International Journal of
Medicinal Chemistry & Analysis
www.ijmca.com
e ISSN 2249 - 7587
Print ISSN 2249 - 7595

ECONOMIC SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME SCHIFF BASES OF 2 NITRO PYRIDINE

P.Venkateswara Rao[1], A.V.G.S. Prasad[*1], P.S.S.Prasad[*2]

[1]Department of Chemistry, Nizam College (Autonomous), Hyderabad, Andhra Pradesh, India.
[2]Drug Control Administration, Hyderabad, India.

ABSTRACT

In the present study an intermolecular reductive Schiff base formation from nitroarenes and benzaldehydes to yield diarylimines is carried out in the presence of iron powder and dilute acid. In the present study new Schiff base compounds derived from 2 nitro pyridine with aldehyde derivatives. Schiff bases were characterized by IR, and 1H NMR spectroscopy. The Schiff base ligands have also been tested *in vitro* for their antibacterial activity. The experimental results suggest that Schiff base ligands are more potent in anti-bacterial activities.

Keywords: Schiff bases, 2 Nitro pyridine, Salicylaldehyde, 5 Bromo salicylaldehyde 5 Methoxy salicylaldehyde, Antibacterial activity.

INTRODUCTION

The increase as well as emergence of bacteria immune to ordinarily used antibiotics has resulted in the need to devolve new categories of antibacterial agents to conflict infections. The chemistry of biological science has produced a number of compounds that are now employed as antibacterial agents. Such type of compounds revealed great promise in this area is the Schiff bases. A Schiff base is the nitrogen analogue of aldehyde in which the C=O group is replaced by a C=N group and is essential for biological activity, several azomethines were reported to possess remarkable antibacterial, antifungal, anticancer and diuretic activities [1].

The reported Schiff bases exhibits antibacterial [2-5], antifungal [6] and antitumor activity [7]. This has led to concentrate deep research on this class of compounds [8]. Similarly, the presence of hetero-atoms in the Schiff bases enhances activity [9].

Current literature reveals that these pyridine compounds possess a variety of biological activities, such as vasodilator, bronchodilator, anti-atherosclerotic, geroprotective, hepatoprotective, anti-diabetic, anti-malarial, anti-inflammatory, anti-asthmatic, antibacterial, and tyrosine kinase inhibiting agents.

Therefore, their synthesis has been the focus of much interest for organic and medicinal researchers. These promising results are encouraging further research in this field, for future applications.

Traditional formation of Schiff bases from nitroarene starting materials requires a two-step process in which the nitroarene is first reduced to the aniline, then isolated, and subsequently condensed with the desired carbonyl [10,11].

Development of non-hazardous synthetic methodologies for organic synthesis is one of the latest challenges to organic chemists. The growing concern for the environment demands the development of eco-friendly and economic processes wherein even less hazardous byproducts are not desirable.

In view of these facts we can clear about that Schiff base are important not only in medical chemistry, but also in organic synthetic chemistry. Schiff base perhaps are synthesized in various method. Recently, catalytic Schiff base formation from nitroarenes and carbonyls has been reported [12,13].

Herein we wish to report our findings of a tandem iron reduction of nitroarenes and subsequent condensation

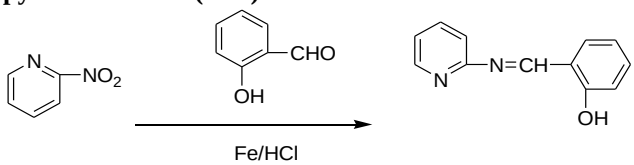
Corresponding Author: - **A.V.G.S. Prasad** Email: avvasiva@gmail.com

iron reduction of nitroarenes and subsequent condensation of arylaldehydes under mild reaction conditions. In the present study an intermolecular reductive Schiff base formation from nitro derivative and benzaldehydes is carried out in the presence of iron powder and dilute acid, characterize them and study their antibacterial activities.

MATERIALS AND METHODS

All the chemicals and solvents were of AR grade. The elemental analyses were performed using vario EL elemental analyzer. IR spectroscopy analysis was recorded on Schimadzu FTIR 8400S spectrometer in 4000 - 200 cm-1 range using KBr pellet technique. 1H-NMR spectra were recorded on JEOL JNM-α 400 spectrometer using DMSO-d6 as solvent and TMS as internal standard.

Synthesis of Schiff bases: N-(2-hydroxylbenzylidene) pyridin-2-amine (SC1)



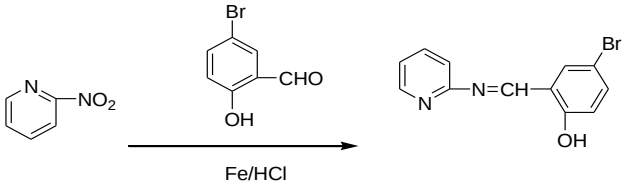
Hydrochloric Acid (4.5 mmol) was added to a mixture of 2 nitro pyridine (0.72 mmol), 2 hydroxy salicylaldehyde (0.72 mmol), and iron powder (7.32 mmol) in 26 mL of EtOH–H2O (2:1 v/v) solution. The reaction was heated to 65°C for 1.5 h before being filtered while hot. The filtrate was extracted using CH2Cl2 (3 × 25 mL) after which the organic layers were combined, dried over MgSO4, filtered, and concentrated in vacuo to yield Yellow-orange crystal; yield 63%; mp 60-62^{0}C.

IR (cm-1): 3434, 1615, 1591, 1281, 1257, 1151, 996, 916, 846, 792, 736, 581.

1HNMR (CDCl3, 400 MHz): 6.91-8.51(m, 8H), 9.41(s, 1H), 13.41(s, 1H).

Anal.calcd. for C12H10N2O: C, 72.72, H, 5.02, N, 14.10.Found: C, 72.38, H, 5.00, N, 14.08.

N-(5-bromo-2-hydroxylbenzylidene) pyridin-2-amine: (SC2)

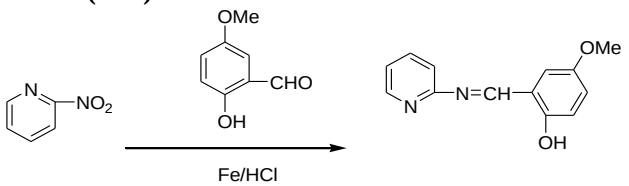


Hydrochloric Acid (0.13 mL, 4.5 mmol) was added to a mixture of 2 nitro pyridine (1.20 gr, 0.72 mmol), 5- bromo 2 hydroxy salicylaldehyde (1.195r, 0.72 mmol), and iron powder (0.409 g, 7.32 mmol) in 24 mL of EtOH–H2O (2:1 v/v) solution. The reaction was heated to 65°C for 1.5 h before being filtered while hot. The filtrate was extracted using CH2Cl2 (2 × 25 mL) after which the organic layers were combined, dried over MgSO4, filtered, and concentrated in vacuo to yield light orange crystal; yield 78 %; mp 135-137^{0}C;

IR (cm-1): 1604,1580, 1430, 1340, 1270, 1180, 1070, 990, 915, 870, 810, 782,740, 698, 625. 1HNMR (CDCl3, 400 MHZ): 6.88-8.48(m, 7H), 9.35(s, 1H), 13.43(s, 1H).

Anal.calcd. for C12H9N2OBr: C,51.98, H, 3.21, N, 10.07. Found: C, 51.95, H, 3.18, N, 9.98

N-(5-methoxy-2-hydroxylbenzylidene) pyridin-2-amine: (SC3)



Hydrochloric Acid (0.13 mL, 4.5 mmol) was added to a mixture of 2 nitro pyridine (1.20 gr, 0.72 mmol), 5-methoxy 2- hydroxy salicylaldehyde (1.195r, 0.72 mmol), and iron powder (0.409 g, 7.32 mmol) in 24 mL of EtOH–H2O (2:1 v/v) solution. The reaction was heated to 65°C for 1.5 h before being filtered while hot. The filtrate was extracted using CH2Cl2 (2 × 25 mL) after which the organic layers were combined, dried over MgSO4, filtered, and concentrated in vacuo to yield dark-orange crystals; yield 73%; mp 80-82^{0}C.

IR (cm-1)*:* 1610,1572, 1550, 1485, 1324, 1270, 1141, 1025, 990,890, 832, 773, 622.

1HNMR (CDCl3, 400 MHZ): 3.74(s, 3H), 6.92 to 8.45(m,7H), 9.35(s, 1H), 12.91(s, 1H). Anal.calcd. for C13H10N2O2: C,68.42, H, 5.24, N, 12.25. Found: C, 68.32, H, 5.22, N, 12.18.

Antimicrobial activity

Antimicrobial activity of the compounds in DMF and 1,4-DIOXANE. Four standard bacteria strains screened were gram positive *S.aureus*, *E.feacalis* and gram negative *E.coli*, *P. aeruginosa*. Antimicrobial activity of the synthesized compounds was screened using the disc diffusion method. The compounds were dissolved in DMSO/1, 4-DIOXANE and sterilized by filtering through 0.45µm millipore filter. Nutrient agar (anti-bacterial activity) and sabouraud dextrose agar medium (antifungal activity) was prepared and sterilized by an autoclave (121ºC and 15 Ibs for 20 min) and transferred to previously sterilized petridishes (9 cm in diameter). After solidification, petriplates were inoculated with bacterial organisms in sterile nutrient agar medium at 45^{0}C, and fungal organism in sterile sabouraud's dextrose agar medium at 45^{0}C in aseptic condition. Sterile whatmann filter paper discs (previously sterilized in U.V lamp) were impregnated with synthesized compounds at a concentration of 25,100 mg/disc was placed in the organism-impregnated petri plates under sterile condition. The plates were left for 30 min to allow the diffusion of compounds at room temperature.

Table 1. Antimicrobial activity of the Schiff bases in DMF

Compound	*S.aureus*						*E.Feacalis*	*E.Coli*						*P.auruginisa*
	Concentration mg/ml													
	40	20	10	5	2.5	1.25	40-1.5	40	20	10	5	2.5	1.25	40-1.5
(SC1)	2	2	1	0	0	0	0	3	2	2	1	0	0	0
(SC2)	3	2	3	2	2	2	0	3	3	3	2	1	1	0
(SC3)	2	3	3	3	3	2	0	3	3	2	3	1	2	0

Table 2. Antimicrobial activity of the Schiff bases in 1, 4-DIOXANE

Compound	*S aureus*						*E.Feacalis*	*E.Coli*						*P.auruginisa*
	Concentration mg/ml													
	40	20	10	5	2.5	1.25	40-1.5	40	20	10	5	2.5	1.25	40-1.5
(SC1)	3	2	3	2	1	1	0	2	2	3	1	2	0	0
(SC2)	3	2	3	2	3	2	0	3	3	3	3	2	2	0
(SC3)	2	3	2	2	3	2	0	3	3	3	2	3	3	0

RESULTS AND DISCUSSION

All compounds are stable and have sharp melting points that indicate the purity of the compounds. The elemental analyses of the compounds are co-operating with the composition suggested for the compounds.

The IR of each compound confirms the formation of imine bond (–C=N-) and absence of the original aldehydic bond (-C=O). A band at 1608-1614 cm-1 is assigned to stretching vibration of the imine group v (C=N). All the compounds displayed a band at 1270-1288 cm-1 which is assigned to v(C-O) stretching vibration of the Phenolic – OH, respectively. The *v* (OH) band at 3435-3438 cm-1 was observed only in compounds I and II.

Proton NMR showed sharp singlet at 9.34-9.53 ppm which further confirmed the formation of C=N-bonds.

All compounds were inactive against E. feacalis and P.aeruginosa and active against *S.aureus* and *E.coli*. The unsubstituted salicylaldehyde Schiff base (SC1) had least activity against bacteria studied in each solvent. Prevention studies of S. aureus in DMF revealed that (SC3) containing the bromo substituent exhibited activity at lowest concentration studied (0.625 mg/ml) with the electron-donating OMe Schiff base (SC3) having the least activity at the highest concentration (5 mg/ml). Screening against the gram negative E. coli in DMF revealed that (SC3) showed activity at concentration of 2.5 mg/ml and both (SC2) and (SC3) were active at 20 mg/ml. The change of solvent to less polar dioxane, (SC2) and (SC3) were active at lower concentrations of 5 mg/ml. respectively. The higher activity reported in less polar solvent may be due to easier diffusion across the cell wall.

CONCLUSION

We developed the new route for Schiff bases in which we maintained the green chemistry parameter. At the same time yield of product is also increased by maintaining purity of products.

This type reaction is economically attractive method for synthesis of Schiff base compounds and their derivatives. This methodology uses only Fe powder in acidic EtOH/H2O as a reducing agent for nitro derivatives which upon reduction spontaneously condense with an aldehyde in situ.

The synthesized compounds therefore, present a new scaffold that can be used to yield potent antimicrobial compounds. It can be concluded that these compounds certainly holds great promise towards good active leads in medicinal chemistry.

REFERENCES

1. Barboiu CT et al. *Eur J Med Chem*, 31, 1996, 597.
2. Murthy SS, Kaur A, Sreenivasalu B. *Indian J Exp Biol*, 36, 1998, 724.
3. William O. Foye, Principles of Medicinal Chemistry, Bombay, 3rd Edi, 1989, 728.
4. Verma M, Gujrati VR, M Sharma. *Arch Pharm*, 317, 1984, 890.
5. Hogale MB and Uthale AC. *Indian J Chem*, 29B, 1990, 592.
6. Udupi RH, Jeeson M. *Indian J Heterocycl Chem*, 5, 1996, 99.
7. Gajare SA, Bhawsar SB, Shinde DB, Shingare MS. *Indian J Chem*, 36B, 1997, 449.
8. Udupi RH, Mayur YC, Bhat AR. *Indian J Heterocycl Chem*, 6, 1997, 281.
9. Khan MH, Nizamuddin BC. *Indian J Chem*, 36B, 1997, 625.
10. Corsaro A, Chiacchio U, Pistara V. *Curr Org Chem*, 8(6), 2004, 511-538.
11. Iqbal AF. *J Org Chem*, 37, 1972, 27-31.
12. Merlic CG, Motamed S, Quinn BJ. *Chem Soc*, 60, 1995, 33-65.
13. Stefancich G, Artico M, Massa S, Corelli F. *Synthesis*, 1981, 321.