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Microwave Induced Synthesis and Biological Evaluation of Some Schiff Bases of 2-Amino-3-(N-Chlorophenyl Carboxamido)-4,5-dimethyl Thiophenes

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The new series of 2-amino-3-(N-chlorophenyl carboxamido)-4,5-dimethyl thiophenes (**I–III**) were synthesized by Gewald reaction. Later, the compounds **I–III** were subjected to treatment with ten different substituted arylaldehydes to yield thirty new Schiff bases (**Ia–j to IIIa–j**). All the compounds were characterized by spectral data. Antimicrobial activity has been performed using cup diffusion method for all the synthesized compounds. The compounds **Ia, IIa** and **IIIa** with 2-chlorophenyl substituent and **Ib, IIb** and **IIIb** with 4-chlorophenyl substituent at X exhibited significant antibacterial activity against *S. aureus, B. subtilis* and *E. coli* comparable to ampicillin.

Key Words: Microwave Synthesis, Thiophenes, Schiff bases, Antibacterial activity.

INTRODUCTION

A variety of thiophenes[1–3] and Schiff bases[4–7] were reported to possess interesting activity like antitubercular, bacteriostatic and antifungal activities. Keeping in view the biological importance of 4,5-substituted thiophene derivatives and Schiff bases, an attempt was made by us to synthesize thirty new 4,5-substituted thiophene Schiff bases using microwave heating with a presumption that Schiff bases of 4,5-substituted thiophene (**I–III**) would produce new compounds of appreciable antibacterial activity.

The synthesis of the starting materials 2-amino-3-(N-chlorophenyl carboxamido)-4,5-dimethyl thiophenes (**I–III**) were conducted in 2 steps by adapting a well known and versatile Gewald reaction[8] in 40–50% yield.

Ten different substituted arylaldehydes reacted with appropriate 2-amino-3-(N-chlorophenyl carboxamido)-4,5-dimethyl thiophenes (**I–III**) in presence of catalytic amount of glacial acetic acid and produced the new title compounds **Ia–j**

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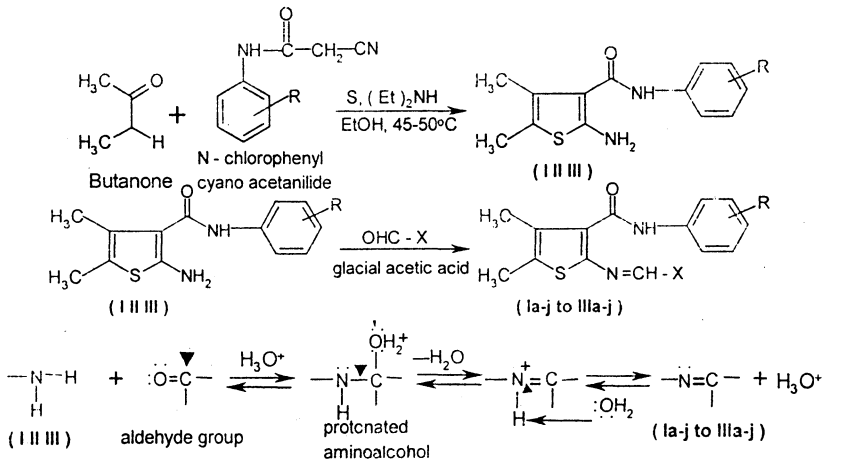
to **IIIa–j,** *via* protonated aminoalcohol intermediate with loss of a molecule of water and formation of —N=C— **(Scheme-1).**



Scheme-1

EXPERIMENTAL

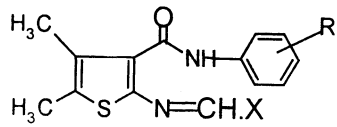
All the compounds are bright coloured solids. Melting points are uncorrected. The UV spectra were recorded on Shimadzu 1601 spectrometer. IR (KBr) were recorded on FT-IR 8201. ^{1}H NMR spectra were recorded on Brucker DPX 200; the chemical shift values are in δ ppm. Purity of the compounds was checked by thin layer chromatography on silica gel G plates. Elemental analyses were within ±0.4% of their calculated values.

The starting compound 2-amino-3-(N-chlorophenyl carboxamido)-4,5-dimethyl thiophene **(I–III)** were prepared according to the literature method[8]. The Schiff bases of corresponding thiophenes were synthesized and characterized in the following manner.

Synthesis of Schiff base of 2-amino-3-(N-*o*-chlorophenyl carboxamido)-4,5-dimethyl thiophene (Ia)

A mixture of 2-amino-3-(N-*o*-chlorophenyl carboxamido)-4,5-dimethyl thiophene **(I)** (2.9 g; 0.01 M) with 2-chlorobenzaldehyde (1.4 g; 0.01 M) and catalytic amount of glacial acetic acid (1 mL) in isopropanol (40 mL) was taken in a beaker, covered with a watch glass and placed inside a Samsung microwave (2450 mHz, 900 W). The compound was irradiated for 1 min. The product separated was cooled, filtered, washed with isopropanol, dried and recrystallised from DMF : water mixture (5 : 1) to yield bright yellow coloured crystalline compound. Yield 72%, m.p. 206°C. Similar procedure was employed in the preparation of other compounds reported in Table-1.

TABLE-1
PHYSICAL AND ANTIBACTERIAL DATA OF COMPOUNDS **Ia-j, IIa-j** and **IIIa-j**



Compd. No.	R	X	m.p. (°C)	Zone of inhibition in mm			
				S.a.	*B.s.*	*E.c.*	*S.t.*
Ia	*o*-Chloro	2-chloro phenyl	206	18	16	10	NA
Ib	*o*-Chloro	4-chloro phenyl	178	22	18	16	NA
Ic	*o*-Chloro	2-hydroxy phenyl	136	23	16	NA	NA
Id	*o*-Chloro	2-nitro phenyl	145	12	10	NA	NA
Ie	*o*-Chloro	3-nitro phenyl	186	14	12	NA	NA
If	*o*-Chloro	4-methyl phenyl	196	NA	NA	NA	NA
Ig	*o*-Chloro	4-methoxy phenyl	140	NA	NA	NA	NA
Ih	*o*-Chloro	3,4-dimethoxy phenyl	152	NA	NA	NA	NA
Ii	*o*-Chloro	3,4,5-trimethoxy phenyl	146	12	12	NA	NA
Ij	*o*-Chloro	4-dimethyl amino phenyl	204	NA	NA	NA	NA
IIa	*m*-Chloro	2-chloro phenyl	188	16	14	12	NA
IIb	*m*-Chloro	4-chloro phenyl	202	20	18	14	NA
IIc	*m*-Chloro	2-hydroxy phenyl	188	14	10	NA	NA
IId	*m*-Chloro	2-nitro phenyl	204	10	10	NA	NA
IIe	*m*-Chloro	3-nitro phenyl	202	12	10	NA	NA
IIf	*m*-Chloro	4-methyl phenyl	186	NA	NA	NA	NA
IIg	*m*-Chloro	4-methoxy phenyl	156	NA	NA	NA	NA
IIh	*m*-Chloro	3,4-dimethoxy phenyl	152	NA	NA	NA	NA
IIi	*m*-Chloro	3,4,5-trimethoxy phenyl	146	12	12	NA	NA
IIj	*m*-Chloro	4-dimethyl amino phenyl	200	NA	NA	NA	NA
IIIa	*p*-Chloro	2-chloro phenyl	202	20	18	12	NA
IIIb	*p*-Chloro	4-chloro phenyl	194	24	20	18	NA
IIIc	*p*-Chloro	2-hydroxy phenyl	203	18	12	NA	NA
IIId	*p*-Chloro	2-nitro phenyl	152	12	12	NA	NA
IIIe	*p*-Chloro	3-nitro phenyl	192	14	14	NA	NA
IIIf	*p*-Chloro	4-methyl phenyl	204	NA	NA	NA	NA
IIIg	*p*-Chloro	4-methoxy phenyl	162	NA	NA	NA	NA
IIIh	*p*-Chloro	3,4-dimethoxy phenyl	180	NA	NA	NA	NA
IIIi	*p*-Chloro	3,4,5-trimethoxy phenyl	148	12	10	NA	NA
IIIj	*p*-Chloro	4-dimethyl amino phenyl	172	NA	NA	NA	NA
Ampicillin				41	36	28	26

S.a. = *S. aureus*, *B.s.* = *Bacillus subtilis*, *E.c.* = *E. coli*, *S.t.* = *S. typh*i, NA = No activity.

The formation of the starting compound 2-amino-3-(N-chlorophenyl carboxamido)-4,5-dimethylthiophenes **(I–III)** has been clearly indicated by the characteristic IR spectra, which show characteristic absorption bands in 3450–3310 cm^{-1} region arising from the asymmetric and symmetric stretching vibrations of the two NH bands (amino group), respectively. Further, the presence of a broad band with a small shoulder at *ca.* 3450 cm^{-1} indicated the presence of an amide group (—CONH—). The appearance of a sharp band at 2940 cm^{-1} is due to the (—S—CH) group and at 700 cm^{-1} is due to the chlorophenyl —C—Cl group.

Since amides have a very strong tendency to self-associate by hydrogen bonding, the band positions have been shifted to lower frequency region. It is observed that the spectra show charateristic sharp band at 1620 cm^{-1} which is due to (C=O) stretching vibration. As a consequence of the mesomeric effect, this amide carboxyl (—CONH) group has less double bond character and hence appeared at lower frequency.

The formation and the purity of the Schiff bases **(Ia–j to IIIa–j)** were confirmed by the difference in m.p., R_f values and characteristic IR peaks at 720 (C—Cl aromatic), 700 (chlorophenyl —C—Cl), 830–810 (*p*-methyl aromatic), 1307 (—OH aromactic), 1370–1330 (—C—NO_2 aromatic), 1660–1640 (—HC=N— of Schiff bases), 2860–2840 cm^{-1} (—OCH_3). The structures of these compounds were also supported by their ^1H NMR spectra as follows:

Ia = 8.2–8.5 (1H, s, —CH= and 1H, d, —NH—), 7.0–7.4 (8H, m, Arom), 2.4 (6H, d, —CH_3 Arom).

If = 8.5 (1H, s, —CH= and 1H, d, —NH—), 7.0–7.8 (8H, m, Arom), 2.4 (9H, d, —CH_3 Arom).

IIb = 8.2–8.5 (1H, s, —CH= and 1H, d, —NH—), 6.9–7.4 (8H, m, Arom), 2.4 (6H, d, —CH_3 Arom).

IId = 8.25 (1H, s, —CH = and 1H, d, —NH—), 7.0–7.75 (8H, m, Arom), 2.4 (6H, d, —CH_3 Arom).

IIIa = 8.2 (1H, s, —CH=), 7.3–7.7 (1H, d, —NH— and 8H, m, Arom), 2.4 (6H, d, —CH_3 Arom).

IIIg = 8.4 (1H, s, —CH=), 7.0–7.8 (1H, d, —NH— and 8H, m, Arom), 4.0 (3H, s, —OCH_3 Arom), 2.4 (6H, d, —CH_3 Arom).

Biological Activity: All the synthesized compounds **(Ia–j to IIIa–j)** were evaluated for antibacterial activity by cup diffusion method[9] at a concentration of 50 μg/mL. Bacterial cultures used for the study were *S. aureus, B. subtilis, E. coli* and *S. typhi*. The zone of inhibition was measured in mm and reported in Table-1. The activity was compared with ampicillin (50 μg/mL) as standard.

A perusal of data presented in Table-1 reveals that the six compounds **Ia, Ib, IIa, IIb, IIIa** and **IIIb** had exhibited interesting activity against *S. aureus, B. subtilis* and *E.coli* only; whereas the compounds **Ic, IIc** and **IIIc** having 2-hydroxy phenyl substituent at X were moderatly active against the Gram +ve organisms only. The compounds with nitro phenyl and trimethoxy phenyl substituents at X exhibited moderate to least antibacterial activity on Gram +ve bacteria; while the compounds with *p*-methyl, *p*-methoxy, dimethoxy and 4-N,N′-dimethyl phenyl substituents showed zero activity against all the organisms employed.

Thus out of the 30 compounds screened none of the compounds were active against *S. typhi* and the compounds with 4-chloro phenyl substituents at X (**Ib, IIb** and **IIIb**) were most active against three strains of bacteria compared to the standard.

Finally, among the title compounds the compounds belonging to the series of **III** had exhibited better activity than the series of **I** and **II**. This activity may be promising and stimulating for further studies on this kind of compounds.

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