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An environmentally benign, solvent free synthesis and antibacterial activity of novel Schiff bases derived from 4,5-diazafluoren-9-one

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ABSTRACT

Ten new heterocyclic moiety containing Schiff bases have been synthesized by the condensation of 4,5-diazafluoren-9-one with substituted amines by using $SnCl_2$ as a catalyst under solvent free condition. The Schiff bases were obtained in good yields and easy to isolate. Some synthesized products were characterized by IR, NMR and MASS and also tested for antibacterial activities by disc diffusion method.

Introduction

The chemistry of the carbon-nitrogen double bond plays a vital role in the progress of chemistry science [1]. Schiff-base compounds have been used as fine chemicals and medical substrates.

Moreover, Schiff bases derived from various heterocycles have been reported to possess cytotoxic [2], anticonvulsant [3], antiproliferative [4], antimicrobial [5], anticancer [6], antifungal [7], anti-inflammatory [8], analgesic [9], CNS depressant [9], antitubercular [10], antitumor [11-12], insecticidal [13], plant growth inhibitor [14] and herbicidal properties [15].

One of the important roles of Schiff bases is an intermediate in the biologically important transmission reaction. Schiff bases are also used as protective agent in synthesis of natural rubber and various organic synthesis reactions.

At present a broad range of methods for synthesizing imines in the presence of catalysts are available: $ZnCl_2$ [16], $TiCl_2$ [17], K-10 [18-19], $MgSO_4$-PPTL [20], $Mg(ClO_4)_2$ [21] and also SiO_2-$NaHSO_4$ (under MW irradiation condition) [22].

More recently, ultrasound irradiation has been used to give rise to the formation of a series of Schiff bases (aryl-aryl and aryl-alkyl), under solvent-free conditions [23] or using SiO_2 as a catalyst in ethanol [24], with short reaction times (10-20 min) and high yields. Harruna et al [25] and Rillema et al [26], reported synthesis of imimes from 4,5-diazafluoren-9-one by using acetic acid as a catalyst in ethanol with long reaction times (17-18 hrs), low yield and difficult to work up.

Thus to overcome this drawback we synthesized novel Schiff bases from 4,5-diazafluoren-9-one by using $SnCl_2$ as a catalyst under solvent free condition. All compounds also assayed for antibacterial activity.

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Experimental:

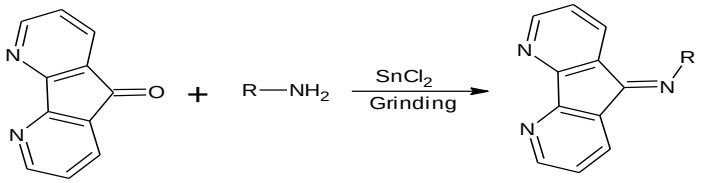
Material and instrumentation:

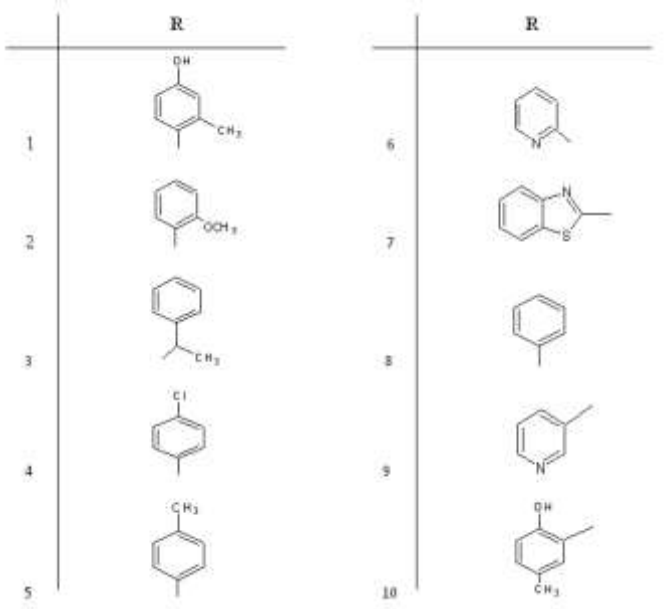
All the chemicals used for this work were obtained from Merck and Aldrich Chemical Companies. Melting points of the synthesized compounds were determined in open-glass capillaries on a stuart-SMP10 melting point apparatus and are uncorrected. IR absorption spectra's were recorded on a Perkin Elmer 1650 FTIR using KBr pellets in the range of 4,000-450 cm^{-1}, ^{1}H-NMR were recorded on a Bruker spectrometer operating at 300 MHz using. The ^{1}H-NMR chemical shifts are reported as parts per million (ppm) downfield from TMS (Me_4Si) used as an internal standard. Mass spectra's were recorded on LCQ ion trap mass spectrometer. Purity of the compounds was checked by thin layer chromatography (TLC) on Merck silica gel 60 F254 precoated sheets in benzene/methanol mixture and spots were developed using iodine vapors as visualizing agents.

Synthesis of Schiff bases:

A mixture of 4,5-diazafluoren-9-one (1 mmol) and substituted amines (1mmol) was grinded in a mortar with a pestle at room temperature and then $SnCl_2$ (20 mol%) was added and crushed, progress of reaction was monitored by TLC. After completion of reaction (3 min) the crude product was washed with water, dried and purified by column chromatography. Synthetic pathway for preparation of title compounds is shown in Scheme 1.

Scheme 1: Synthesis of Schiff bases





3-methyl-4-(5*H*-pyrido[3',2':4,5]cyclopenta[1,2-*b*]pyridin-5-ylideneamino)phenol (1)

Yield: 82 %; mp: 256-258 ^{o}C; IR: (KBr, cm^{-1}) ν 3375, 3025, 2927, 1627, 1529, 1400, 758, 701, 538; ^{1}H NMR: ($CDCl_3$, 300 MHz), δ: 9.84 (s, 1 H), 8.74 (m, 2 H), 8.37 (dd, J = 8.7 Hz, 1 Hz, 1H), 8.28 (dd, J = 8.7 Hz, 1 Hz, 1 H), 7.38 (m, 1H), 7.25 (m, 1 H), 6.98 (d, J = 8.1 Hz, 1 H), 6.77 (s, 1 H), 6.64 (d, J = 8.1 Hz, 1 H), 2.35 (s, 1H); MS (ES): m/z 288.1 (MH^+)

4-chloro-*N*-(5*H*-pyrido[3',2':4,5]cyclopenta[1,2-*b*]pyridin-5-ylidene)aniline (4)

Yield: 86 %; mp: 187-188 ^{o}C; IR: (KBr, cm^{-1}) ν 3046, 2922, 1601, 1591, 1447, 754, 711; ^{1}H NMR: ($CDCl_3$, 300 MHz), δ: 8.85 (m, 2 H), 8.60 (d, J = 7.5 Hz, 1H), 8.22 (d, J = 7.5 Hz, 1 H), 7.82 (d, 8.7 Hz, 2H), 7.45 (d, 8.7 Hz, 2H), 7.32 (m, 1 H), 7.29 (m, 1 H); MS (ES): m/z 291 (MH^+), 292 (MH^{+1})

***N*-(5*H*-pyrido[3',2':4,5]cyclopenta[1,2-*b*]pyridin-5-ylidene)-1,3-benzothiazol-2-amine (7)**

Yield: 82 %; mp: 239-241 ^{o}C; IR: (KBr, cm^{-1}) ν 3029, 2931, 1612, 1595, 1490, 749, 732; ^{1}H NMR: ($CDCl_3$, 300 MHz), δ: 8.89 (dd, J = 7.8 Hz, 1.5 Hz, 1 H), 8.85 (m, 2H), 8.23 (dd, J = 7.8 Hz, 1.5 Hz, 1 H), 7.51-8.10 (m, 4H), 7.31 (m, 1H), 7.20 (m, 1 H); MS (ES): m/z 314 (MH^+)

4-methyl-2-(5*H*-pyrido[3',2':4,5]cyclopenta[1,2-*b*]pyridin-5-ylideneamino)phenol (10)

Yield: 80 %; mp: > 300 ^{o}C; IR: (KBr, cm^{-1}) ν 3365, 3026, 2920, 1611, 1593, 1452, 755, 699, 539; ^{1}H NMR: ($CDCl_3$, 300 MHz), δ: 9.89 (s, 1 H), 8.77 (m, 2 H), 8.38 (dd, J = 9 Hz, 1.2 Hz, 1H), 8.30 (dd, J = 9 Hz, 1.2 Hz, 1 H), 7.35 (m, 1H), 7.26 (m, 1 H), 7.13 (s, 1 H), 7.04 (d, J = 8.1 Hz, 1 H), 6.91 (d, J = 8.1 Hz, 1 H), 2.34 (s, 1H); MS (ES): m/z 287.1 (MH^+)

Antimicrobial activity assay procedure

Disc diffusion method:

The antimicrobial activity of newly synthesized compounds was evaluated according to the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS, 1997) using the disc diffusion method [27].

Briefly, a 24/48 h-old culture of selected bacteria was mixed with sterile physiological saline (0.85%) and the turbidity was adjusted to the standard inoculum of McFarland scale 0.5 [~106 colony forming units (CFU) per milliliter]. Petri plates containing 20 mL of Nutrient Agar (NA, Hi- Media) were used for all the bacteria tested. The inoculums was spread on the surface of the solidified media and Whatman no. 1 filter paper discs (6 mm in diameter) impregnated with the test compound (20 µL/disc) were placed on the plates.

Cephotoxime (10 µg/disc, Hi-Media) and Tetracycline (30 µg/disc, Hi-Media) were used as positive controls for bacteria. A paper disc impregnated with dimethylsulfoxide (DMSO) was used as negative control. Plates inoculated with the bacteria were incubated for 24 h at 37 ºC.

The inhibition zone diameters were measured in millimeters. All the tests were performed in triplicate and the average was taken as final reading.

Result and Discussion

Chemistry:

To overcome the reported drawbacks, we began our study by evaluating the efficiency of grinding in reaction between 4,5-diazafluoren-9-one and substituted amines in solid state under solvent free condition. Initially we ground the mixture of 4,5-diazafluoren-9-one and substituted amines in mortar with a pestle at room temperature under neat condition. However, results demonstrated that the need of catalyst. Since the starting material was recovered. Thus, we chose inexpensive and efficient $SnCl_2$ as a catalyst. $SnCl_2$ was used in 20 mol % which leads to excellent yield of the product.

Anti-bacterial activity:

The anti-bacterial activities of the newly synthesized compounds (1-10) were evaluated against various pathogenic (Gram-negative and Gram-positive) bacterial strains viz., *Escherichia coli* (*E. coli*), *Staphylococcus aureus* (*S. aureus*), *Bacillus subtilis* (*B. subtilis*) and *Klebsiella pneumonae* (*K. pneumonae*). The anti-bacterial activities were evaluated by the disc diffusion method. The solvent used for the preparation of compound solution (DMSO) did not show inhibition against the tested organisms (negative control)

The results of anti-bacterial screening of all newly synthesized compounds are demonstrated in Table 1. In these compounds 7 and 10 showed good activity (Zone of inhibition 11-16 mm at concentration of 250 µg/ml) against all four bacterial strains.

It is interestingly to note that the slight structural difference in 1 and 10 can be observed, but their antibacterial activity is entirely different. The electric property of the compounds has close relations with biological activity [28] and the weak antibacterial activity of compound 1 compared to compound 10 may be explained by their charge density distribution.

Compound 5 with CH_3 substituent at para position showed moderate activity (Zone of inhibition 11-12 mm at concentration of 250 µg/ml) against *E. coli* and *K. pneumonae*. The compound 4 with Cl substituent at para position showed moderate activity (Zone of inhibition 11 mm at concentration of 250 µg/ml) against *S. aureus* and *K. pneumonae.*

Conclusion:

Procedure for synthesis of Schiff bases eliminates the use of organic solvents. Thus we have synthesized a series of new heterocyclic Schiff bases by using $SnCl_2$ as a catalyst.

Reaction completes within 3 minutes with excellent yield. Isolation of product is simple and does not harm the environment. All the compounds more or less active to tested bacteria. Compounds 1, 4, 5, 7 and 10 showed moderate to good anti-bacterial activity. Probably the electric property of these compounds may be a reason for their biological activity.

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Table 1: Anti-bacterial activities of the compounds (1-10)

Compounds	1	2	3	4	5	6	7	8	9	10	S1	S2
E. coli (mm)	11	-	7	-	12	-	12	-	-	16	16	14
S. aureus (mm	-	7	-	11	3	9	15	7	12	14	18	15
B. subtilius (mm)	-	-	-	-	5	7	11	-	-	16	14	17
K. pneumonia (mm)	9	-	7	11	11	-	11	-	-	13	14	15

- : indicates bacteria are resistant to the compounds,
S1:Cephotoxime used as standard drug atconcentration of 10 µg/ml
S2 : Tetracycline used as standard drug at concentration of 30 µg/ml
All compounds tested at concentration of 250 µg/ml