DOI 10.15415/jce.2014.11002

One-Pot Synthesis of Schiff Base Compounds Derived From 2-Nitro Benzoic Acid With Aldehydes

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

Department of Chemistry, Nizam College, Hyderabad, A.P, India

***E-mail: avvasiva@gmail.com**

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 This type of excellent method avoids use of hazardous solvents, longer reaction time and tedious work up procedure. Advantage of this efficient method is excellent yield of products in crystalline form, short reaction time, simplicity of work up procedure and no use of any type of hazardous solvents. Simply this reaction is economically attractive method for synthesis of Schiff base compounds. All these Schiff base compounds were characterized by means of IR, 1H-NMR analysis data. The Schiff base ligands have also been tested in vitro for their antibacterial and anti fungal activity. The experimental results suggest that Schiff base ligands are more potent in anti bacterial and anti fungal activities.

Keywords: Schiff bases, 2-nitro benzoic acid, Antibacterial activity and Antifungal activity.

One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents.Nitrogen containing compounds are very widely distributed in nature and are essential to life, they play a vital role in the metabolism of all living cells.

At present, greater than 75% drugs and drug candidates incorporate amine functionality. The synthesis of these nitrogen-containing compounds by the easily available imine (Schiff base) is one of the most important and convenient routes.

The synthesis and structure assignment by Schiff in 1864 of the first imines was an important event at the beginning of the modern age of chemistry. Schiff's base compounds and their complexes have significant importance in chemistry. Every year number of reports is published on preparation of these compounds and their application in chemical reactions.However, the enormous potential of Schiff bases is far from exhausted and provides an endless opportunity for chemical creativity.

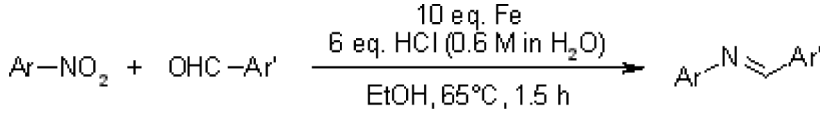
Journal of Chemistry, Environmental Sciences and its Applications
Vol. 1, No. 1
September 2014
pp. 7–14

Schiff bases are important intermediates for the synthesis of various bioactive compounds. Schiff bases are known to have useful biological activity like insecticidal (Jarrahpour et al., 2006), antibacterial (Taggi and Hafez et al., 2002), antituberculosis (Shekarriz and Taslimi, 2004), antimicrobial (Ren et.al., 2002) and anticonvulsant (Hu et al., 2010) activities.

Many derivatives of Schiff bases have found applications in diverse physiological and coordination chemistry area, due promising antibacterial and antivirus activities as well as metal chelating effect and other pharmacological effects (Sandip and Anunay, 2006; Sinha and Tiwari et al., 2008; Sarah and Kelsey et al., 2005).

The present aim of the work is to synthesize a Schiff base derived from 2-nitro benzoic acid with different aldehydes and to characterize them and study their antibacterial activities.

Schiff base formation and mechanism

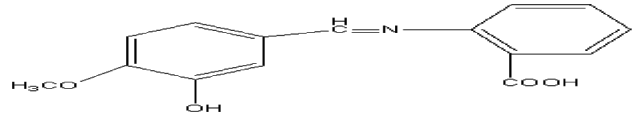


EXPERIMENTAL

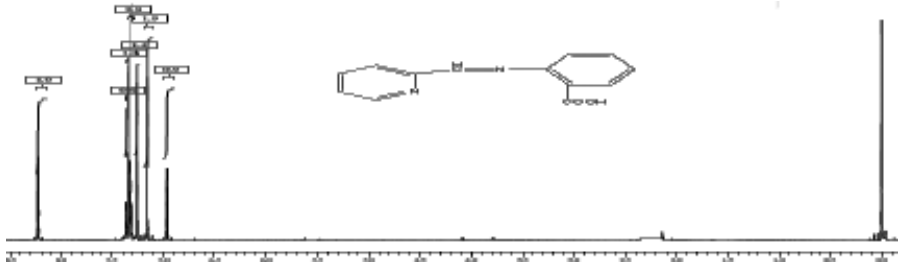
Reagents and Apparatus

All the chemicals used were of AnalaR grade and procured from Sigma-Aldrich and Fluka. The C, H, and N were analyzed on a Carlo-Erba 1106 elemental analyzer. The IR spectra were recorded on Jusco 300 instrument in KBr pellets. 1H NMR spectra of ligands in DMSO solution were recorded on a Bruker DT- 300MHz spectrometer, and chemical shifts are indicated in ppm relative to tetramethylsilane. Mass spectra were recorded using a KRATOS MS50TC spectrometer.

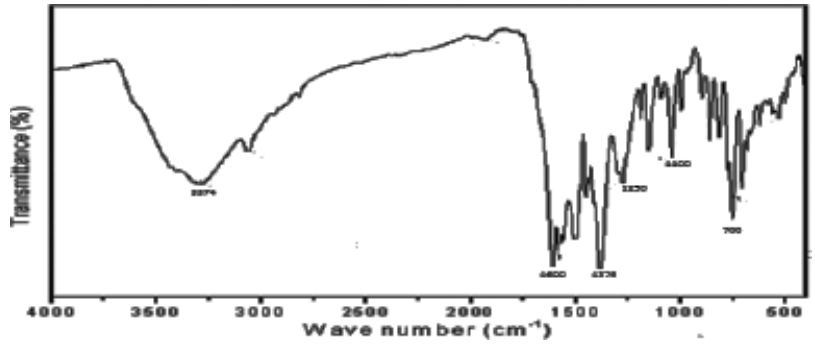
Synthesis of compound (1) **2 (pyridine-2-ylmethyleneamino) benzoic acid**



HCl (0.13 mL, 4.5 mmol) was added to a mixture of 2 nitro benzoic acid (1.2g, 0.72 mmol), pyridine 2 carboxaldehyde (0.78 mL, 0.72 mmol), and iron powder (0.409 g, 7.32 mmol) in 24 mL of EtOH–H_2O (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 CH_2Cl_2 (2 × 20 mL) after which the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 1.48g (75%).

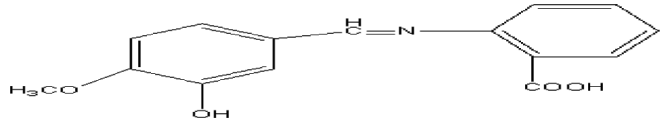


NMR: In the ^{1}H NMR spectra, the aromatic protons (8H), 6.56 to 8.01 ppm. The azomethine proton (1H, N=CH) is observed at 7.49 ppm, and the carboxylic proton appears as a broad signal at 8.4 ppm.



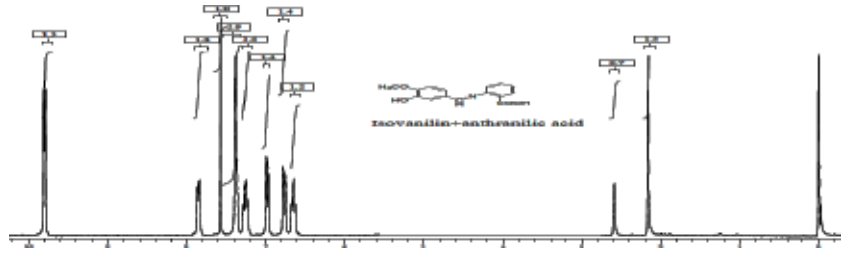
IR: Band at 1600cm^{-1}, which is assigned to v(C=N) stretching vibration, a feature found in Schiff bases. Band at 1379 cm^{-1}, characteristic of the of v(C=O) group. Carboxylic acid group at 3374 cm-1.Mass: m/z=269

Synthesis of compound (2) **2-(3-hydroxy-4-methoxybenzylidineamino) benzoic acid**

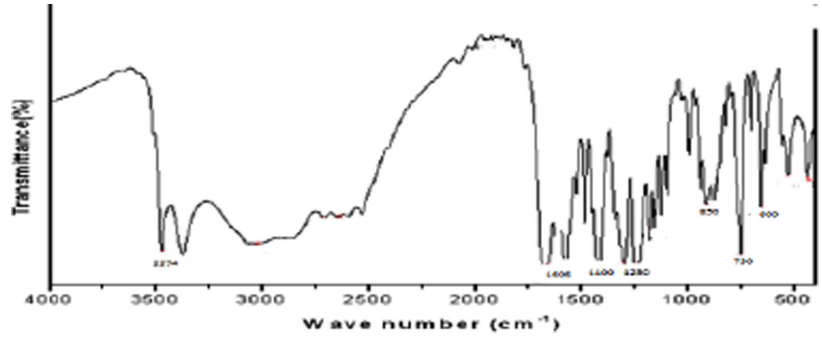


(2)

HCl (0.13 mL, 4.5 mmol) was added to a mixture of 2 nitro benzoic acid (1.2g, 0.72 mmol), isovanilline (1.1 g 0.72 mmol), and iron powder (0.409 g, 7.32 mmol) in 24 mL of EtOH–H_2O (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 CH_2Cl_2 (2 × 20 ml) after which the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 1.95 (85%).

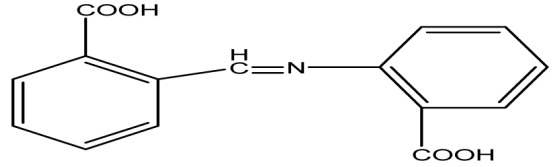


NMR:The aromatic protons (7H) are observed in the range of 6.56 to 7.8 ppm. The azomethine proton (1H, N=CH) is observed at 7.4 ppm, and the carboxylic proton appears as a broad signal at 9.8 ppm. Alcohol proton appears as a broad signal at 2.8 ppm. Methoxy proton appears as a broad signal at 2.2 ppm.



IR:Band at 1606cm-1, which is assigned to v(C=N) stretching vibration, a feature found in Schiff bases. IR absorption 1400 cm-1, characteristic of the of v(C=O) group. IR absorption at 3378 cm-1, characteristic of the of carboxylic acid group. Mass: m/z=271

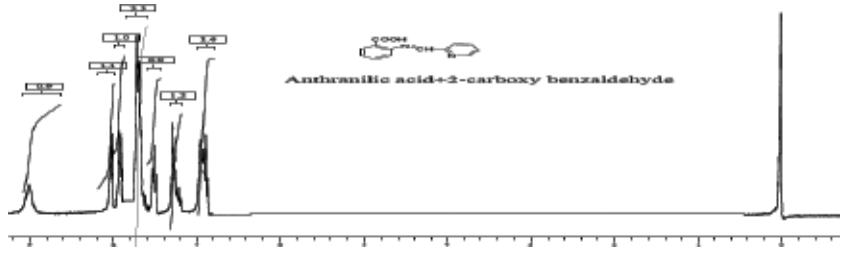
Synthesis of compound (3) **2--(2-carboxylimine) benzoic acid**



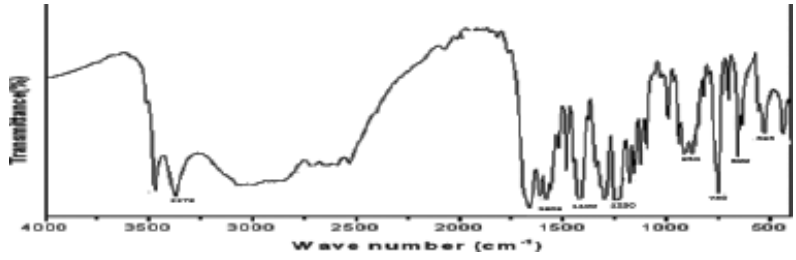
(3)

HCl (0.13 mL, 4.5 mmol) was added to a mixture of 2 nitro benzoic acid (1.2g, 0.72 mmol), 2 carboxy benzaldehyde (1.08g , 0.72 mmol), and iron powder (0.409 g, 7.32 mmol) in 24 ml of EtOH–H_2O (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 CH_2Cl_2 (2 × 20 ml) after which the organic layers were combined, dried over MgSO4, filtered, and concentrated in vacuo to yield 1.53 g (80%).

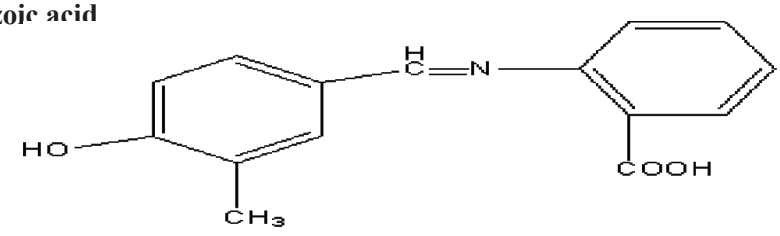


NMR:The aromatic protons (8H) are observed in the range of 6.9 to 7.3 ppm. The azomethine proton (1H, N=CH) is observed at 7.4 ppm, and the carboxylic proton appears as a broad signal at 9 ppm.



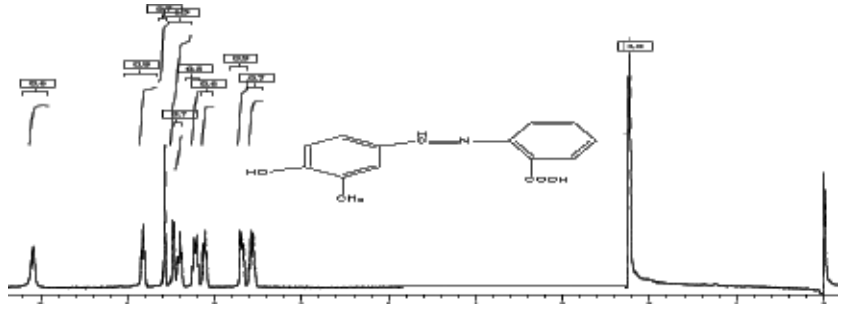
IR:The IR spectral data of the Schiff base showed a band at 1606 cm^{-1}, which is assigned to v(C=N) stretching vibration, a feature found in Schiff bases. IR absorption band at 1400 cm^{-1}, characteristic of the of v(C=O) group. IR absorption band at 3378 cm^{-1}, characteristic of the of carboxylic acid group.Mass m/z=226.

Synthesis of compound (4**) 2-(4 hydroxy-3-methyl benzylidineamino) benzoic acid**

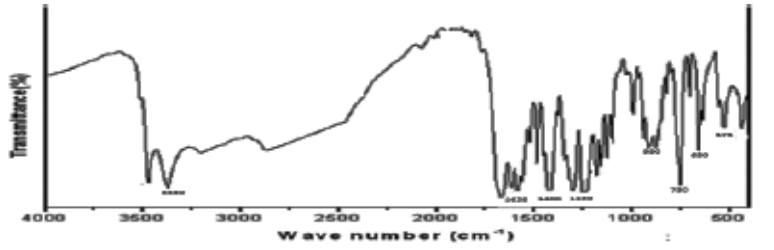


(4)

HCl (0.13 ml, 4.5 mmol) was added to a mixture of 2 nitro benzoic acid (1.2g, 0.72 mmol), 3 methyl-4 hydroxy benzaldehyde (1.0 g, 0.72 mmol), and iron powder (0.409 g, 7.32 mmol) in 24 mL of EtOH–H_2O (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 CH_2Cl_2 (2 × 20 mL) after which the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 1.76 g (80%).



NMR: In the ^{1}H NMR spectra, the aromatic protons (7H) are observed in the range of 6.5 to 7.9 ppm. The azomethine proton (1H, N=CH) is observed at 7.4 ppm, and the carboxylic proton appears as a broad signal at 9 ppm. Methyl proton at 2.2ppm.



IR: The absorption band at 1638cm^{-1}, is assigned to v(C=N) stretching vibration, a feature found in Schiff bases.IR absorption at 3350 cm^{-1}, characteristic of the carboxylic acid group. IR absorption spectrum of the Schiff base ligand shows a band at 1400 cm^{-1}, characteristic of the of v(C=O) group.Mass: m/z 255

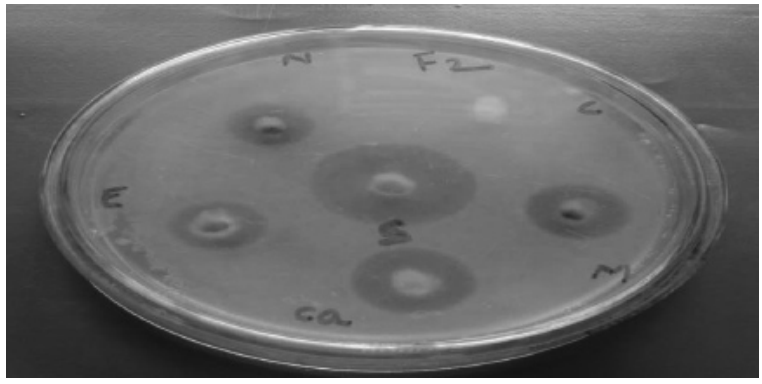
Biological activity

Paper disc diffusion method is used to see what antibiotics or compounds inhibit bacterial growth, or are bacteriostatic. The zones of inhibition are measured around where the disc was placed to determine whether the bacteria were resistant or susceptible to the particular antibiotic or chemical chosen.

The antibacterial activity of the ligands was studied against Gram-negative bacteria Escherichia coli. Each of the compounds dissolved in DMSO at a concentration of 1 mg/ml was prepared. Paper discs of Whatman filter paper no. 1 were cut and sterilized in an autoclave. DMSO as negative control and was placed aseptically in the Petri dishes containing Nutrient agar media inoculated with the above mentioned bacteria. The petridishes were incubated at 37^0C and the inhibition zones were recorded after 24 h of incubation (Drew et al., 1972; Bauer et al., 1996b)

Description of markings on petriplate.

C – Control ca - Standard (amoxicillin)
N - 2 (pyridine-2-ylmethyleneamino) benzoic acid 20 mg of sample
E -2-(3-hydroxy-4-methoxybenzylidineamino) benzoic acid. 20 mg of sample.
M – (3) [2-N-(2-carboxylimine)benzoic acid] 20 mg of sample
S - (4) 2-(4 hydroxy-3-methyl benzylidineamino) benzoic acid 20 mg of sample



RESULTS AND DISCUSSION

Schiff bases shows IR absorption peak at 1600-1675 cm^{-1} (C=N stretching). All the compounds show NMR signals for different kinds of protons at their respective positions. The synthesized compounds were found to be nearly equal or more active than standard antibiotics used for comparison activity against E. coli. The synthesized compound 2-(4 hydroxy-3-methyl benzylidineamino) benzoic acid(compound 4---S) showed more active than standard antibiotic amoxicillin. Hence, further study of antimicrobial activity may become fruitful.

CONCLUSIONS

Diarylimine have been prepared by a simple and environmentally friendly reductive imination procedure. This methodology uses only Fe(0) in acidic EtOH/H_2O as a reductant for nitroarenes, which upon reduction spontaneously condense with an aldehyde *in situ*.

Above Schiff base compounds shows inherent new generation of series of pharmaceutically important compounds. Conclusively, a variety of Schiff bases derivatives with 2-nitro benzoic acid have been successfully synthesized in appreciable yields and screened in vitro for their antimicrobial activities against Gram-negative bacteria E.Coli.

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