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Original scientific paper

One-pot green synthesis of isoxazol-5(4*H*)-one derivatives using Dowex1-x8OH in water

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Abstract: 4-(Arylmethylidene)-3-methylisoxazol-5(4*H*)-ones and 4-(arylmethylidene)-3-phenylisoxazol-5(4*H*)-ones were synthesized in a one-pot three-component procedure in the presence of Dowex1-x8OH as catalyst in water. The products were obtained in high yields (90–95 %) and proper reaction times (1–5 h). The method is eco-friendly and operationally simple.

Keywords: dye; removal; polymeric sorbent; equilibrium; kinetic; thermodynamics; Dowex1-x8OH; isoxazol-5(4*H*)-one; one-pot reaction; green chemistry.

INTRODUCTION

Multi-component reactions (MCRs) play an important role in combinatorial chemistry because of their ability to synthesize diverse and complex organic molecules, natural products, and biologically active compounds. An MCR allows compounds to be synthesized in a few steps and usually in a one-pot operation without the need to isolate any intermediate during the reactions. Other typical benefits from these reactions are simplified work-up, reduced reaction times, saving of energy and raw materials, minimization of waste, easy purification, excellent functional group compatibility, versatility, and eco-friendliness.[1–11]

Isoxazole derivatives possess a variety of biologically activities.[12–30] In addition, isoxazolone moieties have been used for the design of liquid crystals, merocyanine dyes in optical research, and photochromic compounds.[31–35] Furthermore, 4-(arylmethylene)isoxazol-5-ones are used for the preparation of fused heterocyclic compounds.[36–39]

The synthesis of 4-aryl-3-methylisoxazol-5(4*H*)-one derivatives was performed using a variety reagents and catalysts in basic medium, such as *via* pyridine,[40] sodium silicate,[41] sodium benzoate,[42] sodium azide,[43] sodium saccha-

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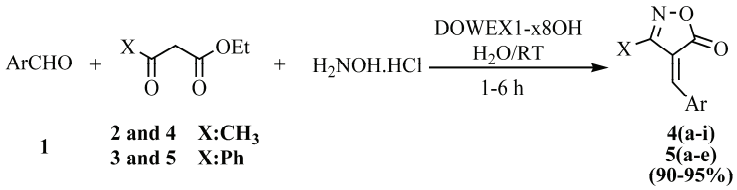
rin,[44] sodium citrate,[45] sodium sulfide,[46] sodium ascorbate[47] and sodium tetraborate.[48] Moreover, some methods were performed at high temperatures and for long reaction times,[49] with minimal yields[50] or under unconventional energies, such as ultrasound irradiation[50] or visible light.[51]

Recently, it was reported that Dowex(R)50WX4 (ion-exchange resin, strong acid) could be used for the regioselective synthesis of oximes in the $NH_2OH·HCl$/Dowex(R)50WX4 system,[52] 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 using the $NaBH_4$/ /Dowex(R)50WX4 system,[53] the synthesis of cyanohydrins using the NaCN/ Dowex(R)50WX4 system,[54] the reductive–amination of a variety of aldehydes and anilines using the $NaBH_4$/Dowex(R)50WX4 system,[55] the reductive acylalation of aldehydes using the borohydrides/Ac_2O/Dowex(R)50WX4-8 systems,[56,57] and for the synthesis of isoxazol-5(4*H*)-one derivatives.[58] Furthermore, Dowex1-x8 (ion-exchange resin, strong base) was used for the reduction of carbonyl compounds.[59]

These achievements encouraged this investigation of a convenient and eco--friendly procedure for the synthesis of 4-(arylmethylidene)-3-substituted isoxazol-5(4*H*)-ones using Dowex1-x8OH as catalyst. Thus, the synthesis of 4-(arylmethylidene)-3-methylisoxazol-5(4*H*)-ones **4a**–**i** and 4-(arylmethylidene)--3-phenylisoxazol-5(4*H*)-ones **5a**–**e** was attempted using equimolecular quantities of ethyl acetoacetate, hydroxylamine hydrochloride, and a variety of aromatic aldehydes in the presence of Dowex1-x8OH in water, as shown in Scheme 1.



Scheme 1. General procedure for the synthesis of 3-methyl- and 3-phenyl-4-(arylmethylidene)-isoxazol-5(4*H*)-ones **4a**–**i** and **5a**–**e**, respectively. For Ar see Table I.

EXPERIMENTAL

General. All substrates and reagents of the best quality were purchased from commercial sources. The FT-IR and ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a PerkinElmer FT--IR RXI spectrometer and a 300 MHz Bruker spectrometer, respectively. The products were characterized by their ^{1}H-NMR or IR spectra and comparison with authentic samples (melting points). The organic layers were dried over anhydrous sodium sulfate. All yields refer to isolated pure products. The purities of the products were determined by ^{1}H-NMR spectroscopy. In addition, the reactions were monitored by TLC using silica gel 60 F_{254} aluminum sheets.

The analytical and spectral data are given in Supplementary material to this paper.

Preparation of the Dowex1-x8OH resin[60]

Dowex1-x8 (10 g) was washed sequentially with 1 M aqueous HCl (3×40 mL), 1 M aqueous NaOH (3×40 mL) and 100 mL of water, and then dried overnight prior to use.

*General procedure for the synthesis of the 4-(arylmethylidene)-3-methylisoxazol-5(4*H*)-ones* ***4a–i***

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 Dowex1-x8OH (1 g) in 10 mL of distilled water was prepared and stirred at room temperature for the required time (given in Table I). After completion of the reaction (monitored by TLC), the precipitate was filtered off and washed with cold distilled water. Then the products were recrystallized from ethanol or acetone (Table I). The 4-(arylmethylidene)-3-methylisoxazol-5(4*H*)-ones were obtained in excellent yields (90–95 %), and characterized by FT-IR, and ^{1}H-NMR and ^{13}C-NMR spectroscopy.

*General procedure for the synthesis of the 4-(arylmethylidene)-3-phenylisoxazol-5(4*H*)-ones* ***5a–e***

In a round-bottomed flask (25 mL) equipped with a magnetic stirrer, a mixture of ethyl 3-oxo-3-phenylpropanoate (10 mmol), hydroxylamine hydrochloride (0.7 g, 10 mmol), aromatic aldehyde (10 mmol) and Dowex1-x8OH (1 g) in 10 mL of distilled water was prepared and stirred at room temperature for the required time (given in Table I). After completion of the reaction (monitored by TLC), the precipitate was filtered off and washed with cold distilled water. Then products were recrystallized from ethanol or acetone (Table I). The 4-(arylmethylidene)-3-methylisoxazol-5(4*H*)-ones were obtained in excellent yields (90–95 %) and characterized by FT-IR, and ^{1}H-NMR and ^{13}C-NMR spectroscopy.

TABLE I. The synthesis of 4-(arylmethylidene)-3-methylisoxazol-5(4*H*)-ones and 4-(arylmethylidene)-3-phenylisoxazol-5(4*H*)-ones with the Dowex1-x8OH/H_2O system

Entry	Product	Ar	Time, h	Yield[a], %
1[b]	**4a**	Ph	2	92
2[b]	**4b**	4-MeO-Ph	1	95
3[b]	**4c**	2-MeO-Ph	1.5	93
4	**4d**	3-Br-Ph	4	90
5[b]	**4e**	4-F-Ph	5	93
6[b]	**4f**	4-Me-Ph	2	94
7	**4g**	4-Me_2N-Ph	1	95
8	**4h**	2-Thienyl	2	92
9[c]	**4i**	Ph-CH=CH	2	92
10[b]	**5a**	Ph	3	94
11[b]	**5b**	4-Me_2N-Ph	2	93
12	**5c**	4-MeO-Ph	2	95
13	**5d**	4-Me-Ph	2.5	90
14[b]	**5e**	2-Thienyl	3	91

[a]Yields refer to isolated pure products after recrystallization from an appropriate solvent; [b]the products were recrystallized from ethanol (96 %); [c]the products were recrystallized from acetone

RESULTS AND DISCUSSION

The synthesis of 4-(arylmethylidene)isoxazol-5(4*H*)-ones is a multi-component reaction (Scheme 1). First, Dowex resin bearing quaternary ammonium hydroxide moieties, *i.e.*, Dowex1-x8OH, was prepared through chloride–hydroxide anion exchange according to a literature procedure.[60] Then, the reaction conditions were optimized. For this purpose, the reaction of benzaldehyde as model compound with hydroxylamine hydrochloride and ethyl acetoacetate in water was performed at room temperature with different amounts of Dowex1-x8OH ranging from 0 to 2 g, as shown in Table II. When the amount of Dowex1-x8OH was increased from 0 to 1 g, the yield of product improved from 40 to 92 % (Table II, entries 1–4). However, when the amount of Dowex1-x8OH was further raised to 2 g, no significant decrease in the time of the reaction was observed (Table I, entry 5). Consequently, the amount of 1 g for Dowex1-x8OH was selected as the optimal amount of catalyst for these reactions.

TABLE II. The optimization reaction conditions for the synthesis of 4-benzylidene-3-methylisoxazol-5(4*H*)-one (**4a**) from benzaldehyde (10 mmol), ethyl acetoacetate (10 mmol) and $NH_2OH{\cdot}HCl$ (10 mmol) in H_2O (10 ml) in the presence of Dowex1-x8OH as shown in Scheme 1

Entry	Dowex1-x8OH, g	Time, h	Conversion[a], %	Yield[b], %
1	0	1	100<	40
2	0.25	1	100<	60
3	0.5	3	100	94
4	1	2	100	92
5	2	1.75	100	94

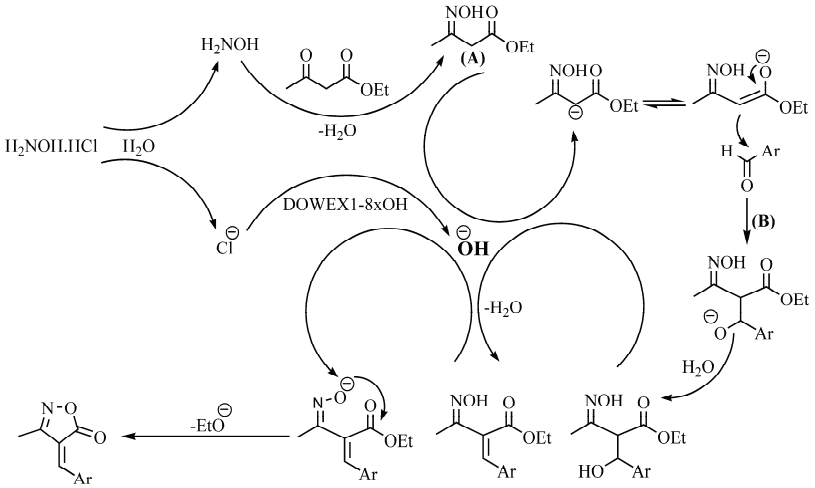
[a]Conversion refers to TLC monitoring; [b]yield refers to isolated pure product

The versatility of this protocol was examined by the reaction of a variety of aldehydes in the presence of Dowex1-x8OH. All reactions were completed within 1–5 h with excellent yields of the products (90–95 %), as shown in Table I.

All of the products are known and were characterized by FT-IR, and ^{1}H- and ^{13}C-NMR spectroscopy. The characterization data are given in the Supplementary data to this paper.

The proposed mechanism for the formation of the products is shown in Scheme 2. The ion-exchange resin Dowex1-x8OH is insoluble in H_2O. Therefore, the reactions took place under heterogeneous conditions. The influences of Dowex1-x8OH are shown in Scheme 2. Thus, the OH groups on Dowex1-x8OH (as an anion-exchange resin, strong base) deprotonate the oxime intermediate (A) that is more susceptible for reaction with aromatic aldehydes. The reaction proceeds *via* an intermolecular Knoevenagel adduct (B) followed by dehydration and ring closure, which is also catalyzed by Dowex1-x8OH.

The reusability of the catalyst was checked using the Dowex1-x8OH recovered from the synthesis of 4-benzylidene-3-methylisoxazol-5(4*H*)-one (**4a**) as shown in Table III. It was observed that the recovered catalyst could be satisfactorily used for a second run without regeneration, whereas, a third run with recovered catalyst led to poor yields and longer reaction times. After regeneration of the Dowex1-x8OH,[60] the reaction proceeded as in first run with fresh catalyst (Table III, entry 4).



Scheme 2. The proposed mechanism for the synthesis of 4-(arylmethylidene)-3-substituted isoxazol-5(4*H*)-ones.

TABLE III. Reusability of Dowex1-x8OH in the synthesis of 4-benzylidene-3-methylisoxazol-5(4*H*)-one (**4a**) from benzaldehyde under the optimized reaction conditions

Entry	Run No.	Time[a], h	Conversion[b], %	Yield[c], %
1	1	2	100	92
2	2	3	100	90
3	3	3	100<	60
4[d]	–	2	100	90

[a]It is the highest time when the reaction ends or does not further progress; [b]conversion refers to TLC monitoring (eluent; CH_2Cl_2); [c]yield refers to the isolated pure products (±3 %); [d]regeneration with 1M NaOH[60]

In order to demonstrate the merit of Dowex1-x8OH in comparison with other catalysts used for the same reaction, some of the obtained results are tabulated and compared in Table IV. As is evident from the shown results, the yield was the highest with a short reaction time in the presence of Dowex1--x8OH. In addition, easy work-up, mild reaction conditions, reuse of catalyst and the use of water from the environment are advantages of the new protocol, while some procedures are strict and complicated.

TABLE IV. The comparison of the synthesis of 4-(4-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (**4b**) using the Dowex1-x8OH and other reported systems

Entry	Catalyst and conditions	Time, h	Yield[a], %	Recyclable catalyst	Reference
1	Dowex1-x8OH/H_2O/R.T.	1	95	Yes	This paper
2	Dowex(R)WX4/H_2O/R.T.	0.5	96	Yes	58
3	Na_2S/EtOH/R.T	1.5	88	no	46
4	Pyridine/EtOH/reflux	3	71	no	40
5[b]	Catalyst-free/grinding	0.8	61	–	49
6[c]	Catalyst-free/105–110 °C	0.25	66	–	49
7	Pyridine/H_2O/ultrasound	1	82	no	50
8	Sodium tetraborate/H_2O/R.T.	0.83	95	no	48
9	Sodium benzoate/H_2O/R.T.	1.5	87	no	42
10	Visible light/aq. EtOH/R.T.	0.16	82	–	51

[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

CONCLUSION

It has been shown that Dowex1-x8OH in water is a convenient catalyst for the preparation of a variety of isoxazol-5(4*H*)-ones using aromatic aldehydes, ethyl acetoacetate and hydroxylamine hydrochloride precursors in a one-pot, three-component condensation reaction at room temperature with excellent yields of the products. The high efficiency, shorter reaction times, easy work-up, mild conditions, reuse of catalyst and use of water as a green and environmentally benign solvent make the new protocol attractive for the synthesis of isoxazol-5-(4*H*)-ones. Therefore, this new system could be a useful addition to the present methodologies.

SUPPLEMENTARY MATERIAL

Characterization data for the synthesized compounds are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА ИЗОКСАЗОЛ-5(4*H*)-ОН ДЕРИВАТА У ВОДИ КАО РАСТВАРАЧУ, У ЈЕДНОМ РЕАКЦИОНОМ КОРАКУ, У ПРИСУСТВУ DOWEX1-X8OH

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Извршена је синтеза деривата 4-(арилметилиден)-3-метилизоксазол-5(4*H*)-она и 4-(арилметилиден)-3-фенилизоксазол-5(4*H*)-она, у једном реакционом кораку, у води као растварачу уз Dowex1-x8OH као катализатор. Производи су добијени у високом приносу (90–95%) у релативно кратком реакционом времену (1–5 h). Описани поступак је еколошки прихватљив и једноставан за примену.

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