Article

J. Mex. Chem. Soc. **2015**, *59(3)*, 191-197

ISSN 1870-249X

DOWEX(R)50WX4/H_2O: A Green System for a One-pot and Three-Component Synthesis of isoxazol-5(4*H*)-one Derivatives

Davood Setamdideh*

Department of Chemistry, Mahabad Branch, Islamic Azad University, Mahabad, Iran.
*E-mail: davood.setamdideh@gmail.com; d.setamdideh@iau-mahabad.ac.ir

Received May 12th, 2015; Accepted August 3rd, 2015

Abstract. A one-pot and three-component synthesis of 3-methyl-4-arylmethyleneisoxazol-5(4*H*)-ones was developed in the presence of DOWEX(R)50WX4 as the catalyst. The products were obtained in high yields (93-96%) and short reaction times (30-60 min). The present method provides an easy and efficient approach for the synthesis of this class of compounds, because of its clean reaction profile and operational simplicity.
Key words: DOWEX(R)50WX4, isoxazol-5(4*H*)-one, one-pot reaction, water, green chemistry.

Resumen. Se describe el desarrollo de una síntesis de 3-metil-4-arilmetilenisoxazol-5(4*H*)-onas a través de un método tri-componente en un solo matraz y en presencia de DOWEX(R)50WX4 como catalizador. Los productos se obtuvieron en elevados rendimientos (93-96%) y en tiempos de reacción cortos (30-60 min). Este método representa una alternative fácil y eficiente para la síntesis de esta clase de compuestos, en razón de un perfil de reacción que evita la formación de subproductos y es de gran simplicidad operacional.
Palabras clave: DOWEX(R)50WX4, isoxazol-5(4*H*)-ona, reacción *one-pot*, agua, química sustentable.

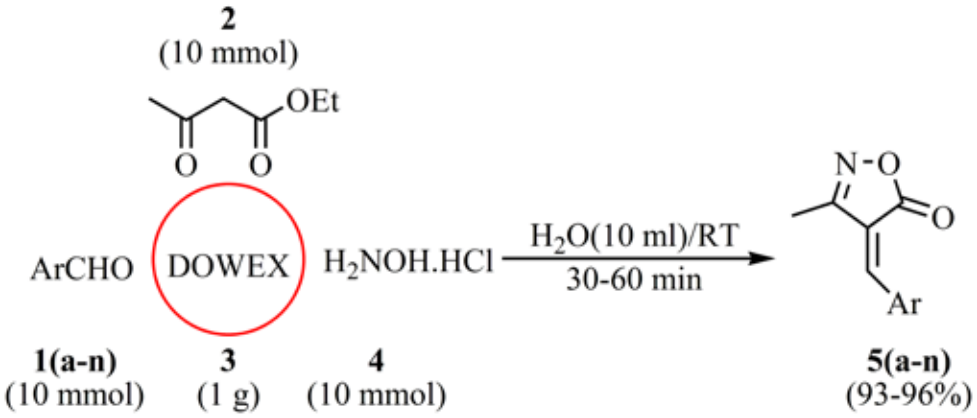
Introduction

Isoxazole derivatives are a class of heterocyclic compounds featuring a variety of biological activities such as treatment of arthritis [1a], treatment of leishmaniasis [1b], inhibition of protein-tyrosine phosphatase 1B [1c], anti-mycobacterial [1d], anti-convulsing [1e], HDAC inhibitory activity [1f], analgesic [1g-h], nematicidal [1i], anti-oxidant [1j-k], anti-microbial [1l], COX-2 inhibitory [1m], anti-inflammatory [1n], anti-cancer [1o], anti-viral [1p], and anti-tuberculosis [1q]. Furthermore, isoxazolone moieties can also be found in compounds used for the design of liquid crystals [1r], merocyanine dyes in optical research [1s-t], and photochromic components [1u-v]. Literature survey shows that the synthesis of aryl-3-methylisoxazol-5(4*H*)-one derivatives involves a coupling of aromatic aldehydes with ethyl acetoacetate and hydroxylamine. This procedure has been performed by different reagents and catalysts in basic medium such as *via* pyridine [2a], sodium silicate [2b], sodium benzoate [2c], sodium azide [2d], sodium saccharin [2e], sodium citrate [2f], sodium sulfide [2g], sodium ascorbate [2h], and sodium tetraborate [2i]. Also some methods have been carried out at high temperature and long reaction times [2j], with moderate yields [2k], or under unconventional energy sources such as ultrasound irradiation [2k], visible light [2l], and microwave irradiation [2m]. On the other hand, multi-component reactions (MCRs) have been used as very powerful method for the synthesis of a variety of molecules in one-pot reactions. This type of reactions is important in the synthesis of natural products and biologically active compounds, because they have many advantages such as excellent functional group compatibility, minimization of waste, versatility, atom economy, environmentally friendly, and easy work-up [3].

Recently, we have reported that DOWEX(R)50WX4 (ion-exchange resin) is a strong acid been used for the regioselective synthesis of oximes by using an $NH_2OH{\cdot}HCl$/DOWEX-(R)50WX4 system [4a], the reduction of a variety of carbonyl compounds such as aldehydes, ketones, α-diketones, acyloins and α,β-unsaturated carbonyl compounds to their corresponding alcohols by applying the $NaBH_4$/DOWEX(R)50WX4 system [4b], the synthesis of cyanohydrins by NaCN/DOWEX-(R)50WX4 [4c], the reductive-amination of a variety of aldehydes and anilines by $NaBH_4$/DOWEX(R)50WX4 [4d], and for the reductive acylalation of aldehydes by borohydrides/Ac_2O/DOWEX(R)50WX4-8 systems [4e-f]. These achievements encouraged us to probe the development of convenient and environmentally benign procedure by DOWEX(R)50WX4 as the catalyst for the synthesis of 4-arylmethylidene-3-substituted-isoxazol-5(4*H*)-ones. Thus, the synthesis of 4-arylmethylidene-3-methyl-isoxazol-5(4*H*)-ones was attempted by using equimolecular quantities of ethyl acetoacetate, hydroxylamine hydrochloride, and a variety of aromatic aldehydes in the presence of DOWEX(R)50WX4 as catalyst in water (Scheme 1).

Results and Discussion

Recognizing the MC-based processes as powerful methods for the synthesis of structurally diverse compounds [3], we conceived the preparation of diverse arylmethylidene-isoxazole-5(4*H*)-ones from the reaction between an aromatic aldehyde, hydroxylamine hydrochloride, and ethyl acetoacetate



Scheme 1. General procedure for the synthesis of (*Z*)-3-methyl-4-arylmethylene-isoxazol-5(4*H*)-ones **(5)** from the corresponding aromatic aldehydes **(1)** with hydroxylamine hydrochloride **(4)** and ethyl acetoacetate **(2)** in the presence of DOWEX(R)50WX4 **(3)** as catalyst in water at room temperature.

(EAA) catalyzed by DOWEX(R)50WX4. In order to determine the optimal reaction conditions, we screened different amounts of DOWEX(R)50WX4 (0-2 g) (Table 1) using benzaldehyde as a model compound. When the amount of DOWEX(R)50WX4 was increased from 0.5 to 1 g, the yield of product was improved from 60 to 95 % (entries 1–2). However, when the amount of DOWEX(R)50WX4 was increased to 2 g, a remarkable increase in the yield of the product was not observed (Table 1, entries 3–4). Consequently, the amount of 1 g for DOWEX(R)50WX4 was selected as the optimized amount of the catalyst for this procedure.

The efficiency of this protocol was examined by the reaction of a variety of aldehydes with electron-donating groups (**5b-e** and **5n**), with electron-withdrawing groups (**5h** and **5k-m**), cinnamaldehyde (**5f**) as an unsaturated aldehyde, and furfural (**5g**) as a heterocyclic aldehyde. In general, aldehydes with donating groups react in shorter times. However, all reactions were completed in appropriate times within 30-60 min in excellent yields (93-96%) (Table 2). The products were characterized by ^{1}H-NMR spectroscopy, considering the chemical shifts of the olefinic proton of the exocyclic methylene group (Table 2, column 7) and the methyl group (Table 2, column 8), which appear around 7.20-8.40 ppm and 2.21-2.33 ppm, respectively, as singlet signals. The C=O stretching frequency in the FT-IR spectrum of the products appears around 1714-1768 cm^{-1} (Table 2, column 9). Melting points of the products (Table 2, column 6) were measured and compared with the literature for the known compounds [2]. Two isomeric products the (*E*) and (*Z*)-arylmethylidene moiety are possible in these products. Characterization and comparison of the formed products with suitable references [**2k** and **2l**] supports the selectivity for the formation of the (*Z*)-isomer. Therefore, the products are assumed to have the double bond with the (*Z*) geometry.

Two proposed mechanism for the formation of the products and the influences of DOWEX(R)50WX4 are shown in Schemes 2 and 3. It is likely that the SO_3H groups on DOWEX-(R)50WX4 (as cation-exchange resin and strong acid catalyst) protonate the carbonyl group of ethyl acetoacetate and the aromatic aldehyde. Therefore, DOWEX(R)50WX4 activates aldehyde and ester moieties to produce oxime intermediate (A, scheme 2 and 3). In the first pathway (Scheme 2), the obtained oxime can react with the aromatic aldehyde. Then, the reaction proceeds *via* the intermolecular Knoevenagel addition to give the corresponding adduct (B), which is followed by a ring closure.

Table 1. Optimization reaction condition for the synthesis of (*Z*)-4-benzylidene-3-methylisoxazol-5(4H)-one **(5a)** from benzaldehyde (10 mmol), ethyl acetoacetate (10 mmol) and $NH_2OH.HCl$ (10 mmol) in H_2O (10 ml) in the presence of DOWEX(R)50WX4 as shown in scheme 1.

Entry	DOWEX(R)50WX4 (g)	time (min)	conversion (%)[a]	yield (%)[b]
1	0	90	100<	40
2	0.25	90	100<	60
3	0.5	70	100	94
4	1	40	100	95
5	2	30	100	95

[a] Conversion refers to TLC monitoring.
[b] Yield refers to isolated pure product.

Table 2. Synthesis of (*Z*)-4-arylmethylidene-3-methyl-isoxazol-5(4*H*)-ones with DOWEX(R)50WX4/H_2O system as shown in scheme 1.

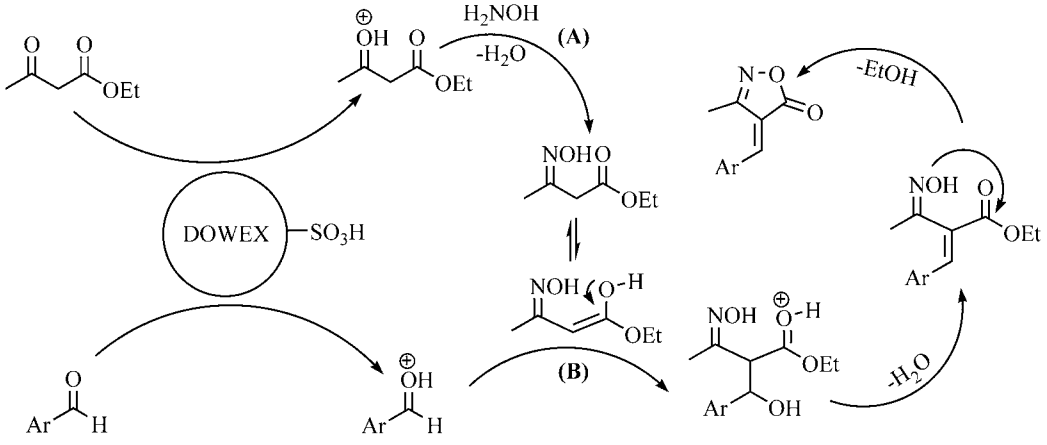
Entry	Product	Ar	time (min)	yield (%) [a]	mp (°C) [b]	^{1}H-NMR ($CDCl_3$)/ppm		FT-IR (KBr)/cm^{-1}
						CH=C	CH_3	C=O
1[c]	5a	Ph	40	95	140-142	7.44	2.31	1732
2[c]	5b	4-MeO-Ph	30	96	177-179	7.34	2.28	1730
3[c]	5c	2-MeO-Ph	30	95	159-160	8.06	2.31	1732
4[c]	5d	4-HO-Ph	35	93	214-216	7.80	2.30	1730
5[c]	5e	2-HO-Ph	35	93	200-202	8.10	2.23	1755
6[c]	5f	Ph-CH=CH	40	96	180-182	-	2.25	1733
7[c]	5g	2-furyl	50	93	240-242	7.85	2.32	1748
8[d]	5h	3-Br-Ph	50	95	141-143	7.35	2.31	1729
9[d]	5i	4-Me_2N-Ph	30	95	206-209	7.27	2.23	1714
10[c]	5j	4-Me-Ph	40	94	129-131	7.40	2.29	1731
11[c]	5k	4-F-Ph	50	93	154-156	8.12	2.23	1768
12[c]	5l	3-F-Ph	50	95	142-144	7.39	2.33	1730
13[d]	5m	4-O_2N-Ph	60	95	163-165	8.25	2.21	1778
14[c]	5n	4-C_2H_5O-Ph	60	93	151-153	7.34	2.28	1735

[a] Yields refer to isolated pure products after recrystallization in appropriate solvent.
[b] The melting points have been compared with the literatures. 5c and 5h are new compounds. [2].
[c] The products have been recrystallized in ethanol (96%).
[d] The products have been recrystallized in acetone.

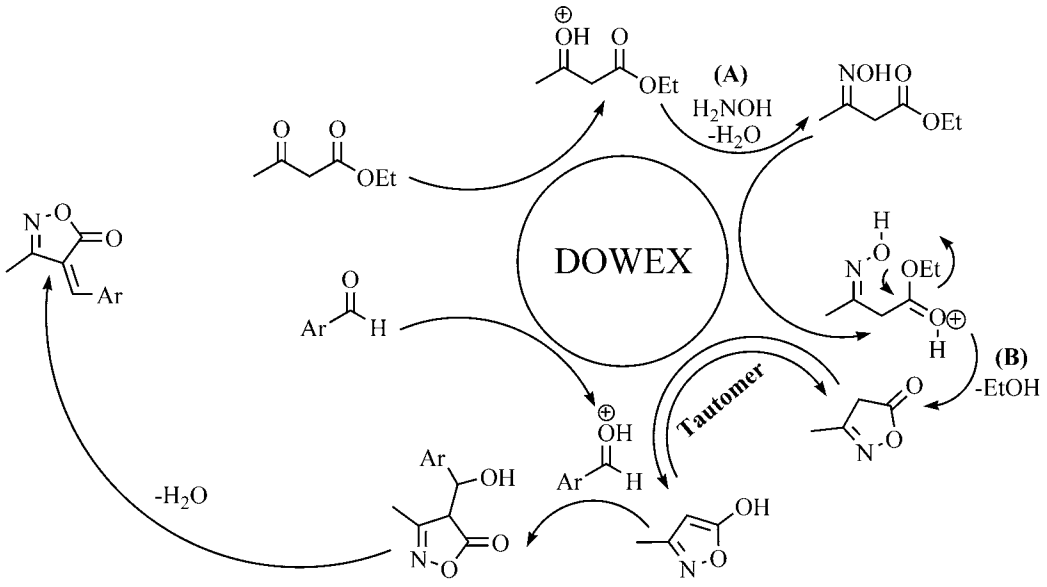
As shown in Scheme 3, an alternative pathway for the mechanism is the formation of the 3-methyl-5(4*H*)-isoxazolone (B) before the alkylidene formation by condensation with the aldehyde. Since the intramolecular attack of the oxime to the ester moiety may be a faster process than the intermolecular Knoevenagel adduct (B, scheme 2), it is expected that the heterocyclic formation were anticipated to the condensation with the aldehyde component.

These mechanisms are supported by carrying the reactions in the absence and presence of the catalyst. As shown in Table 1, without any catalyst, the yields of the products were low even after long periods of time.

In order to show the merit of DOWEX(R)50WX4 in comparison with other catalysts (used for the same reaction), we have tabulated and compared some of the results in Table 3. The comparison shows that the yields and reaction times are improved in the presence of DOWEX(R)50WX4. In addition, the work-up is easier (The ion-exchange resin DOWEX-(R)50WX4 is insoluble in H_2O and its removal is very easy), the reaction conditions milder, the catalyst is reused, and by using water as a green solvent, are clear advantages for this new protocol, in comparison with other reported methods, which use more severe conditions and complicate extraction procedures.



Scheme 2. The proposed mechanism for the synthesis of (*Z*)-3-methyl-4-arylmethylene-isoxazol-5(4*H*)-ones in the presence of DOWEX(R)50WX4.



Scheme 3. The another proposed mechanism for the synthesis of (*Z*)-3-methyl-4-arylmethylene-isoxazol-5(4*H*)-ones in the presence of DOWEX(R)50WX4.

Table 3. Comparison of the synthesis of (*Z*)-4-(4-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one **(5b)** by DOWEX(R)50WX4 and other reported systems.

Entry	Catalyst and conditions	time (min)	yield (%)[a]	Recyclable catalyst	Reference
1	DOWEX(R)50WX4 /H_2O/R.T.	30	96	yes	This context
2	Na_2S/EtOH/R.T	90	88	no	2g
3	Pyridine/EtOH/reflux	180	71	no	2a
4[b]	Catalyst free/grinding	48	61	-	2j
5[c]	Catalyst free/105–110 ˚C	15	66	-	2j
6	Pyridine/H_2O/ultrasound	60	82	no	2k
7	Sodium tetraborate/H_2O/R.T.	50	95	no	2i
8	Sodium Benzoate/H_2O/R.T.	90	87	no	2c
9	visible light/aq. EtOH/R.T.	10	82	-	2l

[a] Isolated yield.
[b] The mixture was allowed to stand 12 h after the completion of the reaction.
[c] The mixture was allowed to stand overnight after the completion of the reaction.

We have checked the reusability of the catalyst by using the recovered DOWEX(R)50WX4 from the synthesis of (*Z*)-4-benzylidene-3-methylisoxazol-5(4*H*)-one (**5a**) as shown in Table 4. We have observed that the recovered catalyst could be satisfactorily used for the second run without regeneration. Whereas, a third run of the recovered catalyst leads to poor yields and longer reaction times. Likewise, the reaction was also efficient like the first run by carrying out the reaction in the presence of the regenerated DOWEX(R)50WX4 (Table 4, entry 4). Regeneration of the latter was achieved by stirring in HCl 5-10% for 30-60 min, then washed with distillated water.

Conclusion

In conclusion, we have shown that DOWEX(R)50WX4 in water is a convenient catalyst for the preparation of a variety of alkylidene isoxazol-5(4*H*)-ones, using aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride precursors in one-pot, three-component condensation reaction at room temperature in excellent yields. High efficiency, shorter reaction times, easy work-up, mild reaction conditions, reuse of catalyst, and using of water as a green solvent make to this new protocol attractive for the synthesis of these heterocycles. Therefore, this

Table 4. Reusability of DOWEX(R)50WX4 in the synthesis of (*Z*)-4-benzylidene-3-methylisoxazol-5(4*H*)-one **(5a)** from benzaldehyde under optimized reaction conditions.

yields (%)[c]	conversion (%)[b]	time (min)[a]	Run Number	Entry
95	100	40	1	1
91	100	50	2	2
60	100<	90	3	3
93	100	40		4[d]

[a] It is the highest time when the reaction ends or dose not further progress.
[b] Conversion refers to TLC monitoring (eluent; CH_2Cl_2);
[c] Yields refer to isolated pure products (±3%).
[d] Regeneration by HCl (5-10%).

new efficient protocol can be added to the list of the currently used methodologies.

Experimental

General. All substrates and reagents were purchased from commercially sources (Merck and Sigma-Aldrich). DOWEX-(R)50WX4 (100-200 mesh)(CAS No. 111134-61-4) was prepared from Sigma-Aldrich company. FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectra were recorded on PerkinElmer FT-IR RXI and 300 MHz Bruker spectrometers, respectively. The products were characterized by their FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectra and comparison with authentic samples. Organic layers were dried over anhydrous sodium sulfate. All yields referred to isolated pure products. The purity of products was determinate by ^{1}H NMR. Also, reactions were monitored over silica gel 60 F_{254} aluminum sheet.

A typical procedure for the synthesis of (*Z*)-4-arylmethylene-3-methyl-isoxazol-5(4*H*)-ones

In a round-bottomed flask (25 mL) equipped with a magnetic stirrer, a mixture of ethyl acetoacetate (1.30 g, 10 mmol), hydroxylamine hydrochloride (0.7 g, 10 mmol), aromatic aldehyde (10 mmol), and DOWEX(R)50WX4 (1 g) in 10 mL of distilled water was prepared and stirred at room temperature for mentioned time in Table 2. After completion of reaction (monitored by TLC), the precipitate was filtered off and washed with cold distilled water. Then products were recrystallized from ethanol or acetone as mentioned in Table 2. Pure (*Z*)-4-arylmethylene-3-methyl-isoxazol-5(4*H*)-ones were obtained as solids after recrystallization from ethanol or acetone and were characterized by ^{1}H-NMR, ^{13}C-NMR, and FT-IR spectroscopy.

Spectral data for prepared compounds:

(Z)-4-benzylidene-3-methylisoxazol-5(4H)-one (5a)
Yellow crystal: mp 140-142 °C (Lit [2k] mp 142-144 °C);^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3), 7.44 (s, 1H, ArCH=), 7.49-7.59 (m, 3H, Ar), 8.35 (dd, J = 1.3, 7.4 Hz, 2H, Ar); ^{13}C-NMR (300 MHz, $CDCl_3$): δ 11.63 (CH_3), 119.65 (C=, inside of isoxazolone ring), 129.03 (Ar), 130.47 (Ar), 132.29 (Ar), 134.01 (Ar), 149.98 (ArCH=), 161.16 (C=N), 167.88 (C=O); IR (KBr) *v*: 1732 (C=O), 1620, 1100, 1216, 879, 763 cm^{-1}.

(Z)-4-(4-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (5b)
Yellow crystal: mp 177-179 °C (Lit [2k] mp 177-178 °C);^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.34 (s, 1H, ArCH=), 7.00 (d, J = 8.7 Hz, 2H, Ar), 8.44 (d, J = 8.7 Hz, 2H, Ar); ^{13}C-NMR (300 MHz, $CDCl_3$): δ 11.63 (CH_3), 55.70 (OCH_3), 114.64 (C=, inside of isoxazolone ring), 116.31 (Ar), 125.82 (Ar), 136.96 (Ar), 149.35 (ArCH=), 161.29 (Ar-O), 164.60 (C=N), 168,77 (C=O); IR (KBr) *v*: 1730 (C=O), 1590, 1267, 1018, 875, 775 cm^{-1}.

(Z)-4-(2-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (5c)
Yellow crystal: mp 159-160 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 6.96 (d, J = 8.4 Hz, 1H, Ar), 7.09 (t, J = 7.8 Hz, 1H, Ar), 7.56 (t, J = 7.05 Hz, 1H, Ar), 8.06 (s, 1H, ArCH=), 8.92 (d, J = 8.1 Hz, 1H, Ar); ^{13}C-NMR (300 MHz, $CDCl_3$): δ 11.67 (CH_3), 55.47 (OCH_3), 110.70 (C=, inside of isoxazolone ring), 118.32 (Ar), 120.84 (Ar), 121.20 (Ar), 133.37 (Ar), 136.27 (Ar), 143.98 (ArCH=), 159.82 (C=N), 161.52 (C=O); IR (KBr) *v*: 1732 (C=O), 1590, 1256, 1103, 887, 765 cm^{-1}. IR (KBr) *v*: 1732 (C=O), 1590, 1256, 1103, 887, 765 cm^{-1}.

(Z)-4-(4-hidroxybenzylidene)-3-methylisoxazol-5(4H)-one (5d)
Yellow crystal: mp 214-216°C (Lit [2k] mp 215-218 °C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 6.95 (d, J=9.3 Hz, 2H, Ar), 7.80 (s, 1H, ArCH=), 8.48 (d, J=9.3 Hz, 2H, Ar), 11.06 (s, 1H, OH); IR (KBr) ν: 1730 (C=O), 1596, 1556, 1515, 1310, 1234 cm^{-1}.

(Z)-4-(2-hidroxybenzylidene)-3-methylisoxazol-5(4H)-one (5e)
Yellow crystal: mp 200-202 °C (Lit [2f] mp 198-201 °C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, CH_3), 6.90 (t, J=6.7 Hz, 1H, Ar), 7.00 (t, J=6.7 Hz, 1H, Ar), 7.48 (t, J=7.4 Hz, 1H, Ar), 8.10 (s, 1H, ArCH=), 8.75 (t, J=7.4 Hz, 1H, Ar); 11.00 (s, 1H, OH); IR (KBr) ν: 1755 (C=O), 1590, 1459, 1369, 1312, 1268 cm^{-1}

(Z)-3-methyl-4-(3-phenylallylidene)isoxazol-5(4H)-one (5f)
Yellow crystal: mp 180-182 °C (Lit [2k] mp 179-181 °C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, CH_3), 7.28-7.36 (m,

2H, CH=CH), 7.36-7.47 (m, Ar (2H) & ArCH= (1H)), 7.64-7,66 (m, 2H, Ar), 8.26-8.35 (m, 1H, Ar); ^{13}C-NMR (300 MHz, $CDCl_3$): δ 11.19 (CH_3), 117.86 (C=, inside of isoxazolone ring), 121.34 (Ar), 122.38 (Ar), 129.31 (Ar), 131.53 (C=C), 134.96 (C=C), 147.53 (Ar), 151.45 (ArCH=), 159.89 (C=N), 168.99 (C=O); IR (KBr) *v*: 1733 (C=O), 1542, 1103, 993, 848, 753 cm^{-1}.

(Z)-4-(2-furylmethylene)-3-methylisoxazol-5(4H)-one (5g)
Yellow crystal: mp 240-242 °C (Lit [2k] mp 240-242 °C), ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H, CH_3), 7.12-7.18 (m, 1H, furyl), 7.85 (s, 1H, furylCH=), 8.11-8.16 (m, 1H, furyl), 8.60-8.67 (m, 1H, furyl); IR (KBr) ν: 1748 (C=O), 1616, 1590, 1318, 1292, 1220, 1176 cm^{-1}.

(Z)-4-(3-bromobenzylidene)-3-methylisoxazol-5(4H)-one (5h)
Yellow crystal: mp 141-143 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3), 7.35 (s, 1H, ArCH=), 7.41 (t, J = 8.1 Hz, 1H, Ar), 7.71 (d, J = 7.80 Hz, 1H, Ar), 8.34 (d, J = 7.8 Hz, 1H, Ar), 8.46 (s, 1H, Ar); ^{13}C-NMR (300 MHz, $CDCl_3$): δ 11.60 (CH_3), 121.12 (Ar-Br), 122.89 (C=, inside of isoxazolone ring), 130.48 (Ar), 131.90 (Ar), 133.87 (Ar), 136.03 (Ar), 136.50 (Ar), 147.71 (ArCH=), 160.86 (C=N), 167.45 (C=O); IR (KBr) *v*: 1729 (C=O), 1544, 1217, 1123, 871, 775 cm^{-1}.

(Z)-4-(4-(dimethylamino)benzylidene)-3-methylisoxazol-5(4H)-one (5i)
Red crystal: mp 206-209 °C (Lit [2k] mp 206-207 °C); ^{1}H-NMR (300 MHz, $CDC1_3$): δ 2.23 (s, 3H, CH_3), 3.15 (s, 6H, $N(CH_3)_2$), 6.71 (d, J = 9 Hz, 2H, Ar), 7.27 (s, 1H, ArCH=), 8.39 (d, J = 9 Hz, 2H, Ar); ^{13}C-NMR (300 MHz, $CDCl_3$): δ 11.71 (CH_3), 40.10 ($(CH_3)_2N$), 111.07 (Ar), 111.50 (C=, inside of isoxazolone ring), 121.51 (Ar), 137.62 (Ar), 149.26 (Ar), 154.22 (ArCH=), 161.59 (C=N), 170.12 (C=O); IR (KBr) *v*: 1714 (C=O), 1557, 1380, 1196, 1095, 867, 765 cm^{-1}.

(Z)-4-(4-methylbenzylidene)-3-methylisoxazol-5(4H)-one (5j)
Lemon crystal: mp 129-131 °C (Lit [2j] mp 126-127 °C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.32 (d, J = 7.8 Hz, 2H, Ar), 7.40 (s, 1H, ArCH=), 8.29 (d, J = 7.8 Hz, 2H, Ar); ^{13}C-NMR (300 MHz, $CDCl_3$): δ 11.65 (CH_3), 22.07 (CH_3), 118.40 (C=, inside of isoxazolone ring), 129.88 (Ar), 134.14 (Ar), 145.73 (Ar), 149.96 (ArCH=), 161.22 (C=N), 168.21(C=O); IR (KBr) *v*: 1731 (C=O), 1594, 1114, 873, 777 cm^{-1}.

(Z)-4-(4-fluorobenzylidene)-3-methylisoxazol-5(4H)-one (5k)
Yellow crystal: mp 154-156 °C (Lit [2k] mp 153-155 °C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, CH_3), 6.80 (d, J=8.1 Hz, 2H, Ar), 8.12 (s, 1H, ArCH=), 8.80 (d, J=8.1 Hz, 2H, Ar); IR (KBr) ν: 1768 (C=O), 1612, 1586, 1470, 1375, 1323, 1274 cm^{-1}.

(Z)-4-(3-fluorobenzylidene)-3-methylisoxazol-5(4H)-one (5l)
Yellow crystal: mp 142-144 °C (Lit [2n] mp 142-144 °C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, CH_3), 7.20 (m, 1H, Ar), 7.33 (t, J = 7.6 Hz, 1H, Ar), 7.62 (m, 1H, Ar), 7.39 (s, 1H, ArCH=), 9.00 (m, 1H, Ar); IR (KBr) *v*:1730 (C=O), 1682, 1590, 1524, 1431, 1255, 879 cm^{-1}.

(Z)-4-(4-nitrobenzylidene)-3-methylisoxazol-5(4H)-one (5m)
Orang crystal: mp 163-165 °C (Lit [2k] mp 164-166 °C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3H, CH_3), 6.71-8.90 (m, 4H, Ar), 8.25 (s, 1H, ArCH=); IR (KBr) ν: 1778 (C=O), 1618, 1596, 1489, 1366, 1340, 1281 cm^{-1}.

(Z)-4-(4-ethoxybenzylidene)-3-methylisoxazol-5(4H)-one (5n)
Yellow crystal: mp 151-153 °C (Lit [2n] mp 150-152 °C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.33 (t, J = 7.2 Hz, 3H, EtO), 2.28 (s, 3H, CH_3), 4.16 (q, J = 7.2 Hz, 2H, EtO), 6.70 (d, J = 8.6 Hz, 2H, Ar), 7.34 (s, 1H, ArCH=), 8.44 (d, J = 8.6 Hz, 2H, Ar); IR (KBr) ν: 1735 (C=O), 1582, 1556, 1275, 890 cm^{-1}.

Acknowledgments

The authors gratefully appreciated the financial support of this work with the grant No. 02-2905/22092-1393/12/17 by the research council of Islamic Azad University branch of Mahabad.

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