

FULL PAPER

KI-Mediated Three-component Reaction of Hydroxylamine Hydrochloride with Aryl/Heteroaryl Aldehydes and Two β -Oxoesters

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Abstract:

A KI-mediated multi-component cyclocondensation of hydroxylamine hydrochloride, aromatic/hetero-aromatic aldehydes, and ethyl acetoacetate or 4-chloroethyl acetoacetate to form isoxazole-5(4H)-one heterocycles is described. The reaction employs readily accessible starting reactants and provides a range of synthetically isoxazole-5(4H)-ones in good to high yields. Reactions were performed in water as a green medium at room temperature (rt) without heating, microwave irradiation or sonication. Reusability of the reaction medium is also a noteworthy characteristic of this reaction.

Keywords: β -dicarbonyl; green; isoxazole-5(4H)-ones; potassium iodide; water

1. Introduction

The Multi-Component Reactions (MCRs) have the privileged position in the synthesis of fine chemical compounds because they are useful tools for the rapid access to a library of organic structures and the synthesis of biologically active heterocyclic motifs with high levels of diversity and complexity. Atom-, structure-, bond-forming economy, energy efficiency, and avoidance of time-consuming and hazardous compounds are other features of MCRs that are consistent with the standards of green chemistry [1-3]. Isoxazole scaffolds, on the other hand, are one of the famous five-membered heterocyclic rings in organic synthesis, which can be traced in medicinally relevant compounds, bioactive natural products and agrochemicals [4-7]. The biological activities exhibited by these valuable heterocyclic derivatives include antifungal [8-11], antimicrobial [12, 13], metastatic activities [14], anticancer [15-17], anti-inflammatory [18], hypoglycemic [19], analgesic [20], HIV-inhibitory [19], antioxidant [21], and monoamine oxidase (MAO) enzyme

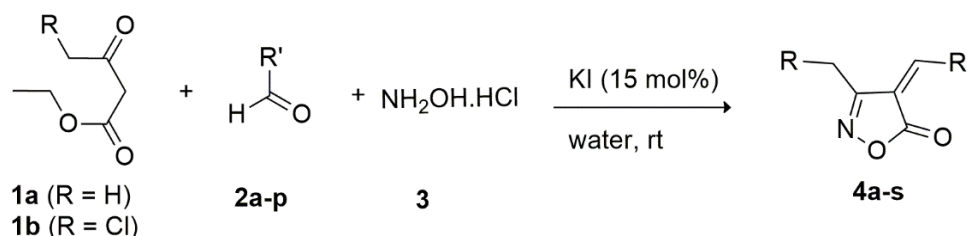
inhibitory [22]. In addition to their biological applications, isoxazoles function as dyes, electric insulating oils, high-temperature lubricants, light-conversion molecular devices, and polyisoxazoles have applications as semiconductors [6, 23]. Furthermore, the isoxazole rings show the power of masked 1,3-dicarbonyl equivalents. Thus, these heterocycles are considered as valuable synthetic intermediates in organic and total synthesis [24-26].

Owing to importance of isoxazole-5(4H)-ones, extensive research has been keen to the development of efficient methods for their synthesis. The conventional methods employed for the synthesis of substituted isoxazole-5(4H)-ones, include cyclization of *O*-propioloyl oximes [27], reaction of ethyl acetoacetate and hydroxylamine hydrochloride followed by the Knoevenagel condensation with aromatic aldehydes in two steps [28-30], condensation of substituted benzaldoximes and 1,3-dicarbonyl compounds [31], and reaction of β -oxoesters with

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hydroxylamine and sodium hydroxide with subsequent addition of aqueous HCl followed by heating [32]. One-pot synthesis involving three-component reaction (3CR) of β -oxoester compounds, hydroxylamine hydrochloride, and diverse aldehydes has been considered as a unique and attractive approach to access this significant class of heterocycles due to the

possibility of forming several bonds in a single operation [33-56]. The 3CR for the synthesis of 3,4-disubstituted isoxazole-5(4*H*)-ones is of particular interest to our laboratory [41-48], and this report describes the one-pot synthesis of several derivatives of isoxazole-5(4*H*)-ones in the presence of KI (Scheme 1).



Scheme 1. The three-component reaction of β -oxoesters (**1a-b**) with aryl/heteroaryl aldehydes (**2a-p**) and hydroxylamine hydrochloride (**3**) catalyzed by KI in water at room temperature (rt).

2. Results and Discussion

Initially, we focused on the optimization of the reaction conditions for the cyclocondensation reaction of ethyl acetoacetate (**1a**), vanillin (**2h**), and hydroxylamine hydrochloride (**3**) as starting substrates, as all of these are commercially available. The results are summarized in Table 1. First of all, we employed water as a solvent; because it is considered the best solvent from the viewpoint of green chemistry and showed the best yields for the reactions showed in Table 1. It was successful to carry out some experiments in water at room temperature (rt) as can be seen in entries 2-5. The addition of catalytic amounts of potassium iodide (3 mol%) was effective in promoting the three-component cyclocondensation leading to **4h** in a 55% yield (entry 1). The reaction yield was improved to several times by increasing the amount of catalyst from 3 to 15 mol% (entries 2-5). In fact, the employment of 15 mol% KI at rt gave the best result (entry 5). Other solvents, such as dimethylsulfoxide (DMSO), acetone, methanol, *n*-hexane, ethanol, and a mixed water-ethanol resulted in poor to modest yields of 78% (entries 6-11). Increasing reaction temperature to 50 and 100 °C did not improve chemical yields (entries 12 and 13). The reaction was also carried out in the solvent-free conditions in the presence of 15 mol% of the KI; and the corresponding isoxazole (**4h**) was obtained with the 25% yield at longer reaction time and solvent-free conditions (Table 1, entry 14).

Table 1. Optimization of the conditions for the synthesis of 4-(4-hydroxy-3-methoxybenzylidene)-3-methylisoxazole-5(4*H*)-one (**4h**) (model reaction).^a

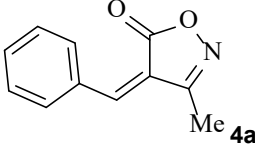
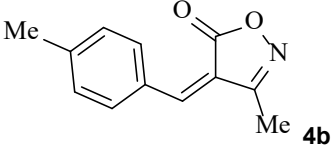
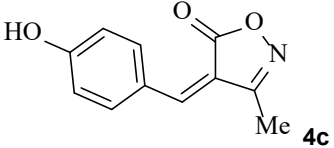
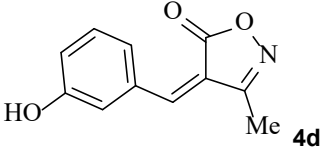
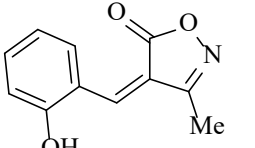
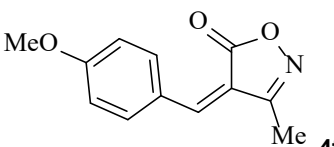
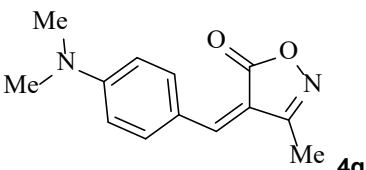
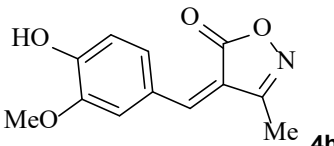
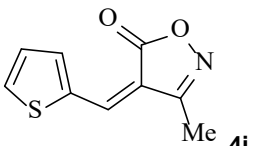
Entry	Solvent	KI (mol%)	Time (min)	Isolated Yields (%)
1	H ₂ O	3	120	55
2	H ₂ O	5	120	68
3	H ₂ O	7.5	120	73
4	H ₂ O	10	100	81
5^b	H₂O	15	90	89
6	DMSO	15	200	Trace
7	CH ₃ COCH ₃	15	20	34
8	MeOH	15	120	64
9	<i>n</i> -hexane	15	200	65
10	EtOH	15	150	70
11	H ₂ O-EtOH (1:1, v/v)	15	120	78
12 ^c	H ₂ O	15	150	53
13 ^d	H ₂ O	15	200	34
14	Solvent-free	15	200	25

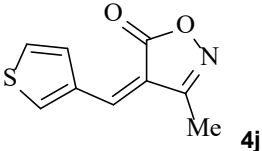
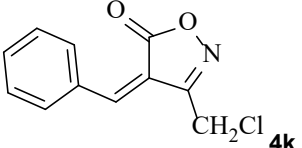
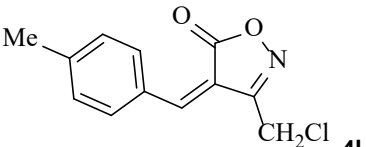
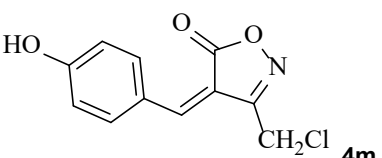
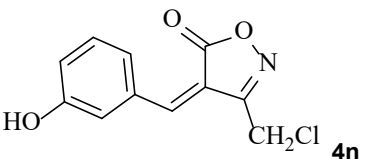
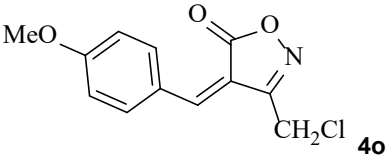
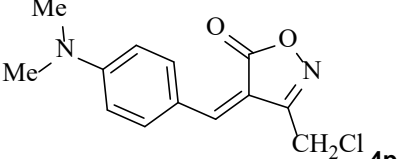
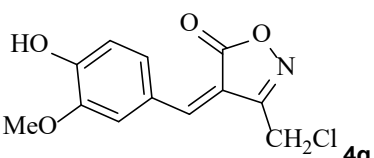
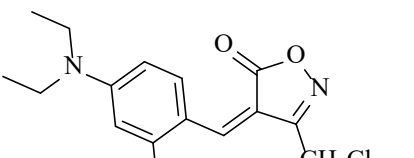
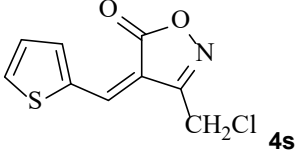
^aReaction conditions: a mixture of ethyl acetoacetate **1a** (1 mmol), vanillin **2h** (1 mmol), hydroxylamine hydrochloride **3** (1 mmol), and a solvent (5 mL) was stirred at room temperature except for entries 12 and 13. ^bOptimized conditions. ^cThe reaction was performed at 50 °C. ^dThe reaction was performed at reflux.

With the optimal reaction conditions in hand, to explore the scope of this three-component reaction various aromatic/hetero-aromatic aldehydes and β -oxoesters were employed, and the results are shown in Table 2. All the products synthesized through this method are precipitated

in the reaction vessel after standing 12h, and the corresponding isoxazoles (**4a-s**) were then obtained in reasonable yields without any chromatographic purification methods.

Table 2. The synthesis of substituted isoxazole-5(4*H*)-ones (**4a-s**).^a

Entry	Structure of products	Time (min)	Isolated yields (%)	Mp (°C)	
				Found	Reported ^b
1		180	80	141-142	141-143
2		125	84	134-136	136-137
3		105	93	211-213	214-215
4		130	85	199-202	201-203
5		150	82	197-200	199-201
6		135	87	174-176	176-188
7		90	86	230-233	228-230
8		90	89	211-214	214-216
9		100	83	144-146	147-148

10		90	80	145-147	147-148
11		135	87	181-183	182-184
12		110	88	172-174	176-177
13		120	88	186-188	185-187
14		145	83	185-188	187-190
15		115	84	173-175	176-177
16		110	85	178-181	177-179
17		100	90	139-141	140-142
18		125	90	204-206	205-207
19		110	88	144-146	146-149

^aReaction conditions: substrates; water (5 mL); KI (15 mol%); stirred at room temperature. ^bMelting points were compared with the literature and matched literature data [33-52].

Electron-donating substituted phenyl rings and hetro-aromatic aldehydes as starting reactants were well tolerated, providing the desired isoxazole-5(4*H*)-ones in good to high yields (Table 2, entries 1-10). The reaction also displays good tolerance of various substitution patterns (*o*-, *m*-, and *p*-). Electron-withdrawing substituted phenyl rings containing starting materials remained unreactive towards the reaction conditions. In another attempt, the reusability of the catalyst was also examined on the model reaction. After the completion of the reaction, the solid product was filtered off and washed with water. The filtrate containing the catalyst was used again as the reaction medium for three subsequent cycles (Table 3). Decreased reaction yields and increased reaction times, probably due to the decreased amount of catalysts in the next step the reactions.

Table 3. The reusability KI for the synthesis of **4h**.^a

No. of recycles	Fresh	Run 1	Run 2	Run 3
Time (min.)	90	120	200	200
Isolated yields (%)	89	84	77	69

^aThe reaction conditions are similar to the optimized conditions described for the model reaction.

3. Material and Methods

All chemicals were purchased from Alfa Aesar and Aldrich as well as were used without further purification, except 4-methylbenzaldehyde, 4-methoxybenzaldehyde, benzaldehyde, thiophene-2-carbaldehyde, and thiophene-3-carbaldehyde which were distilled before use. All solvents were distilled before use. The 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 Buchi 510 melting point apparatus. NMR spectra were recorded at ambient temperature on a BRUKER AVANCE DRX-400 MHz using DMSO-*d*₆ as the solvent. FT-IR spectra were recorded on a Perkin-Elmer RXI spectrometer. The development of reactions was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F₂₅₄ aluminum sheets, visualized by UV light. Elemental microanalyses were performed on an Elementar

Vario EL III analyzer. All of the targeted products are reported in the literature and are characterized by comparison of their spectral and physical data on the basis of literature descriptions.

General procedure for the synthesis of isoxazole-5(4*H*)-ones (4a-s)

A mixture of ethyl acetoacetate/4-chloroethyl acetoacetate (**1**, 1 mmol), aryl/hetro-aryl aldehyde (**2**, 1 mmol), hydroxylamine hydrochloride (**3**, 1 mmol), and 15 mol% of KI was stirred in distilled water (5 mL) at rt. The progress of the reaction was monitored by TLC (EtOAc: *n*-hexane, 3:10) analysis. After the completion of the reaction, the crude products were obtained by filtration followed by washing with distilled water and the corresponding products were obtained as solid materials. The filtrate containing catalyst was reused for subsequent reactions. Data for representative compound **4r** was as follows:

3-(Chloromethyl)-4-(4-(diethylamino)-2-hydroxybenzylidene)isoxazole-5(4H)-one (4r): IR (KBr, cm⁻¹): ν = 3445 (OH), 3070, 1690 (C=O), 1648, 1608, 1580, 1515, 1425, 1135, 1144, 1058, 1030, 755; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 11.08 (s, 1H, OH), 9.14 (d, *J* = 9.6 Hz, 1H, Ar-H), 8.07 (s, 1H, olefinic), 6.52 (dd, *J* = 2.0, 9.6 Hz, 1H, Ar-H), 6.18 (d, *J* = 2.4 Hz, 1H, Ar-H), 4.82 (s, 2H, CH₂Cl), 3.50 (q, *J* = 6.8, 7.2 Hz, 4H, 2×CH₂), 1.17 (t, *J* = 6.8, 7.2 Hz, 6H, 2×CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 170.9 (CO of isoxazole ring), 164.2 (C=N), 162.2 (C_{Ar}-OH), 156.4 (CH-olefinic), 143.1, 136.1, 111.9 (=C of isoxazole), 106.9, 101.2, 95.8, 45.2 (CH₂), 36.4 (CH₂Cl), 13.1 (CH₃). Anal. Calcd. for C₁₅H₁₇ClN₂O₃ (%): C, 58.35; H, 5.55; N, 9.07. Found: C, 58.36; H, 5.54; N, 9.08.

4. Conclusions

In conclusion, this one-pot 3CR giving good to high yields of isoxazole-5(4*H*)-ones using KI as the commercially available catalyst. The approach is simple, efficient, and offers an alternative method for the synthesis of valuable heterocycles. Eco-friendliness, cost-effectiveness, no chromatographic purification, not using microwave irradiation or ultrasound waves are another notable characteristic of this reaction.

Acknowledgments

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