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"An Efficient Synthesis Of Substituted Isoxazole Derivatives Using Ultra Sound Sonication Method"

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Abstract: A series of synthesis of some substituted isoxazole derivatives using efficient ultra sound sonication method in methanol solvent. Firstly the synthesis of different substituted chalcones using substituted aldehydes and substituted acetophenones using triethylamine as base in ethanol solvent under sonication. In second step synthesized substituted chalcones is reacted with two equivalents of hydrochloride salt of ammonium hydroxide, sodium oxalate and methanol under sonication at 30-35^{O}C to afford a substituted isoxazole derivatives in 90-98% of yields. The structures of the synthesized compounds were confirmed on the basis of NMR, and MS analysis. This method has a several advantages over current reaction methodologies, such as shorter reaction times, simple work-up procedure and good percent yields.

Keywords: isoxazole, chalcones, ammonium hydroxide, sodium oxalate, methanol, sonication.

1. INTRODUCTION

Generally the nitrogen, oxygen and sulphur containing heterocyclic scaffolds are immense important in the designing of bioactive molecules[1]. One of the cyclic five member nitrogen and oxygen containing compound is isoxazole. Isoxazole and its derivatives generally possess various biological activities due to its unique chemical and structural properties, they are also playing important role as building blocks for the synthesis of natural products as well as therapeutic agents[2,3,4].

The different substituted isoxazoles derivatives are also attract a growing attention of chemist, due to the high biological activity exhibited by specimens of these compounds[5]. The isoxazole heterocycle is a fragment of molecules of quite a number of pharmaceuticals, e.g., of leflunomid, isocarboxazid, valdecoxib, edonentan, sulfamethoxazole, sulfisoxazole[6,7,8] and lot of others. Along with these isoxazole derivatives are also kinase inhibitors and antitumor agents were reported[9,10,11,12]. Literature survey recently found that the synthesis of substituted isoxazolylureas, and they were found to increase the cytotoxicity of antitumor pharmaceuticals cis platin and carboplatin thus permitting the reduction of the therapeutic dose of these very toxic substances [13]. The complex forming properties of substituted isoxazoles and its biological activity are considerably determined by the functional groups of the heterocycles[14],[15].

A lot of general synthetic methods are also reported for the synthesis of isoxazole derivatives[16]. However, some of these methods suffer from several disadvantages such as multisteps, harsh reaction conditions, long reaction times and large amount of promoters. Therefore, the development of new synthetic approaches using mild reaction conditions remains an active research area. In order to synthesize isoxazole ring systems, various synthetic methods have been reported[17,18].

Nowadays sonochemistry is attracting research activity within the synthetic chemistry, due to it is new approach to the preparation of organic compounds. In the past two decades, sonochemical methods have become widely used in organic synthesis[19,20,21]. Ultrasonic irradiation technique has been employed, not only to improve yields, but also decrease reaction times in a large variety of different heterocycles. As comparing with traditional or conventional methods, this method is easily controllable and more convenient for synthesis. A large number of organic reactions can be carried out within a shorter reaction time, higher yield and milder conditions under ultrasound are also reported[22, 23, 24, 25].

The aim of our present work based on the importance of isoxazole derivatives, consisted in the preparation of substituted isoxazoles derivatives using new synthetic routes continuation of our efforts to develop new synthetic routes of biological active heterocycles[26,27,28,29,30,31].

Experimental

2. MATERIAL AND METHODS

All the chemicals and required raw materials are purchased from commercial suppliers and used without further purification or as it is received. Melting points were determined using a Thermo Scientific Fluke 51 II, model IA 9100 melting point apparatus and reported uncorrected. ^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were recorded at room temperature on a Bruker Ultra Shield 500 using tetramethylsilane (TMS) as the internal standard and deuterated chloroform ($CDCl_3$) as the solvent. EI-MS were run on a Shimadzu GC-MS 2010 spectrometer, which was operating at 70 eV in positive mode. The ultrasonic irradiation was performed by using a Branson ultrasonic cleaner bath, model 1510, AC input 115 V, output 50 W, with capacity of 1.9 liters having a mechanical timer (60 min with continuous hold) and heater switch, 47 KHz.

*General Procedure for the Synthesis of substituted chalcones (**3a-j**):*

The equimolar amount of substituted benzaldehydes **1** (0.5mmol) and different substituted acetophenones **2** (0.5mmol) were taken in two neck 100ml RBF. Then 50ml of ethanol were added under the sonication of reaction mass after well stirring dropwise addition of triethylamine (0.8mmol) were stated and completed in 2 minutes at room temperature. After the formation of solid precipitates TLC was checked using mobile phase n-hexane: ethyl acetate, 8:2 ratios. After the completion of reaction (6-10 minutes) observed by TLC sonication is stopped. The obtained precipitates was poured on ice cold water, stirred well, solid form were filtered, washed with ice cold water and recrystallized from 50% ethanol to give the corresponding chalcones **3a-j** in purest form.

*General Procedure for the Synthesis of isoxazole derivatives (**4a-j**):*

A solution of substituted chalcones **3a-j** (0.05mmol) and methanol 10ml were taken in 50ml 2 necks RBF and well sonicate. After that sodium oxalate (0.01mmol) and hydrochloride salt of ammonium hydroxide (0.1mmol) were added in reaction mass. Then the reaction mass were sonicated for the completion of reaction (5-8 minutes) at 30-35^{O}C temperature. The progress of reaction were monitored by using a TLC (using mobile phase n-hexane: ethyl acetate, 8:2 ratios), after completion observed by TLC to stop the sonication

and reaction mass taken for the final work up. The reaction mixture was then treated with cold methanol and filtered to leave a solid product, which was crystallized from a hexane/methanol mixture to yield pure product **4a-j**. Some of the products were characterized by their physical and spectral data such as MS, ^{1}H NMR, ^{13}C NMR analysis.

*3-(4-Methoxy-phenyl)-5-p-tolyl-isoxazole (**4a**):*
Mass: m/z 266.2 [M+H^{+}]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, 1H), 7.37-7.33 (m, 3H), 7.17 (d, 2H), 6.80 (d, 2H), 6.69 (d, 1H), 3.75 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 157.0, 148.7, 138.1, 130.9, 128.1, 128.0, 127.9, 127.4, 113.9, 113.1, 54.3, 20.3. IR; 3307, 2920, 1605, 1514, 1406, 1268.
*3,5-Bis-(4-methoxy-phenyl)-isoxazole (**4b**):*
Mass: m/z 282.2 [M+H+]. 1H NMR (500 MHz, CDCl3) δ 7.53 (d, 1H), 7.47 – 7.43 (m, 3H), 6.96 (d, 2H), 6.88 (d, 2H), 6.76 (d, 1H), 3.86 (s, 3H), 3.83 (s, 3H). 13C NMR (126 MHz, CDCl3) δ 160.4, 160.3, 157.9, 139.1, 130.5, 128.9, 127.3, 115.1, 114.1, 113.8, 55.3. IR; 3307, 2920, 1605, 1514, 1406, 1268.

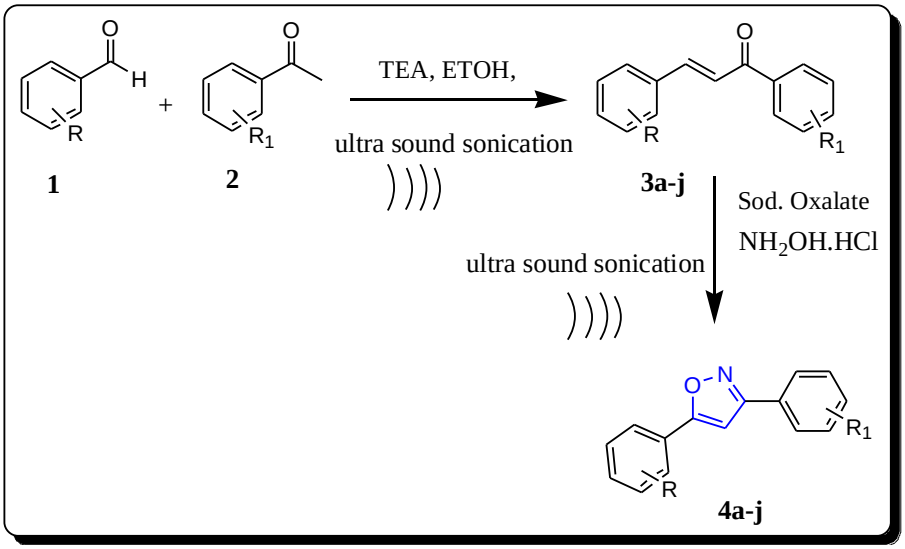
3. RESULTS AND DISCUSSION

In the present study to obtain functionalized heterocycles through the development of ultra sound sonication irradiation synthetic strategies. The syntheses were carried out using a starting compounds substituted benzaldehydes **1** and substituted acetophenones **2**. Initially the condensation of substituted aldehydes and ketones using triethyl amine as base in ethanol solvent to gives substituted chalcones **3a-j.** As a part of our ongoing synthesis on the isoxazole and application of ultrasonic irradiation as a useful and clean technique in organic synthesis, we were synthesized chalcone derivatives in under ultrasound irradiation method (scheme 1).

Secondly, we were examined the cyclocondensation reaction between substituted chalcone derivatives **3a-j** and hydrochloride salt of ammonium hydroxide in presence of catalytic amount of sodium oxalate under a methanol solvent to afford substituted isoxazole derivatives **4a-j** under sonication method (scheme 1).

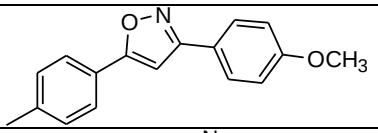
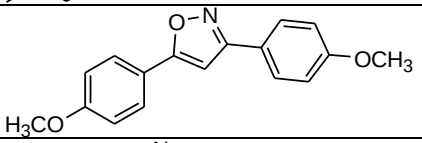
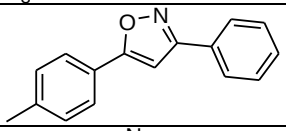
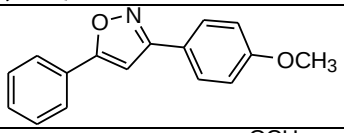
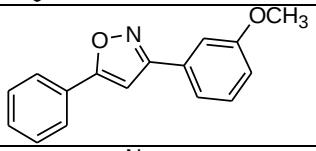
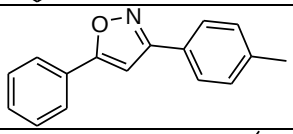
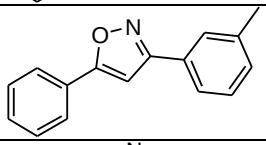
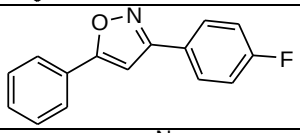
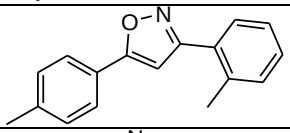
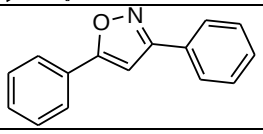
The present reaction were worked best under sonication conditions in methanol solvent at ambient temperature (30-35°C) to provide good yield of the synthesized isoxazole derivatives (90–98%) in a short time, and the results are summarized in Table 1.

Scheme - 1. Synthesis of substituted isoxazole derivatives **(4a-j)**



To the best of our knowledge, this synthetic methodology provides first example of ultrasound-promoted approach for the synthesis of this type of substituted isoxazole derivatives. The structures of the two synthesized compounds were established by their NMR and MS analysis remaining compounds were confirmed by the melting point reported in the literature data.

Table – 1. Physical parameters of the synthesized isoxazole.

Entry	Product	Time (min.)	% yield[a]	M.P. ^{O}C[b]
4a		6	92	
4b		8	90	176-177
4c		8	96	75-77 (76-78)[30]
4d		9	90	120-121 (118-120)[30]
4e		8	95	77-80 (76-78)[30]
4f		10	93	134-135 (134-136)[30]
4g		10	90	105-107 (106-108)[30]
4h		7	98	75-76 (74-76)[30]
4i		6	90	60-61 (59-61)[30]
4j		8	91	141-142 (140-142)[30]

[a] = Isolated yield.

[b] = under bracketed melting points are reported.[32]

The ^{1}H NMR spectrum for compound **4a** in deuterated chloroform solvent showed proton signals of the isoxazole moiety as an ABX-type spin system, and the proton signals were observed as δ 7.47 doublet for one hydrogen, δ 7.37-7.33 multiplates for three hydrogen, δ 7.17 doublet for two hydrogen, δ 6.80 doublet for two hydrogen, δ 6.69 doublet for one hydrogen, δ 3.75 singlet for three hydrogen and δ 2.34 singlet for three hydrogen. ^{13}C

NMR also confirms the formation of particular compound. Positive mode mass spectra are also supports the formation of **4a** i.e. m/z 266.2.

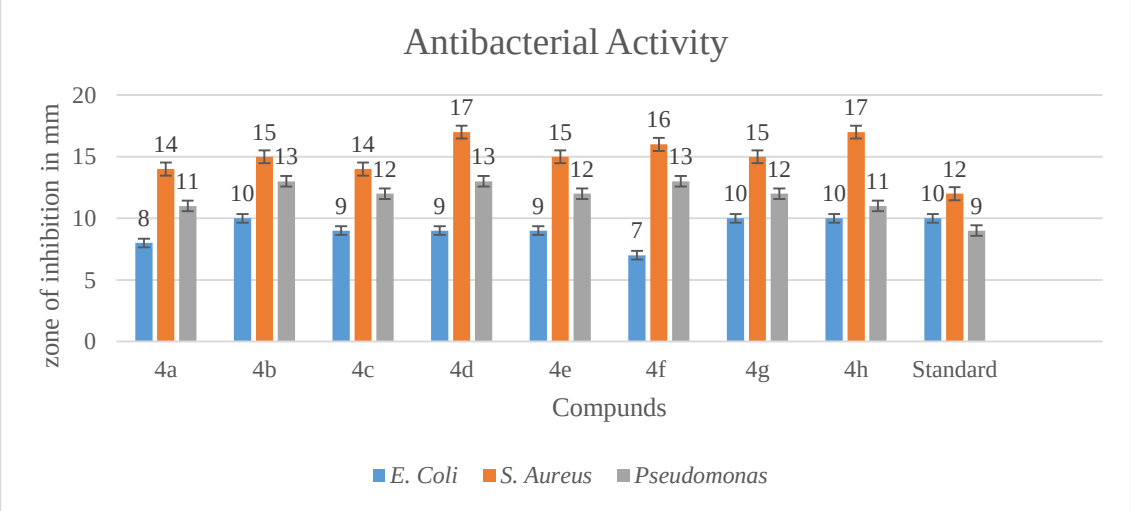
Antibacterial activity

The synthesized compounds (4a-j) were assessed for antibacterial activity using different micro-organisms like *E. Coli*, *S. Aureus* and *Pseudomonas Aerogenosa*. Disc diffusion method was used for antibacterial activity on nutrient agar plates. Briefly, agar (pH = 7.2–7.4; Mueller-Hinton) was placed into Petri dish (100 mm size and 4 mm depth). Discs containing known amounts of an antimicrobial agent were placed on the surface of an agar plate that has been inoculated with a standardized suspension of microorganisms to be tested. The MZI for rifampicin (antibacterial) was used as reference values (in millimeters) as given in Table-1.

Table-1: Antimicrobial activity of synthesized derivative

Compound no	*E. Coli*	*S. Aureus*	*Pseudomonas*
4a	8	14	11
4b	10	15	13
4c	9	14	12
4d	9	17	13
4e	9	15	12
4f	7	16	13
4g	10	15	12
4h	10	17	11
Standard	10	12	9

Figure -1: Antimicrobial activity of synthesized derivative



4. RESULTS OF ANTIMICROBIAL ACTIVITY

All the compounds shoed good antibacterial activity and the results are comparable with standard. Compound 4d and 4h were most active.

5. CONCLUSIONS

Ultrasound promoted reaction of a substituted chalcones with hydrochloride salt of ammonium hydroxide and catalytic amount of sodium oxalates afforded the corresponding substituted isoxazole derivatives in good yields and short reaction times at ambient conditions such as simple, facile and efficient fashion. Due to the broad spectrum of biological activities of isoxazole derivatives present synthetic protocol having immense importance.

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

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