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A mild and efficient synthesis of novel isoxazolyl-benzo[4,5] oxazolo[3,2-*a*]pyrazines

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Synthesis of novel 2(3-methylisoxazol-5-yl)-4,10*a*-diaryl-2,10*a*-dihydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyrazines **5** have been achieved by the reaction of 2,2'-(3-methylisoxaol-5-yl)azanediyl)bis(1-phenylethanones) **3** with *o*-aminophenol **4** in the presence of CAN catalyst in CH_3CN solvent by adopting a new synthetic protocol. The required intermediates **3** are prepared by the interaction of 5-amino-3-methylisoxazole **1** with phenacyl bromides **2** in ethanol in the presence of K_2CO_3. The structures of newly synthesized compounds **3a-j** and **5a-j** have been confirmed by IR, ^1H and ^{13}C NMR, and EI-MS and from microanalytical data.

Keywords: Isoxazolyl benzo[4,5]oxazolo[3,2-*a*]pyrazines, Ceric ammonium nitrate (CAN), Mild and efficient synthesis, New synthetic protocol

Benzoxazole derivatives possess diverse variety of pharmacological activities[1]. Due to this benzoxazole have occupied unique place in the field of medicinal chemistry. Benzoxazole is structurally similar with nucleic bases as well as the isosteres of naturally occurring cyclic nucleotides such as adenine and guanine, that is why it probably interacts with biopolymers in the living systems and show diverse biological activities like antimicrobial[2], anti-inflammatory[3], analgesic[4], anticancer[5], anti-tubercular[6], and anti-HIV agents[7].

Benzoxazoles are synthesized by the condensation of 2-aminophenols with aromatic acids[8], aromatic aldehydes[9], β-diketones[10], or esters[11]. They are also synthesized by the reaction of *o*-haloanilines with acid chlorides, followed by cyclization under the influence of Cu catalyst[12]. Pyrazines are found to act as potential anticancer agents[13]. Molecular hybridization may enhance the biological activity. As a heterocyclic system in which both benzoxazole and pyrazine moiety fused together may assume much biological significance.

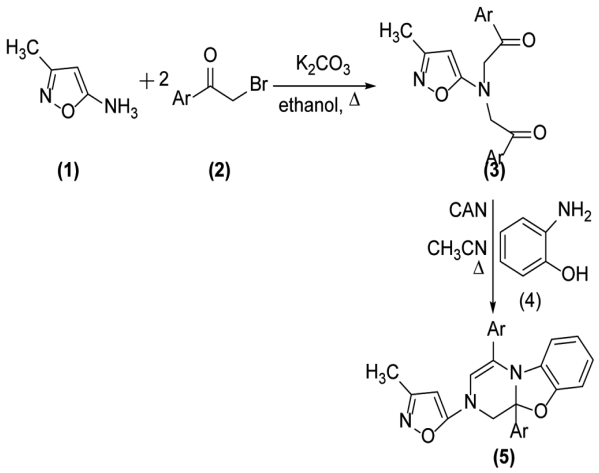
Among aromatic heterocycles, the isoxazole unit constitutes an easily accessible nucleus that is present in a number of natural and pharmacological compounds[14], and displays a wide range of organic reactivities and could be used as an effective means of preparing new molecular scaffolds[15]. Isoxazoles have been repeatedly shown as useful synthons in organic synthesis[16]. Ceric (IV) ammonium nitrate (CAN) is a convenient reagent for affecting a number of synthetic transformations due to its ready solubility in organic solvents, low toxicity, high reactivity, inexpensiveness, eco-friendly nature and easy handling. The use of CAN as Lewis acid in C-C bond forming reactions has attracted attention of synthetic chemists[17-21]. Attracted by these impressive scaffolds *viz*., benzoxazole, pyrazine and isoxazole moieties and their pharmacological properties, we set out to develop a new synthetic route to prepare novel isoxazolyl benzo[4,5]oxazolo[3,2-*a*]pyrazines using CAN as a Lewis acid catalyst. As a sequel to our work on the synthesis of bioactive isoxazole derivatives[22-26], we, report herein, the synthesis of novel isoxazolyl benzo[4,5]oxazolo[3,2-*a*]pyrazines.

Results and Discussion

Chemistry

The synthesis of title compounds **(5a-j)** have been accomplished by the new synthetic protocol outlined in Scheme 1.

The key intermediate, 2,2'-(3-methylisoxaol-5-yl)azanediyl)bis(1-phenylethanones) **3** required for the synthesis of title compound, was prepared by the reaction of 5-amino-3-methylisoxazole (1 mmol) with phenacyl bromide **2** (2 mmol) in the presence of



Compound	Ar	Compound	Ar
3a & 5a	C_6H_5	**3f & 5f**	2-ClC_6H_4
3b & 5b	4-$CH_3C_6H_4$	**3g & 5g**	4-BrC_6H_4
3c & 5c	2-$CH_3C_6H_4$	**3h & 5h**	3-BrC_6H_4
3d & 5d	4-$OCH_3C_6H_4$	**3i& 5i**	4-$NO_2C_6H_4$
3e & 5e	4-ClC_6H_4	**3j & 5j**	3-$NO_2C_6H_4$

Scheme 1 — Synthetic protocol for the synthesis of 5a-j

K_2CO_3 in ethanol. Compound **3** on cyclocondensation with *o*-aminophenols in refluxing ethanol in the presence of Lewis acid catalyst Ceric ammonium nitrate (CAN) (10 mol%) in CH_3CN solvent furnished the novel 2-(3-methylisoxazol-5-yl)-4,10*a*-diaryl-2,10a-dihydro-1*H*-benzo[4,5]oxazolo[3,2-a]pyrazines 5.

Initially the test reaction is carried out with diffirent catalysts including $InCl_3$, $ZnCl_2$, Silica gel, L-proline, *p*-TSA, $AlCl_3$, and CAN (Table 1). The best overall yield (95%) was obtained with CAN (10 mol%). No product was obtained in the absence of catalyst. Further, the test reaction was also explored by using different solvents such as CH_3CN, EtOH, THF, AcOH, DCM, DMF, H_2O, 1,4-dioxane and DMSO. It is noticed that CH_3CN is suitable solvent for this reaction in presence of CAN catalyst, and the desired product was obtained in 95% yield under these conditions (Table 2).

Having established the optimized reaction conditions, the reaction is extended to different substituted phenacyl bromides. It was observed that, by using CAN (10 mol%) as catalyst, in CH_3CN solvent the desired product was obtained in excellent yield, in each case. The results indicate that this method is compatible with different functional groups on the aromatic ring, and the approach proved to be of general applicability. All the reactions are found to proceed with equal efficiency.

Table 1 — Effect of different catalysts on the synthesis of 2-(3-methylisoxazol-5-yl)-4,10a-diaryl-2,10*a*-dihydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyrazine, **5**

Entry	Catalyst	Yield (%)
1	None	–
2	L-proline	30
3	CAN	95
4	$InCl_3$	35
5	$FeCl_3$	45
6	$ZnCl_2$	25
7	Silica gel	40
8	*p*-TSA	60
9	$AlCl_3$	50

[a] Isolated and optimized yields

Table 2 — Effect of amount of catalyst and solvent on the synthesis of 2-(3-methyl isoxazol-5-yl)-4,10a-diaryl-2,10*a*-dihydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyrazine, **5**

Entry	Solvent	Catalyst (mol%)	Yield (%)
1	EtoH	10	30
2	CH_3CN	5	60
3	CH_3CN	10	95
4	CH_3CN	20	95
5	THF	10	50
6	AcOH	10	30
7	DCM	10	60
8	DMF	10	15
9	H_2O	10	–
10	DMSO	10	15

[a] Isolated and optimized yields

Ten new intermediates of 2,2'-(3-methylisoxazol-5-yl)azanediyl)-bis(1-phenylethanones) **3**, and Ten new derivatives of final products *viz*., 2-(3-methylisoxazole-5-yl)-4,10*a*-diaryl-2,10*a*-dihydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyrazines **5** have been reported. The structures of newly synthesized compounds **3a-j** and **5a-j** were confirmed by micro analytical and spectral data (IR, ^{1}H and ^{13}C NMR and MS).

IR spectra of **3** exhibited absorption bands at 1675 cm^{-1} due to C=O functional group stretching vibrations; ^{1}H NMR spectra of **3** revealed the presence of a singlet at δ 4.32 assignable to N-CH_2 protons. Isoxazole methyl and ring hydrogens resonated at δ 2.28 and 6.23 respectively, whereas aromatic protons appeared as a complex multiplet between δ 6.89-7.80; ^{13}C NMR data is in agreement with the proposed structure. The mass spectrum of **3a** displayed the molecular ion $[M+H]^+$ peak at *m/z* 335.

The IR spectra of **5** did not show carbonyl group stretching vibrations at 1675 cm^{-1}, present in its precursor **3**, clearly indicates the cyclization; ^{1}H NMR z

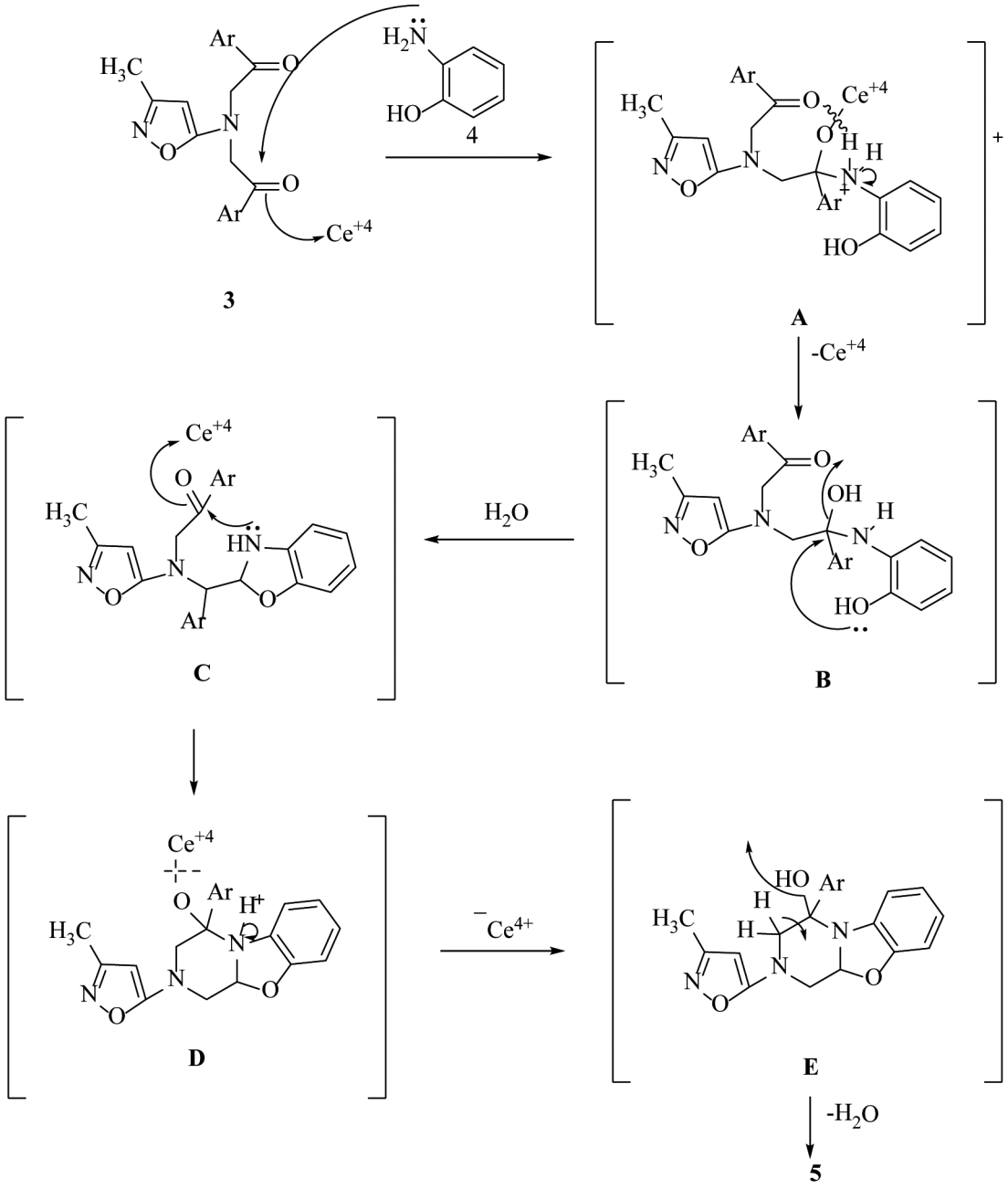
Data from the elemental analyses further confirmed the assigned structures **3** and **5.**

The plausible mechanism for the formation of isoxazolyl benzo[4,5]oxazolo[3,2-*a*]pyrazines is depicted in Scheme 2. Initially 2,2'(3-methylisoxazol-5-yl)azanediyl)bis(1-phenyl ethanone) **3** reacts with *o*-aminophenol **4**, activated by CAN, there by condensation and cyclization takes place to produce **A**. Then, the intramolecular nucleophilic addition of secondary amine to the carbonyl group activated by CAN gives **B**. Compound **B** undergoes spontaneous dehydration by the influence of CAN to give compound **5**.

Experimental Section

Chemistry

All the melting points were determined on a Fisher-Johns melting point apparatus, and are uncorrected. Analytical TLC was performed on Merck precoated 60 F254 silica gel plates. Visualization was carried



Scheme 2 — Plausible mechanism for the formation of novel isoxazolyl benzo[4,5]oxazolo[3,2-*a*]pyrazines 5

out by exposure to iodine vapour. IR spectra (KBr pellet) were recorded on a Perkin-Elmer BX series FT-IR spectrometer; ^{1}H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer; ^{13}C NMR spectra were recorded on a Bruker 75 MHz spectrometer. Chemical shift values are given in δ (ppm) with tetramethyl silane as an internal standard. ESI mass spectra were recorded on a Agilent LC-MSD mass spectrometer. Elemental analyses were performed on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

General procedure for the synthesis of 2,2'-((3-methylisoxazol-5-yl)azanediyl)bis(1-phenylethanones, 3a-j

A mixture of 5-amino-3-methylisoxazole **1** (1 mmol), phenacyl bromide **2** (2 mmol) and K_2CO_3 (1 mmol) in ethanol (20 mL) were refluxed at 80°C with stirring for 3 h. After the completion of the reaction, as indicated by TLC, the reaction mixture was poured on to crushed ice. The separated solid was filtered, and washed with cold alcohol and recrystallized from benzene.

2,2'-((3-Methylisoxazol-5-yl)azanediyl)bis(1-phenylethanone), 3a: Pale Yellow solid. Yield 70%. m.p.128-130°C. IR (KBr): 1671 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, isoxazole CH_3), 4.32 (s, 4H, N-CH_2), 6.23 (s, 1H, isoxazole CH), 6.89-7.80 (m, 10H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.84, 61.92, 62.35, 100.23, 127.32, 128.67, 129.32, 130.11, 130.58, 131.02, 131.65, 132.05, 133.12, 134.21, 135.54, 137.65, 160.32, 163.21, 190.21, 191.35; EI-MS: *m/z* 335 [M+H]$^+$. Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.86; H, 5.39; N, 8.38. Found: C, 71.88; H, 5.37; N, 8.36%.

2,2'-((3-Methylisoxazol-5-yl)azanediyl)bis(1-(4-methylphenyl)ethanone), 3b: Pale Yellow solid. Yield 75%. m.p.133-135°C. IR (KBr): 1674 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, isoxazole CH_3), 2.55 (s, 6H, Ar-CH_3), 4.35 (s, 4H, N-CH_2), 6.20 (s, 1H, isoxazole CH), 6.87-7.85 (m, 8H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.84, 22.32, 23.21, 60.62, 63.05, 101.03, 126.32, 127.77, 128.02, 129.11, 130.32, 131.32, 131.85, 132.65, 133.35, 134.21, 136.24, 137.60, 161.22, 164.01, 191.01, 192.31; EI-MS: *m/z* 363 [M+H]$^+$. Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.93; H, 6.08; N, 7.73. Found: C, 72.91; H, 6.07; N, 7.74%.

2,2'-((3-Methylisoxazol-5-yl)azanediyl)bis(1-(2-methylphenyl)ethanone), 3c: Pale Yellow solid. Yield 77%. m.p.138-140°C. IR (KBr): 1675 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, isoxazole CH_3), 2.52 (s, 6H, Ar-CH_3), 4.33 (s, 4H, N-CH_2), 6.22 (s, 1H, isoxazole CH), 6.83-7.81 (m, 8H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.66, 21.02, 22.11, 61.02, 64.25, 100.06, 126.55, 127.98, 128.22, 129.35, 130.65, 131.88, 132.05, 132.98, 133.58, 134.11, 135.64, 136.80, 162.23, 165.21, 190.31, 192.66; EI-MS: *m/z* 363 [M+H]$^+$. Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.93; H, 6.08; N, 7.73. Found: C, 72.92; H, 6.06; N, 7.75%.

2,2'-((3-Methylisoxazol-5-yl)azanediyl)bis(1-(4-methoxyphenyl)ethanone), 3d: Pale Yellow solid. Yield 80%. m.p.143-145°C. IR (KBr): 1678 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, isoxazole CH_3), 3.68 (s, 6H, Ar-OCH_3), 4.35 (s, 4H, N-CH_2), 6.20 (s, 1H, isoxazole CH), 6.87-7.85 (m, 8H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.68, 58.65, 59.32, 62.12, 65.20, 101.16, 126.75, 127.90, 128.32, 129.15, 130.66, 131.80, 132.36, 133.08, 133.88, 134.01, 135.69, 137.30, 163.23, 166.31, 191.01, 192.55; EI-MS: *m/z* 395 [M+H]$^+$. Anal. Calcd for $C_{22}H_{22}N_2O_5$: C, 67.00; H, 5.58; N,7.11. Found: C, 67.02; H, 5.56; N, 7.10%.

2,2'-((3-Methylisoxazol-5-yl)azanediyl)bis(1-(4-chlorophenyl)ethanone), 3e: Pale Yellow solid. Yield 70%. m.p.150-152°C. IR (KBr): 1678 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, isoxazole CH_3), 4.30 (s, 4H, N-CH_2), 6.20 (s, 1H, isoxazole CH), 6.78-7.83 (m, 8H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.80, 60.92, 61.39, 101.63, 127.87, 128.81, 129.36, 130.11, 130.58, 131.08, 131.69, 132.05, 133.12, 134.21, 135.54, 138.71, 160.32, 164.01, 191.01, 192.15; EI-MS: *m/z* 403 [M+H]$^+$. Anal. Calcd for $C_{20}H_{16}Cl_2N_2O_3$: C, 59.70; H, 3.98; N, 6.96. Found: C, 59.72; H, 3.97; N, 6.95%.

2,2'-((3-Methylisoxazol-5-yl)azanediyl)bis(1-(2-chlorophenyl)ethanone), 3f: Pale Yellow solid. Yield 68%. m.p.171-173°C. IR (KBr): 1675 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, isoxazole CH_3), 4.32 (s, 4H, N-CH_2), 6.22 (s, 1H, isoxazole CH), 6.85-7.89 (m, 8H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.53, 61.12, 62.29, 100.83, 127.21, 128.31, 129.55, 130.41, 130.88, 131.18, 131.88, 132.15, 133.22, 134.20, 136.21, 138.21, 161.62, 163.81, 191.01, 192.25; EI-MS: *m/z* 403

$[M+H]^+$. Anal. Calcd for $C_{20}H_{16}Cl_2N_2O_3$: C, 59.70; H, 3.98; N, 6.96. Found: C, 59.71; H, 3.96; N, 6.94%.

2,2'-((3-Methylisoxazol-5-yl)azanediyl)bis(1-(4-bromophenyl)ethanone), 3g: Brown solid. Yield 70%. m.p.185-187°C. IR (KBr): 1678 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.20 (s, 3H, isoxazole CH_3), 4.30 (s, 4H, N-CH_2), 6.20 (s, 1H, isoxazole CH), 6.82-7.56 (m, 8H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.51, 60.62, 61.89, 101.80, 127.55, 128.11, 129.61, 130.45, 130.96, 131.58, 132.08, 132.85, 133.65, 135.10, 136.23, 138.32, 162.82, 168.81, 192.01, 192.55; EI-MS: *m/z* 493 $[M+H]^+$. Anal. Calcd for $C_{20}H_{16}Br_2N_2O_3$: C, 48.78; H, 3.25; N, 5.69. Found: C, 48.77; H, 3.24; N, 5.67%.

2,2'-((3-Methylisoxazol-5-yl)azanediyl)bis(1-(3-bromophenyl)ethanone), 3h: Brown solid. Yield 72%. m.p.190-192°C. IR (KBr): 1676 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.22 (s, 3H, isoxazole CH_3), 4.32 (s, 4H, N-CH_2), 6.23 (s, 1H, isoxazole CH), 6.91-7.73 (m, 8H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.23, 61.02, 62.19, 100.85, 127.25, 127.91, 128.7, 129.95, 130.92, 131.89, 132.63, 133.25, 134.05, 135.56, 136.87, 139.22, 161.92, 169.88, 191.61, 192.35; EI-MS: *m/z* 493 $[M+H]^+$. Anal. Calcd for $C_{20}H_{16}Br_2N_2O_3$: C, 48.78; H, 3.25; N, 5.69. Found: C, 48.76; H, 3.25; N, 5.68%.

2,2'-((3-Methylisoxazol-5-yl)azanediyl)bis(1-(4-nitrophenyl)ethanone), 3i: Pale yellow Solid. Yield 72%. m.p.215-217°C. IR (KBr): 1679 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, isoxazole CH_3), 4.35 (s, 4H, N-CH_2), 6.25 (s, 1H, isoxazole CH), 6.96-7.83 (m, 8H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.62, 62.02, 63.29, 101.35, 127.51, 128.11, 129.72, 130.25, 131.32, 132.79, 133.43, 134.15, 135.05, 136.50, 137.27, 140.02, 162.62, 169.69, 190.75, 192.52; EI-MS: *m/z* 425 $[M+H]^+$. Anal. Calcd for $C_{20}H_{16}N_4O_7$: C, 56.60; H, 3.77; N, 13.21. Found: C, 56.62; H, 3.78; N, 13.20%.

2,2'-((3-Methylisoxazol-5-yl)azanediyl)bis(1-(3-nitrophenyl)ethanone), 3j: Pale yellow Solid. Yield 75%. m.p.204-206°C. IR (KBr): 1677 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H, isoxazole CH_3), 4.32 (s, 4H, N-CH_2), 6.23 (s, 1H, isoxazole CH), 6.93-7.79 (m, 8H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.55, 61.92, 62.99, 100.56, 126.21, 127.61, 128.52, 129.65, 130.82, 131.79, 132.83, 134.25, 136.95, 137.30, 138.17, 141.12, 161.60, 168.62, 191.65, 192.69; EI-MS: *m/z* 425 $[M+H]^+$. Anal. Calcd for $C_{20}H_{16}N_4O_7$: C, 56.60; H, 3.77; N, 13.21. Found: C, 56.61; H, 3.76; N, 13.20%.

General procedure for the synthesis of 2-(3-methylisoxazol-5-yl)-4,10a-diaryl-2,10a-dihydro-1*H*-benzo[4,5]oxazolo[3,2-a]pyrazines, 5a-j

A mixture of 2,2'-(3-methylisoxazol-5-yl)azanediyl)bis(1-phenylethanones **(3)** (1 mmol) and *o*-aminophenol **4** (1 mmol) 15 mL of CH_3CN in the presence of 10 mol% CAN was refluxed while stirring for 30 min. The reaction was monitored with TLC. After the completion of the reaction, as indicated by TLC, the reaction mixture was poured on to crushed ice, and the resulting solid was filtered, and washed with cold ethanol to give crude product. The product was recrystallized from ethyl acetate.

2-(3-Methylisoxazol-5-yl)-4,10a-diphenyl-2,10*a*-dihydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyrazine, 5a: Pale Yellow solid. Yield 80%. m.p.156-158°C. IR (KBr): 1120 (C-O-C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H, isoxazole CH_3), 4.09 (s, 2H, N-CH_2), 5.92 (s, 1H, pyrazine ring), 6.24 (s, 1H, isoxazole CH), 6.98-7.80 (m, 14H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.85, 73.54, 100.33, 103.25, 107.98, 108.22, 113.51, 119.69, 120.25, 123.54, 125.69, 126.21, 126.87, 127.57, 128.36, 129.54, 130.21, 131.74, 132.25, 134.21, 135.35, 136.37, 141.65, 143.25, 158.65, 160.78; EI-MS: *m/z* 408 $[M+H]^+$. Anal. Calcd for $C_{26}H_{21}N_3O_2$: C, 76.66; H, 5.16; N, 10.32. Found: C, 76.65; H, 5.15; N, 10.30%.

2-(3-Methylisoxazol-5-yl)-4,10a-di-4-methylphenyl-2,10*a*-dihydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyrazine, 5b: Pale Yellow solid. Yield 82%. m.p.162-164°C. IR (KBr): 1126 (C-O-C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, isoxazole CH_3), 2.50 (s, 6H, Ar-CH_3), 4.12 (s, 2H, N-CH_2), 5.96 (s, 1H, pyrazine ring), 6.24 (s, 1H, isoxazole CH), 6.98-7.80 (m, 12H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.85, 22.85, 23.21, 74.14, 99.36, 101.65, 108.63, 109.02, 114.21, 118.69, 119.25, 120.32, 121.39, 123.61, 125.87, 126.35, 127.66, 128.54, 129.61, 130.74, 131.65, 132.91, 134.95, 135.77, 140.75, 143.37, 157.60, 161.28; EI-MS: *m/z* 436 $[M+H]^+$. Anal. Calcd for $C_{28}H_{25}N_3O_2$: C, 77.24; H, 5.75; N, 9.65. Found: C, 77.22; H, 5.76; N, 9.63%.

2-(3-Methylisoxazol-5-yl)-4,10a-di-2-methylphenyl-2,10*a*-dihydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyrazine, 5c: Pale Yellow solid. Yield 78%. m.p.170-172°C. IR (KBr): 1124 (C-O-C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, isoxazole CH_3), 2.52 (s, 6H, Ar-CH_3), 4.15 (s, 2H, N-CH_2), 5.92 (s, 1H, pyrazine ring), 6.20 (s, 1H, isoxazole CH), 6.92-7.89 (m, 12H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.20, 22.76, 23.65, 75.05, 99.32, 100.99, 106.73, 110.62, 114.29, 116.79, 118.35, 120.95, 121.85, 122.92, 124.69, 125.75, 126.87, 127.64, 128.60, 131.98, 130.91, 133.83, 135.15, 136.32, 141.85, 144.01, 159.60, 163.08; EI-MS: *m/z* 436 $[M+H]^+$. Anal. Calcd for $C_{28}H_{25}N_3O_2$: C, 77.24; H, 5.75; N, 9.65. Found: C, 77.21; H, 5.73; N, 9.64%.

4,10a-bis(4-Methoxyphenyl)-2-(3-methylisoxazol-5-yl)-2,10a-dihydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyrazine, 5d: Pale Yellow solid. Yield 80%. m.p.185-187°C. IR (KBr): 1124 (C-O-C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, isoxazole CH_3), 3.68 (s, 6H, Ar-OCH_3), 4.18 (s, 2H, N-CH_2), 5.90 (s, 1H, pyrazine ring), 6.22 (s, 1H, isoxazole CH), 6.86-7.86 (m, 12H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.23, 58.21, 60.68, 74.35, 100.32 101.98, 107.63, 109.12, 113.69, 117.99, 119.35, 120.85, 121.55, 122.81, 124.97, 125.75, 127.67, 128.14, 129.69, 130.58, 131.81, 132.23, 134.85, 136.37, 141.70, 143.21, 158.66, 162.08; EI-MS: *m/z* 467 $[M+H]^+$. Anal. Calcd for $C_{28}H_{25}N_3O_4$: C, 7195; H, 5.35; N, 8.99. Found: C, 71.93; H, 5.36; N, 8.97%.

4,10a-bis(4-Chlorophenyl)-2-(3-methylisoxazol-5-yl)-2,10a-dihydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyrazine, 5e: Pale Yellow solid. Yield 75%. m.p.192-194°C. IR (KBr): 1125 (C-O-C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, isoxazole CH_3), 4.19 (s, 2H, N-CH_2), 5.90 (s, 1H, pyrazine ring), 6.25 (s, 1H, isoxazole CH), 6.85-7.93 (m, 12H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.82, 74.14, 101.03, 102.20, 106.90, 107.32, 114.11, 118.39, 119.22, 122.64, 124.86, 125.61, 126.91, 127.55, 127.96, 128.64, 130.55, 131.88, 133.15, 134.36, 136.95, 137.30, 143.65, 144.65, 159.35, 161.28; EI-MS: *m/z* 476 $[M+H]^+$. Anal. Calcd for $C_{26}H_{19}Cl_2N_3O_2$: C, 65.68; H, 4.00; N, 8.84. Found: C, 65.66; H, 3.99; N, 8.82%.

4,10a-bis(2-Chlorophenyl)-2-(3-methylisoxazol-5-yl)-2,10a-dihydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyrazine, 5f: Pale Yellow solid. Yield 75%. m.p.209-211°C. IR (KBr): 1128 (C-O-C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, isoxazole CH_3), 4.21 (s, 2H, N-CH_2), 5.92 (s, 1H, pyrazine ring), 6.26 (s, 1H, isoxazole CH), 6.92-7.85 (m, 12H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.72, 75.04, 100.23, 101.28, 105.99, 108.92, 115.31, 117.39, 118.62, 123.60, 124.80, 125.98, 126.58, 127.69, 128.36, 129.94, 131.59, 132.78, 133.13, 134.16, 135.65, 138.90, 144.65, 145.65, 158.65, 162.08; EI-MS: *m/z* 476 $[M+H]^+$. Anal. Calcd for $C_{26}H_{19}Cl_2N_3O_2$: C, 65.68; H, 4.00; N, 8.84. Found: C, 65.67; H, 4.01; N, 8.81%.

4,10a-bis(4-Bromophenyl)-2-(3-methylisoxazol-5-yl)-2,10a-dihydro-1*H*-benzo[4,5]oxazolo[3,2-a]pyrazine, 5g: Brown solid. Yield 73%. m.p.219-221°C. IR (KBr): 1128 (C-O-C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, isoxazole CH_3), 4.21 (s, 2H, N-CH_2), 5.90 (s, 1H, pyrazine ring), 6.27 (s, 1H, isoxazole CH), 6.92-7.80 (m, 12H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.70, 75.06, 101.33, 102.18, 104.89, 109.98, 116.81, 118.30, 119.60, 123.69, 124.92, 126.08, 126.88, 127.88, 128.55, 129.96, 132.50, 133.88, 134.63, 134.96, 135.85, 138.96, 145.65, 146.85, 160.65, 163.18; EI-MS: *m/z* 566 $[M+H]^+$. Anal. Calcd for $C_{26}H_{19}Br_2N_3O_2$: C, 55.22; H, 3.36; N, 7.43. Found: C, 55.24; H, 3.34; N, 7.42%.

4,10a-bis(3-Bromophenyl)-2-(3-methylisoxazol-5-yl)-2,10a-dihydro-1H-benzo[4,5]oxazolo[3,2-a]pyrazine, 5h: Brown solid. Yield 71%. m.p.225-227°C. IR (KBr): 1125 (C-O-C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, isoxazole CH_3), 4.24 (s, 2H, N-CH_2), 5.92 (s, 1H, pyrazine ring), 6.24 (s, 1H, isoxazole CH), 6.95-7.87 (m, 12H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.90, 74.66, 100.63, 101.88, 103.79, 110.38, 115.91, 117.90, 118.69, 122.89, 124.65, 125.28, 126.83, 127.25, 128.50, 130.06, 131.30, 132.68, 135.60, 136.36, 137.65, 138.92, 144.95, 147.95, 161.85, 164.28; EI-MS: *m/z* 566 $[M+H]^+$. Anal. Calcd for $C_{26}H_{19}Br_2N_3O_2$: C, 55.22; H, 3.36; N, 7.43. Found: C, 55.20; H, 3.35; N, 7.41%.

2-(3-Methylisoxazol-5-yl)-4,10a-bis(4-nitrophenyl)-2,10a-dihydro-1*H*-benzo[4,5]oxazolo[3,2-a]pyrazine, 5i: Pale Yellow solid. Yield 70%. m.p.235-237°C. IR (KBr): 1120 (C-O-C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, isoxazole CH_3), 4.10 (s, 2H, N-CH_2), 5.92 (s, 1H, pyrazine ring), 6.20 (s, 1H, isoxazole CH), 6.95-7.88 (m, 12H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.80,74.10, 100.16, 102.65, 107.63, 109.02, 114.21, 118.70,

119.25, 120.30, 122.19, 123.61, 125.87, 126.35, 127.98, 128.54, 129.66, 130.78, 131.65, 133.71, 135.95, 136.77, 140.70, 144.37, 158.62, 162.18; EI-MS: *m/z* 498 $[M+H]^+$. Anal. Calcd for $C_{26}H_{19}N_5O_6$: C, 62.78; H, 3.82; N, 14.08. Found: C, 62.76; H, 3.80; N, 14.06%.

2-(3-Methylisoxazol-5-yl)-4,10a-bis(3-nitrophenyl)-2,10a-dihydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyrazine, 5j: Pale Yellow solid. Yield 70%. m.p.241-243°C. IR (KBr): 1126 (C-O-C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, isoxazole CH_3), 4.15 (s, 2H, N-CH_2),5.90 (s, 1H, pyrazine ring), 6.26 (s, 1H, isoxazole CH), 6.98-7.91 (m, 12H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.72, 75.20, 99.96, 100.66, 105.83, 110.82, 115.21, 117.79, 119.25, 120.36, 122.58, 123.95, 125.69, 127.05, 127.99, 128.50, 129.88, 130.96, 131.65, 134.71, 136.90, 137.97, 141.76, 148.97, 159.82, 163.88; EI-MS: *m/z* 498 $[M+H]^+$. Anal. Calcd for $C_{26}H_{19}N_5O_6$: C, 62.78, H, 3.82; N, 14.08. Found: C, 62.77; H, 3.81; N, 14.07%.

Conclusion

In conclusión, we report a mild and efficient synthesis of novel isoxazolyl benzo[4,5]oxazolo[3,2-*a*]pyrazines **5** catalyzed by CAN by a new synthetic protocol. This synthesis benifits from a simple method of purification, which does not require chromatography. This ease of purification compliments this technology practical, easy to perform, and facile. To the best of our knowledge this happens to be the first report on the synthesis of isoxazolyl benzo[4,5]oxazolo[3.2-*a*]pyrazines.

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