electric current. The oscillating electromagnetic field generates an oscillation of electrons or ions in a conductor, resulting in an electric current. This current faces internal resistance, which heats the conductor.

Microwave heating is different from conventional heating in many respects.

Reaction may be carried out with solvent or without solvent in microwave with prevent the use of excessive solvent and are environment friendly.

Advantage and Disadvantage of Microwaves[2,4,5]

Advantages

- Rapid reactions
- High purity of products
- Less side-products
- Improved yields
- Simplified and improved synthetic procedure
- Wider usable range of temperature
- Higher energy efficiency
- Sophisticated measurement and safety technology
- Modular systems enable changing from mg to kg scale.

Disadvantages

- Heat force control is difficult
- Water evaporation
- Closed container is dangerous because it could be burst

Material and Method:

In this research work, the melting points of synthesized compounds were determined by open capillary tubes using paraffin bath and are uncorrected. Thin layer chromatography is among the most useful tools for following the progress of organic chemical reactions and for assaying the purity of organic compounds. Thin Layer Chromatography was performed using Silica Gel coated on glass plates and precoated Aluminum sheets (E-Merck) and the spots were visualized, by exposure to iodine vapors. IR spectra were recorded on a Agilent FTIR (ATR) spectrophotometer Model no.- Cary-630 from Core Analytical Laboratory, Nashik. NMR spectra of the compounds were recorded on a VARIAN, Mercury Plus 300MHz NMR spectrometer, in DMSO solvent, using TMS as an internal standard and GC-MS spectra & chromatogram were recorded on 7890 - AccuTOF GCV Agilent- Jeol instrument from SAIF, IIT, Mumbai.

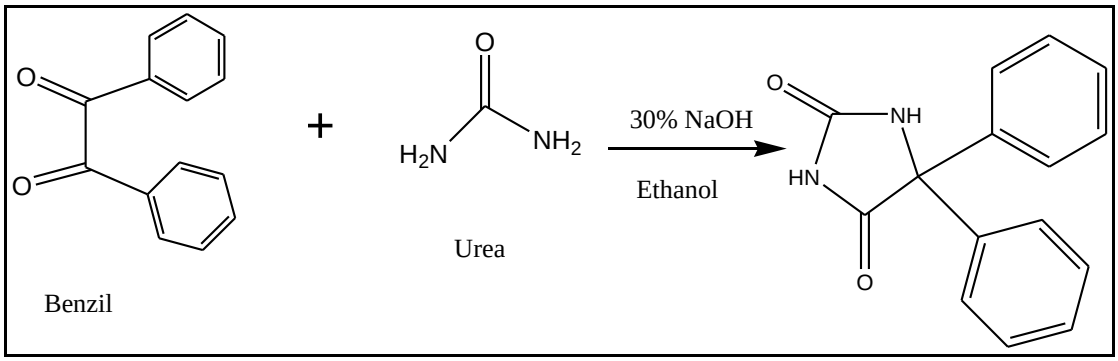
Experimental Work

1. MS-1: Synthesis of Phenytoin[1,6,7]

A. MW assisted reaction: In a 250 ml RBF , a mixture 2.0 gms of benzil and 1.13 gms of urea were taken in ethanol, to it was 30 % NaOH solution was added and the reaction was subjected to microwave at 425W for 10 min, Intermittently TLCs were recorded. Reaction mixture was rendered acidic with conc. HCl. The product obtained was separated by filtration at the pump washed with alcohol.

B. Conventional synthesis: Approximately 3 hrs of reflux is required to obtain the product using the equimolar quantities.

IR (FTIR-ATR)- Vmax (cm^{-1}): 3657.16 (N-H str), 2839.31 (C-H str), 1748.20, 1745.87 (C=O str), 1589.40(N-H bend), 1226.77 (C-N str), 757.55 (C-H Ar); ^{1}H NMR (300MHz) (DMSO), δ (ppm): 7.20-7.62 (m, 10H, Ar-H) 5.84 (s, 1H,N-1), 9.35 (s, 1H,N-3); EI-MS (m/e): 252 (M^{+})

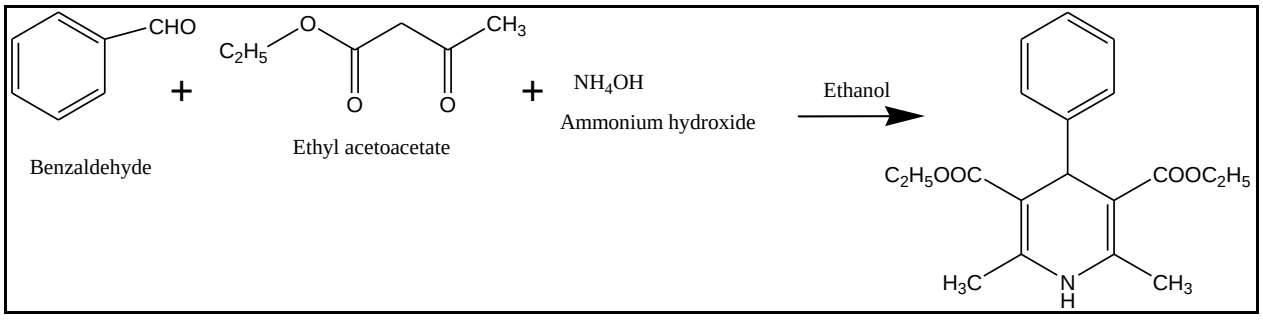


2. MS-2: Synthesis of Hanzsch dihydropyridine[6]

A. Microwave assisted reaction: In RBF a solution of 1.6 ml Benzaldehyde, 2.8 ml Ethyl acetoacetate and 1 ml conc. Ammonium Hydroxide in 6 ml of ethanol at 225 W for 15 min. to resulting solution 10 ml of warm water was added and cooled in ice water to obtain product. The product was purified by 60% aqueous ethanol.

B. Conventional synthesis: 3 hrs of reflux is required to obtain product.

IR (FTIR-ATR)- Vmax (cm^{-1}): 3340.0 (N-H str), 2982.2 (C-H str), 1685.7 (C=O ester), 1648.9 (C-N str), 1452.0 (N-H bend), 1297.6 (C-H Aliphatic), 1207.2 (C-O ester alkyl), 1089.7 (C-O ester acyl), 765.4 (C-H Ar); ^{1}H NMR (300MHz) (DMSO), δ (ppm): 7.08-7.29 (m, 5H, Ar-H), 5.7 (s, 1H, NH), 4.11-4.13 (q, 4H, CH_2), 1.19-1.24 (t, 6H, CH_3), EI-MS (m/e): 327(M^+)



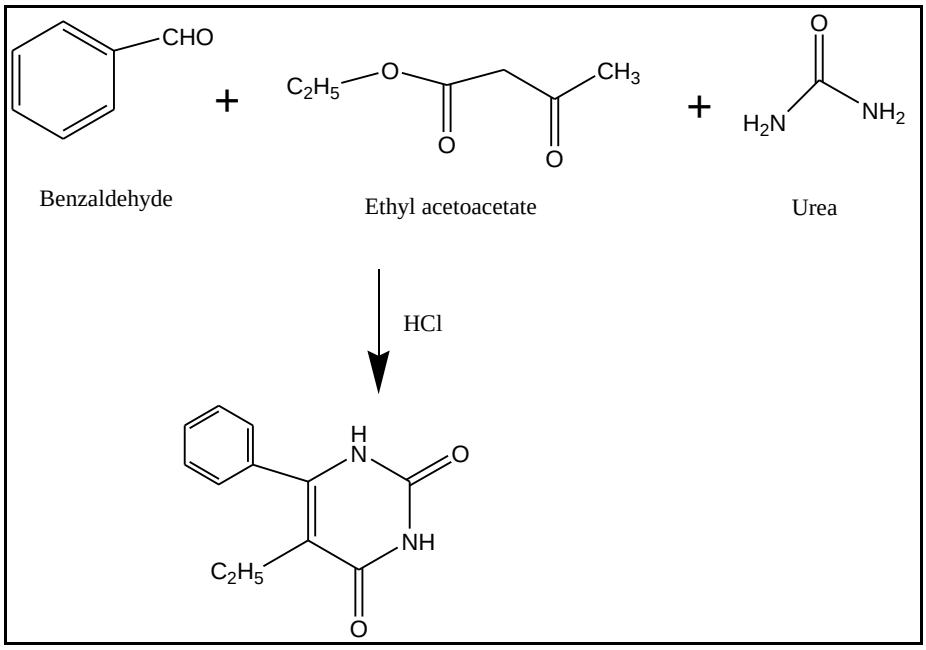
3. MS-3: Synthesis of Tetrahydro pyrimidinedione (Bignelli Condensation) [1,]

A. Microwave assisted reaction: In a 250ml RBF, an equimolar mixture of aromatic aldehyde, ethylacetoacetate and urea were taken. To this few drops of concentrated Hydrochloric acid is added as catalyst. The reaction was subjected to microwave at 225W and monitored on TLC intermittently for 12min. After 12 min, the product was washed with ethyl acetate and alcohol to obtain pure compound. Further recrystalized from ethanol.

B. Conventional synthesis: Approximately 2 hrs of reflux is required to obtain product by using equimolar quantities.

IR (FTIR-ATR)- Vmax (cm^{-1}): 3474.9 (N-H str), 2919.2 (C-H str), 1671.1 (C=O Amide), 1611.7 (N-H bend), 1550.7 (C-N str), 1508.1 (C-O ester acyl), 1341.3 (C-H Aliphatic), 1192.4

(C-O ester alkyl), 816.9 (C-H Aromatic)

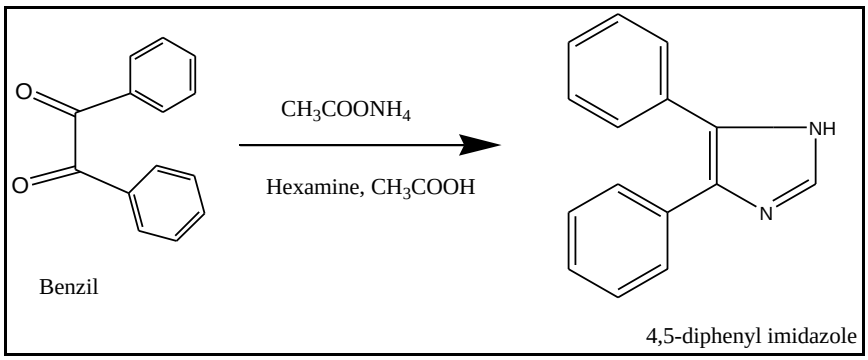


4. MS-4: Synthesis of 4,5-Diphenylimidazole[7]

A. Microwave assisted reaction: In RBF, a solution of 2.1 gms of benzil, 0.26 gm of hexamine and 6 gm of ammonium acetate in 50 ml of Glacial acetic acid heated at 340 W for 7 min. After cooling resulting solution added to water and turbidity was removed by adding carbon followed by stirring and filtration. The product obtained by basifying the filtrate with concentrated ammonium hydroxide.

B. Conventional synthesis: 1 hrs of reflux is required to obtain product.

IR (FTIR-ATR)- Vmax (cm^{-1}): 3266.7 (N-H str), 3143.8 (C-H str, Ar), 3093.7 (C-H str, Aliphatic), 1668.7 (C=C str), 1599.1 (C=N str), 1552.1 (N-H bend), 1496.8 (C-H bend), 1442.2 (C-N str) , 747.3 (C-H Aromatic).



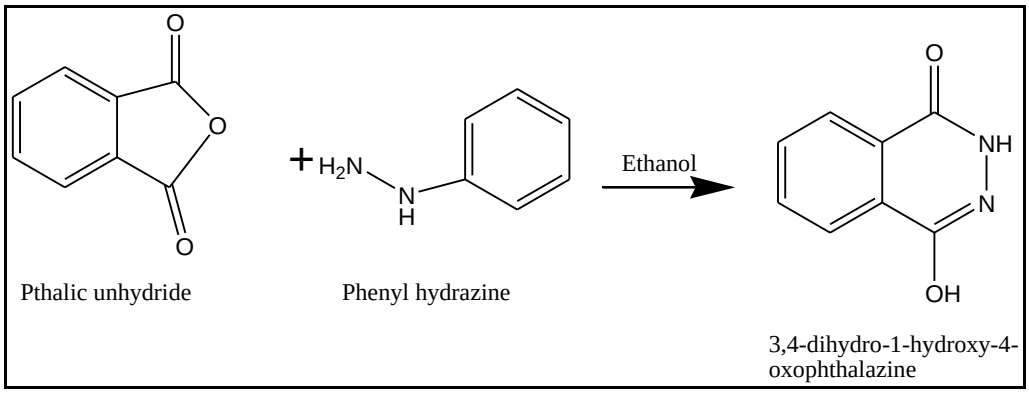
5. MS-5: Synthesis of 3,4-dihydro-1-hydroxy-4-oxophthalazine. [7]

A. Microwave assisted reaction: In RBF a solution of 1ml of hydrazine hydrate and 3 gm phthalic anhydride in 25 ml ethanol heated at 100^0 C for 6 min at 340W. The product obtained by cooling and washed with Petroleum ether.

B. Conventional synthesis: 45 min of reflux is required to obtain product.

IR (FTIR-ATR)- Vmax (cm^{-1}): 3158.2 (O-H str), 3005.1 (N-H Amide), 2882.5 (C-H str Ar),

1655.0 (C=O Amide), 1598.3 (C=N imine), 1489.1 (N-H bend), 1080.5 (C-N Amide), 779.1 (C-H bend Ar); ^{1}H NMR (300MHz) (DMSO), δ (ppm): 7.33-8.38 (m, 4H, Ar-H), 7.26 (s, 1H, NH), 2.51 (s, 1H, OH); EI-MS (m/e): 162 (M^+)

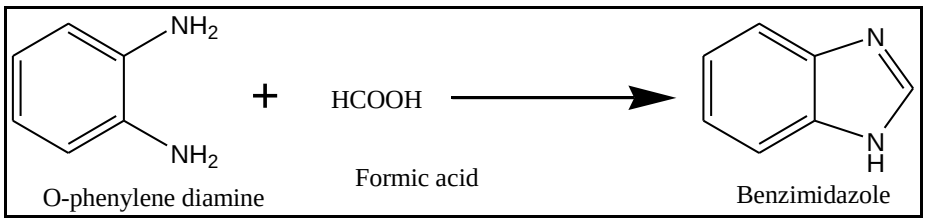


6. MS-6: Synthesis of Benzimidazole. [6,7]

A. Microwave assisted reaction: In RBF a solution of 2.7 gm of o-phenylene diamine and 1.6 ml of 90% formic acid was heated at 595W for 7 min. After 7 min reaction mixture was cooled and 10% sodium hydroxide added to precipitate crude Benzimidazole, which was recrystallised from water using little decolorizing Charcoal.

B. Conventional synthesis: 2 hours of reflux is required to obtain product.

IR (FTIR-ATR)- Vmax (cm^{-1}): 3525.99 (N-H str), 1589.40 (C=N str), 1496.42 (N-H bend), 1250.77 (C-N str), 758.41 (C-H Ar); ^{1}H NMR (300MHz) (DMSO), δ (ppm): 7.26-7.69 (m, 4H, Ar-H), 5.89 (s, 1H, NH), 8.14 (s, 1H, CH); EI-MS (m/e): 118 (M^+)

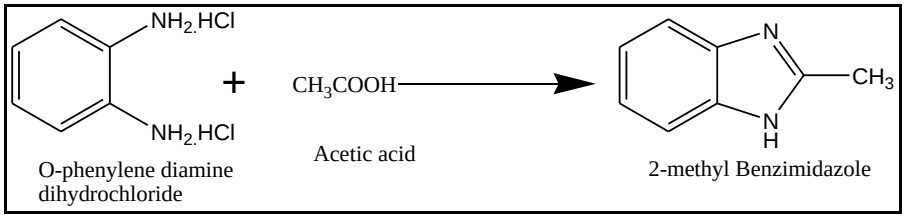


7. MS-7: Synthesis of 2- methyl Benzimidazole. [6,7]

A. Microwave assisted reaction: In RBF a solution of 5.3 gm of o-phenylene diamine dihydrochloride, 5.4 gm glacial acetic acid and 20 ml of water was irradiated at 425W for 8 min. After 7 min reaction mixture was cooled and made basic with gradual addition of conc. Ammonia solution. The product was recrystallised from 10% aqueous ethanol using little decolorizing Charcoal.

B. Conventional synthesis: 45 min of reflux is required to obtain product.

IR (FTIR-ATR)- Vmax (cm^{-1}): 3525.99 (N-H str), 1589.40 (C=N str), 1496.42 (N-H bend), 1250.77 (C-N str), 758.41 (C-H Ar);

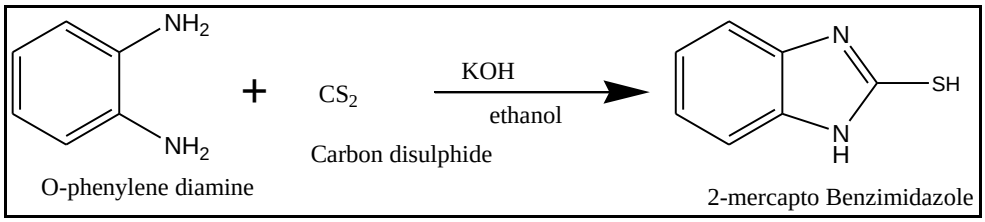


8. MS-8: Synthesis of 2-mercapto Benzimidazole. [6,7]

A. Microwave assisted reaction: In RBF a solution of 1.08 gm of o-phenylene diamine, 0.565 gm of Potassium hydroxide, 0.767 gm of carbon disulfide, 10 ml of 95% ethanol and 5 ml of water was irradiated at 425W for 5 min. 1 gm of charcoal was added and irradiated at 425W for 1 min. The product obtain after cooling by acidifying with dilute acetic acid with good stirring, which was recrystallised from ethanol.

B. Conventional synthesis: 3 hours of reflux is required to obtain product.

IR (FTIR-ATR)- Vmax (cm^{-1}): 3522.13 (N-H str), 2881.75 (C-H str), 2573.13 (S-H str), 2453.54 (C-S str), 1668.46 (C=N str), 1558.63 (N-H bend), 1182.27 (C-N str), 789.43 (C-H Ar).

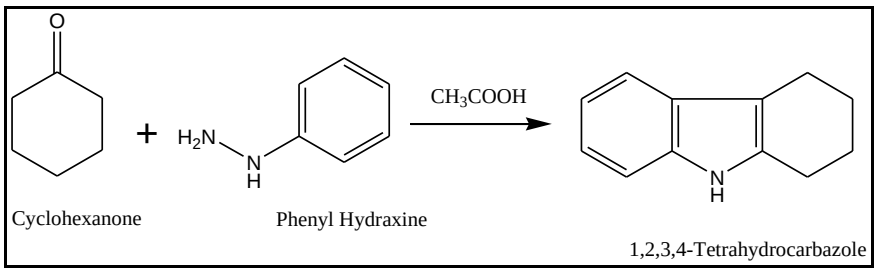


9. MS-9: Synthesis of 1,2,3,4-Tetrahydrocarbazole[1,6,7]

A. MW assisted reaction: In 250 ml RBF, mixture of equimolar quantities of cyclohexanone and redistilled phenyl hydrazine was placed with few drops of glacial acetic acid, then subjected to microwave at 340W for 10 min. then the reaction mixture was cooled to 5^0C. The above mixture was filtered at pump and the filtered solid was washed with cold water.

B. Conventional Synthesis: Approximately 2 hours of reflux followed by procedure remaining same from cooling at 5^oC.

IR (FTIR-ATR)- Vmax (cm^{-1}): 3193.2 (N-H str), 1768.7 (C=C str), 1714.7 (N-H bend), 1396.8 (C-H Alphatic), 743.8 C-H (Aromatic).

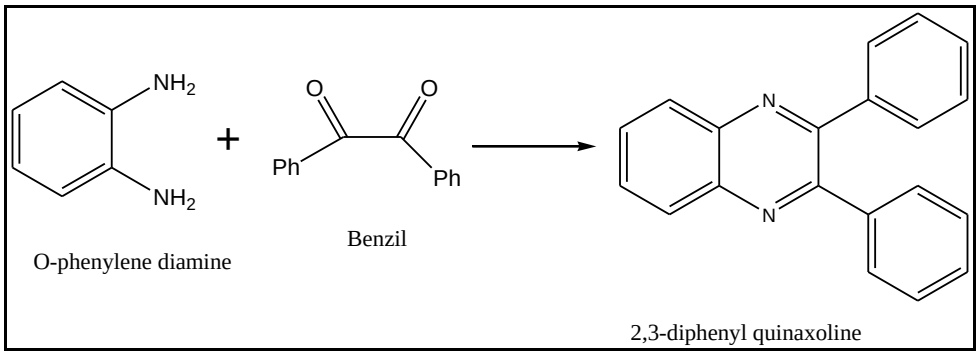


10. MS-10: Synthesis of 2,3-diphenyl quinaxoline[6,7]

A. Microwave assisted reaction: In RBF a solution 1.1 gm of o-phenylene diamine, 2.1 benzil and 8 ml of rectified spirit was irradiated at 525W for 3 min. The product obtains after cooling in ice water, which then recrystallised from ethanol.

B. Conventional synthesis: 30 min of reflux is required to obtain product.

IR (FTIR-ATR)- Vmax (cm^{-1}): 3211.7 (C-H Ar), 1671.6 (C=N imine), 1594.0 (C=C Ar), 771.7 (C-H Ar); ^{1}H NMR (300MHz) (DMSO), δ (ppm): 7.25-7.52 (m, 4H, Ar-H, Quinaxoline), 7.72-8.21 (m, 5H, Ar-H subst); EI-MS (m/e): 282 (M^+)



Result and Discussion:

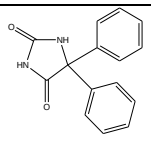
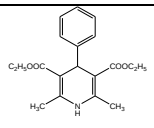
One of the superior alternatives for conventional heating is microwave irradiation. The product obtained by microwave irradiation in shorter time with good yield. Table-1 show the comparison of time required for synthesis of heterocyclic compound by conventional and microwave irradiation. Heterocycle requiring hours of tedious heating by conventional method are obtained in minutes of microwave irradiation with good quality. Some product obtained in better purity than conventional heating.

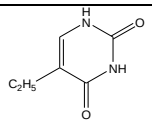
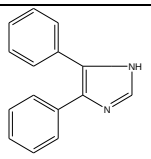
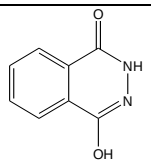
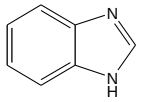
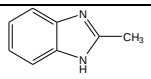
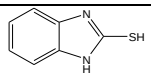
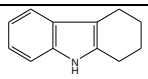
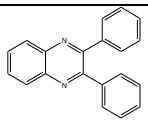
Table-1: Comparison of the Time taken by Microwave Irradiation and time taken by Conventional Synthesis

Comp Code	Name of compound	% yield From MWI	Time taken by	
			Conventional Synthesis in hours	MWI in minutes
MS1	Phenytoin	73	3	10
MS2	Hanzsch tetrahydropyridine	82	3	15
MS3	Tetrahydro pyrimidinedione	80	2	12
MS4	4,5-Diphenylimidazole	65	1	7
MS5	3,4-Dihydro-1-hydroxy-4-oxophthalazine	74	45 min	6
MS6	Benzimidazole	63	2	7
MS7	2- Methyl Benzimidazole	55	45 min	8
MS8	2-Mercapto Benzimidazole	60	3	6
MS9	1,2,3,4-Tetrahydrocarbazole	76	2	10
MS10	2,3-Diphenyl quinaxoline	87	0.5	3

The Physical properties of heterocyclic compound were given in Table-2. The product obtained by microwave irradiation with better quality and in safe environment. In some reaction no need to add solvent and hence reduces the cost. Also toxic fumes are not produced as no solvent needed to carry out reaction.

Table-2: Physical Properties of Heterocyclic Compounds.

Comp Code	Name of compound	Structure	Molecular Formula	Melting Point (^{0}C)	Rf Value
MS1	Phenytoin		$C_{15}H_{12}N_2O_2$	294-296	0.93 (Chloroform: Ethyl acateate 1:1)
MS2	Hanzsch dihydropyridine		$C_{19}H_{23}NO_4$	43-48	0.74 (Chloroform: Ethanol 2:6)

MS3	Tetrahydro pyrimidinedione		$C_6H_8N_2O_2$	300-304	0.67 (Chloroform: Ethanol 2:6)
MS4	4,5-Diphenylimidazole		$C_{16}H_{14}N_2$	233-235	0.54 (Ethanol: Ethyl Acetate 4:1)
MS5	3,4-Dihydro-1-hydroxy-4-oxophthalazine		$C_8H_6N_2O_2$	77-79	0.83 (Chloroform: ethanol 3: 2)
MS6	Benzimidazole		$C_7H_6N_2$	170-172	0.3 (n-Hexane: ethyl acetate 7: 3)
MS7	2- Methyl Benzimidazole		$C_8H_9N_2$	172-175	0.65 (Chloroform: ethanol 7: 3)
MS8	2-Mercapto Benzimidazole		$C_7H_6N_2S$	300-304	0.78 (Chloroform: ethanol 7: 3)
MS9	1,2,3,4-Tetrahydrocarbazole		$C_{12}H_{13}N$	112-116	0.82 (Chloroform: ethanol 4:1)
MS10	2,3-Diphenyl quinaxoline		$C_{20}H_{14}N_2$	129-131	0.8 (Chloroform: ethanol 1:1)

Conclusion:

Microwave assisted synthesis is quicker, better and safer approach of green chemistry to traditional and applied named reactions. The time take for the synthesis is significantly reduced by the microwave assisted organic synthesis. Hence microwave proved to be an efficient tool to conventional heating. It is environment friendly technique to obtain compound in minimal time.

Acknowledgment:

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