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SYNTHESIS OF ARYLIDENEISOXAZOL-5-ONES CATALYZED BY SODIUM CYCLAMATE

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Abstract – The three-component reactions using aryl aldehydes, hydroxylamine hydrochloride, and *β*-ketoesters (ethyl acetoacetate, ethyl 4-chloro-3-oxobutanoate, and ethyl 3-oxohexanoate) as available precursors were performed to synthesize arylideneisoxazol-5-ones. The experiments have been catalyzed using sodium cyclamate and high yields of products were obtained under green conditions at room temperature. Relatively shorter reaction time, free from the use of organic reaction medium, the simplicity of the method, the formation of pure products without using chromatographic methods, and inexpensive are among the advantages of this method. Heating and the use of other devices for energy supply are not required. Also, in this three-component process, using water as a reaction medium is in line with the principles of green chemistry.

In the world of heterocycles, isoxazoles have their special place, probably because of their diversity and also their many applications.[1] The isoxazole cyclic system is documented as an important moiety for a wide variety of pharmaceutical drugs.[2] According to the literature, they are ranked 31st among the 351 ring systems found in synthetic medicinal compounds.[3] The isoxazole core is found in a wide variety of naturally occurring products in nature, agrochemicals, propellant plasticizers, and explosives as well as versatile building blocks in organic synthesis.[4] The isoxazole ring can also be observed in liquid crystalline compounds with interesting optoelectronic properties.[5]

Among the most studied isoxazoles, the isoxazol-5(4*H*)-ones are privileged heterocycles that are found in a wide range of drugs, natural products, as well as biologically active compounds, and are of great interest.[6] Many compounds that have biologically active properties such as antiviral, anti-inflammatory, antioxidant, anticancer, antimicrobial, antifungal, anti-Alzheimer's disease, antineoplastic, and anti-tuberculosis belong to the category of arylideneisoxazol-5-ones.[7] Besides, the

arylideneisoxazol-5-ones are attractive multipurpose precursors used for the synthesis of other heterocyclic and non-heterocyclic compounds.[8] Due to the importance of arylideneisoxazol-5-ones, diverse methods, and catalysts have been used for their synthesis in various numerous conditions. Among these catalysts are pyruvic acid,[9] malic acid,[10] piperazine,[11] succinic acid,[12] deep eutectic solvent,[13] urea,[14] boric acid,[15] nano-SiO_2-H_2SO_4,[16] KI,[17] nano-MgO,[18] $Ni(OAc)_2 \cdot H_2O$,[19] pyridine,[20] salicylic acid,[21] potassium phthalimide (PPI),[22] 2-hydroxy-5-sulfobenzoic acid (2-HSBA),[23] sulfanilic acid,[24] potassium 2,5-dioxoimidazolidin-1-ide,[25] potassium hydrogen phthalate (KHP),[26] 2-aminopyridine (2-AP),[27] guanidine hydrochloride,[28] pyrrolidinium dihydrogen phosphate,[29] Steglich's base,[30] vitamin B1,[31] lipase,[32] Fe_3O_4@chitosan-SO_3H,[33] 1,4-diazabicyclo[2.2.2]octane (DABCO),[34] CeO_2/TiO_2,[35] Brönsted acidic organic salt,[36] ionic liquid [HNMP][HSO_4],[37] fruit juices,[38] KBr,[39] sodium malonate,[40] azolium chloride,[41] nano-GO@$Fe(ClO_4)_3$,[42] acid functionalized Fe_3O_4 nanoparticles (Fe_3O_4@MAP-SO_3H NPs),[43] citrazinic acid,[44] and synzyme.[45]

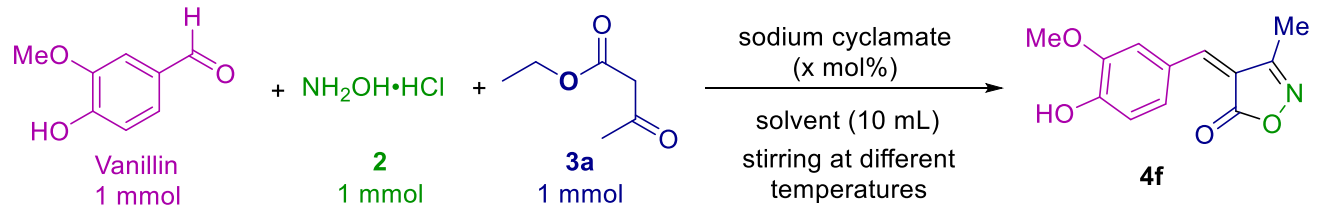
Multi-component organic synthesis, which uses three or more components, can be considered one of the best synthetic methods in chemistry.[46] In other words, the use of safe solvents free from toxic effects can reduce environmental problems. From both economic and environmental viewpoints, employing solvents such as water has a unique position in chemical processes. Thus, carrying out multi-component reactions in water is one of the best ways to reduce environmental risks and make reactions cost-effective.[47]

Concerning the importance and wide applications of arylideneisoxazol-5-ones, in view of some principles of green chemistry, the advantages of three-component reactions, and also the use of sodium cyclamate in the synthesis of tetrahydrobenzo[*b*]pyrans,[48] we decided to explore the catalytic efficiency of sodium cyclamate in the three-component synthesis of these heterocycles (**4a-z**) (Scheme 1).

At first, vanillin is treated with hydroxylamine hydrochloride (**2**) and ethyl acetoacetate (**3a**) (the template reaction) in water at room temperature. The results can be seen in Table 1. The process progressed slightly and the expected product (**4f**) was obtained after 130 min in 60% yield (Table 1, entry 1). After this result, the reaction was allowed to proceed under the same conditions. The continuation of the template reaction did not lead to appreciable improvement in the reaction yield. Next, under aqueous conditions, the model reaction was checked using different amounts of sodium cyclamate as the catalyst. The yield of the reaction increased (85%) and the reaction time decreased (50 min) due to a slight increase (5 mol%) in catalyst loading (Table 1, entry 2). When the amount of the catalyst was doubled (from 5 to 10 mol%), the process proceeded successfully and provided heterocycle product **4f** in 98% isolated yield in 35 min (Table 1, entry 3). Increasing more amounts of catalyst did not significantly affect the yields and reaction times (Table 1, entries 4 and 5). Therefore, the 10 mol% of sodium cyclamate was proven to be the best loading, with the formation of a product of 98% isolated yield. The catalytic efficiency of sodium cyclamate on the model reaction was investigated in other solvents such as acetone,

dichloromethane, ethyl acetate, *n*-hexane, and ethanol. The results of the experiments, as seen in Table 1, indicate that there has been no improvement in the reaction from the point of view of yield or reaction time (Table 1, entries 6-10). Likely, the unusual acceleration in water has been attributed to smaller hydrophobic interactions.[49] The reaction mixture is not completely homogeneous. However, there is also a possibility that the reactions were carried out "on water" conditions and on water effect will lead to the acceleration of the reaction. No significant change in the reaction yield as well as the time of reaction was observed using 10 mol% of the catalyst under solvent-free conditions (Table 1, entry 11). Although the best result was obtained using 10 mol% of the catalyst at room temperature, the temperature parameter was also checked. The template reaction was carried out at 50 ºC and refluxing water. The results were not very favorable (Table 1, entries 12 and 13). Overall, after receiving the above-mentioned results, the optimal conditions for the reaction can be considered as 10 mol% of the catalyst, room temperature, and aqueous conditions (Table 1, entry 3).

Table 1. Optimized the reaction conditions



Entry	Sodium cyclamate/mol%	Solvent	Temp./°C	Time/min.	Isolated yields/%
1	-	H_2O	rt	130	60
2	5	H_2O	rt	50	85
3[a]	**10**	**H_2O**	**rt**	**35**	**98**
4	15	H_2O	rt	40	92
5	20	H_2O	rt	45	90
6	10	acetone	rt	130	20
7	10	CH_2Cl_2	rt	90	25
8	10	EtOAc	rt	100	25
9	10	*n*-hexane	rt	75	20
10	10	EtOH	rt	70	80
11	10	-	rt	115	50
12	10	H_2O	50	70	80
13	10	H_2O	reflux	65	82

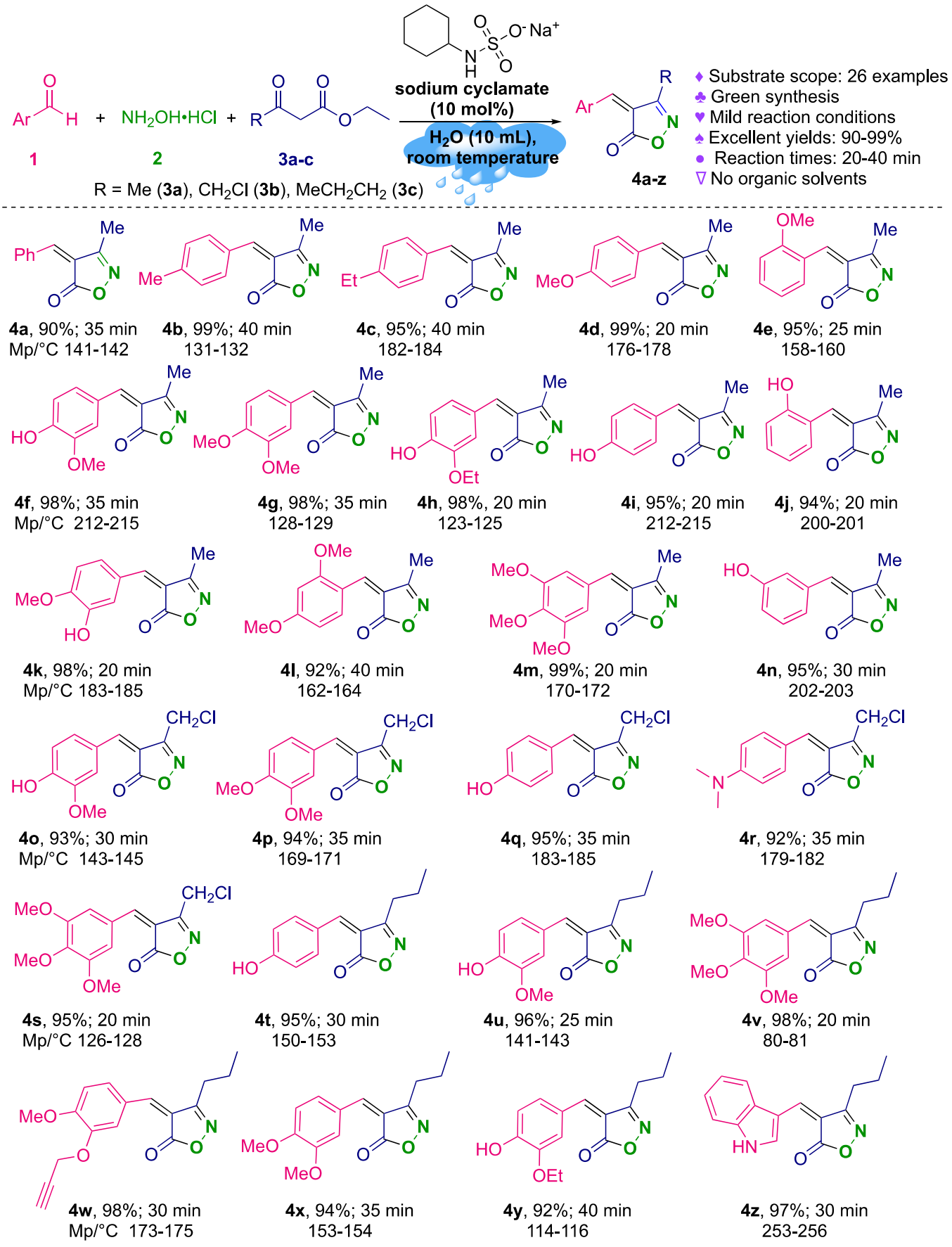
[a] Optimized conditions.

After finding the optimized conditions, the substrate scope and generality of this three-component process were examined with substituted benzaldehydes (Scheme 1). The reactants involve aryl aldehydes, $NH_2OH{\cdot}HCl$ (**2**), and *β*-ketoester compound **3a** underwent the reaction efficiently to deliver the corresponding arylideneisoxazol-5-one derivatives (**4a-n**) in synthetically excellent isolated reaction

yields (90-99%) for 20-40 min.

After the above-mentioned experiments using ethyl acetoacetate (**3a**), the heterocyclization catalytic process was explored with ethyl 4-chloro-3-oxobutanoate (**3b**) as the *β*-ketoester precursor. In these experiments, when **3b** was treated with some aldehydes and $NH_2OH{\cdot}HCl$ (**2**), the expected heterocyclic products (**4o-s**) were formed with excellent isolated yields for times in the range of 20-35 min. After these promising results, another *β*-ketoester, namely ethyl 3-oxohexanoate (**3c**), was used. After running the tests, good results were also obtained. Here, arylideneisoxazol-5-ones **4t-y** were obtained with excellent reaction yields (94-98%) through the three-component reaction of several substituted benzaldehydes, $NH_2OH{\cdot}HCl$ (**2**), and ethyl 3-oxohexanoate (**3c**) in the presence of 10 mol% of sodium cyclamate as a catalyst under aqueous conditions. Furthermore, a three-component reaction of indole-3-carbaldehyde, $NH_2OH{\cdot}HCl$ (**2**), and ethyl 3-oxohexanoate (**3c**) under the optimized reaction conditions to afford the expected heterocyclic compound have been explored. As expected, the reaction proceeded smoothly, yielding compound **4z** in 97% yield. The development of environmentally friendly methods, mild reaction conditions, using the catalyst, energy efficiency, employing non-toxic compounds, and the implementation of reactions in aqueous media are among the goals of green chemistry.[46a, 46g] It should be noted that in the reactions carried out in this work, using a mild catalyst, performing the reactions at room temperature (energy efficiency[50]), and employing a cleaner water solvent (safer solvents[50]) indicate that this method is green.

The melting points of the synthesized heterocycles were recorded and structures were characterized based on of spectral data. For example, the ^1H NMR spectrum of compound **4y** confirms that the hetrocyclization reaction has occurred and the desired heterocyclic compound has been formed. The signals for CH_2O and CH_3 of an ethoxy group on the phenyl ring appeared as a quartet at δ 4.12 ppm and a triplet at δ 1.41 ppm, respectively. The appearance of three separate signals as a triplet (integrated by three protons), sextet (integrated by two protons), and triplet (integrated by two protons) peaks in the chemical shifts at δ 0.99, 1.68, and 2.65 ppm, respectively, indicates the propyl group attached to the isoxazole ring. In addition, the ^1H NMR spectrum revealed three distinct singlet peaks (the area under each peak is equal to one proton) at δ 7.80, 8.53, and 10.69 ppm, which are assigned to CH of vinyl, proton located in the *ortho* position relative to the ethoxy group, and the OH, respectively. The remaining two protons belonging to the phenyl ring appeared as two distinct doublet signals at δ 6.98 and 7.92 ppm. In the ^{13}C NMR spectrum of compound **4y**, three signals in the regions at δ 14.1, 19.9, and 27.5 ppm are assigned to the propyl branch. The two distinct peaks at δ 15.0 and 64.3 ppm are assigned to CH_3 and CH_2O of an ethoxy group, respectively. Two separate resonances at δ 169.7 and 165.2 ppm confirmed the C=O and C=N carbons of isoxazole moiety, respectively. The signals of other carbons resonated in the expected regions at δ 154.5, 151.9, 147.1, 132.0, 125.5, 118.2, 116.3, and 113.5 ppm.



Melting points were in good agreement with values reported in the literature.[11, 14]

Scheme 1. Three-component synthesis of arylideneisoxazol-5-ones (**4a-z**)

To check the efficiency of this catalyst, a comparison has been made with other reported catalysts for the synthesis of **4f** (Table 2). This method is competitive with some other methods in terms of reaction yields, reaction times, catalyst loading, reaction temperature, devices used, reaction media, and commercial availability of the catalyst as well as no need to synthesize it in several steps.

In conclusion, the development of an effective and simple catalyst is important for the synthesis of arylideneisoxazol-5-ones. Therefore, in this work, the heterocyclization process was performed to synthesize arylideneisoxazol-5-ones from available precursors involving aryl aldehydes, $NH_2OH{\cdot}HCl$, and ethyl acetoacetate using sodium cyclamate as the catalyst. Under the optimized reaction conditions, this three-component heterocyclizaton proceeds smoothly if there are electron-releasing groups on the benzaldehyde substrates or electron-rich heteroaryl precursor. Moreover, the formation of arylideneisoxazol-5-ones is not observed for only electron-accepting substituted benzaldehydes. In this catalytic process, we found that sodium cyclamate efficiently catalyzed the reactions under mild conditions and green medium with excellent yield in relatively shorter reaction times. This method is also applicable to the study synthesis of other arylideneisoxazol-5-ones using ethyl 4-chloro-3-oxobutanoate or ethyl 3-oxohexanoate precursors. For this purpose, the synthesis of the related derivatives was investigated and the corresponding heterocyclic products were obtained successfully in high yields. This approach also uses water as a reaction medium, which indicates low risk and compliance with one of the principles of green chemistry.

Table 2. Comparative study of the current catalyst with some other reported catalysts for **4f** synthesis

Entry	Catalyst	Catalyst amount	Reaction conditions	Time/ min.	Yield/%	References
1	pyruvic acid	5 mol%	H_2O, 100 ºC	90	83	9
2	pyruvic acid	5 mol%	H_2O, 50 ºC, US[a]	15	85	9
3	malic acid	10 mol%	H_2O, 50 ºC	45	90	10
4	piperazine	5 mol%	H_2O, 65 ºC	40	99	11
5	succinic acid	10 mol%	H_2O, rt	90	88	12
6	salicylic acid	15 mol%	H_2O, rt	100	93	21
7	potassium phthalimide	10 mol%	H_2O, rt	70	95	22
8	sulfanilic acid	20 mol%	H_2O, rt	70	94	24
9	2-aminopyridine	20 mol%	H_2O, 80 ºC	30	96	27
10	$[H_2\text{-BiPyr}][ClO_4]_2$	0.01 g	H_2O, reflux	15	90	36
11	ABE[b]	3 mL	H_2O, rt	120	86	38
12	nano-GO@$Fe(ClO_4)_3$	500 mg	Solvent-free	60	90	42
13	Fe_3O_4@MAP-SO_3H	20 mg	EtOH-H_2O, 25 °C, US	20	91	43
14	Fe_3O_4@MAP-SO_3H	20 mg	EtOH-H_2O, 25 °C	120	70	43
15	synzyme	50 mg	H_2O, 80 °C	70	86	45
16	sodium cyclamate	10 mol%	H_2O, rt	35	98	this work

[a] Ultrasonication, [b]*Averrhoa bilimbi extract* (ABE)

EXPERIMENTAL

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification, except liquid aldehydes, which were distilled before use. The well-known products were characterized by the comparison of their physical data with those of known samples or by their spectral data. Melting points were measured on a Büchi 510 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian-INOVA 300 MHz at the central laboratory of the Mashhad University of Medical Science, Mashhad, Iran. FT-IR spectra were recorded on a PerkinElmer RXI spectrometer at Damghan University using the KBr disk technique. The development of reactions was monitored by analytical thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F_{254} aluminum sheets, visualized by UV light.

General procedure for the synthesis of arylideneisoxazol-5(4*H*)-ones (4a-z) using sodium cyclamate. In a flat-bottom flask, the mixture of aryl/heteroaryl aldehyde (**1**, 1 mmol), hydroxylamine hydrochloride (**2**, 1 mmol), *β*-ketoester (**3a-c**, 1 mmol), and sodium cyclamate (10 mol%) was stirred in H_2O (10 mL). The reaction mixture was stirred at room temperature until the completion of the reaction (the reaction progress monitored by TLC analysis, 20-40 min). After the reaction was complete, the precipitate formed was removed by filtering with Whatman filter paper and washed with water. Pure heterocyclic products (**4a-z**) were obtained after drying. If needed, the products can be recrystallized in EtOH for further purification.

4-(4-Hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4f). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.28 (s, 3H, Me), 3.91 (s, 1H, MeO), 7.16 (d, *J* = 8.6, 1H, Ar-H), 7.79 (s, 1H, H-vinyl), 7.93 (d, *J* = 8.6, 1H, Ar-H), 8.24 (s, 1H, Ar-H), 9.65 (s, 1 H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.4 (Me), 56.2 (MeO), 111.8, 114.9, 127.2, 128.9, 129.7, 146.7, 151.8, 153.7, 168.8 (C=N), 170.1 (C=O); FT-IR (KBr, cm^{-1}): 3285, 3115, 2842, 1695, 1575, 1452, 1270, 1135, 942.

4-(3,4-Dimethoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4g). ^{1}H NMR (300 MHz, $CDCl_3$): 2.24 (s, 3H, Me), 3.95 (s, 6H, MeO), 6.93 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 7.59 (d, *J* = 7.5 Hz, 1H, Ar-H), 8.67 (s, 1H, H-vinyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.6 (Me), 56.0 (MeO), 56.1 (MeO), 110.7, 115.1, 116.1, 126.3, 131.4, 149.0, 149.9, 154.6, 161.4 (C=N), 169.1 (C=O).

4-(3-Ethoxy-4-hydroxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4h). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.39 (t, *J* = 6.9 Hz, 3H, MeCH$_2$O), 2.22 (s, 3H, Me), 4.10 (q, *J* = 6.9 Hz, 2H, CH$_2$O), 6.95 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.68 (d, *J* = 1.5 Hz, 1H, Ar-H), 7.83 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.48 (s, 1H, H-vinyl), 10.68 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.6 (CH_3), 15.0 (MeCH$_2$O), 64.2 (CH$_2$O), 114.1, 116.3, 118.0, 125.5, 132.0, 147.1, 152.2, 154.4, 162.6 (C=N), 169.4 (C=O).

4-(4-Hydroxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4i). ^{1}H NMR (300 MHz, CDC1$_3$): δ 2.21 (s, 3H, Me), 6.93 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.78 (s, 1H, H-vinyl), 8.43 (d, *J* = 8.8 Hz, 2H, Ar-H), 10.99 (s,

1H, OH); ^{13}C NMR (75 MHz, CDC1$_3$): δ 11.8 (Me). 114.3, 124.5, 125.1, 136.2, 150.9, 162.6, 164.5 (C=N), 169.2 (C=O); FT-IR (KBr, cm^{-1}): 3250, 1725, 1590, 1545, 1373, 1298, 997, 890.

3-(Chloromethyl)-4-(3,4-dimethoxybenzylidene)isoxazol-5(4*H*)-one (4p). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.85 (s, 3H, MeO), 3.92 (s, 3H, MeO), 4.88 (s, 2H, CH_2Cl), 7.21 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.02 (dd, *J* = 1.8, 6.7 Hz, 1H, Ar-H), 8.04 (s, 1H, H-vinyl), 8.47 (d, *J* = 1.8 Hz, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.4 (CH_2Cl), 55.8 (MeO), 56.7 (MeO), 111.8, 112.3, 115.6, 126.3, 132.2, 148.8, 153.1, 155.5, 162.2 (C=N), 168.7 (C=O); FT-IR (KBr, cm^{-1}): 3098, 3025, 2956, 1744, 1609, 1554, 1523, 1429, 1279, 1145, 1013, 886.

3-(Chloromethyl)-4-(3,4,5-trimethoxybenzylidene)isoxazol-5(4*H*)-one (4s). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.84 (s, 3H, MeO), 3.86 (s, 6H, MeO), 4.85 (s, 2H, CH_2Cl), 7.98 (s, 1H, H-vinyl), 8.10 (s, 2H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.8 (CH_2Cl), 56.2 (MeO), 60.4 (MeO), 112.5, 113.4, 127.6, 143.8, 152.5, 152.7, 161.6 (C=N), 167.8 (C=O); FT-IR (KBr, cm^{-1}): 3435, 2943, 1726, 1577, 1427, 1350, 1258, 1136, 900, 781.

4-(3,4-Dimethoxybenzylidene)-3-propylisoxazol-5(4*H*)-one (4x). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.01 (t, *J* = 7.3 Hz, 3H, Me), 1.69 (sext, *J* = 7.4 Hz, 2H, $\underline{CH_2}Me$), 2.64 (t, *J* = 7.4, 2H, $\underline{CH_2}CH_2Me$), 3.85 (MeO), 3.92 (MeO), 7.15 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.84 (s, 1H, H-vinyl), 8.01 (d, *J* = 8.3 Hz, 1H, Ar-H), 8.48 (s, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.2 (Me), 19.7 ($\underline{CH_2}Me$), 27.4 ($\underline{CH_2}CH_2Me$), 55.3 (MeO), 55.8 (MeO), 111.8, 114.8, 116.1, 126.4, 131.5, 148.9, 151.5, 154.9, 165.2 (C=N), 169.5 (C=O).

4-(3-Ethoxy-4-hydroxybenzylidene)-3-propylisoxazol-5(4*H*)-one (4y). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.99 (t, *J* = 7.5 Hz, 3H, Me of propyl), 1.41 (t, *J* = 6.9 Hz, 3H, Me of ethoxy), 1.68 (sext, *J* = 7.5 Hz, 2H, $CH_2\underline{CH_2}Me$), 2.65 (t, *J* = 7.2 Hz, 2H, $\underline{CH_2}CH_2Me$), 4.12 (q, *J* = 6.9 Hz, 2H, $\underline{CH_2}O$), 6.98 (d, *J* = 8.4 Hz, 1H, ArH), 7.80 (s, 1H, Ar-H), 7.92 (d, *J* = 8.1 Hz, 1H, ArH), 8.53 (s, 1H, H-vinyl), 10.69 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1 (Me of propyl), 15.0 (Me of ethoxy), 19.9 ($CH_2\underline{CH_2}Me$), 27.5 ($\underline{CH_2}CH_2Me$), 64.3 (CH_2O), 113.5, 116.3, 118.2, 125.5, 132.0, 147.1, 151.9, 154.5, 165.2 (C=N), 169.7 (C=O).

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