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Research Article

NOVEL ONE POT SYNTHESIS OF PYRIDINE HETEROCYCLIC DERIVATIVES AND BIOLOGICAL STUDIES

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ABSTRACT
In the present study of one pot tandem reductive Schiff base formation from nitroarenes carried out in the presence of iron powder and dilutes acid.A potential method for one-pot synthesis of Schiff base compounds derived from different aldehydes and nitro compounds such as Salicylaldehyde, 3,5-di Tertery butyl 2-Hydroxy Benzaldehyde and 2-nitro Pyridine. 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 environmentally Proactive (non polluted) and economically attractive method for synthesis of Schiff base compound. All these Schiff base compounds were characterized by means of IR, 1H-NMR and their Elemental analysis as (C, H, N, and O) spectral analysis data. Above Schiff base compounds shows inherent new generation of series of pharmaceutically important compounds. The experimental results suggest that Schiff base derivatives are more potent in antibacterial and antifungal activities.

Keywords: *Tandem Reaction, Intermolecular Reductive Schiff Base, Green Chemistry, Salicylaldehyde, 3, 5 di Tertery Butyl 2-Hydroxy Benzaldhyde, 2-nitro Pyridine, Antibacterial Activity, Antifungal Activity*

INTRODUCTION
In an economically expanding world new sustainable concepts have to be developed in order to overcome growing problems of resource availability. Chemists are constantly working to discover new and improved reactions. One of the primary motivating goals of this research is the development of cleaner, more efficient transformations to shorten syntheses and save money on chemicals. The strategy of using reactions in tandem (multistep one-pot reactions) is also aimed at shortening syntheses. Since the intermediates are not isolated it becomes easier to work with sensitive or unstable intermediates. Tandem reactions have several advantages over a series of individual reactions. First, they allow construction of complex structures in as few steps as possible. In theory, they also eliminate the need for a purification step (or steps). Since the intermediates are not isolated it becomes easier to work with sensitive or unstable intermediates.

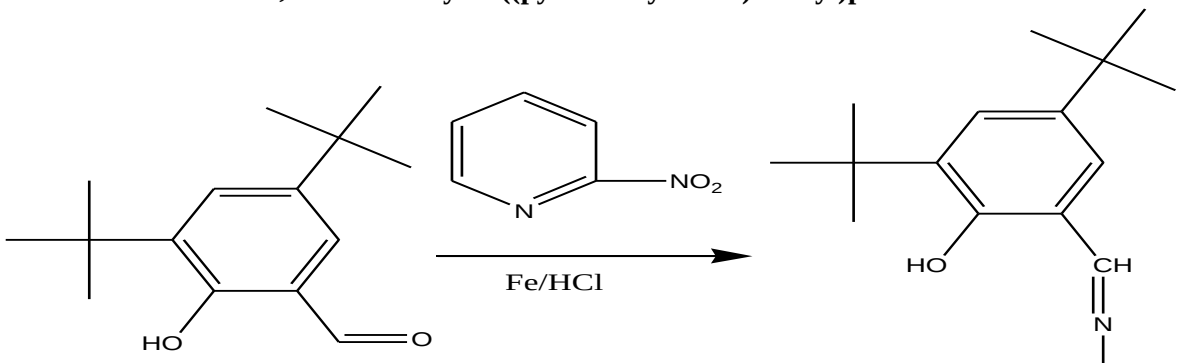
Green Context
In view of human health and environmental concerns, much attention is being paid to 'Green Chemistry', which is a chemical methodology to decrease or eliminate the use or generation of hazardous substances in the design, preparation and application of chemical production. The chemistry 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. Schiff bases are important intermediates for the synthesis of various bioactive compounds. Furthermore, they are reported to show a variety of biological activities including antibacterial, antifungal, anti cancer and herbicidal activities. There has been growing concern over the environmental impact of chemicals so that cleaner green reaction conditions in synthetic processes have been advocated. The tight legislation to maintain greenness requires us to prevent the generation of waste, avoid use of auxiliary substances (e.g., organic solvents, additional reagents), and minimize the energy requirement.
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 (Kidwai *et al.,* 1997).

Schiff base compounds are very popular ligands because of their easy formation and rich coordination chemistry with a large variety of metal ions that has allowed their use as catalysts in different asymmetric reactions (Gagieva *et al.,* 2005; Patti *et al.,* 2009).
Salicylaldehyde-based Schiff bases have been screened for antibacterial activity against several bacterial strains such as Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa (Chohan and Jaffery, 2001).
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 (Song *et al.,* 2008; Bennett *et al.,* 2009).
Over the past few decades, significant research has been directed towards the development of new technologies for environmentally benign processes (green chemistry) (Bhattacharya and Purohit, 2003).
The deep Studies on a new kind of chemotherapeutic Schiff bases are now attracting the attention of biochemists (Shiva *et al.,* 2010; Katia *et al.,* 1995).
Considerable interest attached with the chemistry of Schiff bases (Angellei, 1990), obtained from heterocyclic aldehyde, also various heterocyclic Schiff bases having O,N and S donor atoms, have been reported by several scientists (Campbell, 1974; Dawas and Waters, 1987; Nuria *et al.,* 2008).
In conclusion, we describe a green and efficient method for the synthesis of Schiff bases with easy workup; facile conditions, fast reaction rates, good yields, and selectivity of the reaction make the present methodology attractive.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on a Perkin Elmer Spectrum RX-1 FTIR spectrophotometer. 1H-NMR spectra were measured on Jeol JNM-ECX400P at 400 MHz. All chemicals used were of analytical grade.

Synthesis of Schiff base: 2,4-di-tert-butyl-6-((pyridin-2-ylimino)methyl)phenol



3,5-di-tert-butyl-2-hydroxybenzaldehyde

Hydrochloric Acid (4.5 mmol) was added to a mixture of 2 nitro pyridine (0.72 mmol), 3,5-di-tert-butyl-2-hydroxybenzaldehyde (0.72 mmol), and iron powder (7.32 mmol) in 26 mL of MeOH– H2O (2:1 v/v) solution. The reaction was heated to 65°C for 4-5 h before being filtered while hot. The filtrate was extracted using chloroform (100 ml) after which the organic layers were combined, dried over MgSO4, filtered, and concentrated in vacuo to yield Yellow crystals (68%), Melting Point: 116-118 ^{0}C.
FTIR (KBr pellets):430.05, 466.31, 640, 1048.41, 850.41, 970.16, 1010, 1032.54, 1138.60, 1200, 1270.61, 1353, 1400, 1451, 1481, 1571, 1631, 1790.46, 2926.10, 3056.31, 3600.
1H NMR (200.13 MHz CDCl3):3.92(s, 4H), 6.84(m.4H), 7.20(m, 4H), 8.30 (s, 2H), 13.20 (bs, 2H)
Anal. Calcd. For C20H26N2O: C, 77.38; H, 8.44; N, 9.02; O, 5.15. Found C, 77.01; H, 8.03; N, 8.74; O, 4.84.

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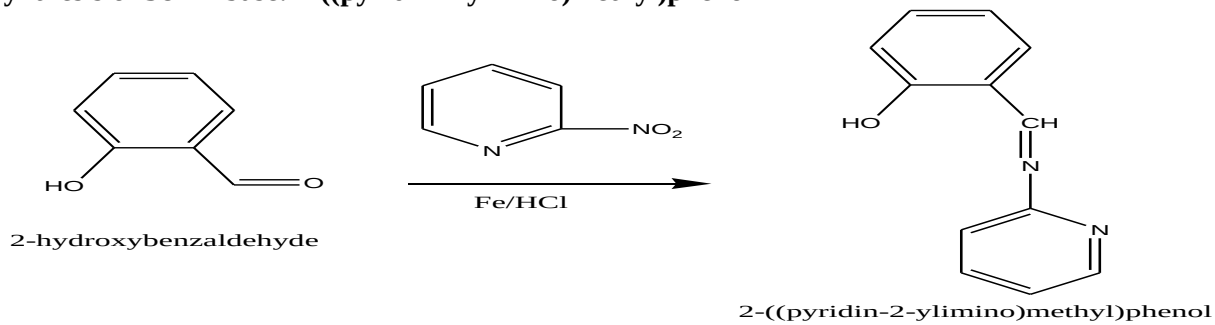
Research Article

Synthesis of Schiff base: 2-((pyridin-2-ylimino)methyl)phenol



Hydrochloric Acid (4.5 mmol) was added to a mixture of 2-nitropyridine (0.72 mmol), salicylaldehyde (0.72 mmol), and iron powder (7.32 mmol) in 26 mL of MeOH– H2O (2:1 v/v) solution. The reaction was heated to 65°C for 4-5 h before being filtered while hot. The filtrate was extracted using chloroform (100 ml) after which the organic layers were combined, dried over MgSO4, filtered, and concentrated in vacuo to yield dark orange crystals, Melting Point: 74-76^{0}C.

FTIR (KBr pellets): 451,502,576,622,675,755,785,845,913,955,996, 1111, 1145, 1186, 1279, 1349,1411, 1429, 1461, 1497, 1552, 1585, 1606, 1837, 1956, 2056, 2108, 2383, 2432, 2483, 2559, 2596, 2731,2800, 2861, 2929, 3051, 3205.76, 3400.12

1H NMR (200.13 CDCl3): 7.0o(m,2H), 7.24-7.51(m,4H), 7.76(dd,1H), 8.48(d,1H), 9.43(s, 1H), 13.45(s, 1H)

Anal. Calcd. For C12H10N2O: C, 72.71; H, 5.08; N,14.13; O, 8.07. Found C, 72.10; H, 4.80; N, 13.76; O, 7.85.

Antimicrobial and Antifungal Screening

The antimicrobial and anti fungal tests were performed by the standard disc diffusion method. The synthesized Schiff base compounds are screened for their antifungal activity against fungi viz. Aspergillus niger. The antibacterial activity of the complexes was studied against Gram-positive bacteria Staphylococcus aureus (MTCC 96)

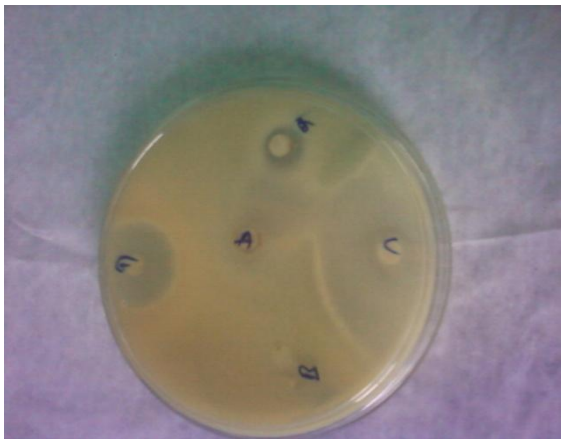


Figure 1: Anti bacterial plate of 2,4-di-tert-butyl-6-((pyridin-2-ylimino)methyl)phenol

C - Standard (amoxycillin)
A – Control
D - 60 mg
E -40 mg
B - 20 mg

Each of the schiff base 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. The paper discs were saturated

with 10 µl of the metal complex compounds dissolved in DMSO solution or DMSO as negative control and were placed aseptically in the Petri dishes containing Nutrient agar media inoculated with the above mentioned two bacteria separately. The petridishes were incubated at 37oC and the inhibition zones were recorded after 24 h of incubation.

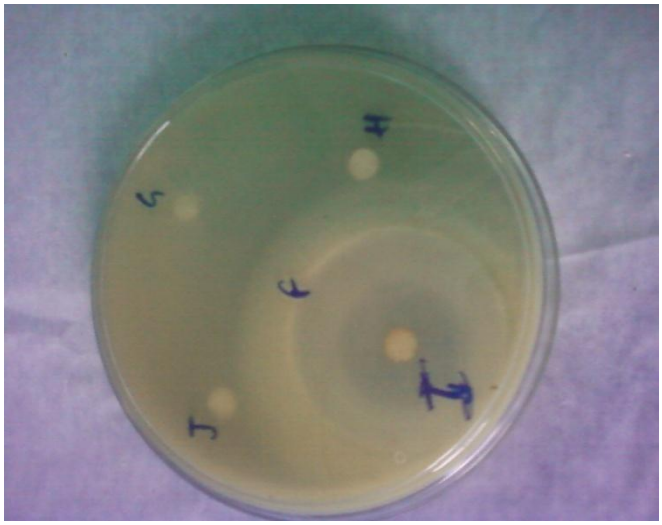


Figure 2: Anti fungal plate of 2,4-di-tert-butyl-6-((pyridin-2-ylimino)methyl)phenol
H – Standard Fluconazole
F –control
G - 20 mg
J-40mg
I- 60 mg

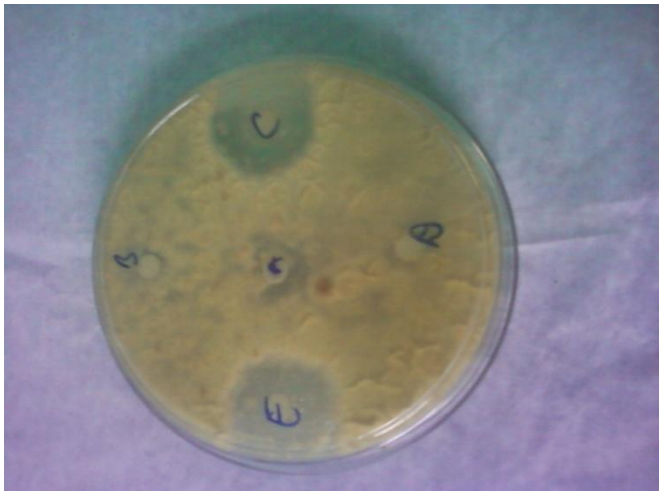


Figure 3: Anti bacterial plate of 2-((pyridin-2-ylimino)methyl)phenol
C - Standard (amoxycillin)
A – Control
D - 60 mg
E -40 mg
B - 20 mg

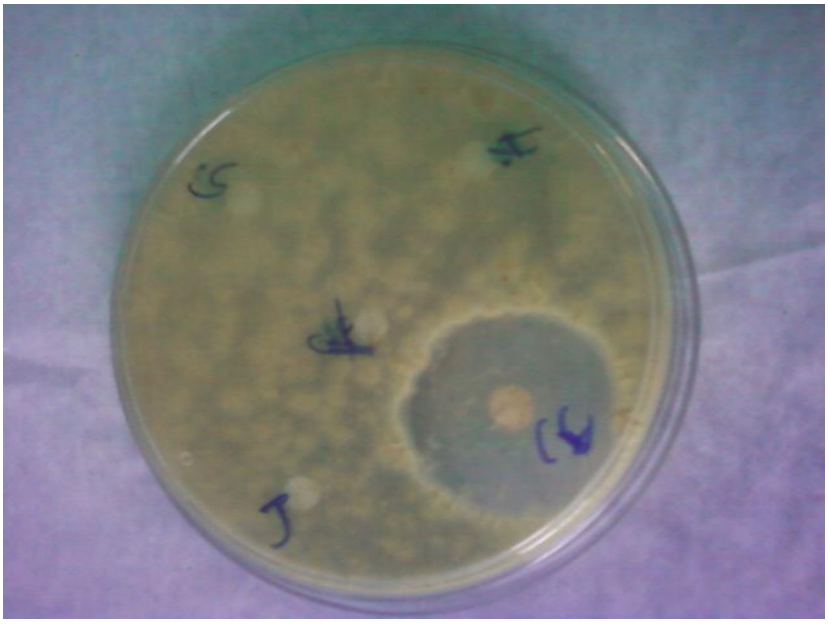


Figure 4: Antifungal plate of 2-((pyridin-2-ylimino)methyl)phenol

H – Standard Fluconazole
F –control
G - 20 mg
J-40 mg
I- 60 mg

Conclusion

Green chemistry for chemical synthesis addresses our future challenges in working with chemical processes and products by inventing novel reactions that can maximize the desired products and minimize by-products, designing new synthetic schemes that can simplify operations in chemical productions, and seeking greener solvents that are inherently environmentally and ecologically benign.

This methodology uses only Fe powder in acidic MeOH/H2O as a reducing agent for nitro derivatives which upon reduction spontaneously condense with an aldehyde in situ.

Our present work brings forth a novel method for the synthesis of Schiff bases n 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, operation simplicity, cleaner reaction and easy work-up. All spectroscopic analysis confirmed the proposed structures for these compounds.

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.

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