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TULSION®-8052 MP RESIN FOR THE SYNTHESIS OF ISOXAZOL-5 (4H)-ONE DERIVATIVES

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Abstract:

In the current investigation, multicomponent reactions (MCRs) were used to condense a variety of substituted aromatic and heteroaromatic aldehydes with hydroxylamine hydrochloride, and ethyl acetoacetate to provide 3-methyl-4-(hetero)aryl methylene isoxazole-5(4H)-ones derivatives. Under ultrawave sonication, a Tulsion®-8052 MP resin accelerated the process at 45°C. The method outlined has the advantages of being safe, environmentally friendly, and economical because it produces isoxazole derivatives with a yield of 90-96% while removing the need for dangerous solvents.

Key Words: Tulsion®-8052 MP Resin, Isoxazol-5 (4H)-One Derivatives, Ultrawave Sonication

Introduction:

In the realm of organic synthesis, the development of efficient and sustainable methodologies using solid acidic catalysts of paramount importance due to their cleanness, economical and hazardless nature [1-2]. The use of heterogeneous catalysts has gained significant attention due to their selective nature, recyclability, and eco-friendly attributes [3-5]. In such era resins attracted researchers more and more now a days for organic transformation due to their unique abilities [6-9].

In which, sulfonic functional group resins are so desired because of their versatility; the resins may be tailored to a given reaction [10]. They work in a wide range of industries, such as plastics, petrochemicals, and pharmaceuticals [11-13]. Tulsion-8052 MP resin catalyst has catalyzed the superior and most effective protocol of a solvent-free synthesis for biologically active isoxazol-5 (4H)-one derivatives.

Isoxazole scaffolds are standing on the top in heterocyclic chemistry as most important pharmacophores and synthons which have played a pivotal role with a solid background [14].This family of compounds has been an integral class in pharmaceuticals where they are most commonly used as antimicrobial, antitubercular, anticancer, anti-HIV and nonsteroidal antiandrogen agents [15].Isoxazole moiety containing common drugs are Oxacillin for obtaining permission to use commercial anti-bacterial drugs [16], Valdecoxib is a non-steroidal anti-inflammatory drug [17], Zonisamide is an anti-convulsant [18], Leflunomide is used to manage rheumatoid arthritis[19].

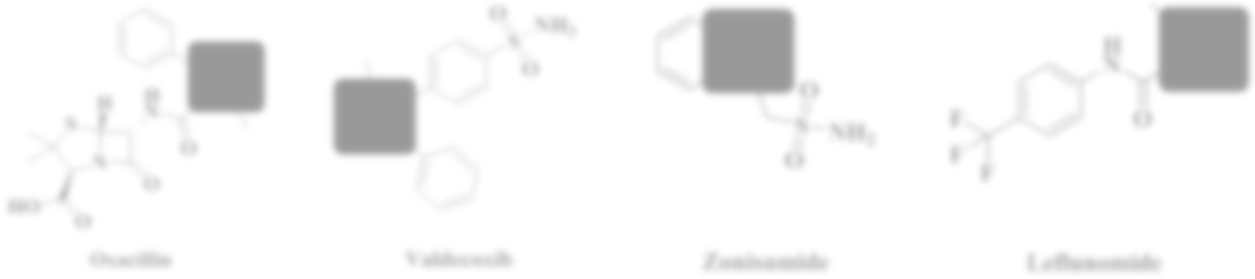

Figure 1: Biological active drugs containing isoxazole moieties.

Due to focus gaining biological activities and great contribution in medicinal chemistry isoxazole moiety are precious and make researchers to develop better and suitable methods for its synthesis.

Previously, enormous methods have been developed for Isoxazol-5 (4H)-one derivatives using acidic catalysts [20-23], ionic liquids [24-25], nano-particles [26-30]. Despite the fact that each of the aforementioned catalytic techniques has advantages of its own, the most of them have drawbacks, such as the need for costly catalysts, issues with the environment, and the creation of unwanted waste, protracted reaction times, difficult reaction circumstances, and low produce product segregation [31].Therefore, there is a great requirement to discover a different pathway for the synthesis of isoxazol-5(4H)-ones derivatives using clean method.

Henceforth, we introducing first time synthesis using Tulsion®-8052 MP resin and ultrasonication. The advantages of the proposed method include its high level of cleanliness, cost-effectiveness, environmental sustainability, and excellent atom efficiency.

Experimental Method:

Materials:

Without being refined, all of the reagents were bought from commercial vendors. Tulsion®-8052 MP resin acquired from Thermax Ltd. Melting points are uncorrected and were measured in open capillaries, thin layer chromatography of preparation glass covered with 20 x 20-inch Silica Gel 60F254 from the German manufacturer Merck. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$/DMSO-d6 solution on a Bruker spectrophotometer at 400 MHz. Using a Water-Micro mass Quattro-II spectrometer, electron spray ionization mass spectra (ES-MS) were captured.

Synthesis of substituted isoxazol-5(4H)-one derivatives:

Amixture of aromatic aldehyde 1 (1 mmol), ethyl acetoacetate 2 (1 mmol), hydroxylamine hydrochloride 3 (1 mmol), and Tulsion®-8052 MP resin (10 mol%) taken in a Borosil beaker and use glass rod for mixing manually in sonication bath. Irradiate reaction mass at 45°C temperature. After completion of reaction as monitored by TLC, the reaction mixture was crystallized using ethanol, filtered to get undissolved resin catalyst and clear filtrate. Obtained filtrates were cool gradually to room temperature then cool to 10°C to get precipitation of product. Obtained products were filtered and subsequently product was washed with cold ethanol to obtain pure products. All the prepared compounds were analyzed by physical and spectral data which was found to be in agreement with that of already reported data.

4-(4-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one (4b):

^{1}H NMR (400 MHz, DMSO-d6): δ 2.26 (s, 3H, CH_3), 6.95-6.98 (d, 2H, Ar-H), 7.80 (s, 1H, H-vinyl), 8.45-8.48 (d, 2H, Ar-H), 11.05 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d6): δ 11.76, 114.34, 116.63, 125.05, 138.00, 199.51, 162.74, 164.33, 169.30, ES-MS m/z 204.2(M^+).

3-methyl-4-(thiophen-2-ylmethylene)isoxazol-5(4H)-one (4i):

^{1}H NMR (400 MHz, CDCl3): δ 2.29 (s, 3H, CH_3), 7.39-7.42 (m, 1H, Ar-H), 8.24 (d, 1H, Ar-H), 8.27 (s, 1H, H-vinyl), 8.34 (d, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.58, 113.5, 129.5, 136.7, 141.6, 142.1, 143.5, 162.1, 169.0.ES-MS m/z 194.2 (M^+).

Result and Discussion:

As we continue to be interested in environmentally friendly processes, we are constantly looking for better alternatives to our established biological active compound approaches [31]. Prior to beginning the synthesis of isoxazol-5(4H)-one derivatives, take into account the catalysts' documented uses and mechanism of action. Taking into account the mechanism, it was discovered that the acidic catalyst is essential to the reaction's advancement. For the purpose of reaction optimization and derivative preparation, Tulsion®-8052 MP resin is selected (Scheme-1). The main scheme depicts the condensation reaction of several aldehydes, hydroxyl amine hydrochloride, and ethyl acetoacetate in the presence of resin catalyst using ultrasonication as an inert energy source.

Scheme 1: General synthetic route of substituted 3-methyl-4-(hetero)-arylmethylene isoxazole-5(4H)-one

An important development in organic synthesis is the solvent-free synthesis of isoxazole-5(4H)-one derivatives, which was catalyzed by a Tulsion®-8052 MP. It is an effective instrument for the productive synthesis of biologically active chemicals due to its selective, recyclable, and environmentally friendly qualities. Researchers in the field of organic chemistry are laying the groundwork for novel and sustainable approaches by utilizing solvent-free methodologies and heterogeneous catalysts. The resin catalyst Tulsion®-8052 MP is light brown in color and granular in form. This copolymer of polystyrene has a sulphonic acid group as its fundamental functional group. The catalyst is quite stable between 0-80°C. A catalyst's wide pore structure and high exchange capacity (1.95 meg/ml.min) are its key characteristics.

In order to synthesize isoxazol-5 (4H)-one, the performance of several resin catalysts was initially examined in this study. Here, a solvent-free reaction was carried out using ultrasonication at 45 degrees Celsius ambient temperature. All collected information was compiled below in Table 1.

Table 1: Comparison data of resin catalysts in the synthesis of (E)-4-benzylidene-3-methylisoxazol-5(4H)-one.[a]

S.No	Catalyst	Temperature	Reaction time	Yield(%)[b]
1.	Amberlyst-15	Ambient	60 min.	64
2	Amberlyst-15	45°C	15 min.	90
3	Indion 130	45°C	12 min.	88
4	Dowex™ 50WX8	45°C	9 min.	91
5	Amberlite™ IR-120(H)	45°C	11 min.	86
6	Indion Ina 225H	45°C	10 min.	85
7	Tulsion®-8052 MP	45°C	5 min.	95
8	Tulsion®-8052 MP	45°C	30 mins	85[c]
9	Tulsion®-A-74 MP	45°C	120 min.	Traces[d]

[a]Reaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol), and resins (10 mol%), ultrawave sonication and [b]Isolated yield, [c]without ultrawave sonication, [d]Traces.

The synthesis of (E)-4-benzylidene-3-methylisoxazol-5(4H)-one was carried out using different resin catalysts, and it was discovered that Tulsion®-8052 MP outperformed all other resins under study when exposed to ultrasonication irradiation at 45 °C. Reaction proceeds without producing any byproducts in a highly orderly and clean manner. However, in the absence of ultrasonication, the reaction takes longer to complete and has an effect on the reaction yield as well (Table 1, entry 8).

This demonstrates unequivocally the significance of ultrasonication irradiation for conducting additional research. We have further investigated catalyst concentration and its impact on reaction time and yield after confirming the reaction catalysts and temperature. Tulsion®-8052 MP resin was evaluated at different concentrations in relation to benzaldehyde (1.0 mmol) in this practice. The collected data were all compiled into Table 2.

Table 2: Tulsion®-8052 MP resin catalyst concentration study in the synthesis of (E)-4-benzylidene-3-methylisoxazol-5(4H)-one.[a]

S.No	Catalyst Concentration (mol%)	Reaction time	Yield(%)[b]
1.	None	60 min.	NR[c]
2	5	20 min.	69
3	10	5 min.	95
4	15	4 min.	95
5	20	3 min.	96
6	25	3 min.	96

[a]Reaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol), and [b]Isolated yield, [c]no reaction.

The data that was seen made it quite evident that resin Tulsion®-8052 MP at a concentration of 10 mol% produces a superior reaction yield of 95% in a shorter amount of time five minutes. However, after 60 minutes of radiation, no reaction occurs in the absence of a catalyst. Reaction rate and reaction yield improved up to a substantial limit as catalyst concentration increased. Although the reaction time is reduced to 4 minutes with a 15mol% catalyst loading, the reaction yield does not significantly improve. Reaction time decreased by 1 minute when loading to 20 mol%, and the reaction yield was about 96%. Reaction time and yield did not significantly change when the catalyst loading was increased to 25 mol%. Therefore, we concluded that a catalyst loading of 10 mol% would be sufficient to complete the derivatization of all isoxazol-5(4H)-one derivatives.

We screened a variety of aldehydes in the synthesis of isoxazol-5(4H)-one derivatives in order to assess the efficiency and compatibility of Tulsion®-8052 MP resin (Table - 3, 4a-4k). The physical constants of each screened derivative were examined, tested, and compared with data from the literature. Different functional groups that donate and withdraw electrons were used to investigate the impact of the substituents on the aromatic aldehyde. While electron withdrawing groups demonstrated a slow rate of reaction to generate the required product, even lengthening the reaction time, aromatic aldehydes with electron donating groups reacted in the right amount of time to produce the desired products with excellent yields. It has been noted that this reaction is generally influenced differently depending on the type of functional group present on aromatic aldehyde.

Some of the heterocyclic aldehydes were also screened and found that catalyst works well on it with better reaction time and yield.

Table 3: Synthesis of the 3-Methyl-4-arylmethylene isoxazol-5(4H)-one derivatives.[a]

Compound	R	Reaction time	Yield(%)[b]	M.P. ^{o}C[C]
4a	C_6H_5	5	95	141-143[20]
4b	4-OH- C_6H_4	4	95	215-217[20]
4c	4-CH_3- C_6H_4	5	94	132-134[20]
4d	4-OCH_3- C_6H_4	4	96	176-178[20]
4e	3,4-OCH_3- C_6H_3	4	96	132-134[20]
4f	4-NO_2- C_6H_4	10	90	166-168[32]
4g	4-Cl- C_6H_4	15	91	160-162[32]
4h	4-N,N-CH_3- C_6H_4	6	93	225-227[32]
4i	2-Thienyl	8	94	145-147[32]
4j	2-Furyl	8	93	240-242[32]
4k	2-pyrrol	10	90	198-200[32]

[a]Reaction conditions: aldehydes (1.0 mmol), ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol), and resins (10 mol%) and [b]Isolated yield, [1]it. reference no.

Experiment with catalyst loading of 10mol% was conducted in accordance with Scheme 1 to verify catalyst efficiency and reusability. After the reaction was completed during the crystallization of ethanol, the catalyst was retrieved using an experimental method, and it was then employed untreated in subsequent cycles. which, when used in the synthesis of isoxazol-5(4H)-one derivatives, demonstrates a higher reusability impact and clearly demonstrates the clean, affordable, and environmentally friendly nature of Tulsion®-8052 MP resin(Table - 4).

Table 4: Tulsion®-8052 MP resin catalyst reusability data.[a]

S.No	Catalyst recycles	Reaction time	Yield(%)[b]
1.	Fresh	5 min.	95
2	1	5 min.	95
3	2	5 min.	95
4	3	6 min.	95
5	4	8 min.	94
6	5	12 min.	92

[a]Reaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol), and resins (10 mol%) and [b]Isolated yield,

The aforementioned study shown that a catalyst can be recycled up to three times without losing its activity or yield. On the other hand, the catalyst for the fourth and fifth recycles takes a little longer to react while losing very little reaction yield.

Conclusion:

In this work we demonstrated, a clean, safe, eco-friendly, and cost-effectiveness process for the synthesis of isoxazol-5(4H)-one derivatives using recyclable Tulsion®-8052 MP resin catalyst. Ultrasonication was used for the reaction because it

improved reaction performance and had a bigger effect on reaction yield. Here, we present an excellent technique for the synthesis of heterocyclic compounds, which will also prove beneficial in the future for other organic transformations.

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