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Microwave Assisted Synthesis and Spectral Studies of Thiophenyl Pyrimidine Derivatives

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ABSTRACT

Series of 4-4(Aryl)-6-(thiophen-2-yl)-pyrimdine-2-amines and its Substituted bromo, methyl, methoxy groups were synthesized by micro wave irradiation and also in conventional method. The synthesized compounds were characterized by FT-IR, One dimentional ^{1}H NMR and ^{13}C NMR spectroscopy and elemental analysis. In FT-IR spectrum the absorption frequencies at 3483 cm^{-1} is due the presence of NH_2 of primary amino group. The absorption frequencies at 1571.99 cm^{-1}, 1367.53 cm^{-1} is due the presence of C=N andC-N of pyrimidine moiety respectively. In ^{1}H NMR spectrum the singlet observed at 5.19 ppm for two protons are primary amino group. The singlet observed at down field region at 7.08 ppm is due H-5 of pyrimidine moiety. In ^{13}C NMR spectrum, the ^{13}C resonance at 165.68 ppm is assigned to the amino group bearing carbon C-2 of pyrimidine moiety. The ^{13}C resonance observed at 160.42 and 101.98 ppm is due to C-4 and C-5 carbons of pyrimidine moiety. The ^{13}C resonance observed at 163.52 ppm is assigned to C-6 carbon of pyrimidine moiety. The synthesized compounds were confirmed by FT-IR, ^{1}H NMR and ^{13}C NMR and elemental analysis.

Keywords: Chalcones, Guanidine nitrate, Conventional method, Microwave Irradiation.

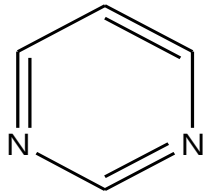
INTRODUCTION

The search for new antibacterial drugs is a continuous process because of the increasing resistance of microbial pathogens. It is enviable to find drugs with more potency with wide activity spectrum. The treatment of bacterial infectious diseases is a never ending challenge because of the increasing number of multi-drug microbial pathogens [1,2,3]. In recent years, the design of new compounds, having new structures and new targets of action, has become one of the most important areas in the antibacterial research purpose[3]. Green Chemistry (environmentally benign chemistry) is not different from traditional chemistry in as much as it embraces the same creativity and innovation that has always been central to classical chemistry. But with an increase in environmental consciousness throughout the world, there is a challenge for chemists to develop new products, processes and services that achieve necessary social, economical and environmental objectives. By using these technologies energy input reduces, improvement of selectivity, shortening of reaction time occurs. Some reactions, which are not possible with single heating, can be possible with above technique. In current aspects development of more sustainable products and energy efficient processes with reducing waste are discussed in emerging green technologies.

Use of energy sources like light, microwave, ultrasound and electricity are more clean, and efficient. Now a days, microwave assisted organic synthesis has gained considerable importance because of its efficiency to lead to the formation of the pure products in high yields [4-9].

The first condensation was reported by Kestanecki [10] and he gave the name "Chalcones". As we know chalcones are valuable intermediates in organic synthesis and exhibit a multitude of biological activities. From a chemical point of view, an important feature of chalcones is the ability to act as activated unsaturated system in conjugated addition reactions of carbanions in the presence of basic catalysts [11]. Chalcones are 1, 3-diphenyl-2-propene-1-one, consist of two aromatic rings linked by a three carbon α, β-unsaturated carbonyl system[12]. Especially interest has been focused on the synthesis and biodynamic activities of chalcones. These are considered to be precursors of flavonoids and isoflavonoids. Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial, anti-inflammatory, analgesic, antiplatel, antiulcerative, antimalarial**,** anticancer, antiviral, antileishmanial, Antioxidant, Antitubercular, antihyperglycemic, activities. The presence of a reactive & unsatutated keto function in chalcones is found to be responsible for their antimicrobial activity. Similar observation has been documented [13, 14].

Nowadays, the main goal of researchers, both academic and industrial is to develop environmentally benign synthetic procedures in organic synthesis. C-C bond formation via condensation of active methylene containing compounds with aromatic aldehydes is a reaction of great significance in organic synthesis. Further, there is a great demand these days on carrying out organic synthesis under environmentally benign reaction conditions and that is why great emphasis is being laid on doing away, whenever possible, with the use of volatile and toxic organic solvents[15-17]. The use of environmentally benign solvents represents a very useful and powerful green chemistry technological procedure. In fact, it would be much better, if feasible, to switch from organic solvents to water as a reaction medium in organic reactions[18-22].



(1)

Pyrimidine is considered to be a resonance hybrid of the charged and uncharged cannonical structures; its resonance energy has been found to be less than benzene or pyridine. The naturally occuring pyrimidine derivatives was first isolated by Gabrial and Colman in 1870, and its structure was confirmed in 1953 as 5-b-D-gluco-pyranoside of divicine. It is revealed from the literature survey that pyrimidine derivatives have been found possessing biological activities reported as under Fungicidal[23], Anticonvulsant[24], Antitubercular[25], Antihypertensive[26], Analgesic[27], Antibacterial[28].

The pyrimidines uracil (2), thyamine and cytosine (3) occur very widely in nature since they are components of nucleic acids, in the form of Nsubstituted sugar derivatives. Several analogues have been used as compounds that interfere with the synthesis and functioning of nucleic acids: examples are fluorouracil (4) and the anti-AIDS drug Zidovudine (AZT). Some diaminopyrimidines, including pyrimethamine (5) and trimethoprim (6) are antimalarial agents; trimethoprim is also an effective antibacterial agent when used in combination with a sulphonamide. Minoxidil (7) is a vasodilator which has been used in the treatment of hypertension. Vitamine B1(8) is also a pyrimidine.

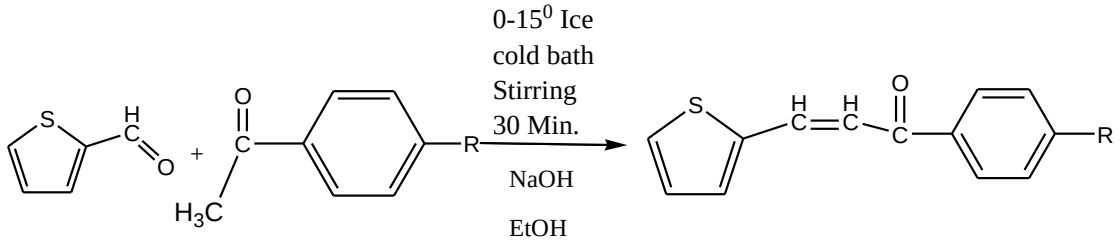
Moreover, the interesting starting material, 2-Thiophenecarboxaldehyde is used as an intermediate to manufacture pharmaceuticals and aroma compounds. In the present work chalcones have been prepared

according to Claisen-schimidt condensation by condensing 2-Thiophenecarboxaldehyde with substituted ketones. These chalcone derivatives were reacted with guanidine nitrate to form 4-4(Aryl)-6-(thiophen-2-yl)-pyrimidine-2-amines. The structures of the synthesized compounds were elucidated on the basis of their elemental analysis, FT-IR, one dimensional ^{1}H and ^{13}C spectroscopic data.

MATERIALS AND METHODS

The starting material, thiopene -2- carboxaldehyde was purchased from Sigma Aldrich. All the reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on E.Merck silica gel (TLC) and visualized by Iodine. The IR spectra were recorded on a Perkin Elmer FT-IR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra are recorded at 400MHz and 100MHz NMR spectrometer(Bruker Biospin International,Ag, Aegeristrasse, Switzerland) using $CDCl_3$ as solvent. All the chemical shift were reported in δ (ppm) using TMS as an internal standard. All reaction carried out below under room temperature.

General Synthesis of Thiophene -2yl - 1- H aryl prop-3 ene -1- ones chalcones(9-12): The one mole thiophene-2-carboxaldehyde, one mole of various substituted acetophenone were taken in a beaker and to this approximately added 30 ml of ethanol containing 2g of NaOH pellets. This mixture is stirred well for 30 minutes in an ice cold bath then it was poured into the crushed ice and this reaction was kept overnight at room temperature. The chalcones were precipitated out as solid. Then it was filtered, Dried and re-crystallized. The reaction was monitered by TLC by using chloroform as the solvent.
IR (KBr)**:** ν max 3066.82, 2931.8, 1653, 1585.49cm^{-1}. **MS**: *m/z* 214 (M+).**(9)**



Scheme1. Synthesis of chalcones 9-12.

Synthesis of Thiophene -2yl -1-(Bromo phenyl) prop-3- ene-1- ones (10): IR (KBr): ν max 3080.32, 3000, 1647.21, 1573.91 cm^{-1}. **MS**: *m/z* 293 (M+).

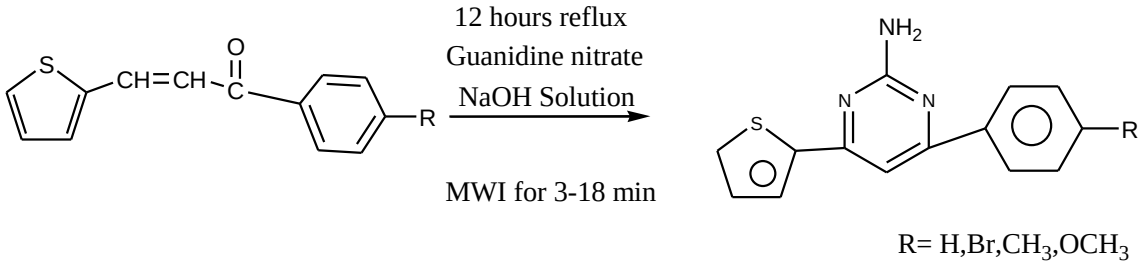
Synthesis of Thiophene -2yl -1-(Methylphenyl) prop-3- ene-1- ones (11): IR (KBr): ν max 3080.32,2914, 1653, 1587.42 cm$^{-1.}$. **MS**: *m/z* 229 (M+).

Synthesis of Thiophene -2yl -1-(Methoxy phenyl) prop-3- ene-1- ones (12): IR (KBr): ν max 3093.82, 2935.66, 1647.21, 1595.13 cm^{-1}. **MS**: *m/z* 244 (M+).

General Synthesis of 4-4(Aryl)-6-(thiophen-2-yl)-pyrimidine-2-amines by Conventional method: (13-16):A mixture of various substituted thiopene chalcones(1mmol), Guanidine nitrate(1mmol), 25 mL of ethanol, a little amount of sodium hydroxide solution, were taken in a dry round bottom flask, the mixture was shaken well and then it was refluxed for 12 h. The reaction was monitored by TLC. After the reaction mixture was cooled to room temperature and poured into crushed ice, the white precipitate was obtained. After filtration, the precipitate was recrystallized from Ethanol.

IR (KBr): ν max 3097.66, 3483.44, 1616.35, 1571.99, 1367.53cm^{-1}. **1H NMR** ($CDCl_3$, 400 MHz): 5.19(NH_2 of pyrimidine moiety), 7.08 (H5 of pyrimidine moiety), 7.92-7.26(ArH and thiophene protons),

^{13}C NMR ($CDCl_3$, 100 MHz) **δ**: 165.68(C-1 carbon), 160.42 (C-4 Carbon), 101.98(C-5 Carbon), 163.52 (C-6Carbon), 128.74-126.15(Ar and thiophene Carbons),142.25, 136.43(Ipso Carbons).**Elemental data**: Calculated for $C_{14}H_{15}N_3S$: C=65.36, H=5.83, N=16.34; Found: C= 65.32, H=5.80, N=16.33. **MS**: *m/z* 257 (M+).



R= H,Br,CH_3,OCH_3

(13-16)

Scheme- 2. Synthesis of pyrimidine derivatives 13-16

General Synthesis of 4-4(Aryl)-6-(thiophen-2-yl)-pyrimidine-2-amines by Microwave assisted method (13-16): A mixture (0.01mol) of chalcone derivative and guanidine nitrate in alkaline medium viz. in sodium hydroxide (0.003mol) in the presence of ethanol (10mL). The entire reaction mixture was microwave irradiated at 180 watts for 3-18 min, then kept aside for 2-3 h and resulted in formation of pyrimidine derivatives. The chemical profile of the compounds is as shown in Table 1.

Synthesis of 4-4(bromo phenyl)-6-(thiophen-2-yl)-pyrimidine-2-amines(14)

IR (KBr): ν max 3086.11, 3483.44, 1622.13, 1562.34, 1350.17 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.24(NH_2 of pyrimidine moiety), 7.17 (H5 of pyrimidine moiety), 7.94-7.28(ArH and thiophene protons).

^{13}C NMR ($CDCl_3$, 100 MHz) **δ**: 164.81(C-1 carbon), 160.87(C-4 Carbon), 102.13(C-5 Carbon), 163.35(C-6Carbon), 129.38-123.21(Ar and thiophene Carbons), 142.89, 136.41, 131.94(Ipso Carbons).**Elemental data**: Calculated for $C_{14}H_{14}N_3SBr$: C=50.14, H=4.17, N=12.53; Found: C= 50.13, H=4.14, N=12.52. **MS**: *m/z 335* (M+).

Synthesis of 4-4(methylphenyl)-6-(thiophen-2-yl)-pyrimidine-2-amines(15)

IR (KBr): ν max 3151.69, 3473.80,1614.42, 1560.41, 1355.96 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 5.26 (NH_2 of pyrimidine moiety), 7.17 (H5 of pyrimidine moiety), 7.97-7.28(ArH and thiophene protons), 2.43(phenylmethyl protons).

^{13}C NMR ($CDCl_3$, 100 MHz) **δ**: 166.02(C-1 carbon), 160.48(C-4 Carbon), 102.21(C-5 Carbon), 163.38(C-6Carbon),129.49-126.84(Ar and thiophene Carbons),143.19, 140.83, 134.73(Ipso Carbons), 21.44 (phenylmethyl carbon). **Elemental data**: Calculated for $C_{15}H_{17}N_3S$: C=66.42, H=6.27, N=15.49; Found: C= 66.40, H=6.24, N=15.45. **MS**: *m/z* 271 (M+).

Synthesis of 4-4(methoxyphenyl)-6-(thiophen-2-yl)-pyrimidine-2-amines(16)

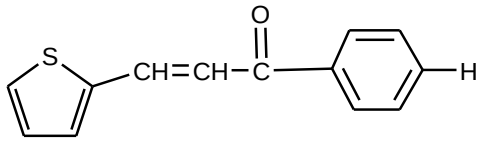
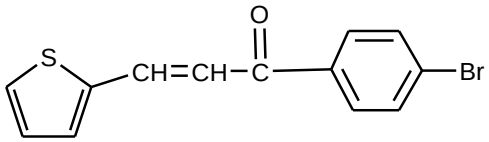
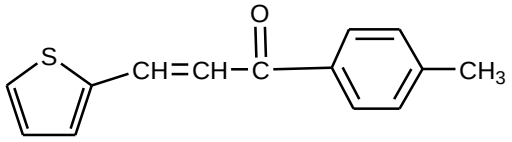
IR (KBr): ν max 3093.82, 3473.80, 1616.35, 1560.41, 1357.89cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 5.17(NH_2 of pyrimidine moiety), 7.02(H5 of pyrimidine moiety), 8.05-7.16(ArH and thiophene protons), 3.90(phenylmethoxy protons).

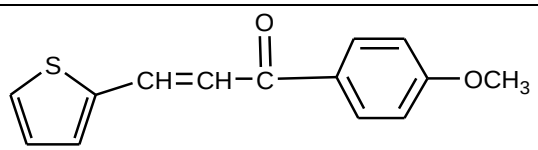
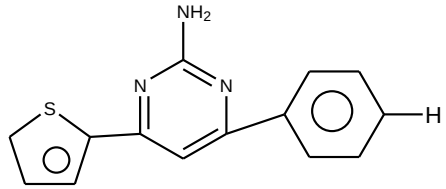
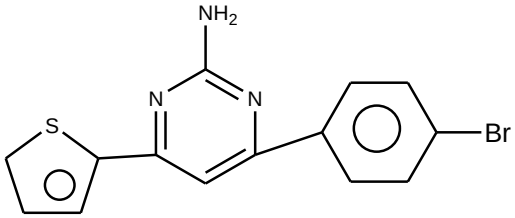
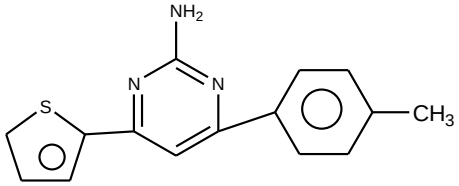
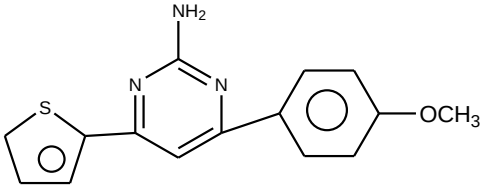
^{13}C NMR ($CDCl_3$, 100 MHz) **δ**: 165.51(C-1 carbon), 160.36(C-4 Carbon), 101.72(C-5 Carbon),163.31(C-6Carbon), 129.92-114.10(Ar and thiophene Carbons), 143.25(Ipso Carbons), 55.41(phenylmethoxy carbon). **Elemental data**: Calculated for $C_{15}H_{17}N_3SO$: C=62.71, H=5.92, N=14.63; Found: C= 62.69, H=5.89, N=14.62. **MS**: *m/z* 287 (M+).

RESULTS AND DISCUSSION

Chemistry: The synthetic route to the target compounds is outlined in scheme 1and 2.The intermediate Chalcones were (9-12) prepared by reacting equimolar aldehyde and ketone in the presence of base by Claisen-Schmidt condensation method. Claisen-schmidt condensation method for the synthesis of chalcones is very attractive since it specifically generates the trans (E)-isomer.4-(4-aryl)-6-(thiophene-2-yl)-pyrimidine-2-amines (13-16) were synthesized by conventional and microwave irradiation method.
Chalcones with guanidine nitrate, NaOH in Ethanol under refluxing for 12 h . In microwave irradiation method the reaction was carried out only in 3-18 min. Microwave irradiation method the yield was high over conventional method. All the compounds were isolated in satisfactory yields (50-90%) and purified by crystallization from ethanol. The purity of the compound was established by Thin layer chromatography (TLC) and elemental analysis. Structures of the synthesized compounds were confirmed by elemental analysis and spectral (FT-IR, ^{1}H NMR and ^{13}C NMR) data, which were in line with the proposed structure.
The FT-IR spectrum of the compound (13-16) afforded pyrimidine C=N stretching (1560.41-1571.99 cm^{-1}), the absorption frequencies around 3473.80-3483.44 cm^{-1} are due to NH asymmetric and symmetric stretching vibrations of the primary amino group. The band at 1614.42-1622.13 cm^{-1} are due to the presence of C=C stretching vibration. The absorption frequency around 3086.11-3151.69 cm^{-1} are due to aromatic C-H stretching. The absorption band at 1350.17-1367.53 $^{cm-1}$ are due to C-N stretching vibration.
In ^{1} H NMR spectrum of Compound 13, the signal at 5.19 ppm is due to the presence of NH_2 proton of pyrimidine moiety. The signal at 7.08 ppm is due to the presence of H_5 proton of pyrimidine moiety. Aromatic protons and thiophene protons appeared at the range of 7.26-7.92 ppm.
In ^{13}C NMR spectrum of Compound 13, the ^{13}C resonance at 165.68 ppm is due the presence of C-1 carbon of pyrimidine moiety, the ^{13}C resonance at 101.98 ppm is attributed to C-5 carbon of pyrimidine moiety. The ^{13}C resonance at 163.52 ppm is due to the presence of C-6 carbon of pyrimidine moiety. The aromatic carbons and thiophene carbons are observed in the range of 126.15 to 128.74 ppm. The ^{13}C resonance at 142.25, 136.43 ppm are due to Ispso carbons. Replacing R group by H, Br, CH_3, OCH_3, gave corresponding products as shown in table 1. As can be noticed from (Table-1) the products were obtained in good yield regardless of various electron donating and withdrawing groups present in the aromatic ketones.

Table 1: The chemical profile of thiophene chalcones and pyrimidine derivatives

Compound structure	Molecular Formula	Molecular Weight	Melting Point	% of Yield	%Yield In MWI
	$C_{13}H_{10}SO$	214	50^0C	70%	-
	$C_{13}H_9SOBr$	293	130^0C	60%	-
	$C_{14}H_{13}SO$	229	80^0C	72%	-

	$C_{14}H_{12}SO_2$	244	100^0C	75%	-
	$C_{14}H_{15}N_3S$	257	94^0C	50%	75%
	$C_{14}H_{14}N_3SBr$	335	160^0C	65%	80%
	$C_{15}H_{17}N_3S$	271	90^0C	69%	86%
	$C_{15}H_{17}N_3SO$	287	170^0C	75%	92%

APPLICATIONS

Microwave Irradiation Synthesis is one of the best applications for Organic Synthesis. MWI is a shorter reaction time, solvent free, experimental simplicity selectivity of products, Easy workup process, environmentally benign process over conventional heating.

CONCLUSIONS

In conclusion the reaction of thiophene chalcone with guanidine nitrate in the presence of inorganic solid support (Sodium hydroxide) under Microwave Irradiation resulted pyrimidine derivatives (13-16) via Michal addition followed by an intra molecular cyclocondensation. This process has advantages over conventional methods, such as shorter reaction time, highly yield, solvent free and environmentally benign. The synthesized compound may serve as useful intermediate for the synthesis of structurally diverse heterocycles. The structures of the synthesized compounds were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis data, which were in line with proposed structure.

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