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EFFICIENT AND AQUEOUS SYNTHESIS OF 3,4-DISUBSTITUTED ISOXAZOL-5(4*H*)-ONE DERIVATIVES USING PIPERAZINE UNDER GREEN CONDITIONS

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Abstract – The one-pot, three-component, as well as expeditious synthesis of 3,4-disubstitted isoxazol-5(4*H*)-ones has been attained from the heterocyclization of various aryl/heteroaryl aldehydes, active methylene compounds, and hydroxylamine hydrochloride in the presence of piperazine as the efficient, low-cost, commercially available, and eco-friendliness basic organocatalyst. This double secondary amine catalyst was found that catalyzed the synthesis of isoxazol-5(4*H*)-ones under green conditions. The additional features of the present catalyst include readily available starting materials, relatively low catalyst loading, using water as a green solvent, broad substrate scope, simplicity, good to excellent reaction yields, faster synthesis, and avoiding the hazardous organic solvents.

The piperazine is a special secondary heterocyclic diamine containing two nitrogen atoms at 1 and 4 positions, which present in pharmaceutical and biological active compounds.[1] Piperazine ranks as the third most common nitrogen heterocycle in drug discovery,[2] and it is an important pharmaceutical intermediate for the synthesis of anticancer, antituberculosis, antibacterial, anti-inflammatory, antipsychotic, antimalarial, anti-Alzheimer, antioxidant, antihistamine, antidepressant, antifungal, and antidiabetic drug candidates.[3] This heterocyclic molecule acts as a transmitter of γ-aminobutyric acid receptor inhibitor, succinic acid formation by parasites inhibitor,[4] and a promoter for CO_2 absorption.[5] Piperazine citrate organosalt as a derivative of piperazine is also used in the treatment, control, and prevention of several worm infections as threadworm, roundworm and pinworm in both human and animals. It is also helps in the treatment of chicken naturally infected with gastrointestinal helminths and can be used in the treatment of ascaris lumbricoides infestation and bacterial infections.[6] Literature survey

revealed that the catalytic activity of piperazine have been used in the cyclocondensation reactions to synthesis 4*H*-pyran annulated compounds.[7]

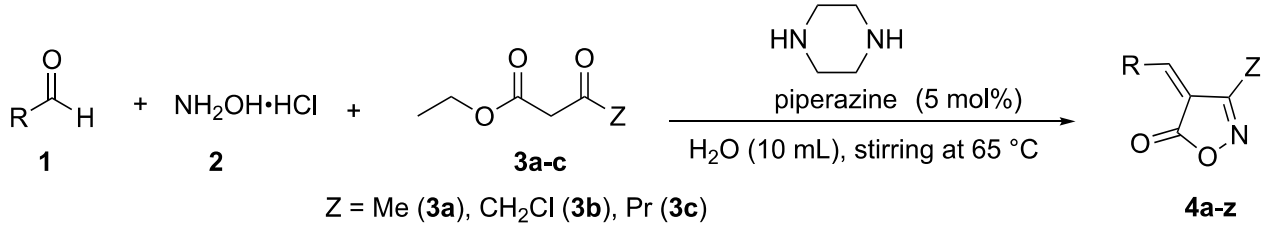
The isoxazole-5(4*H*)-one fragment is a significant framework that has gained special attention in organic synthesis from the point of view of their applications as active synthetic intermediates in organic transformations.[8] Isoxazol-5(4*H*)-ones show myriads of attractive physiological activities such as including anti-obesity,[9] antitumor,[10] anti-HIV-1,[11] anti-inflammatory,[12] antitubercular,[13] anti-androgen,[14] antibacterial,[15] tyrosinase inhibitory,[16] antimycobacterial,[17] analgesic,[18] anti-Alzheimer's disease,[19] antifungal,[20] and antioxidant[21] activities. This class of heterocyclic molecules can also be found in donor−acceptor Stenhouse adducts (DASAs) as new generation of photochromic compounds.[22]

The multicomponent cyclocondensation reaction is one of the most attractive and common synthetic methods to synthesis derivatives of isoxazol-5(4*H*)-ones. In this field, various catalytic systems and approaches have been reported for their synthesis, including deep eutectic solvents,[23] sulfonated graphene oxide (SGO),[24] boric acid,[25] nano-SiO_2-H_2SO_4,[26] ZnO@Fe_3O_4,[27] I_2,[28] $CeCl_3.7H_2O$,[29] silica-TLC grade,[30] KI,[31] nano-MgO,[32] $Ni(OAc)_2.H_2O$,[33] Cu/thiocarbohydrazide-pr@SBA-15,[34] KBr,[35] sulfated tin oxide,[36] and fruit juice.[37] In addition, various organic compounds, such as sodium acetate,[38] salicylic acid,[39] pyridine,[40] starch solution,[41] potassium phthalimide (PPI),[42] 2-hydroxy-5-sulfobenzoic acid (2-HSBA),[43] sulfanilic acid,[44] potassium 2,5-dioxoimidazolidin-1-ide,[45] pyruvic acid,[46] imidazole,[47] succinic acid,[48] potassium hydrogen phthalate (KHP),[49] 2-aminopyridine (2-AP),[50] guanidine hydrochloride,[51] pyrrolidinium dihydrogen phosphate,[52] pyridinium *p*-toluenesulfonate (PPTS),[53] Steglich's base,[54] and sodium benzoate[55] have been used as organocatalysts for the synthesis of a wide variety of 3,4-disubstituted isoxazol-5(4*H*)-ones. Nevertheless, these catalysts have several drawbacks: reactions require a prolonged reaction time, volatile organic solvent, microwave heating, sonication, and expensive or synthesis of some catalysts. Given the importance of substituted isoxazol-5(4*H*)-ones, researchers in synthetic and medicinal chemistry are looking for a useful, inexpensive, environmentally friendly, and efficient catalyst for their synthesis. The use of piperazine in this context partially meets some of these requirements.

On account of the thought-provoking pharmacological properties of the isoxazol-5(4*H*)-one derivatives, we report the synthesis of isoxazol-5(4*H*)-ones (**4a**-**z**) using piperazine as the organocatalyst *via* a three-component cyclocondensation under green conditions (Scheme 1).

A three-component reaction between vanillin (**1a**) as a useful natural product, hydroxylamine hydrochloride (**2**), and ethyl acetoacetate (**3a**) (the model reaction) was carried out in water as a benign solvent in order to obtain 4-(4-hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (**4a**). When the reaction was carried out in the absence of any catalyst at room temperature (rt), the heterocyclic

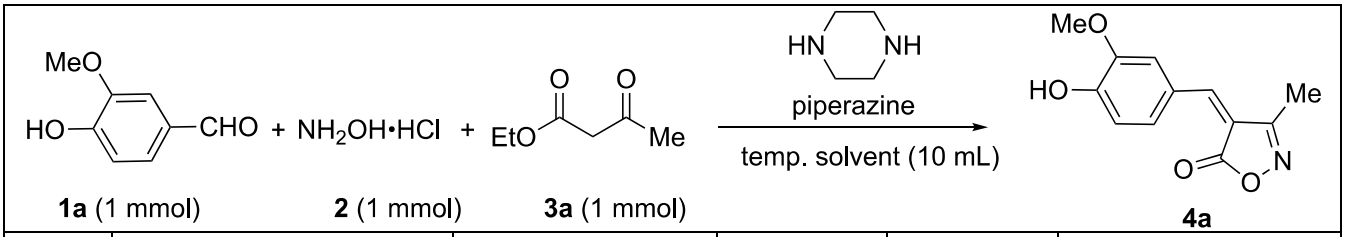
product (**4a**) was obtained in 40% isolated yield after 120 min (Table 1, Entry 1). The model reaction was performed in the presence of 3 mol% of piperazine as an organocatalyst and the product **4a** was obtained with 70% yield after 120 min at rt (Table 1, Entry 2).



Scheme 1. Synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones (**4a**-**z**) using piperazine in H_2O

At the same temperature, in the presence of 5 mol% piperazine, the reaction yield was improved (Table 1, Entry 3). The model reaction was investigated using 5 mol% piperazine organocatalyst at different temperatures such as 40 ºC, 50 ºC, 60 ºC, 65 ºC, 70 ºC, and reflux. The **4a** was isolated in 90%, 95%, 97%, 99%, 85%, and 94% yield, respectively (Table 1, Entries 4-9). This shows that 5 mol% of piperazine and 65 ºC are the best parameters to synthesis the desired product (Table 1, Entry 7).

Table 1. Screening the reaction conditions using piperazine as the organocatalyst



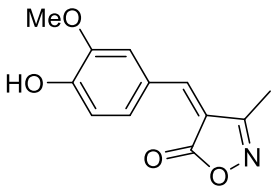
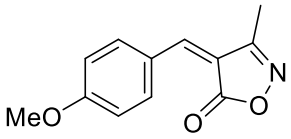
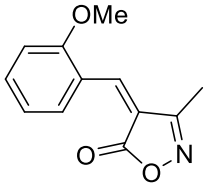
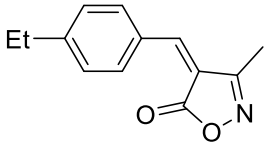
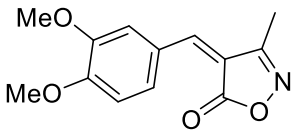
Entry	Piperazine (X mol%)	Solvent	Temp./°C	Time/min.	Isolated yield/%
1	-	H_2O	25	120	40
2	3	H_2O	25	120	70
3	5	H_2O	25	120	85
4	5	H_2O	40	85	90
5	5	H_2O	50	75	95
6	5	H_2O	60	50	97
7[a]	**5**	**H_2O**	**65**	**40**	**99**
8	5	H_2O	70	50	85
9	5	H_2O	reflux	100	80
10	10	H_2O	65	70	98
11	15	H_2O	65	70	95
12	5	EtOH	65	90	83
13	5	acetone	reflux	100	15
14	5	EtOAc	reflux	80	35
15	5	*n*-hexane	reflux	95	60
16	5	EtOH: H_2O (1:1)	65	95	85
17	5	solvent-free	65	115	50

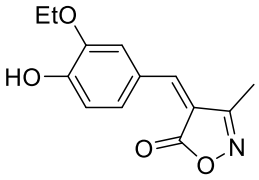
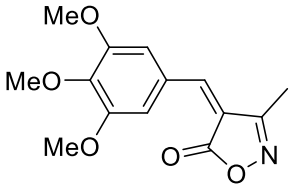
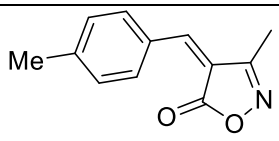
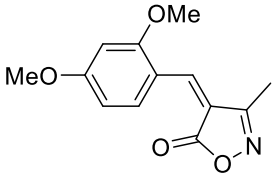
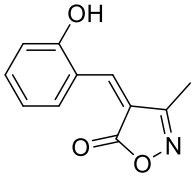
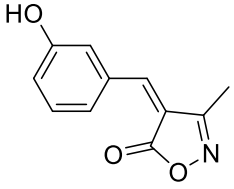
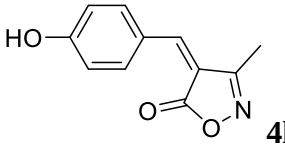
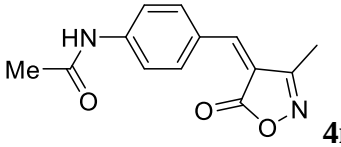
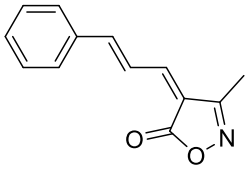
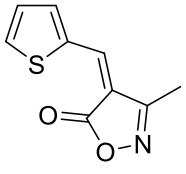
[a] Optimized reaction conditions.

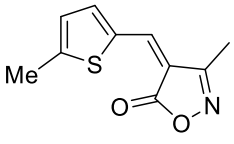
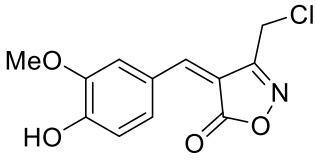
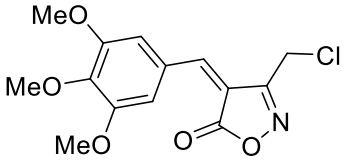
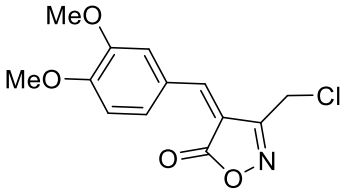
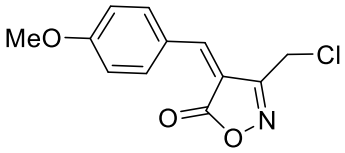
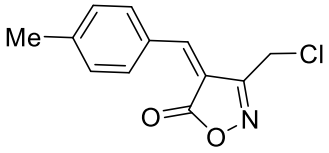
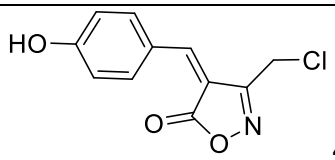
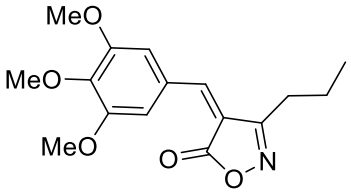
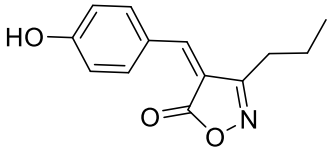
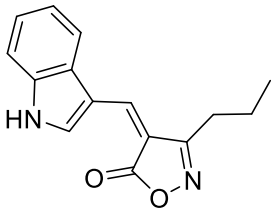
To estimate the solvent effect, many solvents including EtOH, acetone, EtOAc, *n*-hexane, and a mixture of H_2O-EtOH were used in the presence of 5 mol% of piperazine at 65 ºC or reflux conditions and the desired product (**4a**) was obtained in 83%, 15%, 35%, 60%, and 85% reaction yields, respectively (Table 1, Entries 12-16). The reaction under solvent-free conditions at 65 ºC led to 50% isolated yield after 115 min (Table 1, Entry 17). These experimental studies on the model reaction clearly indicates that 5 mol% of piperazine is the best catalyst loading, 65 ºC is the optimum reaction temperature, and H_2O is vital to carry out the reaction. Under aqueous conditions, this three-component cyclocondensaion not only proceeded to completion efficiently but also gave the desired heterocyclic product (**4a**) in high isolated yield and the shortest reaction time (Table 1, Entry 6; the optimized reaction conditions).

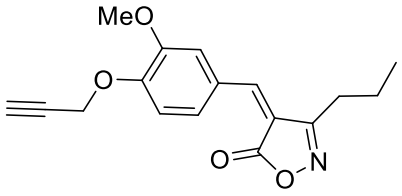
After finding the reaction optimized conditions, the reaction of different derivatives of benzaldehydes having electron-donating groups at the *para*-, *meta*-, and *ortho*-positions proceeded well and the corresponding isoxazol-5(4*H*)-one compounds (**4b**-**m**) were obtained in excellent yields (Table 2, Entries 2-13).

Table 2. Synthesis of various derivatives of isoxazol-5(4*H*)-ones (**4a**-**z**) in the presence of piperazine

Entry	Structure of isoxazol-5(4*H*)-one	Time/ min	Isolated yield/%	Mp/°C	
				Observed	Reported[ref.]
1	 **4a**	40	99	212-214	210-212[26]
2	 **4b**	50	99	175-177	174-176[26]
3	 **4c**	50	95	159-161	153-156[29]
4	 **4d**	60	95	89-91	88-90[50]
5	 **4e**	80	99	163-165	162-165[50]

6	 **4f**	60	99	139-140	123-125[50]
7	 **4g**	60	99	170-172	171-173[26]
8	 **4h**	50	99	131-132	130-132[26]
9	 **4i**	55	95	161-163	128-130[35]
10	 **4j**	70	99	198-200	199-201[26]
11	 **4k**	80	95	202-203	200-202[26]
12	 **4l**	50	95	212-215	210-212[26]
13	 **4m**	60	97	189-191	188-190[26]
14	 **4n**	70	85	183-185	177-179[26]
15	 **4o**	90	85	146-147	144-146[26]

16	 **4p**	100	80	169-172	170-172[26]
17	 **4q**	30	90	143-145	138-140[26]
18	 **4r**	90	95	126-128	128-130[26]
19	 **4s**	70	85	173-175	174-176[26]
20	 **4t**	50	90	182-184	183-185[26]
21	 **4u**	60	90	137-139	136-138[26]
22	 **4v**	100	90	184-186	182-184[26]
23	 **4w**	60	98	80-81	80-82[26]
24	 **4x**	55	95	150-153	151-153[26]
25	 **4y**	45	99	254-257	256-258[45]

26	 **4z**	50	97	174-176	New

When cinnamaldehyde was treated with hydroxylamine hydrochloride (**2**) and ethyl acetoacetate (**3a**) under the optimized conditions, it was reacted well and afford the heterocyclic product **4n** in 85% isolated yield (Table 2, Entry 14). It is noteworthy that heteroaryl aldehyde precursors, including thiophene-2-carbaldehyde and 5-methylthiophene-2-carbaldehyde also gave good yields (Table 2, Entries 15 and 16). In continuation, to further validate the effectiveness and generality of this three-component reaction, the scope of the 1,3-dicarbonyl substrates was probed under the optimized reaction conditions. In these experiments, ethyl 4-chloro-3-oxobutanoate (**3b**) and ethyl 3-oxohexanoate (**3c**) were applied in place of ethyl acetoacetate (**3a**) and the desired isoxazol-5(4*H*)-one products (**4q-z**) were obtained in good to high isolated yields (Table 2, Entries 17-26). Unfortunately, when substituted benzaldehydes containing electron-withdrawing groups and aliphatic aldehydes were involved in this three-component reaction under the optimized reaction conditions, no reaction occurred that could lead to the formation of the heterocycles.

The structures of the isoxazol-5(4*H*)-ones **4a-z** were deduced on the basis of spectroscopic data. For example, in the ^{1}H NMR (300 MHz, DMSO-d_6) spectrum study of 4-(3-methoxy-4-(prop-2-yn-1-yloxy)-benzylidene)-3-propylisoxazol-5(4*H*)-one (**4z**), the resonances of the methoxy group appeared as a sharp singlet at δ 3.87 ppm. The signal of the three protons of the methyl group of propyl substituent observed as a triplet at the chemical shift region 1.02 ppm and coupling constant 7.5 Hz. The characteristic signal for the middle CH_2 of propyl group was observed as a sextet at δ 1.70 ppm and coupling constant 7.2 and 7.5 Hz. The resonance of the methylene protons of the propyl substituent attached to the isoxazolone ring appeared at chemical shift region 2.68 ppm as a triplet and coupling constant 7.2 Hz. A doublet signal at δ 4.99 ppm (J = 2.1 Hz) and a triplet peak at δ 3.69 ppm (J = 2.1 Hz) corresponding to CH_2O and alkyne protons of propargyloxy group, respectively. The signal of the vinylic proton between to rings appeared at δ 7.92 ppm as a singlet. The chemical shifts observed at δ 7.26 (d, J = 8.1 Hz), 8.07 ppm (dd, J = 3.3 and 8.4 Hz), and 8.50 ppm (J = 1.8 Hz) confirmed the aromatic protons of the phenyl ring (Figure 1).

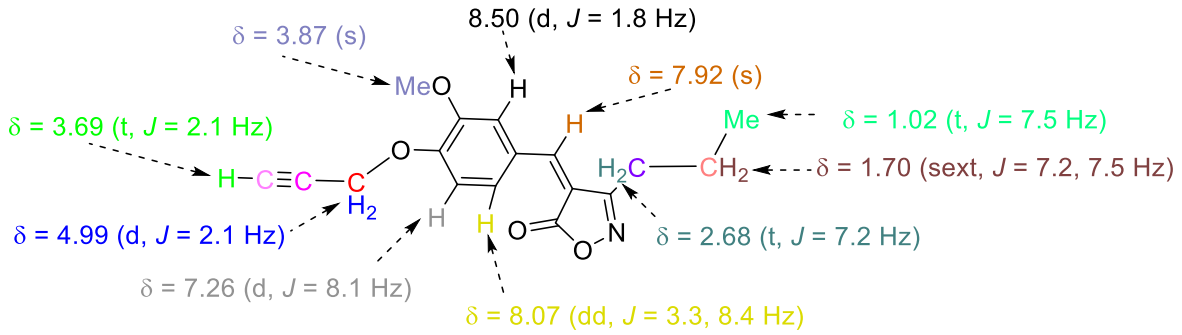
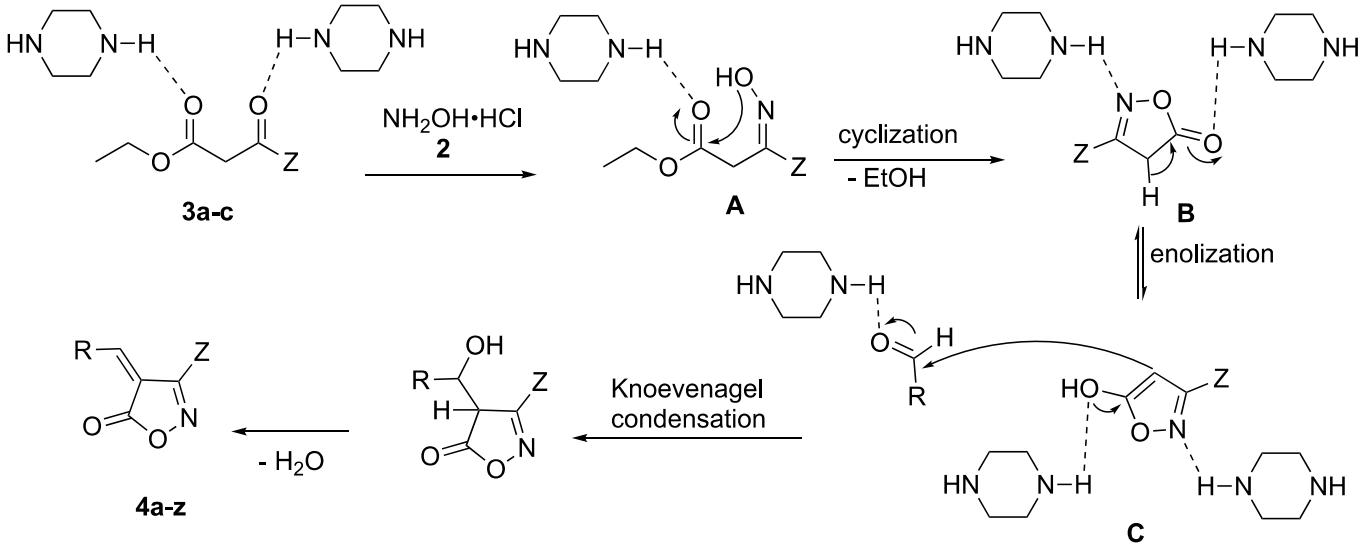


Figure 1. ^{1}H NMR Chemical shifts of 4-(3-methoxy-4-(prop-2-yn-1-yloxy)benzylidene)-3-propylisoxazol-5(4*H*)-one (**4z**) in DMSO-d_6

In ^{13}C NMR spectrum of compound **4z**, the peaks at 14.2 ppm, 19.8 ppm, and 27.5 ppm belonging to the Me, $\underline{CH_2}CH_3$, and CH_2 on the ring carbons of propyl substituent, respectively. The chemical shifts in the region of 113.4-152.3 ppm are assigned to carbons of the phenyl, C-vinyl, and C= of isoxazol ring. The signals at 56.0 ppm and 56.7 ppm belonging to the methoxy group and CH_2O, respectively. The signals of CH terminal and C internal of alkyne moiety appeared at 78.9 ppm and 79.5 ppm, respectively. Two distinct resonances at δ 169.3 ppm and 165.2 ppm confirmed the C=O $_{isoxazole}$ and C=N $_{isoxazole}$ carbons.

On the basis of the related references,[37c,56] the possible reaction mechanism for the formation of 3,4-disubstituted isoxazol-5(4*H*)-one derivatives is outlined in Scheme 2. Briefly, the reaction proceeds *via* activation of the carbonyl carbon of 1,3-dicarbonyl compounds (**3a-c**) by piperazine leading to the formation of oxime intermediates (**A**) on reaction with hydroxylamine (**2**) and the intramolecular heterocyclization was then occurred with the elimination of EtOH, afford the isoxazol-5(4*H*)-one intermediates **B**. The following the Knoevenagel condensation **B** with activated aldehydes gave the final heterocycles (**4a-z**).



Scheme 2. Possible reaction mechanism catalyzed by piperazine

The comparison of piperazine with some previously reported organocatalysts for the synthesis of **4a** is presented in Table 3. The yields of the products were better than those obtained by using some previously reported organocatalysts (Table 3, Entries 1-14). In terms of reaction times, this reaction was performed in relatively shorter reaction times compared to some previously reported methods (Table 3, Entries 1, 2, 4, 5, 7-10, 12 and 14). From the point of view of energy source, this procedure is performed without the need for microwave or ultrasound radiations (Table 3, Entries 6 and 11). Although it is a green reaction in terms of solvent, it is not much different from other methods. However, the best medium for this reaction is water. Regarding the amount of catalyst used, this method requires smaller amounts of catalyst than many other methods (Table 3, Entries 1-9 and 12-14).

Table 3. Comparison of piperazine efficiency with some previously reported organocatalysts for the three-component synthesis of compound **4a**

Entry	Catalyst	Catalyst amount/mol %	Reaction conditions	Time/ min.	Yield /%	References
1	*Averrhoa bilimbi extract* (ABE)	3[a]	H_2O, rt	120	86	37a
2	aq. extract of *Acacia concinna*	20	H_2O, rt	95	85	37d
3	sodium acetate	100	EtOH:H_2O (1:1), *hv*	10	68	38a
4	salicylic acid	15	H_2O, rt	100	93	39
5	starch solution	4[a]	90 ºC	56	86	41
6	starch solution	4[a]	microwave (300 w)	7	94	41
7	potassium phthalimide	10	H_2O, rt	70	95	42
8	2-hydroxy-5-sulfobe-nzoic acid	15	H_2O, rt	70	96	43
9	sulfanilic acid	20	H_2O, rt	70	94	44
10	pyruvic acid	5	H_2O, 100 ºC	90	83	46
11	pyruvic acid	5	H_2O, 50 ºC, US[b]	15	85	46
12	succinic acid	10	H_2O, rt	90	88	48
13	2-aminopyridine	20	H_2O, 80 ºC	30	96	50
14	sodium benzoate	10	H_2O, rt	90	86	55
15	piperazine	5	H_2O, 65 ºC	40	99	This work

[a] Amounts of catalyst in terms of mL. [b] Ultrasonication.

In conclusion, the organocatalytic three-component heterocyclization toward synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones under green conditions has been developed through the reaction of aryl/heteroaryl aldehydes, hydroxylamine hydrochloride, and three 1,3-dicarbonyl derivatives (ethyl acetoacetate, ethyl 4-chloro-3-oxobutanoate, and ethyl 3-oxohexanoate). The corresponding isoxazol-5(4*H*)-ones were obtained in the presence of 5 mol% piperazine in good to excellent isolated

yields. Among the various solvents investigated, the desired heterocycles are produced in higher yields using water medium, which is compatible with the principles of green chemistry.

EXPERIMENTAL

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification, with the exception of liquid aldehydes, which were distilled before using. The well-known products were characterized by 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 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. Elemental microanalyses were performed on an Elementar Vario EL III analyzer at Damghan University. 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 3,4-disubstituted isoxazol-5(4*H*)-ones (4a-z) catalyzed by piperazine. The aryl/heteroaryl aldehyde (**1**, 1 mmol), hydroxylamine hydrochloride (**2**, 1 mmol), *β*-keto ester (**3a-c**, 1 mmol), and piperazine (5 mol%) was stirred in H_2O (10 mL) at 65 ºC. After completion of the reaction as indicated by TLC analysis, the precipitated products were filtered, washed with cold water and dried at rt. If necessary, the crude products were purified by recrystallization from EtOH.

4-(4-Hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (s, 3H, CH_3), 3.92 (s, 1H, OCH_3), 7.15 (d, J = 8.6, 1H, Ar-H), 7.78 (s, 1H, H-vinyl), 7.92 (d, J = 8.6, 1H, Ar-H), 8.23 (s, 1H, Ar-H), 9.63 (s, 1 H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.3 (CH_3), 56.1 (OCH_3), 111.9, 114.8, 127.1, 128.8, 129.6, 146.6, 151.9, 153.8, 168.7 (C=N), 170.2 (C=O).

4-(4-Methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.12 (d, J = 9.3 Hz, 2H, Ar-H), 7.82 (s, 1H, H-vinyl), 8.49 (d, J = 9.0 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.6 (CH_3), 55.6 (OCH_3), 114.5, 125.7, 126.3, 133.8, 149.3, 161.3 (C=N), 168.7 (C=O).

4-(2-Methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4c). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.26 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 6.90-7.05 (m, 2H, Ar-H), 6.45-7.54 (m, 1H, Ar-H), 8.01 (s, 1H, H-vinyl), 8.85 (dd, J = 1.5, 8.9 Hz, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.8 (CH_3), 56.1 (OCH_3), 110.9, 118.5, 121.1, 121.4, 133.7, 136.5, 144.3, 160.1, 161.7 (C=N), 168.5 (C=O).

4-(4-Ethylbenzylidene)-3-methylisoxazol-5(4*H*)-one (4d). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.24 (t, J = 7.5 Hz, 3H, $\underline{CH_3}CH_2$), 2.29 (s, 3H, CH_3), 2.70 (q, J = 7.5 Hz, 2H, CH_2), 7.44 (d, J = 8.1 Hz, 2H, Ar-H),

7.92 (s, 1H, H-vinyl), 8.41 (d, *J* = 8.1 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.7 (CH_3), 15.3 ($\underline{CH_3}CH_2$), 28.8 (CH_2), 118.2, 129.0, 130.9, 134.4, 151.5, 152.2, 162.8 (C=N), 168.6 (C=O).

4-(3,4-Dimethoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4e). ^{1}H NMR (300 MHz, $CDCl_3$): 2.24 (CH_3), 3.96 (s, 6H, OCH_3), 6.92 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.58 (d, *J* = 7.5 Hz, 1H, Ar-H), 8.67 (s, 1H, H-vinyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.6 (CH_3), 56.1 (OCH_3), 56.2 (OCH_3), 110.7, 115.0, 116.0, 126.3, 131.3, 148.9, 149.9, 154.5, 161.5 (C=N), 169.0 (C=O).

4-(3-Ethoxy-4-hydroxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4f). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.40 (t, *J* = 6.9 Hz, 3H, $\underline{CH_3}CH_2O$), 2.22 (s, 3H, CH_3), 4.09 (q, *J* = 6.9 Hz, 2H, $\underline{CH_2}O$), 6.96 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.69 (d, *J* = 1.5 Hz, 1H, Ar-H), 7.83 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.49 (s, 1H, H-vinyl), 10.69 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.7 (CH_3), 15.0 ($\underline{CH_3}CH_2O$), 64.3 (CH_2O), 114.0, 116.2, 117.9, 125.5, 132.0, 147.0, 152.2, 154.5, 162.6 (C=N), 169.4 (C=O).

3-Methyl-4-(3,4,5-trimethoxybenzylidene)isoxazol-5(4*H*)-one (4g). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.33 (s, 3H, CH_3), 3.97 (s, 6H, OCH_3), 4.01 (s, 3H, OCH_3), 7.35 (s, 1H, H-vinyl), 7.85 (s, 2H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.4 (CH_3), 56.4 (OCH_3), 61.2 (OCH_3), 111.8, 117.9, 122.7, 127.9, 149.8, 153.1, 161.3 (C=N), 168.5 (C=O).

3-Methyl-4-(4-methylbenzylidene)isoxazol-5(4*H*)-one (4h). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.58 (s, 1H, H-vinyl), 7.28 (d, *J* = 8.2 Hz, 2H, Ar-H), 8.32 (d, *J* = 8.2 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.5 (CH_3), 22.1 (CH_3-Ar), 127.9, 130.1, 140.2, 150.2, 162.2 (C=N), 168.9 (C=O).

4-(2,4-Dimethoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4i). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.72 (s, 1H, Ar-H), 6.76 (d, *J* = 10.0 Hz, 1H, Ar-H), 7.99 (s, 1H, H-vinyl), 9.02 (d, *J* = 10.0 Hz, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.7 (CH_3), 56.0 (OCH_3), 56.1 (OCH_3), 97.8, 105.9, 114.8, 115.5, 125.2, 136.2, 143.0, 161.8, 167.1 (C=N), 169.3 (C=O).

4-(2-Hydroxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4j). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H, CH_3), 6.96 (t, *J* = 10.0 Hz, 1H, Ar-H), 7.02 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.50 (t, *J* = 9.0 Hz, 1H, Ar-H), 8.08 (s, 1H, H-vinyl), 8.75 (dd, *J* = 2.0, 9.5 Hz, 1H, Ar-H), 10.20 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.2 (CH_3), 116.5, 119.1, 119.5, 132.2, 136.7, 145.0, 146.7, 159.6, 162.1 (C=N), 168.3 (C=O).

4-(3-Hydroxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4k). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (s, 3H, CH_3), 7.09 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.37 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.80 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.85 (s, 1H, H-vinyl), 7.94 (s, 1H, Ar-H), 9.95 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.8 (CH_3), 118.8, 120.0, 121.9, 125.9, 130.1, 134.2, 152.2, 157.9, 162.7 (C=N), 168.1 (C=O).

4-(4-Hydroxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4l). ^{1}H NMR (300 MHz, CDC1$_3$): δ 2.22 (s, 3H, CH_3) 6.92 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.76 (s, 1H, H-vinyl), 8.42 (d, *J* = 8.8 Hz, 2H, Ar-H), 11.0 (s, 1H, OH); ^{13}C NMR (75 MHz, CDC1$_3$): δ 11.7 (CH_3). 114.4, 124.6, 125.0,136.1, 151.0, 162.7, 164.3 (C=N), 169.3 (C=O).

***N*-(4-((3-Methyl-5-oxoisoxazol-4(5*H*)-ylidene)methyl)phenyl)acetamide (4m).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.12 (s, 3H, $COCH_3$), 2.27 (s, 3H, CH_3), 7.79 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.84 (s, 1H, H-vinyl), 8.47 (d, *J* = 9.2 Hz, 2H, Ar-H), 10.53 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.7 (CH_3), 24.8 ($CH_{3\ \text{acetamide}}$), 116.4, 118.7, 127.5, 136.3, 145.3, 151.4, 156.7 (C=N), 162.9 ($C{=}O_{\ \text{acetamide}}$), 170.1 (C=O).

3-Methyl-4-(3-phenylallylidene)isoxazol-5(4*H*)-one (4n). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 7.48-7.51 (m, 4H, Ar-H), 7.68-7.74 (m, 2H, Ar-H, H-vinyl), 7.83 (dd, *J* = 3.6, 11.4 Hz, 1H, H-alkene), 8.15 (dd, *J* = 3.6, 11.7 Hz, 1H, H-alkene).

3-Methyl-4-(thiophen-2-ylmethylene)isoxazol-5(4*H*)-one (4o). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H, CH_3), 7.29 (t, *J* = 4.8 Hz, 1H, Ar-H), 7.65 (s, 1H, H-vinyl), 7.95 (d, *J* = 4.8 Hz, 1H, Ar-H), 8.13 (d, J = 3.6 Hz, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5 (CH_3), 114.5, 128.8, 136.4, 139.2, 139.6, 141.5, 160.7 (C=N), 168.7 (C=O).

3-Methyl-4-((5-methylthiophen-2-yl)methylene)isoxazol-5(4*H*)-one (4p). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24 (s, 3H, $CH_{3\ \text{thiophen}}$), 2.60 (s, 1H, CH_3), 7.14 (dd, *J* = 0.8, 3.8 Hz, 1H, Ar-H), 8.04 (d, *J* = 3.8 Hz, 1H, Ar-H), 8.12 (s, 1H, H-vinyl); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.1 (CH_3), 15.6 ($CH_{3\ \text{thiophen}}$), 111.2, 128.3, 134.4, 141.6, 144.3, 157.1, 161.5 (C=N), 168.7 (C=O).

3-(Chloromethyl)-4-(4-hydroxy-3-methoxybenzylidene)isoxazol-5(4*H*)-one (4q). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.89 (s, 3H, OCH_3), 4.76 (s, 2H, CH_2Cl), 6.95 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.81 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.93 (s, 1H, H-vinyl), 8.54 (d, *J* = 8.4 Hz, 1H, Ar-H), 10.81 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.9 (CH_2Cl), 55.6 (OCH_3), 111.2, 116.8, 121.4, 124.9, 132.5, 148.5, 151.6, 153.4, 162.3 (C=N), 169.4 (C=O).

3-(Chloromethyl)-4-(3,4,5-trimethoxybenzylidene)isoxazol-5(4*H*)-one (4r). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.83 (s, 3H, OCH_3), 3.85 (s, 6H, OCH_3), 4.86 (s, 2H, CH_2Cl), 7.97 (s, 1H, H-vinyl), 8.09 (s, 2H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.9 (CH_2Cl), 56.1 (OCH_3), 60.5 (OCH_3), 112.3, 113.5, 127.5, 143.7, 152.6, 152.8, 161.7 (C=N), 167.9 (C=O).

3-(Chloromethyl)-4-(3,4-dimethoxybenzylidene)isoxazol-5(4*H*)-one (4s). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.87 (s, 2H, CH_2Cl), 7.22 (d, *J* = 8.6 Hz, 1H, Ar-H), 8.01 (dd, *J* = 1.8, 6.7 Hz, 1H, Ar-H), 8.05 (s, 1H, H-vinyl), 8.47 (d, *J* = 1.8 Hz, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.0 (CH_2Cl), 56.2 (OCH_3), 59.5 (OCH_3), 111.5, 111.8, 125.8, 131.7, 148.4, 152.9, 155.1, 161.6 (C=N), 168.3 (C=O).

3-(Chloromethyl)-4-(4-methoxybenzylidene)isoxazol-5(4*H*)-one (4t). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.95 (s, 3H, OCH_3), 4.58 (s, 2H, CH_2Cl), 7.05 (dd, *J* = 2.0, 7.2 Hz, 2H, Ar-H), 7.71 (s, 1H, H-vinyl), 8.52 (dd, *J* = 2.0, 7.2 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.4 (CH_2Cl), 55.8 (OCH_3), 112.5, 114.8, 125.6, 137.5, 151.3, 160.4, 165.3 (C=N), 168.4 (C=O).

3-(Chloromethyl)-4-(4-hydroxybenzylidene)isoxazol-5(4*H*)-one (4v). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.91 (s, 2H, CH_2Cl), 7.10 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.04 (s, 1H, H-vinyl), 8.48 (d, *J* = 8.8 Hz, 2H, Ar-H), 11.28 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.5 (CH_2Cl), 110.8, 116.9, 125.0, 138.7, 153.3, 162.3, 165.0 (C=N), 168.8 (C=O).

3-Propyl-4-(3,4,5-trimethoxybenzylidene)isoxazol-5(4*H*)-one (4w). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.99 (t, *J* = 3.3 Hz, 3H, CH_3), 1.70 (sext, *J* = 7.5 Hz, 2H, $\underline{CH_2}CH_3$), 2.65 (t, *J* = 7.7 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 3.81 (s, 3H, OCH_3), 3.83 (s, 6H, OCH_3), 7.87 (s, 1H, H-vinyl), 7.98 (s, 2H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.7 (CH_3), 19.3 ($\underline{CH_2}CH_3$), 27.2 ($\underline{CH_2}CH_2CH_3$), 55.8 (OCH_3), 60.3 (OCH_3), 112.1, 116.5, 128.0, 142.8, 151.1, 152.4, 164.7 (C=N), 168.6 (C=O).

4-(4-Hydroxybenzylidene)-3-propylisoxazol-5(4*H*)-one (4x). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.01 (t, *J* = 7.3 Hz, 3H, CH_3), 1.70 (sext, *J* = 7.4 Hz, 2H, $\underline{CH_2}CH_3$), 2.68 (t, *J* = 7.4, 2H, $\underline{CH_2}CH_2CH_3$), 6.97 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.85 (s, 1H, H-vinyl), 8.46 (d, *J* = 8.3 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1 (CH_3), 19.8 ($\underline{CH_2}CH_3$), 27.5 ($\underline{CH_2}CH_2CH_3$), 113.7, 116.5, 125.2, 138.1, 151.4, 164.2, 165.3 (C=N), 169.6 (C=O).

4-((1*H*-Indol-3-yl)methylene)-3-propylisoxazol-5(4*H*)-one (4y). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02 (t, *J* = 7.5 Hz, 3H, CH_3), 1.74 (sext, *J* = 7.2, 7.5 Hz, 2H, $\underline{CH_2}CH_3$), 2.77 (t, *J* = 7.2 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 7.31-7.37 (m, 2H, Ar-H), 7.59-7.64 (m, 1H, Ar-H), 8.17-8.19 (m, 2H, H-vinyl and Ar-H), 9.54 (s, 1H, H-2 of indole ring), 12.81 (s, 1H, N-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.2 (CH_3), 20.3 ($\underline{CH_2}CH_3$), 27.4 ($\underline{CH_2}CH_2CH_3$), 108.7, 113.1, 113.6, 119.3, 123.0, 124.4, 128.5, 136.8, 138.9, 140.4, 164.8 (C=N), 171.1 (C=O).

4-(3-Methoxy-4-(prop-2-yn-1-yloxy)benzylidene)-3-propylisoxazol-5(4*H*)-one (4z). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02 (t, *J* = 7.5 Hz, CH_3), 1.70 (sext, *J* = 7.2, 7.5 Hz, 2H, $\underline{CH_2}CH_3$), 2.68 (t, *J* = 7.2 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 3.87 (s, 3H, OCH_3), 3.69 (t, *J* = 2.1 Hz, ≡CH), 4.99 (d, *J* = 2.1 Hz, 2H, CH_2O), 7.92 (s, 1H, H-vinyl), 7.26 (d, *J* = 8.1 Hz, 1H, Ar-H), 8.07 (dd, *J* = 3.3, 8.4 Hz, 1H. Ar-H), 8.50 (*J* = 1.8 Hz, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.2 (CH_3), 19.8 ($\underline{CH_2}CH_3$), 27.5 ($\underline{CH_2}CH_2CH_3$), 56.0 (OCH_3), 56.7 (CH_2O), 78.9 (≡CH), 79.5 ($\underline{C}$≡CH), 113.4, 115.5, 116.5, 127.1, 130.6, 148.9, 151.6, 152.3, 165.2 (C=N), 169.3 (C=O). Anal. Calcd for $C_{17}H_{17}NO_4$ (%): C, 68.22; H, 5.72; N, 4.68. Found: C, 68.25; H, 5.57; N, 4.73.

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