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ONE POT SYNTHESIS OF 5-AMINO-3-PHENYLISOXAZOLE-4-CARBONITRILE DERIVATIVES EMPLOYED BY TIO_2 AS A CATALYST

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ABSTRACT
A straightforward new path way and biological approach of a novel series and followed by conventional process a series of 5-amino-3-phenylisoxazole-4-carbonitrile analogous. These derivatives would obtained by aromatic aldehyde, malononitrile and hydroxylamine hydrochloride in presence of Lews acid catalyst TiO_2 in acetonitrile as a solvent at reflux. All the desired analogous were evaluated the advanced spectroscopic analysis such as ^{1}HNMR, ^{13}CNMR and LCMS and structural determination of titled analogous were determined by elemental analysis. In addition to the obtained synthesized derivatives were examined by their anti-microbial activity.

KEYWORDS: Malanonitrile, hydroxylamine hydrochloride, aromatic aldehyde, 5-amino-3-phenylisoxazole-4-carbonitrile, TiO_2, antibacterial activity.

1. INTRODUCTION
Isoxazole are five-membered heterocyclic compounds that possess two heteroatom such as oxygen and nitrogen atoms. The Isoxazole nucleus system is recognized in a several naturally occurring molecules and biologically active molecules.[1] They are most useful in medicine chemistry and a variety of antibacterial drugs belong to the isoxazole class.[2] Isoxazole and its derivatives are two bacteriostatic sulfonamide antibiotics that was applied either alone or fused with others in the treatment of infections caused Gram-(+Ve) and Gram (-Ve) bacteria.[3,4] Acivicin is a γ-glut amyl transferee's inhibitor is used for anticancer, anti-parasitic and antileishmanial activities.[5] Isoxazole derivatives were containg a wide variety of biological properties viz. antifungal, anti-inflammatory, antiplatelet, anti-HIV, anti-Alzheimer and analgesic.[6–11]

In order to develop applications of titanium dioxide other heterocycles, it was successfully used as catalytic media in the synthesis of series 5-amino-isoxazole-4-carbonitrile analogous via multicomponent reaction of malononitrile, hydroxylamine and different aryl aldehydes In vitro inhibitory activity of all derivatives was evaluated against some pathogenic bacteria including.

2. METHODS AND MATERIALS
2.1. EXPERMENTAL
All reagents, solvents, starting material procured from commercial sources such Fine chemicals and used without further purification. The bacterial culture media were obtained from (HI Media). The melting points newly analogous were estimated with Agrawal 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 (3:7) as mobile phase that were visualized under UV radiation. ^{1}H and ^{13}C NMR spectra were measured 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.

2.2. GENERAL PROCEDURE FOR THE SYNTHESIS OF5-AMINO-3-PHENYLISOXAZOLE-4-CARBONITRILE (4a-4i)
A mixture of malononitrile (1), aromatic aldehydes (2) and hydroxylamine hydrochloride (3) is dissolved in 30 mL ethanol as a 50mL RBF and gradually addition of Lews acid catalyst such as TiO_2(2mmol), during the reaction and continued the reaction 4 hrs. The progress of the reaction was monitored with help of TLC (EtOAc: n-hexane - 5:5). The completion of the reaction added in cold water and also neutralized with a saturated solution of $NaHCO_3$ and extracted with ethylacetae and separated

the organic layer. The organic layer was distilled off vacuum distillation and obtained by product.

2.2.1.5-amino-3-phenylisoxazole-4-carbonitrile (4a)
Orange color compound; Yield: 82 %; M.P : 156–158 °C; ^{1}H NMR (400 MHz, CDCl3) δ ppm: 7.157 (d, J = 7.2 Hz, 2H,Ar-H), 7.712 (d, J = 5.6 Hz, 2H, Ar-H), 8.218 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 74.85, 114.04, 117.15, 120.08 , 126.66, 131.35, 161.18, 167.98; Molecular weight(m/z): 185.57(M+); Molecular formulae $C_{10}H_7N_3O$: Analysis of elements: Calculated : C-64.85, H- 3.81, N- 22.68. Obtained: C- 64.81, H - 3.79, N- 22.72.

2.2.2.5-Amino-3-(4-hydroxyphenyl) isoxazole-4-carbonitrile (4b)
Pale orange color compound; Yield: - 94%; M.P- 151–153°C;^{1}HNMR (400 MHz, $CDCl_3$) δ ppm :7.162 (d, J = 9.0Hz, 2H,Ar-H), 7.681(d, J = 6.4 Hz, 2H, Ar=H′), 8.177(s, 2H, NH_2), 9.915 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δppm : 77.12, 114.08, 117.08, 118.45, 124.50, 135.21, 158.95, 166.47; 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.

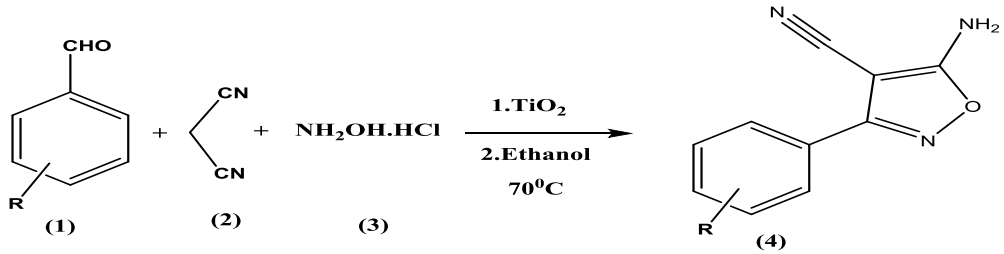
2.2.3.5-Amino-3-(2-hydroxy-3-methoxyphenyl) isoxazole-4-carbonitrile (4c)
Pale orange color solid; Yield- 88%; M.P- 168–170°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.230 (s, 3H, CH_3), 7.270–7.391 (m, 3H, Ar-H), 8.144 (s, 2H, NH_2), 9.254 (s, 1H, OH); ^{13}C NMR (100 MHz, CDCl3) δppm: 56.74, 104.58, 115.47, 118.59, 119.71, 123.05, 126.28, 143.74 , 146.65, 155.47, 158.05; Molecular weight(m/z):232.57 (M+H); Molecular formulae: $C_{11}H_9N_3O_3$: Analysis of elements: Calculated C- 57.14, H- 3.92, N -18.17. Obtained: C -57.08, H- 3.90, N 18.25.

2.2.4.5-Amino-3-(4-tolyl) isoxazole-4-carbonitrile (4d)
Pale orange color solid; Yield:86%; M.P: 170–172°C; ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm : 2.241 (s, 3H, CH_3), 7.320(d, J = 7.2 Hz, 2H, Ar-H), 7.682 (d, J = 7.0 Hz, 2H, Ar-H ′), 8.217 (s, 2H, NH_2); ^{13}CNMR (100 MHz, $CDCl_3$) δppm: 22.77, 82.07, 114.14, 115.86, 128.93, 130.65, 131.58, 148.85, 162.77; Molecular weight(m/z); 166.30(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.

2.2.5.5-Amino-3-(2, 4-dichlorophenyl) isoxazole-4-carbonitrile (4e)
Bright orange color compound; Yield-86%; M.P-175–177°C; ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm : 7.580 (s,1H,Ar-H), 7.842 (s, 1H, Ar-H), 8.124 (d, J = 8.0Hz, 1H, Ar-H), 8.214 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δppm : 87.54, 113.33, 127.57, 128.76, 129.47, 130.88, 132.54, 138.16, 146.87, 158.67; Molecular weight(m/z); 254.74 (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.

2.2.6. 5-Amino-3-(4-nitrophenyl) isoxazole-4-carbonitrile (4f)
Orange colorcompoud; Yield-85%; M.P-179-181°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 7.887 (d, J = 9.0 Hz, 2H, Ar-H), 8.135 (s, 2H, Ar-H), 8.257 (m, 4H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 80.74, 117.45, 124.24, 128.48, 136.16, 148.65, 149.44, 153.65; 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.

3. RESULTS AND DISCUSSION



(4a-4g)

R = H, 4-OH, 4-CH_3, 4-OH-3-OCH_3, 2,4-$(Cl)_2$,4-NO_2

(Scheme-1)

Initially, The route of the reaction 5-amino-3-phenylisoxazole-4-carbonitrile derivatives were prepared 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 TiO_2 (2mmol) slowly added in a RBF. The reaction mixture vigorously stirring for 7hrs at reflux.

The scope and advantages of the synthetic procedure are broad substrate range, easy handling, and easily commercial available inexpensive catalyst. We used a significant variety of derivatives to which optimal

reaction conditions were applied to synthesize a broad range of 5-amino-3-phenylisoxazole-4-carbonitrile as shown by scheme-I.

The reaction condition of these analogous was optimized at different type catalyst, different amount of the catalyst and various typet solvent are used. The maximum yield of the compounds obtained in presence of TiO_2 catalyst than oxidative related catalyst such as AgI, CuI_2 and $CANI_2$ whereas different amount of catalyst utilized during the reaction (Table-1).

Table 1: Effective the various catalysts for the titled derivatives.

Entry	Various catalyst	Time (hrs)	Yield (%)
1	AgI	7	54
2	CuI_2	7	60
3	CAN	7	75
4	TiO_2	7	94

During the reaction, the different amount of catalyst was applied completion of the reaction, initially 0.1 mmol 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 $TiO_2$was used in these reaction better results was obtained compared to same amount of other catalyzed as shown table-2.

Table 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	34
3	2.0	05	94
4	5	08	94

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 ethanol 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-3.

Table 3: The effect of solvents for titled derivatives at reflux (4b).

Entry	Various Solvent	Time (hrs)	Yield (%)
1	Ethanol	05	94
2	MeOH	05	61
3	Acetonitrile	05	71
4	DMF	05	68

CHARACTERIZATION

The structure of the titled analogous was performed by the evidence of spectral analysis such as, ^{1}HNMR, ^{13}CNMR, LCMS and elemental analysis. 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.

4. BIOLOGICAL ACTIVITY

The results of the above table-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.

Table 4: Antimicrobial activity screening activity synthesized scaffold (4a-4i).

Entry	Bacteria			
	S.aureus	**E.coli**	**S. typhi**	**B.substills**
4a	08	06	08	07
4b	21	20	19	19
4c	17	19	21	22
4d	20	17	19	18

4e	22	21	20	22
4f	24	23	23	20
Streptomycin	27	27	25	25
Fluconazole	NA	NA	NA	NA
DMSO	---	----	---	---

5. 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 TiO_2 as Lews acid catalyst reaction proceeded smoothly in an 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 antibacterial activity of the titled derivatives was studied. The derivatives having electron withdrawing groups exhibited excellent active potential.

6. AKOWNLDEMENT

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