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Synthesis and biological evaluation of azetidinone derivatives from 2-α(phenylacetyl) benzohydrazide moiety by microwave method

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ABSTRACT

An expeditious method for preparation of 2-Azetidinones under microwave irradiation is developed. This method has been assessed as greener methodology and found superior to conventional method with higher environmental factor. A series of five novel azetidinones were synthesized by cyclocondensation of various Schiff bases of 2 –α(phenylacetyl) benzohydrazide with chloroacetylchloride in the presence of triethylamine. Schiff's bases preparing from 3-benzylidene phthalide moiety with different aromatic aldehydes under microwave irradiation in DMSO solvent and cyclocondensation of Schiff's bases with chloracetyl chloride in the presence of triethylamine and DMF under microwave irradiation resulted in the formation of corresponding azetidinone derivatives. The newly synthesized compounds were characterized by IR, ^{1}H-NMR spectra. The synthesized compounds were evaluated for antibacterial and antifungal activities by Broth dilution method. All the compounds were screened for their antibacterial activity against Staphylococcus aureus, Bacillus subtilis (Gram positive bacteria) Escherichia coli, Pseudomonas aeruginosa (Gram-negative bacteria). Compounds showed good anti-bacterial activity against Staphylococcus aureus and Bacillus subtilis.

Keywords: Azetidinones, 2 –α(phenylacetyl) benzohydrazide, hydrazine hydrate anti-bacterial, anti-fungal.

INTRODUCTION

The synthesis of heterocyclic compound has always drawn the attention of chemist over the years mainly because of their important biological properties. One such heterocyclic, 2- Azetidinones, a very well known compound for the medicinal chemist, since it forms a part of the antibiotic molecules[1]. They are the carbonyl derivatives of azetidines containing carbonyl group at the position -2.These are known as 2-azetidinones[2]. The earliest use was has Penicillin, Nocardicin, Cephalosporin, contains the β-lactum ring[3]. The utility of azetidinones as synthons for various biologically active compounds, as well as their recognition as antibacterial[4]' anticonvulsant[5], antimicrobial[6], antitubercular[7], anti-inflammatory[8], anthelmintic[9] , anesthetic[10], antioxidant[11]. They also function as enzyme inhibitors[12] and are effective on the central nervous system[13]. Cycloaddition of monochloroacetylchloride with imines (Schiff base) result in formation of 2- azetidinone (ß -lactam). The reaction involves direct acylation of imine with monochloroacetylchloride. The reaction is carried out with base as triethylamine gives b-lactum[14]. Since 2- azetidinones of 2-(α-Phenyl acetyl) benzohydrazide are not available, these derivatives can be done and resulting analogues are tested for their antimicrobial activity.

MATERIALS AND METHODS

Equipments

Melting points were taken in an open capillary tube. The microwave assisted synthesis of 2-azetidinone derivatives were carried out in Godrej SLGX –20 E microwave at 80% power IR spectra were recorded on a Shimadzu Dr-

8031 instrument 1H NMR spectra of the synthesized compounds were recorded on a Bruker-Avance (300 MHz) and Varian-Gemini (200 MHz) spectrophotometer using CDCl3 solvent and TMS as a internal standard. All the synthesized compounds are purified by recrystallization. The reactions were followed up and purity of compounds was monitored on pre-coated TLC plates and visualizing the spots in ultraviolet light.

Materials

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

Methodology

Due to environmental concerns, there has currently been an increasing demand for efficient synthetic processes and solvent –free reactions. Some old and new methodologies are being used to diminish and prevent pollution caused by chemical activities[15] . Microwave-induced organic reaction enhancement (MORE) has gained popularity as a non-conventional technique for rapid organic synthesis in the last few years and 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. Within the framework of 'Green Chemistry' we have now developed an environmentally benign and novel approach for the synthesis of azetidine-2-ones[16]. Hence in this research paper and in my research work I approached to Microwave Methodology .

General Procedure

STEP 1:- SYNTHESIS OF 2(α-Phenyl acetyl) BENZOHYDRAZIDE

To a solution of 3-benzylidene phthalide (2.22 g,1mmole) in ethanol (25 ml) , hydrazine hydrate (80%)(2.5 g 0.05 mol) was added dropwise .The resultant mixture was vigorously stirred for 5 hrs then poured on ice cold water.The white ppt was filtered off and washed thoroughly with water and crystallized from ethanol to give product (fig.1).

M.P 195-196 ^{0}C

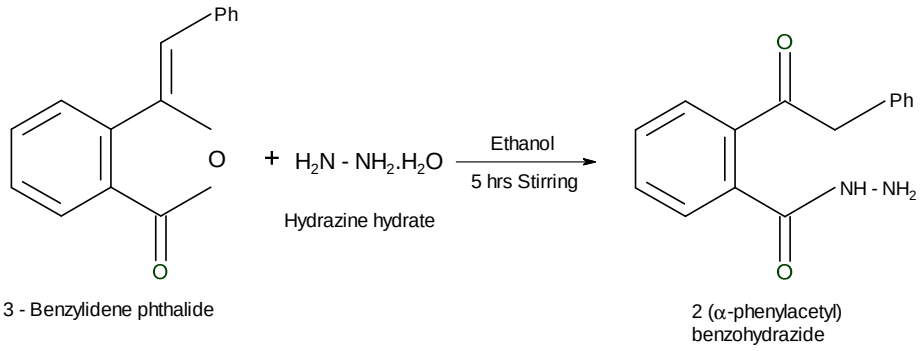


Fig. 1

STEP 2:-SYNTHESIS OF SCHIFF BASE

2(α-Phenyl acetyl) benzohydrazide(0.01mol) is treated with substituted aromatic aldehydes(0.01mol) in DMSO in microwave oven for 2-3 min and then mixture is cooled and poured in ice cold water to obtain Schiff bases (fig.2).

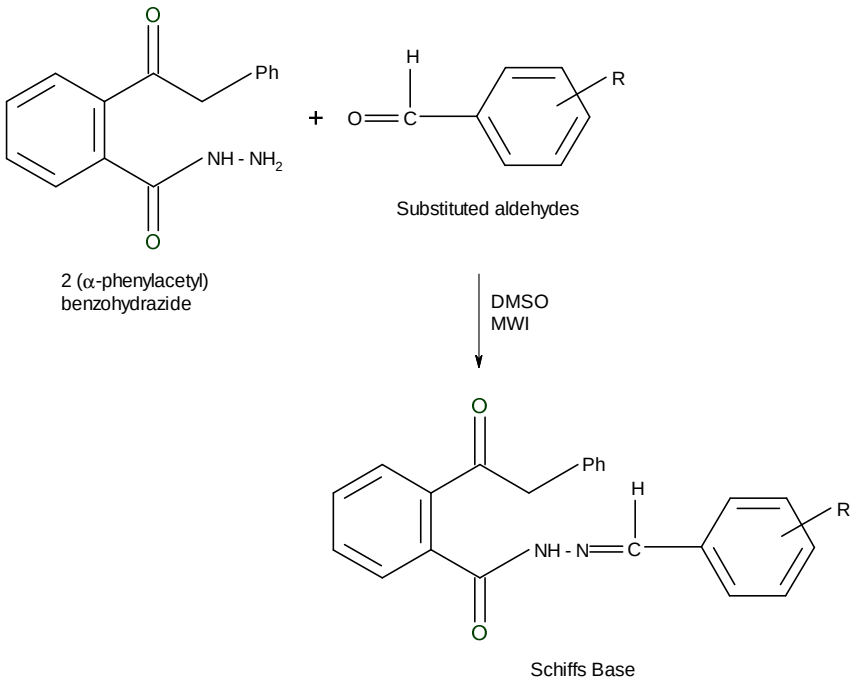


Fig. 2

STEP 3:- SYNTHESIS OF 2-AZETIDINONE DERIVATIVES

Schiff bases obtained in step 2 (0.01mol) in DMF on further treatment with base triethyl amine $N(C_2H_5)_3$ (0.01mol) and acylated with monochloroacetyl chloride(0.01 mol) as cyclising agent in microwave oven for 3 – 4 mins to form 2-azetidinone(fig.3).

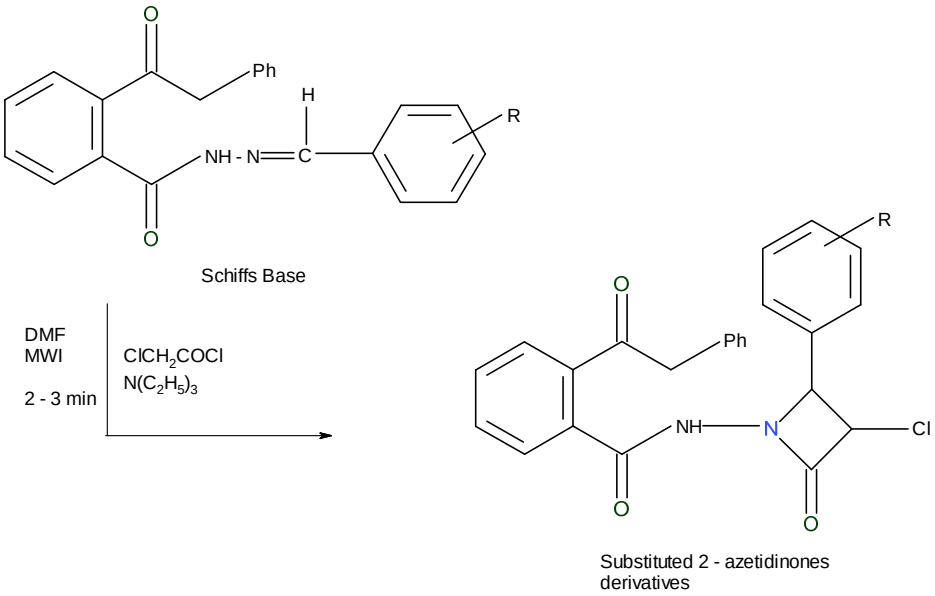


Fig. 3

Where R - is

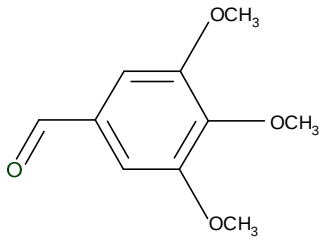
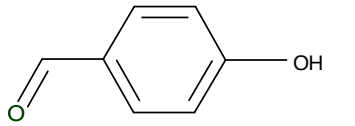
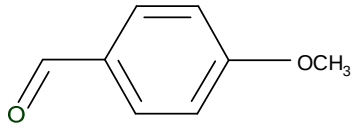
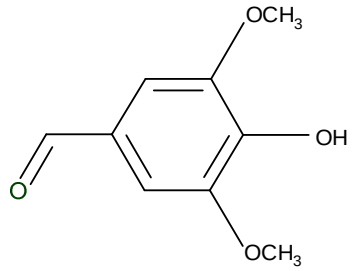
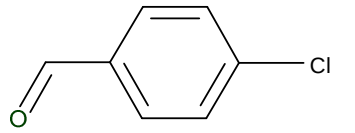
Sr. No.	Compound	Structure
1	3,4,5- trimethoxy benzaldehyde	
2	4- hydroxy benzaldehyde	
3	4- methoxy benzaldehyde	
4	4- hydroxy, 3,5 dimethoxy benzaldehyde	
5	4-chloro benzaldehyde	

TABLE -1 : PHYSICAL DATA OF THE SYNTHESIZED AZETIDINONE COMPOUNDS

COMPOUND	M.P	YIELD	MOLECULAR FORMULA	MOLECULAR WEIGHT
SDT1	180-185 ^{0}C	80 %	$C_{24}H_{18}N_2O_3Cl_2$	452
SDT2	170-180 ^{0}C	68 %	$C_{27}H_{25}N_2O_6Cl$	484
SDT3	180-190 ^{0}C	70 %	$C_{24}H_{19}N_2O_4Cl$	434
SDT4	180-185 ^{0}C	75 %	$C_{25}H_{21}N_2O_4Cl$	448
SDT5	170-175 ^{0}C	75 %	$C_{26}H_{23}N_2O_6Cl$	462

Spectral data of the synthesized derivatives is given below

TABLE -2 : FTIR PEAK ASSIGNMENTS OF SYNTHESIZED COMPOUNDS

Compounds	IR absorption bands (cm^{-1})								
	Ar-H str	C = C str	C = O str	C – N str	N – H str	β – C- Cl str	-OCH_3 str	-OH str	
SDT 1	3016	1449	1655	1338	3405	762	-	-	
SDT 2	3018	1490	1658	1336	3401	764	2401	-	
SDT 3	3013	1445	1655	1333	3405	769	-	2904	
SDT 4	3019	1453	1660	1384	3401	757	2400	-	
SDT 5	3017	1488	1657	1336	3403	763	2903	3162	

^{1}H NMR DATA OF SYNTHESIZED COMPOUNDS

SDT 1 : 2- α(phenylacetyl)benzamido-(4-chloro phenyl)-3 chloro azetidin-2one

Aromatic protons (Ar – H) appeared as a cluster at δ 7.1 – 8.4 , proton CH – Cl appear at δ 4.3 , proton NH appear at δ 10.73 , proton CH_2 appear at δ 2.88 .

SDT 2 : 2- α(phenylacetyl)benzamido-(3,4,5 trimethoxy phenyl)-3 chloro azetidin-2one
Aromatic protons (Ar – H) appeared as a cluster at δ 7.1 – 8.4 , proton CH – Cl appear at δ 4.31 , proton NH appear at δ 10.67 , proton CH_2 appear at δ 1.68 .

SDT 3 : 2- α(phenylacetyl)benzamido-(4 hydroxy phenyl)-3 chloro azetidin-2one
Aromatic protons (Ar – H) appeared as a cluster at δ 7.1 – 8.4 , proton CH – Cl appear at δ 4.31 , proton NH appear at δ 10.81, proton CH_2 appear at δ 2.95 .

SDT 4 : 2- α(phenylacetyl)benzamido-(4 methoxy phenyl)-3 chloro azetidin-2one
Aromatic protons (Ar – H) appeared as a cluster at δ 7.1 – 8.4 , proton CH – Cl appear at δ 4.31 , proton NH appear at δ 10.51 , proton CH_2 appear at δ 2.95 .

SDT 5 : 2- α(phenylacetyl)benzamido-(4- hydroxy, 3,5 dimethoxy benzaldehyde)-3 chloro azetidin-2one
Aromatic protons (Ar – H) appeared as a cluster at δ 7.1 – 8.4 , proton CH – Cl appear at δ 4.31 , proton NH appear at δ 10.97 , proton CH_2 appear at δ 2.95, proton OCH_3 appear at δ 1.77

Antimicrobial Activity :
All the prepared compounds are screened for antimicrobial activity. From the microbial study it can be concluded that compounds bearing chloro, methoxy 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

NO_2 > Cl > Br > OH > OCH_3 > H > CH_3

RESULTS 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 . Characteristic IR bands show several functional vibrational modes which confirm the completion of reaction. All the test compounds showed good, moderate and poor biological activity.

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