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An efficient Synthesis of an isoxazole-5(4H)-one's derivatives in presence of sodium hypophosphite as a catalyst using microwave irradiation

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Abstract: one-pot three-component reactant system contains ethyl acetoacetate, hydroxylamine hydrochloride with various aromatic aldehyde, gives isoxazole derivatives by using sodium hypophosphate as a catalyst using the microwave method. The reaction is carried out in ethanol as a solvent medium, under mild conditions gives a good yield in a very short period. The cyclo condensation reaction was carried out in ethanol during the product formation process. The catalyst uses in this reaction act as a non-toxic, easy setup process, short periods, and soluble in ethanol with easily removed by washing with water.

Key-words: aldehyde, microwave, sodium hypophosphite, isoxazole. etc

Introduction:

Isoxazole structure contains a five-member ring contained nitrogen and oxygen. The nitrogen as a heteroatom is more pronounced for electron-withdrawing, while the oxygen atom is more pronounced for the electron-donating effect. In multi-component reactions (MCRs) have been proven to be a very powerful tool for the synthesis of molecules in a one-pot reaction. With the help of MCRs reaction synthesis of biologically active compounds and the natural products due to their significant role such as high productivity, minimization of waste, atom economy, etc. large number of different products could be synthesized by this method.[1-3]

The isoxazole structure its derivatives have many pharmaceutical drugs attracting considerable interest in the field of medicinal chemistry, such as anti-inflammatory [4], antibacterial[5], anti-tuberculosis[6], antiviral[7], anticancer[8], etc. several methods have been reported for the synthesis of isoxazole and its derivatives. out of them, some of the isoxazoles areas in the presences of reagents and catalyst in a basic medium as well as an acidic medium such as Pyridine[9], Sodium silicate[10], Boric

acid [11], sodium benzoate [12], potassium phthalimide [13], citric acid [14], etc. moreover, some of the methods are carried out at high temperatures and long reaction time, under unconventional energies, such as ultrasound irradiation[15] or visible light [16].

The catalyst used in the present work is sodium hypophosphite (sodium salt of hypophosphorous acid) is a common, safe and one of the main advantages of sodium hypophosphite (SHP) as a catalyst was a clean reaction without any siding product. The catalyst sodium hypophosphite (SHP) Could be water-soluble and efficiently removed without any appreciable loss in the yield. This reagent has been used in several reactions such as etherification of treatment of cotton fabric with 3,3,4,4-benzophenone tetracarboxylic acid (BPTCA)[17]. Sodium hypophosphite is used for plating metals, plastics, and ceramics known as electroless plating [18]. In terms of acidity, it shows pKa=1.1 [19]. Sodium hypophosphite was considering a non -hazardous substances for both human and the environment

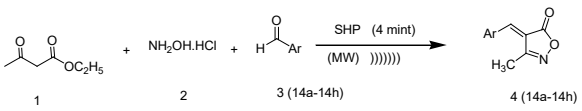
Although microwave irradiation is a safe source of heating, uncontrolled reaction conditions involving volatile reactants and/or solvents at high pressure may result in undesirable results. This problem has been addressed and organic syntheses have been made more sustainable processes through the use of an open-vessel solvent or solvent-free microwave conditions. Microwave irradiation produces efficient internal heating by direct coupling of microwave energy with the bulk reaction mixture. The magnitude of the energy transfer depends on the dielectric properties of the molecules. As a guide, compounds with high dielectric constants tend to absorb microwave energy whereas less polar substances and highly ordered crystalline materials are poor absorbers. In this way, absorption of the radiation and heating can be very selective [20].

The presence of solvents in reactions leads to a clean, efficient, and economical technology; safety is increased significantly, the work-up is simplified considerably, costs are reduced, larger amounts of reactants can be employed, the reactivity is enhanced and, in some cases, the selectivity is modified without dilution. In summary, the reaction gives with the high yields and short reaction times that are characteristic of microwave-assisted processes make these procedures very effective for sustainable synthesis [21].

In 1993, Loupy reported that potassium acetate can be alkylated in the absence of solvent in a domestic oven using equivalent amounts of salt and an alkylating agent in the presence of Aliquat 336 (10% mol). Yields are practically quantitative within 1–2 min regardless of the chain length, the nature of the halide leaving group, and the scale (up to 500 mmol) [22].

Serial no	SHP,mol %	Percent yield	Time in minutes
1	No catalyst	10	4
2	5	60	4
3	10	95	4
4	20	80	4

Reaction:-



Scheme 1 :- Synthesis of isoxazole derivatives in presence of sodium hypophosphite as a catalyst with ethanol as solvent using microwave irradiation.

Table 02 : Following Isoxazole Derivatives were Synthesized

SR NO	Entry	Compound No	Product	Melting point(mp)	Reported (mp)[23]	% Yield
1	14a	4-methoxy benzaldehyde	4-methoxybenzylidene-3-methylisoxazole-5(4*H*)-one	170-175	178-179 [23]	95
2	14b	2-hydroxybenzaldehyde	4-2-hydroxybenzylidene-3-methylisoxazole-5(4*H*)-one	195-200	198-202 [23]	85
3	14c	4-hydroxy-3-methoxybenzaldehyde	4-hydroxy-3-methoxylidene-3-methylisoxazole-5(4*H*)-one	215-220	212-214 [23]	95
4	14d	4-chloro benzaldehyde	4(4-chlorobenzylidene-3-methylisoxazole-5(4*H*)-one	----------	--------	trace
5	14e	benzaldehyde	4-(benzylidene)-3-methylisoxazole-5(4*H*)-one	140-142	142-144 [2]	85
6	14f	4-methyl benzaldehyde	4-methylbenzylidene-3-methylisoxazole-5(4*H*)-one	140-142	141-142 [2]	80
7	14g	di-methylamino benzaldehyde	4-di-methylaminobenzylidene-3-methylisoxazole-5(4*H*)-one	225-230	220-221 [24]	85
8	14h	3-nitro benzaldehyde	4-(3-nitrobenzylidene-3-methylisoxazole-5(4*H*)-one	----------	--------	-------

1. MATERIAL AND METHODS

All chemicals were purchases from Merck, SD Fine Mumbai were commercially available and were used as received without further purification. The melting point was measured by the open capillary method and was uncorrected. IR data were collected on Agilent Cary 630 FTIR (range 4000–450), ^{1}H NMR data were recorded on Bruker Avance Neo 500 MHz ^{1}H NMR DMSO-d6 MHz spectrometer. Mass spectra were recorded on Model Q-ToF micro water. All reactions were carried out in a microwave oven having a maximum output of 800 watts (W).

General Procedure for the Synthesis of isoxazole derivatives (14a-14h):

A dry 50 ml flask was charged with a mixture of ethyl acetoacetate 1.30 g (1 mol), hydroxylamine hydrochloride 0.7g, (1 mol), (2-hydroxybenzaldehyde) or salicylaldehyde

(1 mol) in presences of sodium hypophosphite (10 mol) which mix with 5 ml ethanol as a solvent which stirred at room temperature, after 5 minutes later it is placed in microwave irradiation chamber for 4 mints, after the completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, the formed solid was washed with cold distilled water. Then the crude product was recrystallized from ethanol or acetone to afford the pure products 4-(2-hydroxybenzylidene)-3-methylisoxazole-5(4H)-one (14b) m.p.198^{0}C, yield 75 %. All the products were confirmed by comparing their melting points, IR, ^{1}H NMR, ^{13}C NMR, CHNS analysis, and LCMS-Mass spectral data with literature data.

Entry:1-Structureof4-(4-methoxybenzylidene)-3-methylisoxazole-5(4H)-one (14a)
Yield- 95 %.,Melting point (^{0}C):180-185^{0}C,Color: yellow powder
^{1}HNMR(500MHz, DMSO-d_6) : δ8.53-8.51(d,), δ 7.86(s.ArCH), δ 7.16-7.14, δ 3.90(s,3H,OCH_3), δ 3.28 , δ 2.51, δ 2.26(3H,CH_3)
^{13}C NMR(125MHz, DMSO-d_6) : δ168.46(C=O), δ 164.11(C=N), δ162.11(Ar-O), δ 151.07(Ar-CH=)136.75(Ar), δ 125.66(Ar), δ 115.09 (Ar), δ 114.53(C=inside isoxazoles), δ 55.69(O-CH_3), δ 39.90, δ 38.89, δ 11.12(CH_3)
FTIR:-3454, 3095, 2973, 2831, 1741(C=O), 1621, 1433, 1311, 1180, 1024, 937, 864, 785. cm^{-1}
LC MS: MS(ESI):- 218.10 m/z, Elemental

analysis: $C_{12}H_{11}NO_3$,Calculated: C-66.62, H-05.51, N-6.96., Found: C-60.183, H-04.45, N-06.49,

Entry :-3 -Analytical date of 4-(2-hydroxybenzylidene)-3-methylisoxazole-5(4H)-one(14b)
Yield: 95 %., Melting point (^{0}C):198-200^{0}C, Color : yellow powder
^{1}HNMR(500MHz, DMSO-d_6) :δ10.99-10.20, δ 8.76-8.74, δ 8.10-8.08, δ 7.57-7.02, δ 6.99-6.10, δ 5.98, δ 4.99, δ 2.51, δ 2.34, δ 1.59.
^{13}C NMR(125MHz, DMSO-d_6) :δ168.18(C=O), δ162.00(C=N), δ159.59 (ArCH=), δ 144.84 (Ar) δ136.60(Ar), δ132.25 (Ar), δ119.44 (Ar), δ118.99 (C=inside of isoxazole), δ116.33, δ116.07 (Ar), δ39.76, δ11.09 (CH_3)
FTIR (cm^{-1}):- 3790 (O-H), 3468(N-H), 1772(C=O), 1625((C=C), 1477, 1288, 1033, 796(C-Cl)
LC MS: MS(ESI);- 204.09 m/z, Elemental analysis: $C_{11}H_9NO_3$, Found: C-60.10, H-04.43, N-06.90, Calculated: C-65.02, H-04.46, N-6.89.,

2. RESULTS AND DISCUSSION

The results obtained are presented in (table 02) .high yields were obtained by using the microwave irradiation method at 4 minutes with utilizing ethanol as a cheap solvent. The scheme carried out the model reaction with different amounts of the catalyst (Table 01) and found that 10 mol % of the catalyst is good enough; further increasing the amount of catalyst does not affect the yield. One of the main advantages of sodium hypophosphite (SHP) as a catalyst was a clean reaction without any siding product. The catalyst sodium hypophosphite (SHP) could be water-soluble and efficiently removed without any appreciable loss in the yield. Hence 10 mol % catalyst in ethanol is enough to push the reaction forward.

The efficacy of this protocol was evaluated using no of aldehyde a series of compounds were synthesized with the simple procedure. The nature and position of functional groups on phenyl rings have affected the yields of the product and reaction time. The results indicated that aromatic aldehydes bearing electron-donating groups (such as CH_3,-OCH_3,-OH, etc) give high yields. It is also found that the steric hindrance of the hydroxyl group in 2-hydroxybenzaldehyde (14b) gives a slightly lower yield and longer reaction time. Aromatic

aldehydes containing electron-withdrawing functional groups (such as chlorine or nitro) were ineffective and failed to convert to the target product (14d, 14h). The reaction is carried out in two steps; firstly in presence of catalyst ethyl acetoacetate reacts with hydroxylamine hydrochloride to afford ethyl 3-hydroxyimino. In the second step, Knoevenagel reactions give intramolecular cyclization, obtained 4-arylmethylene-3 methyl-isoxazole-5(4H)-ones.

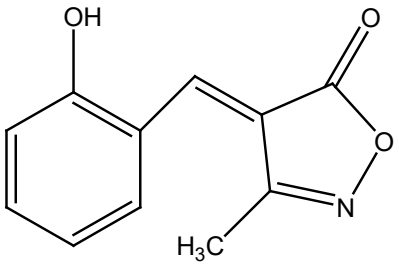


Fig 1: Structure of 4-(2-hydroxybenzylidene)-3-methylisoxazole-5(4H)-one (14b)

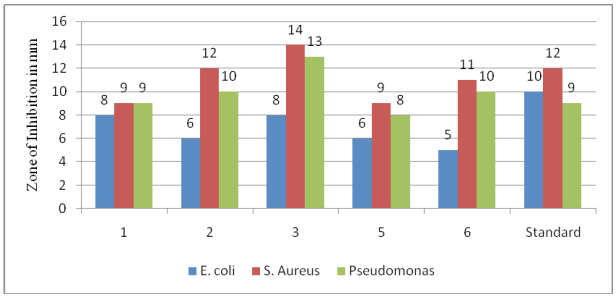
The structure of 4-2-hydroxybenzylidene-3methylisoxazole-5(4H)-one was determined from the physical data and supporting spectral data. The ^{1}HNMR spectrum of the above compound (14b) showed singlet peaks at δ2.34 ppm for a methyl group, and double for C=C bond at δ 8.53 ppm. Aromatic protons of (14c) resonate at δ8.76 ppm and multiples at δ7.57-7.23 ppm. ^{13}CNMR spectrum of compound (14c) showed characteristic signals at 159.59 ppm for C=CH-Ar, 162.00 ppm for C=N, and 168.18 ppm for C=O of the isoxazole ring. IR spectrum shows absorption 3790(OH), 3468 (NH), 1772 (C=O), 1625(C=C), 1288, cm^{-1}. The mass spectra show an intense peak at 204.09 (M+) confirms the formation of 4-(2-hydroxybenzylidene)-3-methylisoxazole-5(4H)-one (14b). Similarly, all other synthesized compound was identified b melting point and comparison with the reported melting point.

In vitro antibacterial activity of the synthesized compounds (14a-14h) has been screened against bacterial species Escherichia coli, Pseudomonas aeruginosa (gram-negative), and Staphylococcus aureus (gram-positive) using rifampicin as standard. The disk diffusion process was used for antibacterial activity on nutrient agar plates. The observation was recorded at 37 C^{0} for 24 h, after a specific time interval with measuring zone of inhibition was measured in mm. from the table it is clear that synthesized compounds show good antibacterial activity

Table 3: zone of Inhibition in mm of Synthesized Isoxazole Derivatives

Compound	E. coli	S. Aureus	Pseudomonas
1	08	09	09
2	06	12	10
3	08	14	13
5	06	09	08
6	05	11	10
Standard	10	12	09

Fig 2: Graphical Zone of Inhibition in mm of Synthesized Isoxazole Derivatives



Compound 2, 3, 6 shows excellent biological activity against to S. aureus and Pseudomonas while another compound 1, 2,3 shows moderate activity aginst to E.coli and pseudomonas

3. CONCLUSIONS

In the present work, the synthesis of isoxazole and its derivatives carried out in a short reaction time gives a high yield. We have used a convenient catalyst that is inexpensive, easily handle, and soluble in ethanol for the synthesis of isoxazole. The microwave technique is really

helpful over the conventional technique.

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5. Conflict of Interest

The authors declare no conflict of interest in the present work.

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