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ONE POT MULTICOMPONENT SYNTHESIS OF A SERIES OF 5-AMINO-3-PHENYLISOXAZOLE-4-CARBONITRILE EMPLOYED BY LEWS ACID CATALYST

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ABSTRACT

In the present study and followed by conventional method, an efficient and design synthesis a novel series of 5-amino-3-phenylisoxazole-4-carbonitrile derivatives. These derivatives can be obtained by substituted aromatic aldehyde, malononitrile and hydroxylamine hydrochloride in presence of Lews acid catalyst ceric ammonium sulphate in isopropyl alcohol as a solvent at reflux. All the titled analogous were evaluated by the advanced spectroscopic analysis such as ^{1}HNMR, ^{13}CNMR and LCMS and structural determination of titled analogous were calculated by elemental analysis. In addition to the newly synthesized compounds were examined by their anti-microbial activity.

KEYWORDS

Malanonitrile, Hydroxylamine hydrochloride, Aromatic aldehyde, 5-amino-3-phenylisoxazole-4-carbonitrile, CAS and Bioevluation.

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INTRODUCTON

Isoxazoles are five-membered aromatic heterocycles containing adjacent oxygen and nitrogen atoms. The isoxazole ring system is found in a variety of naturally occurring compounds and biologically active molecules[1]. They are especially useful in medicine, since many antifungal drugs belong to the isoxazole class[2]. Sulfisoxazole and sulfamethoxazole are two bacteriostatic sulfonamide antibiotics that applied alone or combined with others in the treatment of infections caused Gram-positive and Gram-negative bacteria[3,4]. Acivicin is a γ-glutamyl transferase inhibitor with anticancer, anti-parasitic and antileishmanial activities[5]. Isoxazole derivatives

possess a broad variety of biological activities viz. antifungal, anti-inflammatory, antiplatelet, anti-HIV, anti-Alzheimer and analgesic[6-11].

In order to develop applications of ceric ammonium sulphate other heterocycles, it was successfully used as catalytic media in the synthesis of novel 5-amino-isoxazole-4-carboni-trile derivatives via multicomponent reaction of malononitrile, hydroxylamine and various aryl aldehydes In vitro inhibitory activity of all derivatives was evaluated against some pathogenic bacteria including.

MATERIAL AND METHODS

Experimental

All reagents, solvents, antibiotics, and antifungal agents were purchased from commercial sources such Merck, Sigma and Aldrich and used without further purification. The bacterial and fungal culture media were obtained from (HI Media). The melting points desired analogous were determined with Aggarwal melting point meter and are uncorrected. The reaction progress was identified by TLC plates precoated by SiO_2 with fluorescent indicator F254 using EtOAc/n-hexane (4:6) as mobile phase that were visualized under UV radiation (255 nm). . FT-IR spectra of the products were collected using a Bruker Tensor-27 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker FT-NMR Ultra Shield-400 spectrometer. Elemental analyses (CHNS/O) were performed on a Thermo Finnigan Flash EA micro analyzer.

General procedure for the synthesis of5-amino-3-phenylisoxazole-4-carbonitrile (4a-4i)

A mixture of malononitrile (1), substituted aromatic aldehydes (2) and hydroxylamine hydrochloride (3) is dissolved in 25mL isopropyl alcohol in a 50mL RBF and gradually addition of Lews acid catalyst such as ceric ammonium catalyst (2mmol), during the reaction and continued the reaction 5 hrs. The progress of the reaction was examined with help of TLC (as a mobile system = EtOAc: n-hexane -4:6). The completion of the reaction poured in cold water and neutralized with a solution of $NaHCO_3$ and extracted with ethylacetae and separated the organic layer. The organic layer was distilled with vacuum distillation and obtained by product.

5-amino-3-phenylisoxazole-4-carbonitrile (4a)

Pale orange red; Yield: 84%; M.P : 154–156°C; IR (KBr, cm^{-1}) ν: 3512, 3405, 3341, 2223, 1615, 1267; ^1H NMR (400 MHz, CDCl3) δppm: 7.124 (d, J = 8.8 Hz, 2H, Ar-H), 7.884 (d, J = 7.6 Hz, 2H, Ar-H), 8.224 (s, 2H, NH_2); 13C NMR (100 MHz, $CDCl_3$) δppm: 76.07, 113.36, 116.78, 119.08, 125.66, 132.35, 162.18, 166.98; Molecular weight(m/z): 185.28(M+); Molecular formulae $C10H7N_3O$: Analysis of elements: Calculated: C- 64.86, H- 3.81, N- 22.69. Obtained: C- 64.80, H - 3.79, N- 22.75.

5-Amino-3-(4-hydroxyphenyl) isoxazole-4-carbonitrile (4b)

Pale orange red; Yield: - 92%; M.P- 165–1167°C; IR (KBr, cm-1) ν: 3515, 3414, 3318, 2234, 1618, 1265; ^{1}HNMR (400 MHz, $CDCl_3$) δppm: 7.128 (d, J = 9.2Hz, 2H, Ar-H), 7.687(d, J = 6.8 Hz, 2H, Ar=H′), 8.147 (s, 2H, NH_2), 9.985 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 77.66, 114.87, 117.08, 118.58, 124.55, 136.21, 159.95, 165.47; Molecular weight(m/z); 201.47 (M+); Molecular formulae: $C_{10}H_7N_3O_2$: Analysis of elements: Calculated: C-59.70, H-3.51, N -20.89. Obtained: C -59.63, H-3.50, N-20.96.

5-Amino-3-(2-hydroxy-3-methoxyphenyl) isoxazole-4-carbonitrile (4c)

Pale orange red; Yield- 88%; M.P- 228–230°C; IR (KBr, cm-1) ν: 3502, 3412, 3340, 2213, 1604, 1285; 1H NMR (400 MHz, CDCl3) δppm: 2.254 (s, 3H, CH3), 7.277–7.394 (m, 3H, Ar-H), 8.138 (s, 2H, NH2), 9.147 (s, 1H, OH); 13C NMR (100 MHz, CDCl3) δppm: 56.15, 103.57, 115.58, 117.27, 118.78, 122.58, 125.28, 144.74, 147.65, 154.47, 158.58; Molecular weight (m/z): 232.14 (M+H); Molecular formulae: C11H9N3O3: Analysis of elements: Calculated C- 57.14, H- 3.92, N -18.17. Obtained: C -57.08, H- 3.90, N 18.25.

5-Amino-3-(4-tolyl) isoxazole-4-carbonitrile (4d)

Pale orange red; Yield: 89%; M.P: 174–176°C; IR (KBr,cm-1) ν: 3417, 3327, 2228, 1603, 1218; 1H NMR (400 MHz, CDCl3) δppm: 2.258 (s, 3H, CH_3), 7.327(d, J = 7.6 Hz, 2H, Ar-H), 7.82 (d, J = 7.2 Hz, 2H, Ar-H ′), 8.248 (s, 2H, NH_2); 13C

NMR (100 MHz, $CDCl_3$) δppm: 21.23 , 81.03, 114.07, 115.85, 128.98, 130.44, 132.12, 147.85, 162.65; Molecular weight(m/z); 166.32 (M+H); Molecular formulae: $C_{11}H_9N_3O$: Analysis of elements: Calculated: C-66.32, H- 4.55, N-21.09. Obtained: C- 66.27, H- 4.53, N 21.16

5-Amino-3-(2, 4-dichlorophenyl) isoxazole-4-carbonitrile (4e)

Pale orange red; Yield-90%; M.P-171–173°C; IR (KBr, cm-1) ν: 3428, 3345 , 2218, 1649, 1288; 1H NMR (400 MHz, $CDCl_3$) δppm: 7.589 (m, 1H, Ar-H), 7.846 (s, 1H, Ar-H), 8.118 (d, J = 8.5Hz, 1H, Ar-H), 8.258 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 87.44, 113.07, 127.88, 128.76, 129.19, 130.17, 132.08, 139.16, 145.87, 157.66; Molecular weight (m/z); 254.58 (M+H); Molecular formulae; $C_{10}H_5Cl_2N_3O$: Analysis of elements: Calculated: C -42.27, H-1.98, N-16. 54. Obtained: C -42.20, H- 1.96, N-16.62.

5-Amino-3-(4-nitrophenyl) isoxazole-4-carbonitrile (4f)

Pale orange red; Yield-83%; M.P-225-227°C; IR (KBr,cm-1) ν: 3419, 3372 , 2226, 1604, 1539, 1363, 1286; 1H NMR (400 MHz, $CDCl_3$) δppm: 7.892 (d, J = 9.2 Hz, 2H, Ar-H), 8.132 (s, 2H, Ar-H), 8.254 (m, 4H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 80.28, 116.47, 124.21, 128.47, 136.17, 147.65, 148.44, 153.64; Molecular weight (m/z): 231.54 (M+); Molecular formulae: $C_{10}H_6N_4O_3$: Calculated: C-52.18, H- 2.63, N-24.34. Obtained: C- 52.12, H-2.59, N- 24.37.

5-Amino-3-(furan-2-yl) isoxazole-4-carbonitrile (4g):

Pale orange red; Yield- 85%; M.P: 241–243°C; IR (KBr, cm-1) ν: 3420, 3364, 2217, 1604, 1286; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 6.874 (m, 1H, furyl), 7.123-7.214 (m, 1H, furyl), 8.012 -8.217 (m, 1H, furyl), 8.234 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 76.55, 110.91, 114.27, 117.05, 135.66, 147.24, 153.54, 162.87; Molecular weight(m/z): 174.22 (M+H); Molecular formulae: C8H6N4O: Analysis of elements: Calculated: C -55.17, H- 3.47, N- 32.17. Obtained: C -55.10, H-3.46, N- 32.22.

5-Amino-3-(thiophen-2-yl) isoxazole-4-carbonitrile (4h)

Orange red; Yield- 85%; M.P- 204–206°C: IR (KBr, cm-^{1}) ν: 3425, 3363, 2204, 1601, 1281; 1H NMR (400 MHz, $CDCl_3$) δppm: 7.214-7.258 (m, 1H, Thiophene), 7.451-7.495 (m, 1H, Thiophene), 7.817 (s, 1H, Thiophene), 8.208 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 81.25, 116.18, 128.66, 129.06, 132.11, 140.54, 153.58, 165.47; Molecular weight (m/z):191.88 (M+) Molecular formulae: $C_8H_5N_3OS$: Analysis of elements: Calculated: C- 50.25, H- 2.64, N- 21.98,Obtained: C -50.19, H- 2.62, N- 22.04.

5-Amino-3-(pyridin-4-yl) isoxazole-4-carbonitrile (4i)

Pale red solid; Yield- 86%; M.P- 212–214°C; IR (KBr,cm-1) ν: 3430, 3325, 2215, 1601, 1284; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 7.341–7.514(m, 2H, Pyridyl), 8.125 (s, 2H, NH_2), 8.276 (d, J = 8.0 Hz, 2H, Pyridyl′); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 81.24, 114.54, 124.14, 142.06, 150.39, 153.17, 162.58; Molecular weight (m/z): 186.65(M+); Molecular formulae: $C_9H_6N_4O$: Analysis of elements: Calculated: C- 58.06, H - 3.25, N -30.09. Found: C 58.00, H 3.27, N 30.15.

RESULTS AND DISCUSSION

Initially, The path of the reaction 5-amino-3-phenylisoxazole-4-carbonitrile analogous were obtained from by the reaction mixture of malanonitrile (1mmol), substituted aryl aldehyde (1.2mmol) and hydroxylamine hydrochloride (1mmol) taken in ethanol (30ml) in 50mL RBF and fitted on the magnetic stirrer. The catalytic amount of ceric ammonium sulphate (2mmol) slowly added in a RBF. The reaction mixture vigorously stirring for 5hrs at reflux

The advantages of the synthetic protocol are wide substrate range, easy handling and commercial available inexpensive catalyst. We used a wide variety of compounds to which optimal reaction conditions were applied to synthesize a wide range of benzothiazole as shown by Scheme No.1.

The reaction condition of these derivatives optimized at different catalyst, different amount of the catalyst and different solvent are used. The

maximum yield of the compounds obtained in presence of ceric ammonium sulphate (CAS) catalyst than oxidative related catalyst such as AgI, CuI and I_2 whereas different amount of catalyst utilized during the reaction (Table No.1).

During the reaction, the different amount of catalyst was applied completion of the reaction, initially 0.1mmol added in the reaction, traces of product was obtained and gradually increase the amount of catalyst added and slowly increases product obtained. This indicated that 2.0mmol of the CAN was used in these reaction better results was obtained compared to same amount of other catalyzed as shown Table No.2.

Usually, the various solvents used in during this reaction, ethyl alcohol is suitable solvent and perfectly maintained reaction compared to the other solvents such as methanol, DMF and Acetonitrile. An isopropanol is the best solvent utilizing during the reaction, the advantages of the reaction are no pollution effects, easy to work up and there is no wastage of yield as shown Table No.3.

Characterization

The structure of the titled analogous was performed by the evidence of spectral analysis such as IR, ^{1}HNMR, ^{13}CNMR, LCMS and elemental analysis. The study of IR evidences of desired compound such as 3430 (NH_2) and 2229 (CN). In this study, proton NMR of titled derivatives exhibited by various values of respective groups such as hydroxyl proton is 8.147 δppm, furan is 6.874-8.217δppm, Thiophene is 7.214-7.817δppm, pyridine protons 7.3141-8.276 δppm, methyl protons 2.258 δppm, 9.982 δppm of NH_2 protons as well as aromatic protons 7.892-8.254δppm appeared at various range of values.13CNMR of these derivatives appeared at different values.

Biological activity

The results of the above Table No.4 represented that the anti-bacterial activity of derivatives 4b, 4c, 4d mostly electron donating group of compound viz; these derivatives exhibited good active potent while electron withdrawing group of compounds "4e and 4f" exhibited an excellent active potent. The compound 4e and 4f exhibited moderate active potential due to Nitro groups present in the compound. We also observed the Antifungal Activity of compound (4a-4g) exhibited different activity compound 4g, 4h and 4i d showed good "4a" activity and rate of the compound showed low to moderate activity.

Table No.1: Effective the various catalysts for the titled derivatives

Entry	Various catalyst	Time (hrs)	Yield (%)
1	KIO_4	08	68
2	AgI	12	54
3	CuI_2	10	60
4	CAN	05	92
5	TiO_2	09	45

Table No.2: Different amounts of catalyst in Isopropanol at reflux (4b)

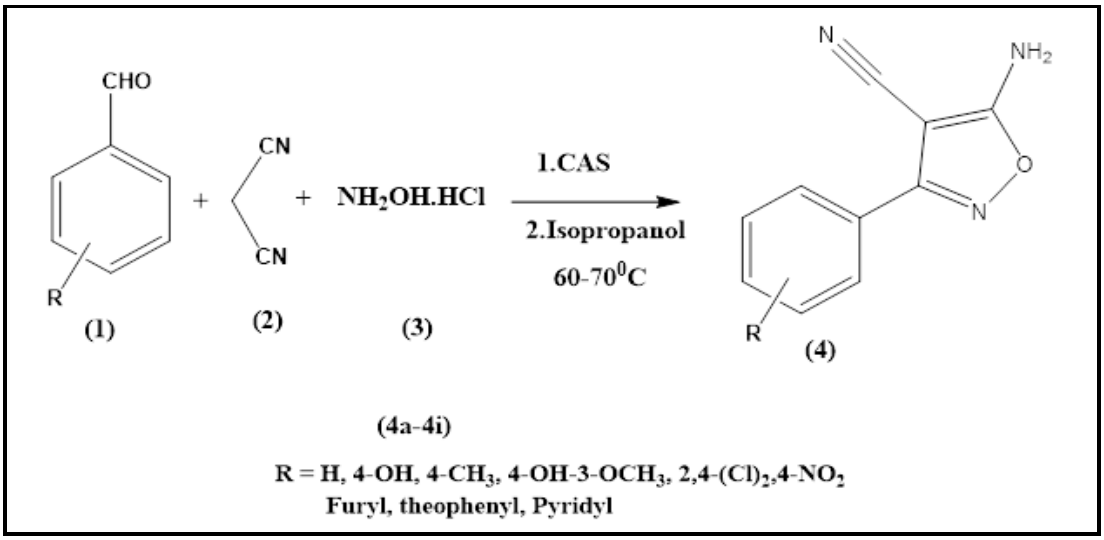
Entry	Amount of catalyst (%)	Time (hrs)	Yield (%)
1	0.1	10	Traces
2	1.0	12	35
3	2.0	05	92
4	5	08	92

Table No.3: The effect of solvents for titled derivatives at reflux (4b)

Entry	Various Solvent	Time (hrs)	Yield (%)
1	Isopropanol	05	92
2	MeOH	08	58
3	Acetonitrile	10	61
4	DMF	10	67

Table No.4: Antimicrobial activity screening activity synthesized scaffold (4a-4i)

S.No	Compound Code	*Zone of inhibition in (mm)					
		Bacteria				Fungi	
		S.aureus	***E.coli***	***S. typhi***	***B.substills***	***A. niger***	***C. albicans***
1	4a	08	05	06	07	05	06
2	4b	18	18	19	20	15	14
3	4c	17	19	19	16	16	13
4	4d	20	17	19	18	16	17
5	4e	23	22	20	22	17	16
6	4f	21	22	23	20	17	16
7	4g	14	15	15	14	08	07
8	4h	15	17	15	17	10	11
9	4i	16	09	07	11	08	06
10	Streptomycin	27	27	25	25	NA	NA
11	Fluconazole	NA	NA	NA	NA	22	22
12	DMSO	---	----	---	---	---	---



Scheme No.1

CONCLUSION

In conclusion, this study of titled derivatives has disclosed a novel and convenient one-pot synthesis of 5-amino-3-phenylisoxazole-4-carbonitrile analogues via multi-component reactions. This ceric ammonium sulphate Lews acid catalyst reaction proceeded smoothly in good to excellent yields and offered different other advantages including short reaction time, simple experimental workup procedures, and no toxic by-products. The approach to titled derivatives systems presented herein avoids the use of catalyst, toxic organic solvent. This protocol represents a promising green route for the synthesis of this class of compounds. Further, the antimicrobial activity of the titled derivatives was studied. The derivatives having electron withdrawing groups exhibited excellent active potential.

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CONFLICT OF INTEREST

We declare that we have no conflict of Interest.

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