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The rapid synthesis of schiff-bases without solvent under microwave irradiation and their antimicrobial activity

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ABSTRACT

*Microwave assisted synthesis, a green chemistry approach, is now a days widely practiced in the synthetic laboratories. In the present work, some Schiff's bases were synthesized using microwave irradiation. They were purified and characterized by means of spectral data and subsequently subjected to the in vitro antibacterial activity against few pathogenic strains of microbes. It was observed that meta-substituted compounds like **3d**, **3e** and **3f** exhibited good activity against almost all the organisms used in the study.*

Keywords: Microwave synthesis, Schiff's base, antibacterial.

INTRODUCTION

Recently, Microwave heating has emerged as a powerful technique to promote a variety of chemical reactions [1]. Microwave reactions under solvent-free conditions are attractive in offering reduced pollution, low cost and offer high yields together with simplicity in processing and handling [2]. The recent introduction of single-mode technology [3] assures safe and reproducible experimental procedures and microwave synthesis has gained acceptance and popularity among the synthetic chemist community. The application of microwave irradiation to organic synthesis has been the focus of considerable attention in recent years and is becoming an increasingly popular technology [4]. Microwave irradiation has been also applied to carry out synthesis in open vessel [5], using organic solvents such as ethanol, N,N–Dimethylformamide(DMF), 1,2–Dichloroethane (DCE), 1,2–dichlorobenzene etc. as energy transfer media which absorb microwave energy efficiently through dipole rotation. The salient features of microwave approach are shorter reaction times, simple reaction conditions and enhancements in chemical yields [6,7].

MATERIALS AND METHODS

Under the work of Green Chemistry we have developed an environmentally benign method for synthesizing some Schiff bases, **3a–h** (Scheme 1) and hope to obtain a few compounds having better anti–bacterial activity. The chemistry of the carbon-nitrogen double bond plays a vital role in the progress of chemical science. Schiff-base compounds are used as fine chemicals and medical substrates [8]. In our effort for the synthesis of Schiff bases, we have synthesized them by both microwave and conventional methods for a comparative study. Synthesis of Schiff base is often carried out by acid-catalysis or generally by refluxing the mixture of aldehyde (or ketone) and amine in organic medium [3]. However, with the assistance of microwave irradiation, it was found that the condensation

reaction of various aromatic aldehydes and various anilines could proceed fast and efficiently without solvent. The products could be purified simply by re-crystallization in an appropriate solvent or a mixture of solvents. The yields of products were high.

Materials

All chemicals and solvents were purchased from Sd Fine Chem ltd. (Mumbai, India) and Hi Media Laboratories (Mumbai, India). The various microbial strains used in the study like *Staphylococcus aureus*, (MTCC 96), *Pseudomonas aeruginosa* (MTCC 2453), *Escherichia coli* (MTCC 739) and *Bacillus subtilis* (MTCC 121) were procured from Institute of Microbial Technology (Chandigarh, India).

Method

The synthesis of new Schiff bases **3a–h** was achieved by cycloaddtion of aromatic aldehydes (10 mmol) and various aromatic amines (10 mmol) in presence of catalytic amount of glacial acetic acid under microwave irradiation (Scheme-1, Table-1). The same compounds were also synthesized using conventional approach. A comparative study in terms of yield and reaction period has been reported using conventional method (Table-2). The reaction carried out using conventional method required about 1.0–2.0 hr, while microwave irradiation method required only 2.0–3.0 min. [9-10] All the compounds synthesized were characterized by IR and Mass data.

Spectral Data Analysis

4-bromo-N-(4-methoxybenzylidene)aniline (3a)

IR (KBr pellet) (Ar) C=C str, 1571.88 cm-1; C=N str, 1602.74 cm-1; C-N str, 1286.43 cm-1; C-O str, 1240.14 cm-1; C-Br str, 1080.00 cm-1. ESI MS (m/z, % int.) 291.17 (100) $[M+H]^+$

4-fluoro-N-(4-methoxybenzylidene)aniline (3b)

IR (KBr pellet) (Ar) C=C str, 1595.02 cm-1; C=N str, 1606.59 cm-1; C-N str, 1288.36 cm-1; C-O str, 1238.36 cm-1; C-F str, 1164.92 cm-1. ESI MS (m/z, % int.) 230.28 (100) $[M+H]^+$

4-fluoro-N-(4-fluorobenzylidene)aniline (3c)

IR (KBr pellet) (Ar) C=C str, 1616.24 cm-1; C=N str, 1627.81 cm-1; C-N str, 1211.21 cm-1; C-F str, 1188.07 cm-1. ESI MS (m/z, % int.) 218.20 (100) $[M+H]^+$

4-((3-chlorophenylimino)methyl)phenol (3d)

IR (KBr pellet) (Ar) O-H str, 3469.70 cm-1; C=C str, 1585.38 cm-1; C=N str, 1627.81 cm-1; C-N str, 1344.29 cm-1; C-Cl str, 1091.63 cm-1. ESI MS (m/z, % int.) 232.68 (100) $[M+H]^+$

3-chloro-N-(4-methoxybenzylidene)aniline (3e)

IR (KBr pellet) (Ar) C=C str, 1571.88 cm-1; C=N str, 1602.74 cm-1; C-N str, 1286.43 cm-1; C-O str, 1242.07 cm-1; C-Cl str, 1164.92 cm-1. ESI MS (m/z, % int.) 246.70 (100) $[M+H]^+$

3-chloro-N-(4-fluorobenzylidene)aniline (3f)

IR (KBr pellet) (Ar) C=C str, 1604.66 cm-1; C=N str, 1618.17 cm-1; C-N str, 1255.57 cm-1; C-F str, 1193.56 cm-1; C-Cl str, 1027.99 cm-1. ESI MS (m/z, % int.) 234.67 (100) $[M+H]^+$

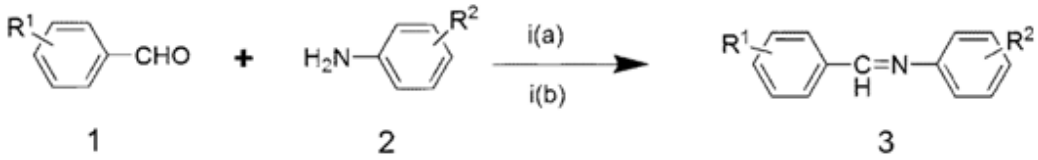
4-fluoro-N-(3-methoxybenzylidene)aniline (3g)

IR (KBr pellet) (Ar) C=C str, 1577.66 cm-1; C=N str, 1606.59 cm-1; C-N str, 1288.36 cm-1; C-O str, 1188.07 cm-1; C-F str, 1164.92 cm-1. ESI MS (m/z, % int.) 230.25 (100) $[M+H]^+$

4-((4-fluorophenylimino)methyl)phenol (3h)

IR (KBr pellet) (Ar) O-H str, 3469.70 cm-1; C=C str, 1573.81 cm-1; C=N str, 1627.81 cm-1; C-N str, 1342.26 cm-1; C-F str, 1089.71 cm-1. ESI MS (m/z, % int.) 216.22 (100) $[M+H]^+$

SYNTHESIS



1 2 3

i(a) Conventional method: *Ethanol / acetic acid, reflux, 1.0-2.0 hours*
i(b) Microwave method: *Acetic acid, mw, 2.0-3.0 mins*

Table 1: Characteristic data of compounds 3a-3h

Compound No.	*R^1*	*R^2*	*M.P.(°C)*	*Molecular formula*
3a	4-OCH_3	4-Br	154-156	$C_{14}H_{12}BrNO$
3b	4-OCH_3	4-F	163-164	$C_{14}H_{12}FNO$
3c	4-F	4-F	178-180	$C_{13}H_9F_2N$
3d	4-OH	3-Cl	172-174	$C_{13}H_{10}ClNO$
3e	4-OCH_3	3-Cl	158-160	$C_{14}H_{12}ClNO$
3f	4-F	3-Cl	162-164	$C_{13}H_9ClFN$
3g	3-OCH_3	4-F	186-188	$C_{14}H_{12}FNO$
3h	4-OH	4-F	176-178	$C_{13}H_{10}FNO$

Table 2: Comparison of Conventional and Microwave synthesis for 3a-3g

Compound No.	*Conventional method*		*Microwave method*	
	% Yield	*Time(hours)*	*% Yield*	*Time(min.)*
3a	65-67	1.0	91-93	2.0
3b	70-72	1.5	94-96	1.5
3c	76-78	45 min.	89-91	1.5
3d	64-66	1.0	92-94	3.0
3e	72-74	2.0	87-89	2.5
3f	68-70	1.5	92-94	2.0
3g	78-80	1.0	88-90	2.5
3h	66-68	1.5	89-91	2.0

Biological Evaluation

Antimicrobial Activity:

The antimicrobial activity of the prepared compounds was determined by agar diffusion method in concentrations of 200, 400, 600 and 800 µg/mL in 10% DMSO against the microbial strains, *Staphylococcus aureus*, and *Bacillus subtilis* were used as Gram positive strains whereas *Pseudomonas aeruginosa* and *Escherichia coli* as Gram negative strains. The selected strains were preserved by sub culturing them periodically on nutrient agar slants and storing them under frozen condition. For the study, fresh 24 hour broth cultures were used after standardization of the culture [11-12].

Screening for antibacterial activity:

The test organisms were inoculated in nutrient broth and were incubated for 48 hours. A definite volume of this suspension was mixed with nutrient agar (cooled to 40 ºC) and poured into petri plates to obtain a uniform thickness. Wells were prepared in the agar and filled with equal volume of respective solution of synthesized compounds. After a period of pre-incubation diffusion, the plates were incubated in the specified conditions. Zones of inhibition were measured with the help of zone reader and are reported in Table 3.

The compound **3e** showed excellent activity while compound **3d** exhibited good activity against *S. aureus* at conc. 800 µg/ml. Compound **3e** was also found to be active against *B. subtilis* at concentration 600 and 800 µg/ml. Compound **3f** exhibited good activity against *E. coli* but none of the compound showed good activity against *P. aeruginosa* [13].

Table 3: Zone of inhibition of compounds 3a-3h

S. No	*Compound code*	*Concentration (ug/ml)*	*Zone of Inhibition diameter (mm)*			
			Gram+ve bacteria		*Gram-ve bacteria*	
			SA	*BS*	*EC*	*PA*
1	Standard (ciprofloxacin)	100	19	18	18	20
2	3a	200	10	5	5	5
		400	10	5	5	5
		600	11	7	5	8
		800	12	8	5	8
3	3b	200	5	5	5	8
		400	5	5	7	10
		600	5	12	9	10
		800	5	13	8	10
4	3c	200	5	5	9	5
		400	10	5	9	5
		600	10	8	10	5
		800	11	8	12	10
5	3d	200	11	5	5	5
		400	12	5	7	9
		600	13	7	10	8
		800	15	7	10	10
6	3e	200	14	10	5	5
		400	14	14	5	5
		600	16	15	8	8
		800	16	15	10	10
7	3f	200	5	5	12	8
		400	11	5	12	10
		600	12	5	14	10
		800	12	5	15	10
8	3g	200	5	5	5	5
		400	5	5	5	5
		600	11	5	5	5
		800	12	5	8	5
9	3h	200	5	5	5	5
		400	5	10	5	8
		600	8	10	8	11
		800	9	11	8	11
10	Control (DMSO)	10% v\v	-	-	-	-

SA: Staphylococcus aureus; BS: Bacillus subtilis; EC: Escherichia coli; PA: Pseudomonas aeruginosa

CONCLUSION

Our present work brings forth a novel method for the synthesis of eight Schiff bases **3a–h** using microwave irradiation which offers significant improvements over existing conventional procedures. This simple technique affords various Schiff base derivatives with short reaction times, excellent yields and without formation of undesirable side products. From data of antimicrobial activity, it could be observed that compounds of the series, **3d** and **3e** showed good activity against Gram positive bacteria whereas **3f** showed moderate activity against Gram negative bacteria comparable to that of standard. Microwave assisted synthesis could be used as an important tool for the synthesis of various medicinally important agents.

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