ISSN: 2249 –4820

Chemistry & Biology Interface, 2011, 1, 1, 116-122

Chemistry & Biology Interface

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Research Article

Synthesis and Pharmacological Evaluation of Novel Aldimines containing Aryl Sulfonate moiety

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Received 27 July 2011; Accepted 16 August 2011

Key Words: Aldimines, aryl sulphonate, aldehydes, heterocyclic amines, antibacterial, antifungal activity.

Abstract: A mild and efficient method for the synthesis of novel aldimine derivatives containing aryl sulphonate moiety is described. The synthesized aldimine molecules were screened for their antibacterial and antifungal activity.

Introduction

The aldimines are pharmaceutically important compound used as substrate for the synthesis of several biologically active compounds [1]. They are an active class of ligands [2] and frequently co-ordinate with metal ions through azomethine nitrogen atom [3]. The aldimines derived from aromatic aldehydes and aromatic or heterocyclic amines were showed a wide spectrum of pharmacological activities. They have a wide range of applications in the field of biology, agriculture [4] and industry [5]. Schiff bases are associated with characteristic biological activities including anti-bacterial [6-9], anti-fungal [10], anti-HIV [11], anti-anxiety and anti-depressant [12], analgesic and anti-inflammatory [13-14] activities. Besides, the compounds containing aryl sulfonate moiety have been received considerable attention during last two decades as they are endowed with variety of biological activities like papillomavirus microbicidal [15], anti-human immunodeficiency virus-1 [16] and anti-neoplastic [17] activity. Polystyrene sulfonate was evaluated as a preventive agent for conception and several sexually transmitted diseases. The aldimines are the chief precursor of medicinally active azetidin-2-one and thiazolidin-4-one derivatives [18].

The ecosystem is highly disturbed by the huge hazardous wastages generated by chemical processes, which have posed a serious challenge to the chemists. The development of safer chemical processes is one of the key requirements for green chemistry. The use of safer solvents and facile methods is the urgent demand for the preservation of ecosystem. Synthesis of aldimines was mostly carried out in solvent medium which were catalyzed by acids, this increases the risk of heavy hazardous chemicals and solvents to

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ISSN: 2249 –4820

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waste. Thus, organic chemists in need to search such alternative methods which could be helpful to produce green environment. The solvents such as dry ethanol and water were proved to be best solvent for the synthesis of aldimines. Also the organic synthesis using microwave technique is much easier and produces excellent yields of the products. The use of microwave heating in organic synthesis is rapidly growing area [19]. Microwave heating not only reduces the reaction time but also increases the product yields and to open up new avenues for organic synthesis. Recently, microwave technique is conveniently used for carrying out chemical transformations which are pollution free and eco-friendly. Keeping in view the immense biological importance of aldimines, we thought to synthesize novel aldimines containing aryl sulphonate moiety by conventional method using ethanol as solvent as well as by non conventional domestic microwave irradiation and mortar pestle techniques under solvent-free conditions. However, with the assistance of microwave technique, it was become possible to prepare the novel aldimines in good to high yields at short reaction time under solvent free conditions.

2. Materials and methods

Experimental

The entire chemicals were purchased from Sigma-Alrich, Spectrochem companies and were of analytical grade. Melting points were performed in open capillary tubes and were uncorrected. The purity of compounds was checked by TLC. IR spectra were recorded on a Perkin-Elmer-2000 FTIR spectrometer using KBr discs and ^{1}H-NMR spectra in DMSO-d6 and $CDCl_3$ on a Varian 200 MHz instrument using TMS as an internal standard. The microwave irradiations were carried out in domestic microwave oven.

2.1 Synthesis of 2-formylphenyl-4-methyl benzenesulfonate (2):

A mixture of substituted 2-hydroxy benzaldehyde (0.01 mol), p-toluene sulfonyl chloride (0.01 mol) and anhydrous K_2CO_3 (0.012 mol) was grinded well into mortar for 6-7 minutes. The reaction mixture becomes pasty and in the end it turns into the solid form. To this mixture water (20 ml) was added and stirred for 10 minutes, a white solid obtained was filtered, washed with water, dried and crystallized from ethanol to get the pure products **2**.

2.2 General procedure for the synthesis of Aldimines (3a-l) (Method A):

A mixture of 2-formylphenyl-4-methylbenzenesulfonate (0.01 mol) and aryl or heteroaryl amine (0.01 mol) was stirred in dry ethanol (2 ml) for 5 minutes and solvent was evaporated. The resultant mixture was subjected to microwave irradiation at low-high power setting for 4-5 minutes. It was then crystallized by ethanol to get the pure aldimine products (3a-l).

2.3 General procedure for the synthesis of aldimines (3a-l) (Method B):

A mixture of 2-formylphenyl-4-methylbenzenesulfonate (0.01 mol) and aryl or heteroaryl amine (0.01 mol) was grinded well in mortar and pestle in dry ethanol (5 ml) for 10-15 minutes. The resultant pasty mixture was allowed to leave for 24 hrs. It was then crystallized by ethanol to get the pure aldimine products (3a-l).

3. Results and discussion

The substrates 2-formylphenyl-4-methyl benzenesulfonate **2** were synthesized by the condensation of 2-hydroxy

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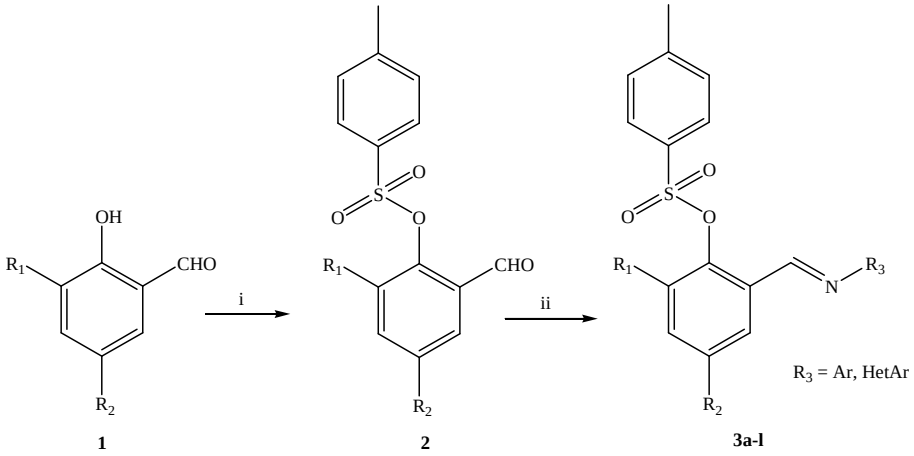
benzaldehyde **1** with p-toluene sulfonyl chloride using anhydrous K_2CO_3. The condensation was carried out by simple grinding procedure in short reaction time. The excellent yield, maximum purity, easy isolation of product and simple procedure are the advantages of this method over the reported methods. The novel aldimines (3a-l) were synthesized by conventional and non conventional methods including microwave and grinding techniques. A mixture of 2-formylphenyl-4-methyl benzenesulfonate was refluxed with aromatic or heterocyclic amines in dry ethanol a product separated out after 4-5 hrs. The separated product on cooling was filtered and crystallized using ethanol which yields 50-55 % pure product. Synthesis of aldimines was also carried out by MW technique it gives better yield of product under solvent free conditions at moderate power. Also aldimines are synthesized in good yields at mild reaction conditions by mortar and pestle technique. The synthesis of aldimines by microwave has got special value because of high yield, easy work up, excellent purity and rapid reactivity. The methods described in present paper are completely eco-friendly (Scheme-1). The synthesized compounds were characterized by IR and ^{1}H-NMR spectroscopic data. The compounds were tested for their antibacterial and antifungal activities.



1 **2** **3a-l**

Scheme-1: Reaction Conditions (i) *p*-Toluene sulfonyl chloride, K_2CO_3, solvent-free, grinding 7-8 min.; (ii) Method-A: Aryl / Heteroaryl amine, MW, solvent-free, 4-5 min, Method-B: Aryl / Heteroaryl amine, ethanol, grinding 10-15 min.

3.2 Antimicrobial activity

The antibacterial activity of the test samples (3a-l) was determined by agar cup plate method using tetracycline (10 µg/ml) as a standard drug and pathogenic bacteria such as *B. subtilis, S. aureus, E. coli and P. aeruginosa.* The method was based on diffusion of antibacterial component from reservoir bore to the surrounding inoculated nutrient agar medium so that the growth of microorganisms was inhibited as circular zone around the bore. The concentration of test compounds was 5 µg/ml and was prepared in dimethyl sulfoxide. The test samples and standard drug were placed in a bore made in Petri dishes, which is already inoculated with different pathogens and were incubated at 37 °C for 24 hours. The zone of inhibitions around the bore was measured after 24 hours. The antibacterial activity was classified as standards (>22 mm), highly active (15-22 mm), moderately active (10-15 mm), least active (7-10 mm) and less than 7 mm was taken as inactive (Table-2). The antifungal activity of synthesized compounds was determined by using

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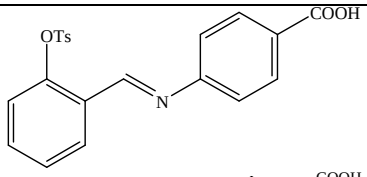
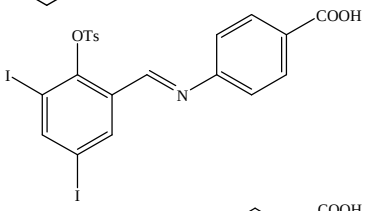
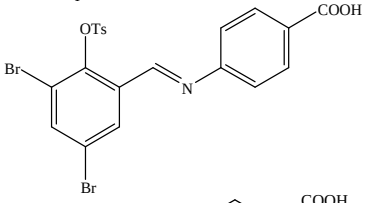
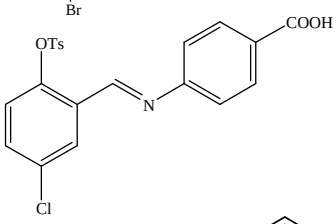
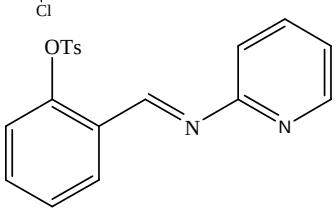
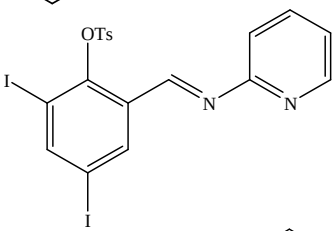
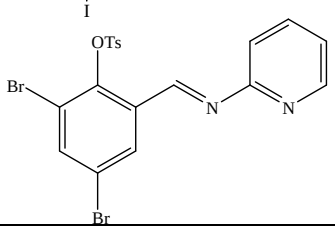
Aspergillus niger, Aspergillus flavus, Penicillium chrysogenium and Fusarium oxysporium pathogenic strains. Dextrose agar as culture medium and dimethyl sulphoxide was used as control for antifungal activity. Norcadin (10 μg/ml) was used as standard drug for the comparison and determination of their antifungal activities (Table-3).

Table 1: Synthesis of Aldimines containing aryl sulfonate moiety (3a-l)

Entry	Product[a]	Yield (%)		MP (°C)
		Method A	Method B	
3a		84	60	204-206
3b		85	65	234-237
3c		84	62	108-110
3d		81	60	213-216
3e		80	63	130-132
3f		83	63	121-123
3g		80	65	83-86

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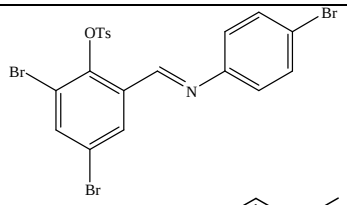
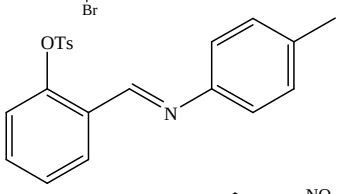
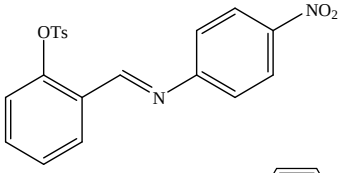
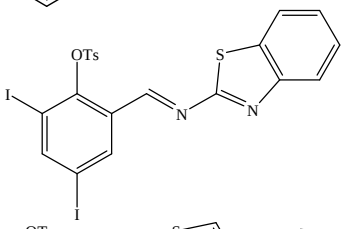
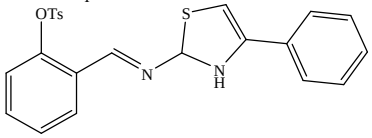
3h		83	60	133-135
3i		87	61	173-175
3j		80	64	185-188
3k		81	65	86-90
3l		85	63	135-137

[a]All the products were confirmed by IR, ^{1}H NMR and mass spectra.

4. Conclusion

Some novel aldimines containing aryl sulfonate moiety were synthesized and compounds were evaluated for their antibacterial and antifungal activities against various microorganisms. The synthesized aldimines with iodine, bromine and chlorine substituent on the benzene ring were found to be more potent against various pathogens. Aldimines obtained by the condensation of aromatic aldehydes and heterocyclic amines have showed powerful antibacterial and antifungal activities against tested microorganisms.

5. Acknowledgement

We are thankful to Dr. P. L. More, Principal, Dnyanopasak College, Parbhani and Dr. R. K. Ippar, Principal, Vaidyanath College, Parli Vaijnath for providing necessary facilities to the research work and the Department of Microbiology, Science College, Nanded for providing antimicrobial activity data.

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Table 2: Antibacterial activity of the synthesized compounds (3a-l)

Entry	Zone of inhibition in mm			
	E. coli	*B. subtilis*	*P. aeruginosa*	*S. aureus*
3a	05	04	05	07
3b	15	08	12	16
3c	16	09	11	14
3d	13	07	14	10
3e	04	03	04	03
3f	11	07	10	07
3g	10	09	13	12
3h	04	04	03	04
3i	02	05	03	03
3j	05	02	04	03
3k	16	09	10	14
3l	19	10	14	15
Control	-	-	-	-
Standard	22	12	14	18

Standard: - Tetracycline, Control- DMSO

Table 3: Antifungal activity of the synthesized compounds (3a-l)

Entry	Zone of inhibition in mm			
	F. oxysporium	*P. chrysogenium*	*A. flavus*	*A. niger*
3a	13	10	07	12
3b	18	15	12	17
3c	21	16	10	15
3d	17	07	14	10
3e	15	19	12	16
3f	10	07	10	14
3g	14	08	13	09
3h	20	14	09	13
3i	19	17	13	12
3j	15	10	07	13
3k	22	16	15	20
3l	25	16	12	22
Control	-	-	-	-
Standard	29	22	14	24

Standard: Norcadine, Control: DMSO

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