



# Synthesis of 4-arylmethyleneisoxazole-5-one derivatives *via* a one-pot three-component reaction in water catalyzed by sodium azide

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## ABSTRACT

An efficient one-pot protocol to generate 4-arylmethyleneisoxazol-5-one derivatives from ethyl acetoacetate, hydroxylamine hydrochloride, and various aromatic aldehydes using sodium azide catalyst in water as environmentally benign solvent has been developed.

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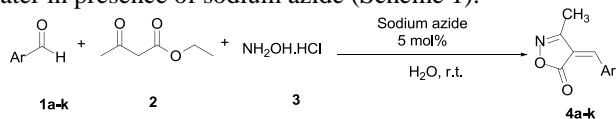
## Introduction

Heterocyclic compounds are frequently employed for numerous bioactive molecules, drugs and natural products.<sup>1</sup> Among them, synthesis of isoxazol derivatives are attractive because their multipurpose properties in chemistry and pharmacology.<sup>2</sup> These compounds exhibit significant properties like<sup>2</sup> anti-androgens, immunosuppressive, hypoglycemic, analgesic, anti-psychotics in the treatment of depression, anti-inflammatory, anticancer, anti-bacterial activity, inhibitors in the therapy of diverse diseases, herbicides and soil fungicidal activity. In addition, 4H-isoxazol-5-ones are powerful proarmotic acceptors and applied in optical storage and nonlinear optical research.<sup>3</sup> Also 4H-isoxazol-5-ones as applicants for stable vinylnitrene equivalents.<sup>4</sup>

Sodium azide has been used to inhibit bacterial contamination in laboratories and hospitals and capable to prevent bacteria from growing in biological fluids. Also used as a soil sterilizing agent, fungicide, herbicide, or pesticide and is used the rubber industry.<sup>5</sup> In addition, sodium azide is useful reagent for synthesis of triazole ring by "click reaction" strategy<sup>6</sup> and other synthetic work such as preparation of 3,5-disubstituted isoxazoles via 1,3-dipolar cycloaddition.<sup>7</sup> Although 4H-isoxazol-5-ones were synthesized so far,<sup>2g-h, 8</sup> to the best of my knowledge, no reports that including sodium azide as a catalyst for condensation of aromatic aldehyde, ethyl acetoacetate (EAA), and hydroxylamine hydrochloride have been reported.

## Results and Discussion

In the present study, 4-arylmethyleneisoxazol-5(4H)-ones, synthesized by three-component condensation reaction of EAA, hydroxylamine hydrochloride with available aromatic aldehydes in water in presence of sodium azide (Scheme 1).



Ar: C<sub>6</sub>H<sub>5</sub>, 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>, 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 4-OH-3-CH<sub>3</sub>OC<sub>6</sub>H<sub>3</sub>, 2-Furyl, 2-Thienyl, 3-thienyl, 2-OHC<sub>6</sub>H<sub>4</sub>, 3-OHC<sub>6</sub>H<sub>4</sub>, 4-OHC<sub>6</sub>H<sub>4</sub>, 4-(NMe)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>

**Scheme 1. Synthesis of 4-arylmethyleneisoxazol-5-ones (4a-k)**

At the beginning, reaction of 4-hydroxybenzaldehyde (1j), EAA (2), hydroxylamine hydrochloride (3) in water in presence of sodium azide at room temperature were performed (Table 2, entry 10). 4j was formed in excellent yield. Since this compound is known, determining the melting point and comparison with formerly described melting point<sup>8b</sup> shows that compound 4j is formed. This result encouraged us to perform the other similar reactions with the goal to attain the appropriate products.

In order to examination to improve the reaction conditions for condensation, reaction using 4-hydroxybenzaldehyde, EAA, and hydroxylamine hydrochloride as a model was carried out in the presence of different amount catalyst and various solvents at room temperature (Table 1). As shown in Table 1, 5 mol% catalysts gave better results than the other amounts of catalyst. It was observed that changing the amount of sodium azide from 1 mol% to 2, 10, and 15 mol% no significant improvement of the yield and rate (Table 1, entries 1-5).

**TABLE 1: Effects of solvents and catalyst amount on the condensation of 4-hydroxybenzaldehyde 1j, EAA<sup>a</sup> 2, and NH<sub>2</sub>OH.HCl<sup>b</sup> 3**

Entry	Solvent	Catalyst amount (mol %)	Yield (%) <sup>c</sup>
1	H <sub>2</sub> O	1	70
2	H <sub>2</sub> O	2	75
3	H <sub>2</sub> O	5	92
4	H <sub>2</sub> O	10	93
5	H <sub>2</sub> O	15	85
6	C <sub>2</sub> H <sub>5</sub> OH	5	51
7	Acetone	5	20
8	1,4-Dioxane	5	10
9	H <sub>2</sub> O/C <sub>2</sub> H <sub>5</sub> OH (1 : 1)	5	65
10	Solvent free	5	42

<sup>a</sup> ethyl acetoacetate, <sup>b</sup> Conditions: 4-OHC<sub>6</sub>H<sub>4</sub>CHO 1j (1 mmol), EAA (1 mmol), and NH<sub>2</sub>OH.HCl (1 mmol), solvent (5 mL). <sup>c</sup> Isolated yields.

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The optimal loading of catalyst was 5 mol% in which case 4j obtained 92%. Therefore 5 mol% of catalyst is satisfactory for performing this reaction. When the reaction was performed in absence of catalyst, trace amount of product was formed. As shown in Table 1, the best results were obtained with water as a solvent and sodium azide (5mol %) as a catalyst. Moderate to poor yields were obtained when reaction carried out in organic solvents (Table 1, entries 6-8) and solvent free conditions (Table 1, entry 10). Also the use of two solvent systems (Table 1, entries 9) could not significant effect on the reaction yield. Hence water and sodium azide (5 mol%) was chosen for perform the other experiments at ambient conditions. Selection of water as a solvent having several advantages including safe, non-toxic, clean, green, non-flammable, low cost, readily available, environmentally friendly<sup>8-9</sup> properties.

**Table 2: Synthesis of 4-arylmethyleneisoxazol-5-ones 4 in water<sup>a</sup>**

Entry	Ar	Time (h)	Yield (%)	mp (°C)	
				Found	Reported
1	C <sub>6</sub> H <sub>5</sub> 1a	5.0	83	141-142	141-143 <sup>[8]</sup>
2	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> 1b	3.5	90	171-172	174-176 <sup>[8]</sup>
3	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> 1c	4.0	85	134-135-	
4	4-OH-3-CH <sub>3</sub> OC <sub>6</sub> H <sub>3</sub> 1d	3.2	92	215-216	211-214 <sup>[8]</sup>
5	2-Furyl 1e	4.5	80	239-241	238-241 <sup>[8]</sup>
6	2-Thienyl 1f	3.2	90	142-143-	
7	3-Thienyl 1g	3.1	89	146-147-	
8	2-OHC <sub>6</sub> H <sub>4</sub> 1h	6.0	81	195-196	198-201 <sup>[8]</sup>
9	3-OHC <sub>6</sub> H <sub>4</sub> 1i	3.5	90	200-201-	
10	4-OHC <sub>6</sub> H <sub>4</sub> 1j	3.2	92	209-212	214-216 <sup>[8]</sup>
11	4-(NMe) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> 1k	4.2	87	226-228-	
12	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> 1l	14.0	nil	-	-
13	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> 1m	12.0	trace	-	-
14	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> 1n	12.0	trace	-	-

<sup>a</sup> Conditions: aldehyde 1 (1 mmol), EAA 2 (1 mmol), hydroxylamine hydrochloride 3 (1 mmol), and sodium azide (5 mol%), H<sub>2</sub>O (8 mL). <sup>b</sup> Isolated yields.

Under the optimized reaction conditions, condensation reactions were investigated. The results are summarized in Table 2. Choices of aromatic aldehydes containing electron-donating and electron-withdrawing substituents were reacted. As shown in Table 2, aromatic aldehydes with electron-donating substituents produced the corresponding products in good to excellent yields (Table 2, entries 2-4 and 8-11). Only a trace amount of products 4m and 4n (Table 2, entries 12 and 13) was formed when the aromatic aldehydes having electron-withdrawing substituents such as chlorine and nitro was used, which possibly due to electronic effects. When salicylaldehyde were condensed with EAA and hydroxylamine hydrochloride, corresponding product 4h was created in good yield (Table 2, entry 8), which may be due to the steric hindrance of the hydroxyl group. Interestingly, when thiophene-2-carbaldehyde and thiophene-3-carbaldehyde were used, the reactions progressed efficiently and give products in excellent yields (Table 2, entries 6 and 7). Such argument about furfural is true. The catalyst can be recovered by evaporating the solvent from the aqueous phase and reused after drying. Catalyst reusability was evaluated in the reaction of 4-hydroxybenzaldehyde, EAA and hydroxylamine hydrochloride. The catalyst can be reused four times without noteworthy lessening of the reactivity (Table 3).

## Experimental

Melting points were measured on a Buchi 510 melting point apparatus and are uncorrected. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded at ambient temperature on a Bruker AVANCE

DRX-400 MHz using CDCl<sub>3</sub> as solvent. FT-IR spectra were recorded on a PerkinElmer RXI spectrometer. Chemicals were purchased and used without further purification. The development of reactions was monitored by thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F<sub>254</sub> aluminum sheets, visualized by UV light.

**Table 3. Reuse of the catalyst**

Cycle	1	2	3	4
Yield (%) <sup>b</sup>	92	90	89	86

<sup>b</sup> Isolated yield.

General procedure for the synthesis of 4-arylmethyleneisoxazol-5(4H)-ones

A mixture of ethyl acetoacetate 2 (0.130 g, 1 mmol), hydroxylamine hydrochloride (0.069 g, 1 mmol), aromatic aldehyde (1 mmol) and sodium azide (5 mol%) in 5 mL of distilled water was stirred at ambient temperature for mentioned time in Table 2. After completion of reaction (TLC), the precipitate was filtered off, and washed with cold distilled water and dried in air. The title pure products were obtained without further purification. Spectral data for some compounds as follows:

3-Methyl-4-(4-methylbenzylidene)-4H-isoxazol-5-one (4c), pale yellow solid, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.32 (s, 3H), 2.49 (s, 3H), 7.35 (d, J = 8.0 Hz, 2H), 7.43 (s, 1H), 8.33 (d, J = 8.4 Hz, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 11.6, 22.0, 118.1, 129.8, 129.9, 134.1, 145.7, 150.3, 161.3, 168.2.

3-Methyl-4-thiophen-2-ylmethylene-4H-isoxazol-5-one (4f), yellow solid, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.33 (s, 3H), 7.29 (t, J = 4.8 Hz, 1H), 7.63 (s, 1H), 7.96 (d, J = 4.8 Hz, 1H), 8.12 (d, J = 3.6 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 11.5, 114.6, 128.9, 136.5, 139.1, 139.6, 141.5, 160.7, 168.7.

3-Methyl-4-thiophen-3-ylmethylene-4H-isoxazol-5-one (4g), yellow solid, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.29 (s, 3H), 7.41 (dd, J = 5.2, 2.8 Hz, 1H), 7.48 (s, 1H), 7.96 (dd, J = 4.8, 1.6 Hz, 1H), 8.98 (dd, J = 2.8, 0.8 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 11.5, 117.1, 126.8, 131.4, 135.2, 139.5, 141.0, 161.3, 168.4.

4-(3-Hydroxybenzylidene)-3-methyl-4H-isoxazol-5-one (4i), yellow solid, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 2.29 (s, 3H), 7.08 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.84 (s, 1H), 7.96 (s, 1H), 9.95 (s, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ 11.7, 119.0, 119.9, 121.7, 125.9, 130.1, 134.1, 152.4, 157.7, 162.6, 168.3.

4-(4-Dimethylaminobenzylidene)-3-methyl-4H-isoxazol-5-one (4k), red solid, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.28 (s, 3H), 3.20 (s, 6H), 7.25 (s, 1H), 6.76 (dd, J = 8.4, 1.2 Hz, 2H), 8.43 (d, J = 8.4 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 11.7, 40.2, 111.0, 111.6, 121.5, 137.8, 149.2, 154.3, 161.8, 170.3.

## Conclusion

In summary, a facile, efficient, and green method has been developed for the one-pot three-component preparation of 4H-isoxazol-5-one derivatives. Also 4H-isoxazol-5-ones were synthesized in high to excellent yields from readily available substrates. Utilizing of water and sodium azide system overcome the some limitations such as low yield, reflux and ultrasound irradiation.<sup>8</sup> Also, improvements in yields were observed by carrying out the reactions with sodium azide and the catalyst remained active. Catalyst recovery without a significant loss of activity can be used for about four cycles.

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