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Greener and Efficient Synthesis of Some Novel substituted Azitidinones With 4-Amino Pyridine via Heterogenous catalyst

Kalpana Avasthi*, Ritu Yadav and Takallum Khan

*Green-Synthetic Organic Laboratory, Department of Chemistry, Dr. Hari Singh Gour central University, SAGAR (M.P.) 470003, **INDIA**

Email: kalpana.avasthi@gmail.com

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ABSTRACT

A new series of (3-chloro-2-oxo-4-substituted-Aryl-N-pyridine-4-yl-azetidinone) β –lactams ***(3a-3j)*** *were synthesized via heterogeneous catalysed reaction between 4 amino- pyridine and substituted aromatic benzaldehyde as a starting material by conventional method in two steps. All the synthesized compounds* ***(3a-3j)*** *were screened for their antibacterial and antifungal activities against some selected bacteria and fungi. . The structure of all the synthesized compounds were confirmed by chemical and spectral analysis such as IR,* ^{1}*H NMR,* ^{13}*C NMR and FAB-Mass.*

Keywords: Heterogeneous catalyst, Conventional green Synthesis, 4-Aminopyridine, Azitidinone, Antimicrobial.

INTRODUCTION

Organic reactions promoted by a solid heterogeneous catalyst have attracted wide spread interest and are advantageous because of operational simplicity, high selectivity and clean separation of the product. Metal oxides impregnated over silica has been recognized as a remarkably useful green heterogeneous catalyst to promote a wide range of organic reactions[1]. Herein we report a rapid and green approach to achieve highly substituted Azetidinones with pyridine in excellent yields in the presence of catalytic amount of SiO2/Fe2O3 under controlled. Pyridine derivatives of different heterocyclic nucleus have shown very important pharmacological properties like antifungal[2-4],antitubercular[5], antibacterial[6], antimi crobial[7], insecticidal[8] etc. Furthermore, different moieties of thiadiazole[9,10], thiazoli dinone [11,12] and azetidinone[13,14] have also been reported to exhibit potent antifungal activities by several scientists. In the light of these observations, compounds of series were synthesized incorporating azetidinone moieties at 4-position of pyridine nucleus with a hope to develop better antifungal agents[15]. These compounds have been screened for their antifungal activity. 2-Azetidines have been extensively investigated by the organic chemists due to their close association with various types of biological activities[16,17]. Azetidineones also have great importance because of the use of β-lactam derivatives as antibacterial agents. Recently, some other types of biological activity beside the antibacterial activity have been reported in compounds containing 2-azetidinone ring[18,19]. Such biological activities

include antimicrobial, anti tubercular, anti inflammatory, anticonvulsant, local anaesthetics and hypo glycaemic agents[20].

MATERIALS AND METHODS

All Melting points were taken in open glass capillaries and are uncorrected. Progress of the reaction was monitored by TLC on pre-coated Silica gel-aluminium plates (Type 60 F254, Merck, Darmstadt, Germany) in MeOH: CHCl3 system (1:9). The spot was visualized by exposing exposure to UV-light (254 nm) or dry plate in iodine vapours. The IR spectra were recorder on Schimadzu FT-IR 8300 Spectrophotometer using (KBr disc) .^{1}HNMR and ^{13}C-NMR spectra were measured on a JEOL DELTA-300 were spectrometer in DMSO-d6 at 300 MHz using TMS as an internal standard. Chemical shifts reported on δ scales. The FAB mass spectra were recorded on a JEOL SX-102 mass spectrometer. Elemental analyses were performed on a Carlo Erba-1108 analyser. The analytical data of all the compounds were highly satisfactory. For column chromatographic purification of the products, Merck silica Gel 60 (230-400 Mesh) was used. All chemicals were purchased from Sigma-Aldrich and the reagent grade chemicals were purchased from commercial sources and further purified before use.

General procedure for synthesis of Schiff bases compound (2a-2j): 4-Amino-pyridine (0.05 mol) was dissolved in 5 mL of ethanol in a 250mL conical flask and was stirred at room temperature for 15 min to get a clear solution. To this solution, equi-molar quantity (0.05 mol) of each substituted aryl aldehydes (in Ethanol) were added in presence of heterogenous catalyst SiO2/Fe2O3 (in catalytic amount (0.01 mole%) and reaction mixture was refluxed with stirring up to 6–8 h at 70°C on magnetic stirrer. The reaction progress was monitored by TLC using mobile phase as chloroform: methanol (6:4).On completion of reaction, then allowed to cool. The product was purified over a column chromatography. The purified product was recrystallized from methanol at room temperature to give compound (2a-2j), Characterization data of compounds (2a-2j) are presented below.

Synthesis of N-Benzylidenepyridin-4-amine , 2a : Yield:75.0%,m.p.91–93°C,Rf 0.75, IR (KBr, ν cm^{-1}) 1632 (C=N), 1615(C=N,pyridine), 1474(C=C,aromatic);1HNMR(DMSO-d6)(δppm):8.2(s,^{1}H,N=CH),8.7–7.8 (m,9H,aromatic); ^{13}C-NMR:162.1(=CH),154.1,151.4,113.7 (pyridine), 135.2, 132.4, 131.1, 130.2 (benzene) .Anal. calcd for C12H10N2: C 79.10, H 5.56, N 15.34; found C 83.24, H 6.56, N 12.16 .

Synthesis of N-(4-Methoxybenzylidene) pyridin-4-amine , 2b: Yield: 72.8%, m.p.: 110–112°C, Rf 0.45, IR (KBr, ν cm- 1):3031 (CH,CH3),1630 (C=N), 1615 (C=N, pyridine),1476(C=C, aromatic);^{1}H-NMR (DMSO-d6)(δ ppm): 8.3 (s,1H,N=CH), 8.7–7.1 (m,8H, aromatic), 3.6 (s,3H,OCH3);13C-NMR: 163.2 (N=CH), 153.2, 151.6, 113.4 (pyridine),165.2, 131.1, 127.4, 115.1 (benzene), 56.2 (OCH3). Anal. calcd for C13H12N2O: C 73.56, H 5.70, N 13.20; found C 69.84, H 6.52, N 15.36 .

Synthesis of N-(3,4-Dimethoxybenzylidene)pyridin-4-amine, 2c: Yield: 88.4%, m.p.: 125–127°C, Rf 0.58, IR (KBr, ν cm- 1): 1244 (Ar–OCH3),1630 (C=N), 1615 (C=N, pyridine), 1476(C=C, aromatic);^{1}H-NMR (DMSO-d6)(δ ppm): 8.3 (s,1H,N=CH), 8.7–7.1(m, 7H,aromatic), 3.6 (s, 6H, OCH3);^{13}C-NMR: 163.2 (=CH), 153.1, 151.6, 113.1 (pyridine), 153.9,150.4, 129.4, 115.8, 114.7 (benzene), 56.1 (OCH3). Anal. calcd for C14H14N2O2: C 69.41, H 5.82, N 11.56; found C 72.56, H 7.42, N 14.25.

Synthesis of N-(4-Bromobenzylidene) pyridin-4-amine, 2d: Yield: 78.2%, m.p.: 135–138°C, Rf 0.68, IR (KBr, ν cm- 1): 1630 (C=N), 1615 (C=N, pyridine), 1474(C=C, aromatic);^{1}H-NMR (DMSO-d6)(δ ppm): 8.3 (s,1H,N=CH), 8.4–7.1(m, 8H,aromatic),13C-NMR: 161.2 (=CH), 153.1,148.2,114.2 (pyridine),135.3,131.5, 126.5, 124.4,(benzene), Anal. calcd for C12H9N2Br: C 55.20, H 3.42, N 10.73, Br 30.60 ; found C 62.56, H 4.42, N 12.15, Br 36.53.

Synthesis of N-(2 –Bromo -benzylidene) pyridin-4-amine, 2e : Yield:68.5%, m.p.: 131–134°C,Rf 0.63, IR (KBr, νcm-^{1}): 1630 (C=N), 1618 (C=N, pyridine), 1478(C=C,aromatic);^{1}H-NMR(DMSO-d6)(δppm):8.3(s,1H,N=CH),8.4–7.3(m,8H,aromatic), ^{13}C-NMR:160.1(=CH).153.1,148.2,114.2(pyridine), 135.3,132.4,130.1,127.3,121.4,(benzene Anal. calcd for C12H9N2Br: C 55.20, H 3.47, N 10.73,Br 30.60; found C 62.56, H 4.42, N 12.15,Br 32.44.

Synthesis of N-(3 -Bromobenzylidene) pyridin-4-amine, 2f: Yield:62.5%, m.p.: 136–138°C, Rf 0.77, IR (KBr, ν cm- 1): 1630 (C=N), 1618 (C=N, pyridine), 1474(C=C, aromatic);^{1}H-NMR (DMSO-d6)(δ ppm): 8.3 (s,1H,N=CH), 8.4–7.4(m, 8H,aromatic),13C-NMR: 160.0 (=CH), 153.2,148.2,114.5 (pyridine),135.8,133.6, 132.4,128.8,127.2,123.3,(benzene), Anal. calcd for C12H9N2Br: C 55.20, H 3.47, N 10.73,Br 30.60; found C 57.56, H 2.42, N 11.25,Br 22.64.

Synthesis of N-(3, 4,5,Trimethoxy-benzylidene) pyridin-4-amine, 2g : Yield:70%, m.p.: 142–145°C, Rf 0.74,IR(KBr, ν cm- 1): 2865& 1170 (CH,OCH3), 1630 (C=N), 1617(C=N,pyridine), 1472 (C=C, aromatic);1H-NMR(DMSO-d6),(δppm):3.84(s,9H,OCH3),8.3(s,1H,N=CH)8.2–7.0(m,6H,aromatic),^{13}C-NMR:160.0(=CH),153.1,148.7,114.1 (pyridine),153.1,140.5, 132.8,104.0 (benzene), Anal. calcd for C15H16N2O3: C 66.16,H 5.92, N 10.23,O 17.60; found C 65.19, H 4.52, N 15.25,O 20.62.

Synthesis of N-(3-methyl-benzylidene) pyridin-4-amine, 2h : Yield:64.5%, m.p.: 138–140°C, Rf 0.64, IR (KBr, ν cm-^{1}):1581(CH=N, azomet.) 2927(CH3), 1618(C=N, Pyridine),1474(C=C Aromatic); ^{1}HNMR (DMSOd6)(δppm);2.51(s,3H,CH3)8.29(s,1H,N=CH),8.47.2(m, 8H,aromatic), ^{13}CNMR:160.0 (N=CH), 153.1,141.3,114.0(5C,pyridine),138.4,133.6,131.3,129.3,128.7,126.1 (6C of benzene), Anal. calcd for C13H12N2: C 79.56, H 6.16, N 14.27, found C 85.12, H 7.51, N 15.22 :

Synthesis of N-(2-methoxy-benzylidene) pyridin-4-amine, 2i : Yield:79.5 %, m.p.: 178–180°C, Rf 0.74, IR (KBr, ν cm- 1): 2860, 1165 (OCH3) 1598(N=CH, azomet), 1618 (C=N, Pyridine),1478 (C=C Aromatic);^{1}HNMR(DMSO-d6)(δppm);3.66(s,3H,OCH3),7.9(s,1H,N=CH),8.4-7.2(m,8H,aromatic, 13CNMR: 154.5 (N=CH),151.3,147.7,116.2(5C,Pyridine),157.4,111.2,131.2,120.1,125.5,122.4(6C of benzene)Anal. calcd for C13H12N2O : C,73.56; H 5.70; N,13.20; O 7.54 ; found C 73.12, H 4.16; N, 14.11, O 6.98.

Synthesis of N-(4-Chloro-benzylidene) pyridin-4-amine, 2j : Yield:77.4 %, m.p.: 168–169°C, Rf 0.79, IR (KBr, ν cm^{-1}): IR: 747(C-Cl), 1560 (N=CH, azomet), 1618 (C=N, Pyridine),1478 (C=C Aromatic);^{1}HNMR (DMSO-d6) (δppm)7.9 (s,1H,N=CH),8.4-7.2(m,8H,aromatic), 13CNMR :159.5(N=CH), 152.3,146.4,117.2(5C,Pyri- dine),134.4,130.2,128.1,134.6 (6C of benzene) Anal. Calcd for C12H9ClN2 : C 66.52; H 4.19; N,12.93; Cl,16.36; found C 63.42, H 5.20; N, 16.21 ; Cl, 14.33.

General conventional method for synthesis of compound (3a-3j): A mixture of compound 2a-2j (0.01 mol) and Et3N (0.01 mol) in ethanol, $ClCH_2COCl$(0.01 mol) was added drop wise. The well stirred (2 h) reaction mixture was refluxed on a steam bath for 5 h. The reaction mixture was cooled and excess of solvent was evaporated under reduced pressure. The solid obtained was purified by passing it through a chromatographic column packed with Silica gel using chloroform/methanol (6:4 v/v) as eluant and recrystallised from ethanol to give compounds (3a-3j).

Synthesis of N-(2-oxo-3-Chloro-4-phenyl-azetidine)pyridin-4-amine (3a) : Yield:73.6 %, m.p.: 108–109°C, Rf 0.69, IR (KBr, ν cm^{-1}): IR: 3068(C–H), 1731 (C=O),1618 (C=N, Pyridine),1478 (C=C Aromatic);^{1}HNMR (DMSO-d6) (δppm): 8.51–7.26 (m,9H, Ar),5.02 (d, 1H,N–CH–Ar), 5.22 (d,1H,CH–Cl),^{13}CNMR:162.22 (C=O),155.19,150.1,109.0 (5C Of Pyridine), 62.6 (CH–Cl), 68.5 (N–CH–Ar).143.4,126.8,128.4,126.7 (6C of benzene), M/S, m /z: 258(M)$^{+}$, 260,259,261,260,Anal. Calcd for C14H11ClN2O: C, 65.00; H, 4.29; Cl, 13.70; N, 10.83.O, 6.18 Found: C, 66.71; H, 5.07; Cl,15.66; N, 11.64; O, 6.27 .

Synthesis of N-[{4-(4-methoxyphenyl) 3-Chloro-2-oxo-azetidine)pyridin-4-amine (3b): Yield:63.7%, m.p.: 98–93°C, Rf 0.70, IR (KBr, ν cm^{-1}): IR: 3097 (C–H),1741 (C=O),1244 (Ar–OCH3).1617 (C=N, Pyridine),1478 (C=C Aromatic);^{1}HNMR (DMSO-d6) (δppm): 8.56 –6.96 (m,8H,Ar),5.08 (d,1H,N–CH–Ar),5.42(d,1H,CH–Cl),3.73 (s, 3H, OCH3), ^{13}C NMR: 162.22 (C=O),155.2,150.1,109.0 (5C Of Pyridine),62.2 (CH–Cl), 68.1 (N-CH –Ar).135.4,126.8,158.4,126.7,114.0,126.4 (6C of benzene), M/S, m /z: 288$(M)^{+}$, 290,289,291,290,Anal. Calcd for C15H13ClN2O2: C, 62.40; H, 4.54; Cl, 12.28; N, 9.70.O, 11.08 Found: C, 64.11; H, 6.07; Cl,14.55; N, 14.24; O, 13.27 .

Synthesis of N-[{4-(3,4-Dimethoxyphenyl) 3-Chloro-2-oxo-azetidine)pyridin-4-amine (3c): Yield : 63.7%, m.p.: 98–93°C, Rf 0.70, IR (KBr, ν cm^{-1}): IR: 3031 (CH,CH3),1728 (C=O),1241 (Ar–OCH3).1618 (C=N, Pyridine),1475 (C=C Aromatic);^{1}HNMR (DMSO-d6) (δppm): 8.56 –6.76 (m,7H,Ar), 5.08 (d,1H,N–CH–Ar),5.44(d,1H,CH–Cl),3.83(s,6H,OCH3),^{13}CNMR:162.22(C=O),155.2, 150.1,109.1(5C Of Pyridine),62.0 (CH–Cl),68.7(N-CH–Ar).136.4,109.8,148.4, 121.7,118.0,147.8(6C of benzene),M/S, m /z: 318$(M)^{+}$, 318,320,319,321,320 Anal. Calcd for C16H15ClN2O3: C,60.40;H, 4.74; Cl,11.12; N,8.79.O, 15.08 Found: C, 66.11; H, 8.07;Cl,17.81; N, 12.24; O,19.17 .

Synthesis of N-[{4-(4-Bromophenyl) 3-Chloro-2-oxo-azetidine)pyridin-4-amine (3d): Yield:63.4%, m.p.: 98–99°C, Rf 0.72, IR (KBr, ν cm^{-1}): IR: 3031 (CH,CH3),1728 (C=O), 642(Ar–Br).1618(C=N, Pyridine),1475 (C=C Aromatic);^{1}HNMR (DMSO-d6) (δppm): 8.56 –7.96(m,8H,Ar),5.08(d,1H,N–CH–Ar),5.44(d,1H,CH–Cl),^{13}CNMR:162.2(C=O),155.2,150, 109.1 (5C Of Pyridine),62.0 (CH–Cl), 68.3 (N-CH -Ar).144.5,127.2,131.4,121.3, (6C of benzene), M/S, m /z: 335$(M)^{+}$, 337,335,339,336,338,338,9,340 Anal. Calcd for C14H10BrClN2O: C, 49.80; H, 2.99; Br, 23.67; Cl, 10.50; N, 8.30.O, 4.74Found: C, 46.81; H, 2.07; Br,24.55; Cl,11.56; N, 9.34; O, 5.72 .

Synthesis of N-[{4-(2-Bromophenyl) 3-Chloro-2-oxo-azetidine)pyridin-4-amine (3e): Yield:75.6%, m.p.: 97–99°C, Rf 0.76, IR (KBr, ν cm^{-1}):IR: 3091 (C–H,CH3),1735(C= O),644 (Ar–Br),1617 (C=N, Pyridine),1475 (C=C Aromatic);^{1}HNMR (DMSO-d6) (δppm):8.56 –7.16(m,8H,Ar),5.08(d,1H,N–CH–Ar),5.44(d,1H,CH–Cl),^{13}CNMR:162.22(C=O),155.3, 150.2,109.1(5C Of Pyridine),61.8(CH–Cl),64.7(N-CH–Ar).145.2,121.7,132.5,128.7 ,127.5, 129.0(6C of benzene), M/S, m /z: 318$(M)^{+}$, 318,320,319,321,320 Anal. Calcd for C14H10BrClN2O: C, 49.81; H, 2.99; Br, 23.67; Cl, 10.50; N, 8.30; O, 4.74 Found: C, 43.11; H, 2.07; Br, 19.56, Cl,11.21; N, 7.96; O, 3.99.

Synthesis of N-[{4-(3-Bromophenyl) 3-Chloro-2-oxo-azetidine)pyridin-4-amine (3f): Yield:75.6%, m.p.: 93–95°C, Rf 0.72, IR (KBr, ν cm^{-1}): 3094 (C–H,CH3),1745(C= O),636(Ar–Br),1615 (C=N, Pyridine),1478 (C=C Aromatic);^{1}HNMR (DMSO-d6) (δppm):8.56 –7.26(m,8H,Ar),5.08(d,1H,N–CH–Ar),5.41(d,1H,CH–Cl), ^{13}CNMR:162.21(C=O),155.3, 150.2,109.1(5C Of Pyridine),63.8(CH–Cl),69.7(N-CH–Ar).145.7,131.9,121.9,129.7 ,129.3, 125.0(6C of benzene), M/S, m /z: 335$(M)^{+}$, Anal. Calcd for C14H10BrClN2O: C, 49.81; H, 2.99; Br, 23.67; Cl, 10.50; N, 8.30; O, 4.74 Found: C, 41.11; H, 2.77; Br, 29.46, Cl, 9.56, N, 10.96; O, 4.16.

Synthesis ofN-[{4-((3,4,5-Trimethoxyphenyl)3-Chloro-2-oxo-azetidine)pyridin-4-amine (3g): Yield: 73.7%, m.p.: 97–99°C, Rf 0.73, IR (KBr, ν cm^{-1}): IR: 3073 (CH,CH3),1747 (C=O),1248 (Ar–OCH3) 1620 (C=N, Pyridine),1479 (C=C Aromatic); ^{1}HNMR (DMSO-d6) (δppm): 8.56 –6.66 (m,6H,Ar), 5.03 (d,1H,N–CH–Ar),5.44(d,1H,CH–Cl),3.89 (s,9H, OCH3), ^{13}C NMR: 162.2 (C=O),159.2, 150.1,109.1 (5C Of Pyridine), 62.0 (CH–Cl), 69.7 (N-CH –Ar).139.4,104.8, 158.7,131.6, 158.7,104.8 (6C of benzene), M/S, m /z: 318$(M)^{+}$, 318,320,319,321,320 Anal. Calcd for C17H17ClN2O4: C, 58.54.; H, 4.94; Cl, 10.14; N, 8.10.O, 18.08 Found: C, 63.11; H, 8.97; Cl, 16.24; N, 10.44; O, 23.27.

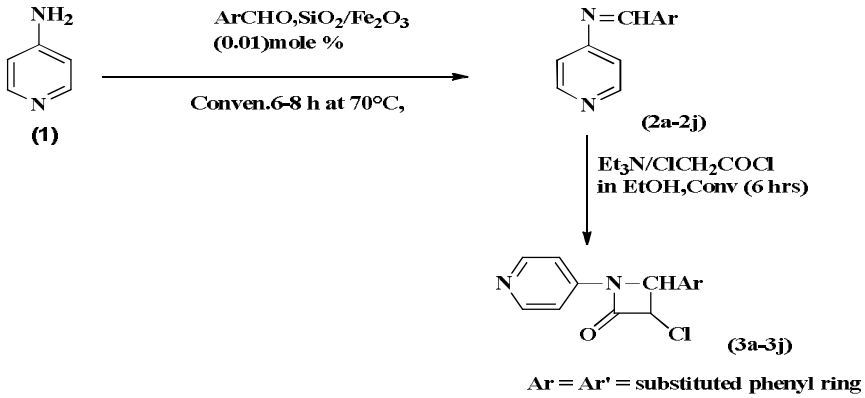
Synthesis of N-[{4-((3 –methyl-phenyl)3-Chloro-2-oxo-azetidine)pyridin-4-amine (3h): Yield:61.2%, m.p.: 145–148°C, Rf 0.69, IR (KBr, ν cm-^{1}): IR: 1547(N -CH)**,)**,2929 (CH3), 1612(C=N, Pyridine), 1469(C=C Aromatic); ^{1}HNMR (DMSO-d6) (δppm);2.31(s,3H,CH3), 8.59,7.02(m,8H,aromatic), 5.06

(d,1H, N–CH–Ar),5.44(d,1H,CHCl),^{13}CNMR:162.2(C=O), 158.1,150.7,109.1(5C Of Pyridine),62.0 (CH–Cl), 68.7 (N-CH –Ar). 147.4,124.8,138.7, 122.6,128.7,124.8 (6C of benzene), M/S, m /z: 272(M)$^+$, Anal. Calcd for C15H13ClN2O: C, 68.54.; H, 4.84; Cl, 13.34; N, 10.20.O, 5.87 Found: C, 71.19; H, 8.36; Cl,16.73; N, 14.34; O, 7.37.

Synthesis of N-[{4-((2 –methoxyphenyl)3-Chloro-2-oxo-azetidine)pyridin-4-amine (3i): Yield:64.8%, m.p.: 108–110°C, Rf 0.71, IR (KBr, ν cm^{-1}): 3097 (C–H),1738 (C=O),1249(Ar–OCH3).1614 (C=N, Pyridine),1472(C=CAromatic);^{1}HNMR (DMSO-d6)(δppm): 8.56 –6.92 (m,8H,Ar),5.08 (d,1H,N–CH–Ar),5.46(d,1H,CH–Cl),3.83 (s, 3H, OCH3), ^{13}C NMR: 162.12 (C=O),155.7,150.4,109.0 (5C Of Pyridine),62.8 (CH–Cl), 62.1 (N-CH–Ar).125.4,154.8,113.4,126.7,124.0,126.4 (6C of benzene), M/S, m /z: 288(M)$^+$, Anal. Calcd for C15H13ClN2O2: C, 62.40; H, 4.54; Cl, 12.28; N, 9.70.O, 11.08 Found: C, 61.41; H, 4.57; Cl, 10.15; N, 6.94; O, 11.21.

Synthesis of N-[{4-((4–Chlorophenyl) 3-Chloro-2-oxo-azetidine)pyridin-4-amine (3j): Yield: 67.4%, m.p.:155159°C,Rf 0.81,IR (KBr,νcm^1): 745(CCl),1618(C=N,Pyridine), 1478 (C=CAromatic); ^{1}HNMR (DMSO-d6) (δppm):8.56–7.43(m,8H,Ar),5.08 (d,1H,N–CH–Ar),5.48(d,1H,CH–Cl), ^{13}C NMR: 162.12 (C=O),155.2,150.4,109.0 (5C Of Pyridine),62.2 (CH–Cl),69.1(N-CH-Ar).140.6,127.1, 128.4,132.2, 128.4, 127.1 (6C of benzene), M/S, m /z: 288(M)$^+$, Anal. Calcd for C14H10Cl2N2O: C, 57.40; H, 3.44; Cl, 24.28; N, 9.60; O, 5.48 Found: C, 60.44; H, 4.17; Cl, 26.15; N, 11.94; O, 7.21.

SCHEME-1



Scheme: Synthesis of some azitidinone via heterogeneous catalyst

RESULTS AND DISCUSSION

The Schiff bases from 4-Amino-Pyridine with various substituted aromatic aldehydes were synthesized according to reaction scheme and Table. All the Schiff base and Azitidinone derivatives characterized by FTIR, ^{1}H-NMR,^{13}C-NMR and Mass, and elemental analysis in order to verify their purity. All the spectral characterization data were found to support the Schiff base of amino pyridine. FTIR data proved the formation of Schiff's bases as the N=C peak appeared in the region of 1615–1638 cm^{-1}and diminished of the peaks for –NH_2 and –C=O groups. In case of ^{1}HNMR and ^{13}C-NMR, the δ values 8.3 and 163–175 for N=C group confirmed the formation of 4-amino pyridine Schiff-base and its Azitidinone derivatives.
Azitidinone derivatives (3a-3j) were prepared from 4 amino pyridine by the Schiff base cyclization in presence of tri-ethylamine and chloroacetylchloride .Earlier methods described for Schiff base synthesis

involved the use of few drops of glacial acetic acid or sulphuric acid to trigger the reaction. Under these conditions Schiff bases were obtained only in 30% yield. Here we planned to use Lewis acid catalyst for the formation of Schiff base derivatives. Initially, we tried the reaction with series of Lewis acids such as $ZnCl_2$, $AlCl_3$, $FeCl_3$ and SiO_2/Fe_2O3 also. The range of yield observed were 50–55, 45–47, 45–48, 40–42 and 50–75% respectively. Thus, SiO_2/ Fe_2O_3 were found to be highly efficient catalyst for the synthesis of imines and imine derived Azitidinone derivatives also. The formation of (2a-j) was supported by the appearance of signals at d 8.62-7.93 ppm due to -N=CH in the ^{1}H NMR spectra and IR spectra, the bands at 1598-1647 cm^{-1} (N=CH- , acyclic),Azetidinone derivatives (3a-3j) exhibited CHCl proton of β -lactam ring as doublet at δ 3.77–4.62 ppm. and N-CH proton as multiplet at δ 4.85–5.64 ppm. The structures were further confirmed by the mass spectra which exhibited the molecular ion peaks at their respective molecular weights.

APPLICATIONS

Evaluation of antimicrobial screening: All the synthesized compounds of series (3a–j) were tested for antibacterial screening a gram-positive bacterium Staphylococcus aureus and two gram-negative bacteria, Escherichia coli and Streptococcus pneumoniae were used. For antifungal activity Candida albicans, Aspergillus fumigates and Aspergillus Niger was taken. Antibacterial and antifungal screenings were performed by dilution method using nutrient agar media. MIC was determined at five concentrations (in lg /ml) ranging from 0.5l g, 1.0lg, 5.0l g,10.0lg, 25.0l g and 50.0lg of each compounds. The tubes were incubated at 37 °C for 48 h. DMSO was used as solvent. The lowest concentration, which showed no visible growth, was taken as an end point for minimum inhibitory concentration (MIC). Oflaxacin was used as standard drug for antibacterial screening in a concentration 0.1 l $g^{-1}mL^{-1}$disc and miconazole was used as standard drug for antifungal screening in a concentration 0.1 lg $^{-1}mL^{-1}$disc. The MIC level of some active compounds (3a–3j) against these organisms is given in Table 1.

All the synthesized compounds of series (3a–j) were screened against some micro-organisms for their antimicrobial activities. Generally compounds possessing electron withdrawing groups showed good antibacterial activity. Some derivatives (3d, 3e, 3f, 3j,) containing electron withdrawing groups (–Cl, –Br) have shown promising activity against some bacteria. Compounds possessing electron donating groups (3a, 3b, 3c, 3g, 3h, 3i) have shown good antifungal activity. Activity data are given in Table 1.

Table 1. Antibacterial and antifungal activity of compounds 3a–3j (MIC lg $^{-1}$mL)

Compound	Ar=Ar1=Ar2 Substituted phenyl Ring	S. aures	E. coli	S. pneumoe	C. albicas	A. fumigats	A. niger
3a	C_6H_5	0.1	0.1	0.1	0.5	0.5	0.5
3b	4-$CH_3OC_6H_4$	0.1	0.1	0.1	1.0	1.0	1.0
3c	3,4,$(CH_3O)_2C_6H_3$	0.5	0.1	0.0	0.5	1.0	0.5
3d	4-BrC_6H_4	1.0	1.0	0.5	0.5	0.5	0.0
3e	2-BrC_6H_4	0.5	1.0	0.5	0.0	0.1	0.1
3f	3-BrC_6H_4	0.5	0.5	1.0	0.1	0.1	0.1
3g	3,4,5$(CH_3O)_3C_6H_2$	0.0	0.1	0.5	1.0	0.5	1.0
3h	3-$CH_3C_6H_4$	1.0	0.5	0.5	0.5	1.0	1.0
3i	2-$CH_3OC_6H_4$	0.0	0.0	0.5	1.0	1.0	1.0

3j	**4-ClC_6H_4**	**0.5**	**1.0**	**1.0**	**0.5**	**0.0**	**0.0**
Oflaxacin		**0.1**	**0.1**	**0.1**			
Miconazole					**0.1**	**0.1**	**0.1**

CONCLUSIONS

We have synthesized some 4 amino pyridine Schiff base and its Azetidinone derivatives by green conventional method. With the help of heterogenous catalyst, the yield of product was increased from 60% upto 85% as compared to without green conventional method. By using heterogenous catalyst the reactions were completed within 6-8 h, and the products were obtained in good to high yields, which reduced the time and formation of By-product. Here catalyst assisted synthesis is simple eco-friendly and can be used as an alternative to the existing conventional heating method. From the results of antibacterial studies it was concluded that the tested compounds exhibited significant antibacterial activities against both gram positive and gram negative organisms. Among the tested compounds, compound substituted with electron withdrawing group in 4-Amino pyridine derivatives preferably at para-position showed promising antibacterial activities; this may be attributed to their enhanced electronic character which favours greater penetration through microbial membrane.

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