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RESEARCH ARTICLE

RAPID AND AN EFFICIENT ONE-POT THREE-COMPONENT SYNTHESIS OF ISOXAZOLES PROMOTED BY CAS

Dr. K. Prathap[1], Dr. Sirisha D.V.L[2]., Durgarao B.V.[3], Dr. Krishnarao N.[2] and Dr. Shaik Lakhman[4]

1. Department of Chemistry, Government Degree College, Dornala, A.P, India, 523331.
2. Department of Chemistry, PRISM PG & amp; DG College (Affiliated to Andhra University), Visakhapatnam, India, 530016.
3. Department of DFS (Chemistry), ONGC, RJY, AP, India, 533105.
4. GSS, GITM (Deemed to be University), Visakhapatnam, India.

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Abstract

A straightforward, practical, and economical process for producing isoxazole derivatives is described. It makes use of ethylacetoacetate, hydroxylamine hydrochloride, and substituted aromatic aldehydes with promoted camphor sulfonic acid as a catalyst in a solvent. No toxic organic solvents are used in the current procedure. Shortest reaction time, high product yields, easy work-up process, and non-chromatographic product purification are only a few of this catalyst's encouraging reaction response characteristics. The derivatives of desired compounds were analyzed advanced spectroscopic data by ^{1}H NMR, ^{13}CNMR and mass spectrometry was used to verify the products' structures. Products were chosen, and their antibacterial activity was examined.

Introduction:-

The ability of heterocyclic compounds to bridge the gap between the chemical and biological sciences has garnered a great deal of interest. These moiety are the subject of much modern research being conducted globally at the moment. According to a review of the literature, the various groups can be substituted on the isoxazole ring to provide distinct activities. There are several commercially available medications containing the isoxazole nucleus fall into various groups and have a variety of therapeutic effects, which has led to the creation of different methods for synthesizing this important partThe field of medicinal and organic chemistry relies heavily on N-containing heterocyclic compounds, a significant class of heterocyclic compounds with a wide range of uses in the search for novel pharmacologically active molecules.

In particular, isoxazole are five-membered heterocycles with an N, O content that are widely found in a wide range of natural products and pharmaceuticals with relevant pharmacological and medical applications. The broad range of bioactivities of synthetic pathways always piques the curiosity of scientists and researchers. In this approach, it has been shown that one pot synthesis provides a practical and eco-friendly strategy to produce these bioactive heterocycles. This approach has a well-established impact on drug discovery, catalysis, combinatorial chemistry, and pharmaceuticals. The production of multicomponent reactions that yield oxazoles and isoxazoles has increased dramatically during the past few decades.

Corresponding Author:- Dr. Shaik Lakhman
Address:- GSS, GITM (Deemed to be University), Visakhapatnam, India.

There are numerous ways to prepare this class of chemicals in the literature. The most popular technique for creating isoxazoles is to use different catalysts in one-pot multicomponent reactions (MCRs) involving aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride subjected to an organic acid in polar solvent . It has been found that MCRs are an effective synthetic tool for the synthesis of a variety of naturally occurring chemicals and physiologically active substances. MCRs have proven to be significantly more advantageous than traditional synthetic techniques. Good yields, great atom economy, cheap costs, shortened reaction times, reduced waste, energy, and labor, ease of operation, and avoidance of time-consuming purification procedures are all guaranteed by this. Important components of the perfect green synthesis are MCR, the utilization of non-conventional energy sources like ultrasonic irradiation, and green solvents like water.

One significant class of nitrogen- and oxygen-containing heterocycles having a variety of uses in organic chemistry, medicinal chemistry, and the pharmaceutical sector is isoxazole and its derivatives.2, 3 Isoxazole derivatives are widely recognized for their extensive biological and pharmacological properties[1-4],including their Antibacterial [5], anti-inflammatory [6], DGAT1 inhibitors [7],anti-ulcer [8], anticancer [9],antioxidant [10],Antihypertensive [11], antitubercular [12], antimalarial [13] etc.The numerous catalysts were applied for the synthesis of isoxazoles and their derivatives such as catalysts, Dowex1-x8OH[14], Pyruvic acid[15], Fruit juice[16], Citric Acid[17]..

Many of these protocols have limitations and drawbacks, though, like highly basic or acidic conditions, low yields, lengthy reaction times, and the use of toxic reagents, harsh reaction conditions, costly catalysts, and laborious workup procedures that limit their applicability in real-world scenarios. Furthermore, due of its low cost, abundance, ease of handling, high stability, non-flammability, compatibility with the environment, and lack of toxicity, water is the best green solvent for organic reactions when compared to other frequently used organic solvents. Taking into account the aforementioned considerations, new and environmentally friendly techniques that circumvent harsh reaction conditions and provide an effective pathway for the synthesis of isoxazole derivatives are still required to meet the growing needs of contemporary synthetic chemistry.

Camphor Sulphonic acid is a highly effective catalyst for the production of titled moiety as we have recently reported. Our evaluation of this acids catalytic potential in the synthesis of isoxazol-5(4H)-one derivative was prompted by this discovery. In order to investigate CSA catalytic utility, we report here the synthesis of isoxazol-5(4H)-one derivative via the one-pot method, a three-component process catalyzed by organ acids under conventional method. Our literature survey revealed that there is no report on the use of camphor Sulphonic acid as a catalyst in the synthesis of isoxazol-5(4H)-one derivative.

Apart from this, the most important organ acids are camphor Sulphonic acid, which is essential to the metabolism of energy in living things. It functions as a strong antimicrobial activity, efficiently lowers cholesterol, enhances exercise endurance, and lessens the generation of free radicals and anoxic damage.

Methods and Materials:-

Experimental:

The firms Merck, Fluka, and Aldrich Chemical were bought out for chemicals. Unless otherwise indicated, all yields relate to isolated products. On a Bruker DRX-400 Avance at room temperature, ^{1}HNMR(400MHz) and ^{13}CNMR (100MHz) spectra were acquired using tetramethylsilanes as the internal standard and $CDCl_3$ as the solvent. Using a Shimadzu spectrometer, Fourier transforms of infrared (IR) spectra were produced as KBr discs. A Varion Saturn 2000 gas chromatograph–mass spectrometer was used to determine the mass spectra. Using a Perkin Elmer 2400 CHN elemental analyzer flowchart, elemental analyses were carried out.

General procedure for the synthesis of Titled derivatives under the conventional condition

The following materials were refluxed for the specified amount of time: substituted benzaldehyde (0.5 g, 4.71 mmol), hydroxylamine hydrochloride (0.327 g, 4.71 mmol), ethyl acetoacetate (0.613 g, 4.71 mmol), and camphor sulfonic acid catalyst (0.02 g, 0.023 mmol) in ethanol (15 mL). Ethyl acetate (2 X 10 mL) was used to extract the reaction mixture once it had reached room temperature following the conclusion of the reaction (TLC analysis). The crude product was obtained by drying the organic layer over anhydrous Na_2SO_4 and concentrating it under reduced pressure. The pure product was then obtained by column chromatography with ethyl acetate:n-hexane (40–60%) used as the eluent.

(Z)-4-benzylidene-3-methylisoxazol-5(4H)-one (4a):
Yellow solid; Yield-86%; M.p.: 185-187^{0}C; IR (KBr): 3482, 3054, 2327, 1735, 1626, 1452, 1355, 1227, 1128, 877, 766, 688, 577 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$)δppm: 8.384 (d, J = 7.6 Hz, 2H), 7.915 (s, 1H), 7.682- 7.636(m, 1H), 7.557 (t, J = 8.0 Hz, 2H), 2.419 (s, 3H) ppm; 13C NMR (100 MHz, $CDCl_3$)δppm : 169.34, 161.86, 153.87, 133.48, 134.87, 131.66, 129.27, 128.85, 128.45, 120.38, 12.78 ppm; LCMS (m/z) : calcd for $C_{11}H_{10}NO_2$ [M+H] 188.0687 found 188.0725.

(Z)-4-(4-hydroxybenzylidene)-3-methylisoxazol5 (4H)-one (4b):
Yellow solid; Yield-94%; M.p: 204-206^{0}C; IR (KBr): 3263, 3035, 1729, 1556, 1311, 1234, 1131, 984, 894, 771, 654 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$)δppm :10.234 (s, 1H), 8.287 (d, J = 9.2 Hz, 2H), 7.881 (s, 1H), 7.912 (d, J = 6.8 Hz, 2H), 2.286 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$)δppm : 169.04, 164.87, 161.17, 152.38, 136.84, 126.84, 117.89, 115.32, 12.07; LCMS (m/z) : calcd for C11H10NO3 [M+H] 204.0685 found 206.0641.

(Z)-3-methyl-4-(4-methylbenzylidene) isoxazol5 (4H)-one (4c):
Light yellow solid; Yield-89%; M.p.: 187-188^{0}C; IR (KBr): 3454, 3091, 2597, 1738, 1601, 1504, 1404, 1356, 1147, 874, 774, 586 cm-1 ; 1 H NMR (500 MHz, $CDCl_3$)δppm: 8.29 (d, J = 8.2 Hz, 2H), 7.39 (s, 1H), 7.33 (d, J = 8.1 Hz, 2H), 2.45 (s, 3H), 2.30 (s, 3H)δppm; ^{13}C NMR (100 MHz, $CDCl_3$)ppm: 167.87, 160.27, 148.08, 146.44, 134.28, 131.64, 128.87, 119.74, 23.47, 12.78; LCMS (m/z) : calcd for $C_{12}H_{12}NO_2$[M+H] 202.0867 found 202.0865.

(Z)-4-(2-hydroxybenzylidene)-3-methylisoxazol5 (4H)-one (4d):
Yellow solid; Yield-91%; M.p: 197-199^{0}C ; IR (KBr): 3190, 1954, 1751, 1605, 1457, 1268, 1092, 901, 774, 585 cm^{-1} ; 1H NMR (400 MHz, CDCl3)δppm: 10.258 (s, 1H), 8.574 (dd, J = 8.0, 1.6 Hz, 1H), 8.064 (s, 1H), 7.551-7.418 (m, 1H), 7.052 (d, J = 7.6 Hz, 1H), 6.984 (m, 1H), 2.310 (s, 3H) ppm; 13C NMR (100 MHz, $CDCl_3$)δppm: 168.22, 161.84, 159.02, 145.44, 136.74, 131.87, 119.56, 117.84, 115.84, 114.61, 12.06 ppm; LCMS (m/z) calcd for C11H10NO3[M+H] 204.0668 found 204.0657.

(Z)-4-(3,4-dimethoxybenzylidene)-3- methylisoxazol-5(4H)-one (4e):
Yellow solid; Yield-89%; M.p.: 204-206^{0}C; IR (KBr): 3447, 3084, 2887, 1730, 1512, 1246, 1165, 974, 856, 784, 624 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$)δppm: 8.546 (d, J = 6.4 Hz, 1H), 7.745 (dd, J = 8.4, 5.4 Hz,1H), 7.451 (s, 1H), 7.123 (d, J = 9.6 Hz, 1H), 3.124 (s, 3H), 2.949 (s, 3H), 2.354 (s, 3H) ;^{13}CNMR(100 MHz, $CDCl_3$)δppm :167.56, 160.64, 155.58, 150.65, 147.46, 130.02, 127.56, 117.28, 114.15, 111.27, 55.15, 51.25, 12.47; LCMS (m/z) : calcd for $C_{13}H_{14}NO_4$[M+2] 248.096 found 248.092.

(Z)-4-(4-methoxybenzylidene)-3-methylisoxazol5 (4H)-one (4f):
Yellow solid; Yield-91%; M.p.: 189-1910C; IR (KBr): 3424, 3056, 2904, 2359, 1729, 1519, 1438, 1271, 1189, 877, 787, 638 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$)δppm : 8.247 (d, J = 7.6 Hz, 2H), 7.478 (s, 1H), 7.082 (d, J = 9.2 Hz, 2H), 3.554 (s, 3H), 2.324 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$)δppm :166.47, 165.74, 160.78, 148.65, 137.18, 127.84, 116.65, 114.48, 56.74, 12.65 ; LCMS (m/z) : calcd for C12H12NO3[M+H] 218.0814 found 218.0812.

(Z)-4-(4-hydroxy-3-methoxybenzylidene)-3- methylisoxazol-5(4H)-one (4g):
Yellow solid; Yield-90%; M.p: 210-212^{0}C; IR (KBr): 3275, 3011, 2145, 1934, 1736, 1554, 1315, 1281, 1174, 1009, 881, 755, 560 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$)δppm: 10.544 (s, 1H), 8.407 (d, J = 2.4 Hz, 1H), 7.892 (dd, J = 8.6, 2.4 Hz, 1H), 7.840 (s, 1H), 6.894 (d, J = 8.0 Hz, 1H), 3.567 (s, 3H), 2.256 (s, 3H) ; 13C NMR (100 MHz, $CDCl_3$)δppm : 168.50, 161.78, 155.35, 151.38, 148.56, 132.44, 125.12, 118.14, 116.35, 114.18, 56.04, 11.24; LCMS (m/z) : calcd for $C_{12}H_{12}NO_4$[M+H] 234.0762 found 234.0760.

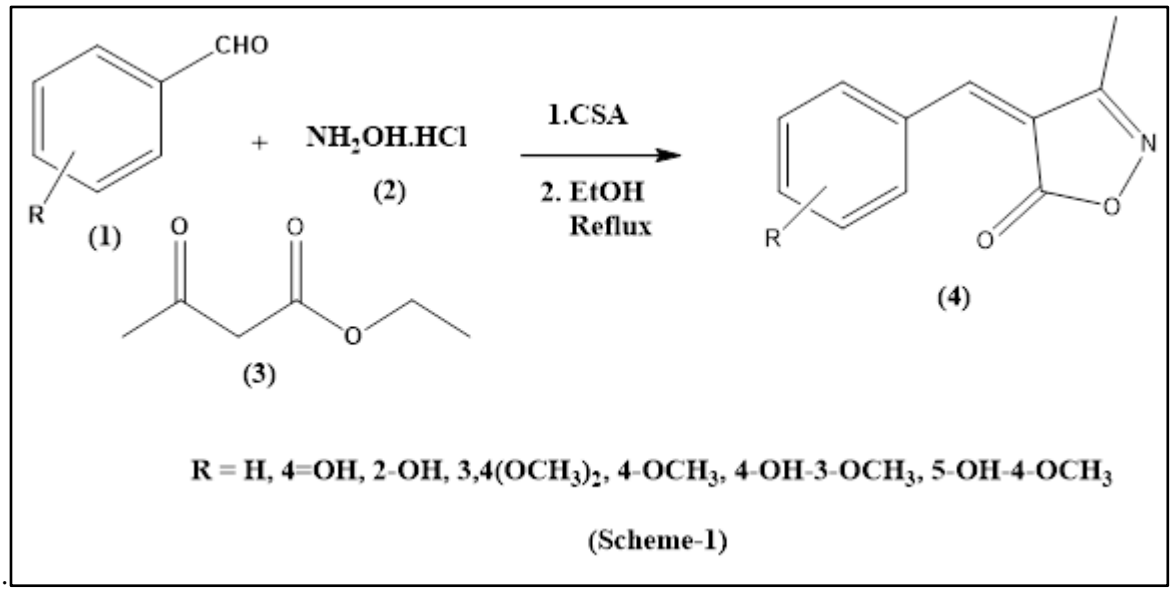
(Z)-4-(3-hydroxy-4-methoxybenzylidene)-3- methylisoxazol-5(4H)-one (4h):
Orange solid; Yield-92%; M.p.: 217-219^{0}C; IR (KBr): 3285, 3056, 2014, 1698, 1571, 1518, 1445, 1285, 1132, 1018, 874, 774, 584 cm^{-1} ; 1 H NMR (400 MHz, $CDCl_3$)δppm : 8.234 (dd, J = 8.0, 2.8 Hz, 1H), 8.024 (d, J = 2.4 Hz, 1H), 7.340 (s, 1H), 6.958 (d, J = 8.8 Hz, 1H), 5.287 (s, 1H), 3.784 (s, 3H), 2.258 (s, 3H) ;13C NMR (100 MHz, CDCl3)δppm : 166.47, 160.08, 150.84, 148.45, 144.75, 128.16, 127.28, 119.05, 117.45, 111.75, 56.25, 12.74; LCMS (m/z) : calcd for $C_{12}H_{12}NO_4$[M+H] 234.0762 found 234.0760

Results and Discussion:-

We first observed into the reaction of substituted benzaldehyde, ethylacetoacetate and hydroxylamine hydrochloride in the presence of camphor sulfonic acid (CAS) under different conditions in order to optimize the reaction

parameters. We also recognized that the good results were obtained (Scheme-1). On the other hand, when the catalyst was used less, the product's yield reduced. Only 28% of the comparable product was produced when the same reaction was carried out without the catalyst.

This outcome encouraged further investigation into a various substituted aldehydes under ideal circumstances, the outcomes of which are displayed in above characterization. It is also observed that several of aromatic aldehydes with substituents in Meta and para-positions that either electron withdraw orelectron releasing groups, them provide a high yield of the product. The ability of various functional groups to survive in these reaction circumstances is another crucial aspect of this process. In this case, we discovered that, in contrast to aldehydes with electron-donating groups, aromatic aldehydes with electron-withdrawing groups reacted more quick.



(Scheme-1)

These derivatives' reaction conditions were improved using several catalysts, catalyst amounts, and solvent compositions. In contrast to oxidative related catalysts like silica-supported sulphuric acid (SSA), methane-sulphonic acid (MSA), p-toluene-sulphonic acid (PTSA), camphor-Sulphonic acid (CSA), and trichlorosalicylic acid (TCSA), the maximum yield of the compounds was obtained in the presence of camphor-Sulphonic acid (CSA), catalyst (Table-I).

Table I:- The reaction of aryl aldehydes, Ethyl acetoacetate, and hydroxylamine hydrochloride effecton catalysis.

Entry	Catalyst	Time (hrs)	Yield (%)
1	SSA	9	52
2	MSA	6	71
3	PTSA	12	66
4	CSA	7	75
5	TCSA	4	94

The model reaction that was examined involved the use of various solvents, including DMF, acetonitrile, isopropanol, methanol, ethanol, and cyclohexane. With a 94% product yield, it was determined to be the most effective medium for the reaction. As a result, it was employed as the solvent for further reactions due to its greater yield, environmentally friendly nature, and simplicity of setup.

Table II:- The reaction of aryl aldehydes, Ethyl acetoacetate, and hydroxylamine hydrochloride: effect of solvent.

Entry	Catalyst	Time (hrs)	Yield (%)
1	DMF	4	42
2	IPA	4	94
3	CH_3CN	4	58

4	EtOH	4	51
5	MeOH	4	68

The yield of 4c was found to have significantly improved, reaching 94%. It took only 1.5 m mol% to advance the process in just 2.0 hours. The outcomes were not improved by using the maximal amounts of the catalyst. Table III illustrates how the yield unexpectedly dropped to 77% even though the reaction time may be shortened to one hour by using 2.0 mmol% camphorsulphonicacidacids.

Table III:- The various amounts of catalyst in IPA at reflux:

Entry	Amount catalyst(mmol)	Time (hrs)	Yield (%)
1	0.5	4	Traces
2	1.0	4	39
3	1.5	4	55
4	2.0	4	94
5	2.5	4	77

Biological Activity

The results of the above table-IV represented that the anti-bacterial activity of derivatives **(4b-4h)** 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 EDG groups present in the compound. We also observed the Antifungal Activity of compound (4a-4h) exhibited different activity compound 4g, 4h and 4i d showed good "4a" activity and rate of the compound showed poor activity.

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

Derivatives	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substills	A. niger	C. albicans
4a	09	05	11	08	06	07
4b	19	17	19	17	14	14
4c	20	15	18	18	15	17
4d	18	19	20	19	14	15
4e	22	21	22	23	14	15
4f	21	22	23	19	15	18
4g	14	15	15	14	08	07
4h	15	17	15	17	10	11
Streptomycin	27	27	25	25	NA	NA
Fluconazole	NA	NA	NA	NA	22	22
DMSO	---	----	---	---	---	---

Conclusions:-

With camphorsulphonic acid acting as an effective catalyst, we have created a novel, simple, and effective method for synthesizing substituted isoxazoles derivatives through a one-pot, three-component condensation of substituted aromatic aldehydes, ethylacetoacetate, and hydroxylamine hydrochloride in an isopropanol medium. This technique is appealing for the synthesis of a range of such derivatives due to the mildness of the conversion, the ease of the work-up procedure, compatibility with different functional groups, and the simplicity of the experiment

Akownldement:-

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