Synthesis of New Series of Isoxazolines via [3+2]-Cycloaddition reaction of Mercury (II) Acetate Generated Nitrile Oxide and Olefins

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Abstract: Mercury (II) acetate is Oxidatively cyclize the aromatic aldoximes with olefins via nitrile oxide intermediate. The method is adopted to successfully synthesize a Series of heterocycles bearing both isoxazoline and imidazole moieties with high purity and good yield. ^{1}HNMR, ^{13}CNMR, IR and elemental analyses characterized the synthesized compounds. Also compounds were evaluated for the antibacterial and antifungal activities and were compared with the standard drugs. The compounds show potent to weak antimicrobial activity.

***Index Terms*: Biheterocycles; Antimicrobial activity; Mercury (II) acetate**

I. INTRODUCTION

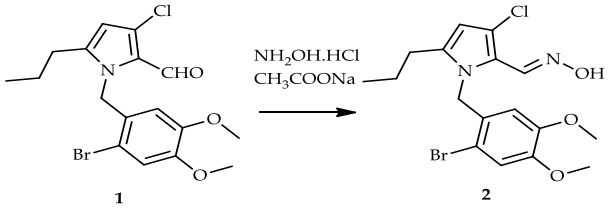
In field of heterocyclic chemistry isoxazoline and imidazole are represents a class of compounds of great importance in biological chemistry. For instance, isoxazoline possess biological activities like[1,2] (insecticidal, antibacterial, antibiotic, antitumour, antifungal). Isoxazoline also serves as anti-influenza virus activity[3] , inhibition of human leukocyte elastase and cathepsin G[4]. In fact, Valdecoxib an isoxazoline derivative is now widely used in the market as anti-inflammatory drug[5]. Imidazole derivatives are gaining synthetic interest in recent years due to their broad spectrum of biological activities like anti-inflammatory[6], analgesic[7], antibacterial[8] and antifungal[9]. 2-n-Butyl-4-chloro-5-farmyl-imidazole is a key intermediate for the synthesis of Losartan a nonpeptide angiotensin antagonist, which is an orally active antihypertensive drug[10].

Literature survey reveals that biheterocycles bearing isoxazoline[11,12] were synthesized via 1,3-dipolar cycloaddition of aldoxime to divinyl ketone / sulfone using chloramine-T as dehydrogenating agent. 1,3-Dipolar cycloaddition reactions are useful tools for constructing biologically potent five membered heterocycles[2] and nitrile oxides serves as excellent 1,3-dipoles. Cycloaddition of nitrile oxide to olefinic compounds are of synthetic interest, since the product isoxazoline obtained are the versatile intermediate for the bifuctional Synthesis and antimicrobial Studies of Biheterocycle compounds.[13] Nitrile oxides can be generated by dehydrogenation of aryl aldoximes with mercuric acetae[14], manganese dioxide[15], tert-butyl hypo chlorite[16], chloramine-T etc. In our laboratory Rai et.al[17] extensively used chloramine-T for the generation of nitrile oxide and nitrile imine from aldoxime and aldehyde hydrazone respectively.

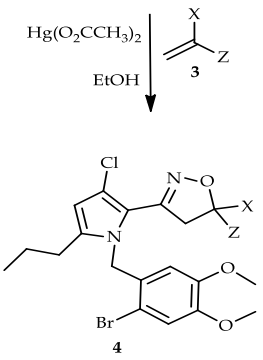
With this background, it is considered worthwhile to prepare biheterocycles starting from 2-n-butyl-4-chloro-(Nsubstituted)–imidazole-5-carbaldehyde and screen them for antimicrobial activity.

II. EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AM 300 MHz spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were measured on Jeol 400 (100MHz) instrument. The chemical shifts are expressed in δ and following abbreviations were used: s = singlet, d = doublet, t = triplet and m = multiplet. Infrared (IR) spectra were measured on Shimadzu 8300 spectrometer. Elemental analyses were obtained on a Vaio-EL intrument. Thinlayer chromatography (TLC) was done with pre-coated silica gel G plates using chloroform-acetone as eluent.



4	X	Z
a	H	Ph
b	CH_3	Ph
c	H	CH_2CN
d	H	CH_2Cl
e	H	CH_2Br
f	H	CH_2OH
g	H	COOMe
h	H	COOEt



Scheme

Antimicrobial activity: All the synthesized compounds were evaluated for antimicrobial activity by the disc diffusion method[18] and microdilution method.[19] Five bacteria and five fungal species were used as the antimicrobial test strains namely: Bacillus substilis, Escherichia coli, Pseudomonas fluorescens, Xanthomonas campestris pvs, Xanthomonas oryzae, Aspergillus niger, Aspergillus flavus, Fusarium oxysporium, Trichoderma species, Fusarium and monaliforme. Streptomycin and tetracycline were used as standard drugs against bacteria and nystatin was used against fungi. In all the determinations tests were performed in triplicate and the results were taken as a mean of at least three determinations.

III. RESULTS AND DISCUSSION

The general synthetic pathway discussed hereafter is depicted in Scheme. The farmyl function of 1 was converted into the aldoxime 2. When oxidative dehydrogenation of 2 by Mercury(II) acetate afforded nitrile oxide, which was in situ trapped by the different olefins 3 (a-h) under refluxing condition in ethanol. Thus produced compound was identified by NMR spectroscopy as 4,5-dihydro-3-(substituted-imidazole)-5- substituted-isoxazoline 4 (a-h) in good quality and yield. The starting substrate 2-n-butyl-4- chloro-(N-substituted)–imidazole-5-carbaldehyde 1 was prepared according to literature procedure.[20] Compound 2 was prepared by standard procedure[21].

Antimicrobial activity of all the compounds was shown in Table 1 and 2. Among the series of synthesized compounds, 4d and 4e shown better inhibition. Remaining compounds shown moderate inhibition. The better inhibition shown by 4d and 4e may be due to the presence of chloro and bromo group in the compound.

Preparation of 4'-(2-Butyl-4-chloro-5-oxime-imidazol-1-ylmethyll-4,5-dimethoxybenzene (2): A mixture of 2-Butyl-5-chloro-3H-imidazole-4-carbaldehyde 1 (1.0 g, 5.37 mmol) in ethanol and hydroxyl amine hydrochloride and Sodium acetate (0.90 g, 6.52 mmol) in water (10 mL) was stirred for 15 min at rt. and the mixture was warmed at rt for 1 hr. After completion of the reaction obtained solid was filtered, washed with water and dried. White crystalline solid. Yield 1.15 g (82%), m.p 122-124 ^{O}C. ^{1}H NMR $CDCl_3$: δ 0.91 (t, 3H, CH_3), 1.30 (m, 2H, CH_2), 1,62 (m, 2H, CH_2), 2.61 (t, 2H, CH_2), 3.70 (s, 6H, OCH_3), 4.06 (s, 1H, OH), 4.88 (s, 2H, CH_2), 6.49 (s, 1H, ArH), 6.82 (s, 1H, ArH), 8.50 (s, 1H, CH), ^{13}C NMR $CDCl_3$: δ 13.9 (C), 23.2 (C), 24.5 (C), 33.1 (C), 33.9 (C), 57.5 (2C), 116.1 (C), 117.6 (C), 118.2 (C), 134.2 (C), 136.6 (C), 140.9 (C), 147.2 (C), 148.4 (C), 156.2 (C), 189.2 (C). IR (KBr pellets cm-1) v 3310, 3069, 2961, 1764, 1667, 1485. Anal.Calcd. For $C_{17}H_{21}BrClN_3O_3$: C, 49.12, H, 4.85, N, 6.74%. Found: C, 49.19, H, 4.87, N 6.70 %.

Synthesis of 4,5-dihydro-3-(substituted-imidazole)-5-phenylisoxazole (4a) A mixture of substituted-imidazole aldoxime 3 (1.0 g, 2.55 mmol), 4a (0.265 g, 2.55 mmol) and mercuric(II) acetate (0.45 g, 1.41 mmol) in ethanol (20 mL) was stirred for 2-3 hr at 65oC. The progress of the reaction was monitored by TLC. After completion of the reaction the solvent was evaporated in vacuum. The residual mass was extracted into ether (25 mL), washed successively with water (2 x 20 mL), 5% HCl (1x10 mL), brine solution (2 x 15 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent afforded crude oily substance, which was purified by column chromatography using chloroform-acetone (9:1) as eluent to gave the product as yellow solid (0.94 g, 69% yield), m.p.124-126 ^{O}C. ^{1}H NMR $CDCl_3$: δ 0.97 (t, 3H, CH_3), 1.35 (m, 2H, CH_2), 1,64 (m, 2H, CH_2), 2.57 (t, 2H, CH_2), 3.21 (dd, 1H, J=8.2, 4-H), 3.28 (dd, 2H, J=8.2, 4-H), 3.73 (s, 6H, OCH_3), 5.02 (s, 2H, CH_2), 5.20 (dd, 1H, J=4.0, 5-H), 6.42 (s, 1H, ArH), 6.78 (s, 1H, ArH), 7.21 (m, 5H, ArH), ^{13}C NMR $CDCl_3$: δ 14.2 ©,

23.0 ©, 25.7 ©, 33.4 ©, 34.8 ©, 41.6 ©, 56.3 (2C), 81.1 ©, 116.3 ©, 117.7 ©, 118.5 ©, 122.2 ©, 126.2 ©, 127.2 (2C), 127.8 ©, 128.9 (2C), 134.5 ©, 140.7 ©, 148.0 ©, 148.7 ©, 149.0 ©, 164.7 ©. Anal.Calcd. For $C_{25}H_{27}BrClN_3O_3$; C, 56.35; H, 5.11; N, 7.89; Found: C, 56.37; H, 5.13; N, 7.87 %.

4,5-Dihydro-3-(substituted-imidazole)-5-methyl-5-phenylisoxazole (4b): Obtained from substituted-imidazole aldoxime 3 (1.0 g, 2.55 mmol), 4b (0.30 g, 2.55 mmol) and mercuric(II) acetate (0.45 g, 1.41 mmol) as yellow solid (0.99 g, 71% yield), and m.p.130-132 $_O$C. $_1$H NMR $CDCl_3$: δ 0.95 (t, 3H, CH_3), 1.33 (m, 2H, CH_2), 1.59 (s, 3H, CH_3), 1,62 (m, 2H, CH_2), 2.55 (t, 2H, CH_2), 3.18 (s, 2H, 4-CH_2), 3.74 (s, 6H, OCH_3), 5.02 (s, 2H, CH_2), 6.40 (s, 1H, ArH), 6.76 (s, 1H, ArH), 7.19 (m, 5H, ArH), ^{13}C NMR $CDCl_3$: δ 14.3 (C), 23.1 (C), 25.6 (C), 29.7 (C), 33.5 (C), 37.7 (C), 56.3 (2C), 87.1 (C), 116.3 (C), 117.5 (C), 118.6 (C), 122.2 (C), 126.1 (2C), 126.2 (2C), 126.4 (C), 128.5 (2C), 134.3 (C), 148.2 (C), 148.7 (C), 149.0 (C), 150.1 (C), 164.6 (C). Anal. Calcd. For $C_{26}H_{29}BrClN_3O_3$ C, 57.10; H, 5.34; N, 7.68; Found: C, 57.12, H, 5.32, N, 7.63 %.

4,5-Dihydro-3-(substituted-imidazole)isoxazole-5-carbo nitrile (4c): Obtained from substituted-imidazole aldoxime 3 (1.0 g, 2.55 mmol), 4c (0.135 g, 2.55 mmol) and mercuric(II) acetate (0.45 g, 1.41 mmol) as yellow oil (0.78 g, 62% yield). ^{1}H NMR $CDCl_3$: δ 0.94 (t, 3H, CH_3), 1.32 (m, 2H, CH_2), 1,60 (m, 2H, CH_2), 2.53 (t, 2H, CH_2), 3.42 (dd, 1H, J=8.0, 4-H), 3.49 (dd, 2H, J=8.0, 4-H), 3.79 (s, 6H, OCH_3), 4.96 (s, 2H, CH_2), 5.24 (dd, 1H, J=4.0, 5-H), 6.34 (s, 1H, ArH), 6.70 (s, 1H, ArH). ^{13}C NMR $CDCl_3$: δ 14.2 ©, 23.0 ©, 25.7 ©, 33.4 ©, 33.7 ©, 40.8 ©, 56.3 (2C), 68.8 ©, 116.4 ©, 117.4 ©, 118.2 ©, 118.6 ©, 122.1 ©, 126.7 ©, 134.5 ©, 148.2 ©, 148.6 ©, 149.1 ©, 164.7 ©. Anal.Calcd. For $C_{20}H_{22}BrClN_4O_3$; C, 49.86; H, 4.60; N, 11.63; Found: C, 49.89, H, 4.67, N, 11.53 %.

5-(Chloromethyl)-4,5-dihydro-3-(substituted-imidazole) isoxazole (4d): Obtained from substituted-imidazole aldoxime 3 (1.0 g, 2.55 mmol), 4d (0.194 g, 2.57 mmol) and mercuric(II) acetate (0.45 g, 1.41 mmol) as yellow solid (0.84 g, 65% yield), m.p.138-140 ^{O}C. ^{1}H NMR $CDCl_3$: δ 0.97 (t, 3H, CH_3), 1.34 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 2.56 (t, 2H, CH_2), 3.38 (dd, 1H, J=8.4, 4-H), 3.42 (dd, 2H, J=8.4, 4-H), 3.46 (dd, 1H, J=7.6, CH_2Cl), 3.69 (dd, 1H, J=7.6, CH_2Cl), 3.75 (s, 6H, OCH_3), 5.02 (s, 2H, CH_2), 5.12 (m, 1H, 5-H), 6.40 (s, 1H, ArH), 6.78 (s, 1H, ArH). ^{13}C NMR $CDCl_3$: δ 14.1 (C), 22.8 (C), 25.5 (C), 33.4 (C), 33.7 (C), 37.8 (C), 51.8 (C), 56.2 (2C), 69.8 (C), 116.4 (C), 117.5 (C), 118.6 (C), 121.9 (C), 126.2 (C), 134.5 (C), 148.1 (C), 148.6 (C), 149.1 (C), 164.7 (C). Anal.Calcd. For $C_{20}H_{24}BrCl_2N_3O_3$; C, 47.55; H, 4.79; N, 8.32; Found: C, 47.53, H, 4.78, N, 8.35 %.

5-(Bromomethyl)-4,5-dihydro-3-(substitutedimidazole) isoxazole (4e): Obtained from substituted-imidazole aldoxime 3 (1.0 g, 2.55 mmol), 4e (0.31 g, 2.56 mmol) and mercuric(II) acetate (0.45 g, 1.41 mmol) as yellow solid (1.02 g, 73% yield), and m.p.144-146 $_O$C. $_1$H NMR $CDCl_3$: δ 0.95 (t, 3H, CH_3), 1.33 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 2.55 (t, 2H, CH_2), 3.35 (dd, 1H, J=8.4, 4-H), 3.40 (dd, 2H, J=8.4, 4-H), 3.44 (dd, 1H, J=7.2, CH_2Br), 3.64 (dd, 1H, J=7.2, CH_2Br), 3.73 (s, 6H, OCH3), 5.00 (s, 2H, CH_2), 5.04 (m, 1H, 5-H), 6.38 (s, 1H, ArH), 6.75 (s, 1H, ArH). ^{13}C NMR $CDCl_3$: δ 14.3 (C), 22.8 (C), 25.6 (C), 33.6 (C), 33.8 (C), 38.8 (C), 41.0 (C), 56.4 (2C), 70.9 (C), 116.4 (C), 117.4 (C), 118.7 (C), 122.2 (C), 126.3 (C), 134.4 (C), 148.2 (C), 148.8 (C), 149.1 (C), 164.7 (C). Anal.Calcd. For $C_{20}H_{24}Br_2ClN_3O_3$; C, 43.70; H, 4.40; N, 7.64; Found: C, 43.71, H, 4.42, N, 7.62 %.

(4,5-Dihydro-3-(substituted-imidazole)isoxazol-5-yl)) methanol (4f): Obtained from substituted-imidazole aldoxime 3 (1.0 g, 2.55 mmol), 4f (0.148 g, 2.55 mmol) and mercuric(II) acetate (0.45 g, 1.41 mmol) as yellow oil (0.78 g, 63% yield). $_1$H NMR $CDCl_3$: δ 0.97 (t, 3H, CH_3), 1.34 (m, 2H, CH_2), 1,63 (m, 2H, CH_2), 2.32 (dd, 1H, OH), 2.57 (t, 2H, CH_2), 3.28 (dd, 1H, J=8.0, 4-H), 3.34 (dd, 1H, J=8.0, 4-H), 3.52-3.79 (m, 2H, CH_2), 3.74 (s, 6H, OCH_3), 4.98 (s, 2H, CH_2), 5.04 (m, 1H, 5-H), 6.41(s, 1H, ArH), 6.77 (s, 1H, ArH). ^{13}C NMR $CDCl_3$: δ 14.2 (C), 23.0 (C), 25.7 (C), 33.5 (C), 33.8 (C), 36.8 (C), 56.3 (2C), 70.6 (C), 77.5 (C), 116.3 (C), 117.4 (C), 118.4 (C), 121.9 (C), 126.2 (C), 134.5 (C), 148.1 (C), 148.7 (C), 149.0 (C), 164.7 (C). Anal.Calcd. For $C_{20}H_{25}BrClN_3O_4$; C, 49.35; H, 5.18; N, 8.63; Found: C, 49.33, H, 5.19, N, 8.64 %.

4,5-Dihydro-3-(substituted-imidazole)isoxazole-5-yl acetate (4g): Obtained from substituted-imidazole aldoxime 3 (1.0 g, 2.55 mmol), 4g (0.22 g, 2.55 mmol) mercuric(II) acetate (0.45 g, 1.41 mmol) as yellow solid (1.0 g, 76% yield), m.p.148-150 ^{O}C. ^{1}H NMR $CDCl_3$: δ 0.94 (t, 3H, CH_3), 1.35 (m, 2H, CH_2), 1,64 (m, 2H, CH_2), 2.04 (s, 3H, CH_3), 2.57 (t, 2H, CH_2), 3.30 (dd, 1H, J=8.2,

4-H), 3.37 (dd, 1H, J=8.2, 4-H), 3.78 (s, 6H, OCH_3), 5.02 (s, 2H, CH_2), 5.68 (dd, 1H, J=3.8, 5-H), 6.39 (s, 1H, ArH), 6.77 (s, 1H, ArH). ^{13}C NMR $CDCl_3$: δ 14.3 (C), 21.1 (C), 23.0 (C), 25.6 (C), 33.4 (C), 33.8 (C), 56.3 (2C), 69.5 (C), 96.3 (C), 116.3 (C), 117.5 (C), 118.6 (C), 121.9 (C), 1.26.2 (C), 134.4 (C), 148.0 (C), 148.6 (C), 149.1 (C), 164.6 (C), 170.4 (C). Anal.Calcd. For $C_{21}H_{25}BrClN_3O_5$; C, 48.99; H, 4.89; N, 8.16; Found: C, 48.99, H, 4.88, N, 8.17 %.

4,5-Dihydro-3-(substituted-imidazole)isoxazole-5-yl propionate (4h): Obtained from substituted-imidazole aldoxime 3 (1.0 g, 2.55 mmol), 4h (0.255 g, 2.55 mmol) and mercuric(II) acetate (0.45 g, 1.41 mmol) as yellow solid (1.05 g, 78% yield), m.p.158-160 ^{O}C. ^{1}H NMR $CDCl_3$: δ 0.95 (t, 3H, CH_3), 1.13 (t, 3H, CH_3), 1.33 (m, 2H, CH_2), 1,64 (m, 2H, CH_2), 2.28 (q, 2H, CH_2), 2.54 (t, 2H, CH_2), 3.31 (dd, 1H, J=8.0, 4-H), 3.38 (dd, 1H, J=8.0, 4-H), 3.75 (s, 6H, OCH_3), 4.99 (s, 2H, CH_2), 5.66 (dd, 1H, J=4.0, 5-H), 6.35 (s, 1H, ArH), 6.74 (s, 1H, ArH). ^{13}C NMR $CDCl_3$: δ 9.5 (C), 14.1 (C), 22.8 (C), 25.6 (C), 30.1 (C), 33.4 (C), 33.7 (C), 56.3 (2C), 69.4 (C), 96.5 (C), 116.4 (C), 117.4 (C), 118.4 (C), 122.0 (C), 126.3 (C), 134.3 (C), 148.0 (C), 148.7 (C), 149.1 (C), 164.5 (C), 173.4 (C). Anal.Calcd. For $C_{22}H_{27}BrClN_3O_5$; C, 49.97; H, 5.15; N, 7.95; Found: C, 49.99, H, 5.13, N, 7.93 %.

Table 1. Minimal inhibitory concentration in µg mL-1 and Inhibitory zone in (diameter) mm of the synthesized compounds against tested bacterial strains by micro dilution method and disk diffusion method respectively

Compound	*Bacillus substilis*		*Escherichia coli*		*Pseudomona fluorescens*		*Xanthomonas campestris pvs*		*Xanthomonasoryzae*	
4a	22µg	8mm	25µg	13mm	23µg	16mm	24µg	11mm	23µg	12mm
4b	23µg	10mm	22µg	12mm	25µg	14mm	21µg	11mm	24µg	10mm
4c	20µg	13mm	18µg	13mm	21µg	17mm	18µg	14mm	23µg	12mm
4d	18µg	15mm	12µg	14mm	14µg	15mm	24µg	10mm	11µg	10mm
4e	18µg	12mm	14µg	14mm	13µg	16mm	12µg	11mm	14µg	12mm
4f	23µg	8mm	22µg	14mm	28µg	13mm	26µg	12mm	23µg	10mm
4g	23µg	8mm	22µg	14mm	26µg	13mm	22µg	10mm	23µg	12mm
4h	23µg	8mm	21µg	14mm	29µg	13mm	24µg	11mm	22µg	11mm
Streptomyc	19µg	8mm	13µg	14mm	12µg	13mm	-	-	-	-
Tetraccline	-	-	-	-	-	-	9µg	12mm	13µg	12mm

Table 2. Minimal inhibitory concentration in µg mL-1 and Inhibitory zone in (diameter) mm of the synthesized compounds against tested fungal strains by micro dilution method and disk diffusion method respectively

Compound	*Aspergillus niger*		*Aspergillus flavus*		*Fusarium oxysporium*		*Trichoderma species*		*Fusarium monalifome*	
4a	18µg	8mm	18µg	9mm	15µg	10mm	24µg	12mm	13µg	11mm
4b	19µg	7mm	18µg	7mm	17µg	11mm	21µg	13mm	14µg	09mm
4c	16µg	8mm	18µg	10mm	12µg	14mm	18µg	14mm	11µg	12mm
4d	15µg	9mm	13µg	12mm	10µg	14mm	24µg	10mm	11µg	12mm
4e	16µg	9mm	14µg	11mm	10µg	15mm	12µg	11mm	14µg	12mm
4f	20µg	8mm	20µg	7mm	16µg	16mm	26µg	16mm	13µg	10mm
4g	20µg	7mm	22µg	8mm	22µg	22mm	22µg	10mm	23µg	12mm
4h	22µg	8mm	19µg	10mm	24µg	20mm	24µg	12mm	22µg	11mm
Nystatin	15µg	8mm	13µg	8mm	14µg	11mm	11µg	15mm	10µg	12mm

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