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Microwave assisted synthesis and anti bacterial activity of p- toludine fused 2-azetedonone derivatives

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ABSTRACT

Non-classical, High-speed, environmentally benign synthesis with microwaves has attracted researchers for organic synthesis was a considerable amount of attention in recent years. An expeditious one pot microwave irradiation method for preparation of 2-azetidinones is developed. This method has been assessed as greener methodology. In our present study, A series of six novel 2-azetidinones were synthesized, compounds were identified by melting point and thin layer chromatography, functional groups of synthesized compounds were confirmed by IR spectroscopy, compounds were evaluated for their antimicrobial activities. The activities were due to cyclic carbonyl group in 2-azetidinones. Some of the compounds have shown comparative antimicrobial activities against all the microbial strains

INTRODUCTION

2-Azetidines have been extensively investigated by the organic chemists due to their close association with various types of biological activities It is a four-membered cyclic lactam (ß-lactam) skeleton has been recognized as a useful building block for the synthesis of large number of organic molecules by exploiting the strain energy associated with it.

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The Staudinger reaction ([2+2] ketene-imine cycloaddition reaction) is regarded as one of the most fundamental and versatile methods for the synthesis of structurally diverse 2-azetidinone derivatives. Azetidine-2-ones also have great importance because of the use of ß -lactam derivatives as antibacterial agents recently, some other types of biological activity beside the antibacterial activity have been reported in compounds containing 2- azetidinone ring.

Efforts have been made in exploring such new aspects of β-lactam chemistry versatile intermediates for their synthesis of aromatic β- amino acid and their derivatives, peptides, polyamines, polyamino alcohols, amino sugars and polyamino ethers. The cyclic 2-azetidinone skeleton has been extensively used as a template to build the heterocyclic

structure fused to the four membered rings. The β-lactam heterocycles are still the most prescribed antibiotics used in medicine. They are considered as an important contribution of science to humanity[1]

The biological activity of β lactam antibiotics such as penicillins and cephalosporins are attributed to the presence of 2-azetidinone ring in them [2]. Compounds carrying azetidin-2- one ring are reported to exhibit certain biological activities likeantagonists [3], hypoglycemic [4], anti-inflammatory [5], Antitubercular [6], anaesthetic[7], analgesic [8], antimalarial [9], antidepressant [10] and enzyme inhibition activity[11]

Cycloaddition of monochloroacetylchloride with imine (schiff base) result in formation of 2-azetidinone (β-lactam).The reaction involves direct acylation of imine with monochloroacetylchloride. The reaction is carried out with base as triethylamine gives β- lactam [12].

Equipments

Melting points were taken in digital melting point apparatus. The microwave assisted synthesis of 2-azetidinone derivatives were carried out in IFB 17 PG2S, 2450MHz, 90° C , Infrared spectra of the prepared compounds were recorded in KBr disc method on SHIMADZU IR 8000 series spectrometer All the synthesized compounds are purified by recrystallization. The reactions were followed up and purity of compounds was monitored on pre- coated TLC plates using different solvent system and visualizing the spots in iodine chamber.

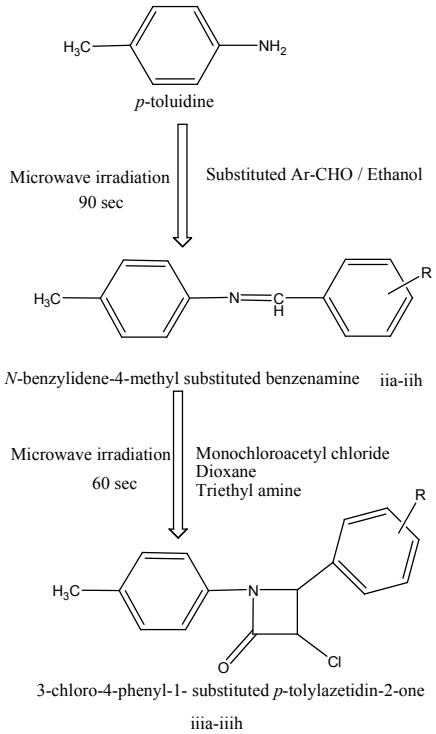


Figure 1. Scheme of synthesis

MATERIALS AND METHODS

All the chemicals and solvents were obtained from E-Merck and S.D. Fine India (AR grade) and were used without further purification.

Methodology

Microwave-enhanced chemistry is based on the efficient heating of materials by "microwave dielectric heating" effects. This phenomenon is dependent on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert it into heat[13]. Microwave irradiation has gained popularity in the past decade as a powerful tool for rapid and efficient synthesis of a variety of compounds because of selective absorption of microwave energy by polar molecules. The application of Microwave irradiation to provide enhanced reaction rate and improved product field in chemical synthesis and it is providing quite successful in the formation of a variety of carbon- heteroatom bonds [14]. Many researchers have described accelerated reaction rates, with a large number of papers that have appeared proving the synthetic utility of MORE chemistry in day to day organic synthesis. It can be termed as 'e- chemistry' because it is easy, effective, economical, and eco-friendly, and is believed to be a step toward achieving green chemistry objectives[15]. Within the framework of 'Green Chemistry' we have now developed an environmentally benign and novel approach for the synthesis of azetidine-2-ones.

General method for the preparation of compounds IIa-IIh

P- toludine 0.01mol (1.2 gms)was dissolved in 30 ml of ethanol containing few drops of glacial acetic acid .The appropriate aromatic aldehyde (0.01 mol) was added to the reaction mixture. It was heated in microwave for 90 seconds cooled and then poured into crushed ice .The solid obtained was filtered, washed with water and re crystallized with ethanol. Different aldehydes are shown in Table 1. Mobile phase for TLC Chloroform: Ethanol (9:1)

General method for the preparation of final compounds IIIa-IIIh

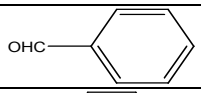
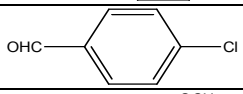
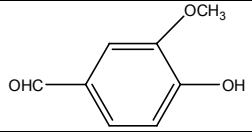
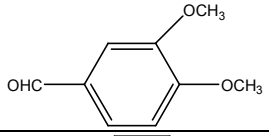
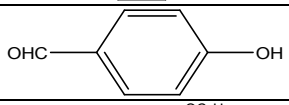
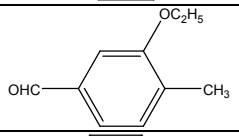
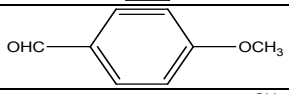
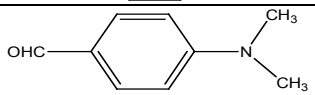
To a stirred solution of step II products of P-nitro aniline (0.01 mol) ,tryethylamine (0.02 mol) in dioxan (dry 50ml) and monochloro acetyl chloride (0.02mol) was added drop wise at room temperature .The reaction mixture was stirred for 30 min and heated in micro wave for 60 seconds .A solid was obtained on removal of dioxan which was re crystallized from a mixture of ethanol and water. Functional groups of synthesized compounds were confirmed by performing IR spectroscopy, results were shown in Table No.3

Physical properties of synthesized compounds were shown in Table No.2. Mobile phase for TLC Benzene: ethanol (7:3).

Antimicrobial activity

The in-vivo Antimicrobial activity was performed by Agar diffusion method. The new compounds were evaluated for *invitro* anti bacterial activity against Gram-positive bacteria like Streptococcus Aureus,. Bacillus Subtilis, and Gram Negative bacteria like*Vibrio cholerae, Pseudomonas aeruginosa,* Agar nutrient broth was employed for bacterial growth.

Table 1. : Different aromatic aldehydes used for the preparation of Schiff's bases

S.No	Name of the aldehyde	Structure
1.	Benzaldehyde	
2.	4-chlorobenzaldehyde	
3.	3-Methoxy4-hydroxy benzaldehyde	
4.	3,4 dimethoxy benzaldehyde	
5.	4-hydroxy benzaldehyde	
6.	3-ethoxy 4-methyl benzaldehyde	
7.	4-methoxy benzaldehyde	
8.	4-N ,N dimethylamino benzaldehyde	

From the microbial study it can be concluded that compounds bearing chloro, , hydroxy Di methyl amino groups are more potent than remaining substituted compounds against Gram (+) and Gram (-) bacterias. All the synthesized compounds have structure activity relationship (SAR) because activity of compounds varies with substitution. On the basis of SAR it can be concluded that activity of compounds depends on electron withdrawing nature of substituted group. The sequence of the activity is as follow; Chloro>Hydroxy>N-Dimethylamino>3,4 Dimethoxy>methoxy , Hydroxy > Ethoxy, methyl >Hydrogen.

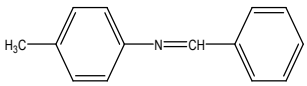
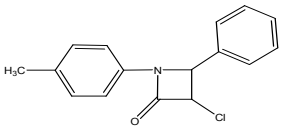
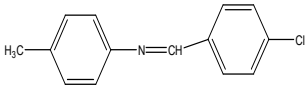
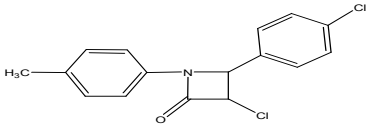
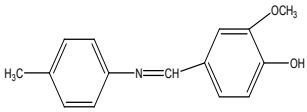
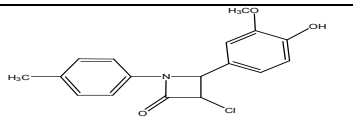
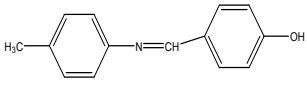
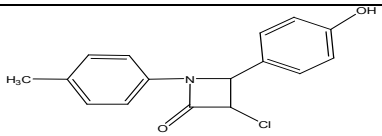
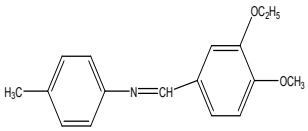
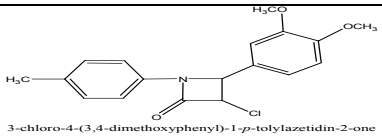
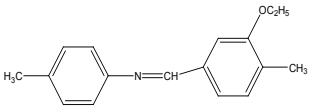
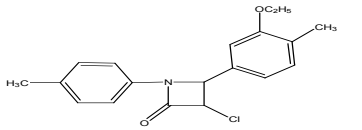
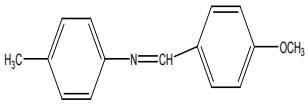
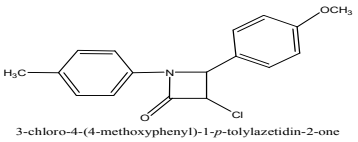
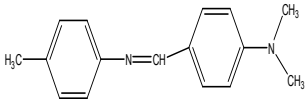
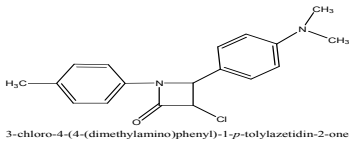
RESULT AND DISCUSSION

A new method for the synthesis of various above azetidin-2-one derivatives using microwave irradiation offers significant improvements over existing procedures and thus helps facile entry into a synthesis of variety of azetidin-2-one derivatives. Also, this simple and reproducible technique affords various azetidin-2-one derivatives with short reaction times, excellent yields, and without formation of undesirable side products. The yields of different synthesized compounds were found to be in the range of 60-80% and the characterization was done by melting point, thin layer which confirm the completion of reaction. Functional groups were identified by performing IR spectroscopy , All the tested compounds showed good, moderate and poor biological activity.

Table 2. Physical properties of synthesized compounds

S.No	Compound code	% yield	Molecular formula	Molecular weight	Melting point °C	solubility	Rf value
1.	IIIa	72	*C14H13NCl*	*195*	*140-143*	Benzene, Acetone	0.72
2.	IIIb	71	*C14H12NO2Cl*	*228*	*146*	Benzene, Acetone	0.68
3.	IIIc	70	*C15H15NO2Cl*	*241*	142	Benzene, Chloroform Acetone	0.75
4.	IIId	65	$C_{16}H_{17}NO_2Cl$	255	*151*	Benzene, Ethyl acetate , Acetone	0.77
5.	IIIe	70	C14H13NO2Cl	*211*	*161*	Benzene, Acetone	0.70
6.	IIIf	62	$C_{17}H_{19}NO_2Cl$	269	*155*	Benzene, Acetone	0.65
7.	IIIg	70	$C_{15}H_{15}NOCl$	225	*140*	Benzene, Chloroform Acetone	0.68
8.	IIIh	71	$C_{16}H_{18}N_2Cl$	226	*144*	Benzene, Acetone, Ethylacetate	0.67

Table 3. IR spectral values of synthesized compounds both Intermediates and final compounds

Intermediate structure	IR Values	Final structure	IR Values
 *N*-benzylidene-4-methylbenzenamine	(ArCHstr)2943.3 ,(CN)14061,(NH -str)3277.06.	 3-chloro-4-phenyl-1-*p*-tolylazetidin-2-one	(Ar-CHstr)2943.3,(C=O) 1685.7,(C-Cl)852.59, (C-N)1406.1, (NH -str)3277.06.
 *N*-(4-chlorobenzylidene)-4-methylbenzenamine	(ArCHstr)2933.5 2, (CN)1471.1, (NH-str)3323.06.	 3-chloro-4-(4-chlorophenyl)-1-*p*-tolylazetidin-2-one	Ar-CH str)2941.44, ,(C=O)1685.7, (C-Cl)852.59,(C-N)1406.1, (NH -str)3277.06
 4-((*p*-tolylimino)methyl)-2-methoxyphenol	(ArCHstr)2958.8 0, (C-N)1406.1, (NH -str)3363.06.	 3-chloro-4-(4-hydroxy-3-methoxyphenyl)-1-*p*-tolylazetidin-2-one	Ar-CH str)2941.44, ,(C=O)1685.7, (C-Cl)852.54,(C-N)1406.1,(NH -str)3277.06.
 4-((*p*-tolylimino)methyl)phenol	(Ar-CHstr)2941.44, (C-N)1406.1, (NH -str)3280.92.	 3-chloro-4-(4-hydroxyphenyl)-1-*p*-tolylazetidin-2-one	Ar-CH str)2941.44, ,(C=O)1685.7, (C-Cl)852.59,(C-N)1406.1, (NH -str)3277.06
	(Ar-CHstr)2870.0, (C-N)1477.47, (NH -str)3254.2	 3-chloro-4-(3,4-dimethoxyphenyl)-1-*p*-tolylazetidin-2-one	Ar-CH str)2941.44, ,(C=O)1624.7, (C-Cl)852.54,(C-N)1406.1,(NH -str)3280.92.
 *N*-(3-ethoxy-4-methylbenzylidene)-4-methylbenzenamine	(Ar-CHstr)2870.06, (CN)1477.47,(NH -str)3254.2,,(Arnitrile)2012.36	 3-chloro-4-(3-ethoxy-4-methylphenyl)-1-*p*-tolylazetidin-2-one	Ar-CH str)2941.44, ,(C=O)1624.7, (C-Cl)852.54,(C-N)1406.1,(NH -str)3280.92,(Ar nitrile) 2012.36
 *N*-(4-methoxybenzylidene)-4-methylbenzenamine	(Ar-CHstr)2870.0, (C-N)1477.47, (NH -str)3254.2	 3-chloro-4-(4-methoxyphenyl)-1-*p*-tolylazetidin-2-one	Ar-CH str)2941.44, ,(C=O)1624.7, (C-Cl)852.54,(C-N)1406.1,(NH -str)3280.92.
 *N*-(4-(dimethylamino)benzylidene)-4-methylbenzenamine	(Ar-CHstr)2870.0, (C-N)1477.47, (NH -str)3254.2	 3-chloro-4-(4-(dimethylamino)phenyl)-1-*p*-tolylazetidin-2-one	Ar-CH str)2941.44, ,(C=O)1624.7, (C-Cl)852.54, (C-N)1406.1,(NH -str)3280.92.

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