ISSN: 0974 - 7516 Volume 9 Issue 3

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 9(3), 2013 [97-101]

Synthesis of 4-arylmethylidene-3-methyl-isoxazol-5(4H)-ones via a three-component reaction in water catalyzed by sodium ascorbate

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ABSTRACT

An efficient procedure for the one-pot synthesis of 4-arylmethylene-3-methylisoxazol-5-ones from ethyl acetoacetate, hydroxylamine hydrochloride, and various aromatic aldehydes using sodium ascorbate as a safe, clean, and green catalyst in water is reported. The advantages of this work are clean, easy work-up, high yields, and the use of water as environmentally benign solvent.

KEYWORDS

4-arylmethylene-3-methylisoxazol-5-ones;
Sodium ascorbate;
Three-component;
Isoxazol;
One-pot.

INTRODUCTION

Multicomponent reactions (MCRs) have been developed widely as powerful strategy and useful tool to create various chemical compounds. Also these processes diminish the synthetic steps, and amount of waste produced, which are significant factors in "green" chemistry[1]. On the other hand, heterocyclic compounds are extensively utilized for many bioactive molecules, drugs and natural products[2]. Among them, synthesis of isoxazol ring are attractive because their multipurpose properties in chemistry and pharmacology[3]. Versatile activities of isoxazol ring have been reported to include[3] 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, isoxazol-5(4*H*)-ones are powerful proarmoatic acceptors and applied in optical storage and nonlinear optical research[4].

Sodium ascorbate together with copper salts is used to synthesis of triazole ring by "click reaction" strategy[5]. Also sodium ascorbate and $CuSO_4$ pentahydrate in a mixture of *tert*-butanol/water was applied for preparation of 3,5-disubstituted isoxazoles *via* 1,3-dipolar cycloaddition[6]. Although 4*H*-isoxazol-5-ones were synthesized so far[3g-h, 7],to the best of my knowledge, no reports that including sodium ascorbate as a catalyst for condensation of aromatic aldehyde, ethyl acetoacetate (EAA), and hydroxylamine hydrochloride have been reported.

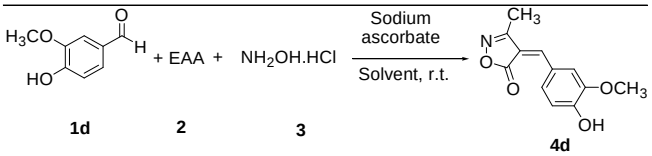
RESULTSAND DISCUSSION

In the present study, isoxazol-5(4*H*)-ones, synthesized by three component condensation reaction of EAA, hydroxylamine hydrochloride with available aromatic aldehydes and premade aldehydes (1l[8] and 1m[9]) in water in presence of sodium ascorbate. At first the reaction of 4-methoxybenzaldehyde (1b), EAA (2), hydroxylamine hydrochloride (3) in water in presence of sodium ascorbate at ambient conditions were performed (TABLE 2, entry 2). 4b was produced in

excellent yield. Since this compound is known, measuring the melting point and comparison with previously reported melting point[7b] indicates that compound 4b is formed. This result encouraged me to perform the other reactions with the aim to obtain the suitable products.

In order to explore to optimize the reaction conditions for condensation, reaction using vanillin, 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% catalyst gave better results than the other amounts of catalyst. It was observed that increasing the amount of sodium ascorbate from 5 mol% to10, 12, 15, 18, and 20 mol% no advance enhancement of the yield and rate (TABLE 1, entries 2-6).

TABLE 1: Effects of solvents and catalyst amount on the condensation of vanillin 1d, EAA[a] 2, and $NH_2OH.HCl$[b] 3



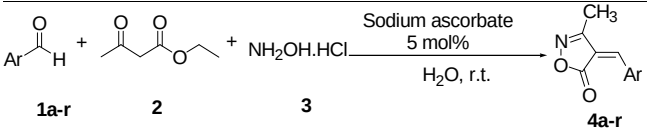
1d 2 3 4d

Entry	Solvent	Catalyst amount (mol %)	Yield (%)[c]
1	H_2O	5	95
2	H_2O	10	97
3	H_2O	12	96
4	H_2O	15	95
5	H_2O	18	95
6	H_2O	20	97
7	C_2H_5OH	5	60
8	C_2H_5OH	10	68
9	THF	5	45
10	Acetone	5	18
11	1,4-Dioxane	5	34
12	Cyclohexane	5	52
13	Hexane	5	38
14	H_2O/C_2H_5OH (1 : 1)	5	75
15	H_2O/Acetone (1 : 1)	5	25
16	H_2O/1,4-Dioxane (1 : 1)	5	50
17	Solvent free	5	40

[a]ethyl acetoacetate, [b] Conditions: vanillin 1d (2 mmol), EAA (2 mmol), and $NH_2OH.HCl$ (2 mmol), solvent (8 mL), [c] Isolated yields

The optimal loading of sodium ascorbate was 5 mol% in which case 4d obtained 95%. Therefore 5 mol% of catalyst is sufficient for increasing the conversion rate and yield. 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 ascorbate (5mol %) as a catalyst. Moderate to poor yields were obtained when reaction carried out in organic solvents (TABLE 1, entries 7-13) and solvent free conditions (TABLE 1, entry 17). Also the use of two solvent systems (TABLE 1, entries 14-16) could not significant effect on the reaction rate and resulted in only moderate to low yields. In order to study effect of temperature on yield and rate, reaction was carried out different temperatures (0, 50, 70, 100 °C).

TABLE 2 : Synthesis of 4-arylmethylidene-3-methyl-isoxazol-5(4*H*)-ones 4 in water[a]



1a-r 2 3 4a-r

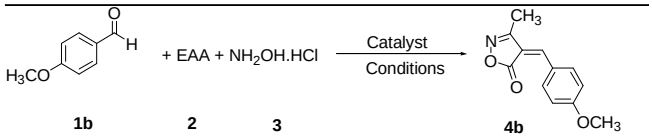
Entry	Ar	Time (min)	Yield (%)[b]	mp (°C) Found	mp (°C) Reported
1	C_6H_5 1a	115	85	141-143	141-143[7]
2	4-$CH_3OC_6H_4$ 1b	60	93	171-173	174-176[7]
3	4-$CH_3C_6H_4$ 1c	80	88	135-136	-
4	4-OH-3-$CH_3OC_6H_3$ 1d	70	95	215-216	211-214[7]
5	2-Furyl 1e	120	80	240-242	238-241[7]
6	2-Thienyl 1f	70	90	146-147	-
7	3-Thienyl 1g	70	90	146-147	-
8	2-OHC_6H_4 1h	130	75	198-200	198-201[7]
9	3-OHC_6H_4 1i	120	92	202-203	-
10	4-OHC_6H_4 1j	125	92	211-213	214-216[7]
11	4-$(NMe)_2C_6H_4$ 1k	80	88	227-228	-
12	3-Br-4-OH-5-$CH_3OC_6H_2$ 1l	145	nil	-	-
13	4-OH-3-$NO_2C_6H_3$ 1m	30	78	267-268	-
14	3-Indolyl 1n	120	79	240-241	239-241[4b]
15	5-methoxy-1*H*-indolyl 1o	110	72	234-235	235-237[4a]
16	4-$NO_2C_6H_4$ 1p	720	trace	-	-
17	2-Pyridyl 1q	900	trace	-	-
18	4-ClC_6H_4 1r	720	trace	-	-

[a]Conditions: aldehyde 1 (2 mmol), EAA 2 (2 mmol), hydroxylamine hydrochloride 3 (2 mmol), and sodium ascorbate (5 mol%), H_2O (8 mL), r.t., [b] Isolated yields

Results indicated that decreasing or rising to the re-

action temperature had not only considerable influence on the yield of 4d, but also decrease yield, and no effect on the reaction rate. Hence water and sodium ascorbate (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[7,10] properties.

TABLE 3 : Comparison of the results of the reaction of 4-methoxybenzaldehyde 1b, EAA 2, and $NH_2OH.HCl$ 3 using sodium ascorbate with those obtained by reported catalysts



1b 2 3 4b

Catalyst/ conditions	Catalyst amount (mol%)	Time (min)	Yield (%)	Ref.
Sodium ascorbate/H_2O/r.t.[a]	5	70	94	-
Na_2S/EtOH/r.t.	5	90	88	7b
Pyridine/EtOH/reflux	100	180	71	7c
Catalyst free/grinding	0	48	61	7c
Catalyst free/105–110 ? °C	0	15	66	7c
Pyridine/H_2O/ultrasound	100	60	82	7c
Sodium benzoate/H_2O/r.t.	10	90	87	7a
Sodium silicate/ H_2O/r.t.	5	90	91	7c

[a]**This work**

Under the optimized reaction conditions, condensation reactions were investigated. The results are summarized in TABLE 2. A range 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) in short reaction times. Only a trace amount of products 4p and 4r (TABLE 2, entries 16 and 18) was formed when the aromatic aldehydes having electron-withdrawing substituents such as chlorine and nitro was used. Furthermore, It was found that the yield was satisfactory when the reaction was carried out with 4-hydroxy-3-nitro benzaldehyde (TABLE 2, entry 13), whereas the yield of the product was unsatisfactory when the reaction was performed with 4-nitrobenzaldehyde even for 24 h, which possibly due to electronic effects. When salicylaldehyde were condensed with EAA and hydroxylamine hydrochloride, corresponding product 4h was produced in relatively lower yield (TABLE 2, entry 8), which may be due to the steric hindrance of the hydroxyl group. Fascinatingly, when thiophene was used, the reaction proceeded efficiently and afford product in 90% yield (entries 6 and 7, TABLE 2). Such argument about furfural is true.

To compare the effectiveness of sodium ascorbate with other catalysts in the synthesis of 4-arylmethylene-3-methyl-isoxazol-5(4*H*)-ones, results of the reaction of 4-methoxybenzaldehyde, EAA, and $NH_2OH.HCl$ have tabulated in TABLE 3. As shown in TABLE 3, sodium ascorbate, comparative to the formerly reported methods, is reasonably better in terms of time reactions and yields.

EXPERIMENTAL

Melting points were measured on a Buchi 510 melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at ambient temperature on a Brucker AVANCE DRX-400 MHz using $CDCl_3$ as solvent. FT-IR spectra were recorded on a PerkinElmer RXI spectrometer. Chemicals were obtained from Merck, Fluka and Alfa-Aesar. The development of reactions was monitored by thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F_{254} aluminum sheets, visualized by UV light. 3-bromo-4-hydroxy-5-methoxybenzaldehyde and 4-hydroxy-3-nitrobenzaldehyde was prepared according to reported procedures[8,9].

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

A mixture of ethyl acetoacetate 2 (0.260 g, 2 mmol), hydroxylamine hydrochloride (0.139 g, 2 mmol) and sodium ascorbate (5 mol%) in 8 mL of distilled water was stirred at room temperature for 8 min, then aromatic aldehyde (2 mmol) was added to the mixture. The reaction mixture 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. Crude products was recrystallized from ethanol (95%) to afford the title pure compounds. Also, the filtrate solution was allowed to room temperature overnight, which caused the product to precipitate. The solid was fil-

tered, washed with cold water, and dried in air gave further the title pure compounds. Spectral data for some compounds as follows:

3-Methyl-4-(4-methylbenzylidene)-4*H*-isoxazol-5-one (4c), pale yellow solid, ^{1}H NMR (400 MHz, $CDC1_3$): δ 2.33 (s, 3H), 2.48 (s, 3H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.42 (s, 1H), 8.32 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDC1_3$): δ 11.6, 22.1, 118.2, 129.8, 129.9, 134.2, 145.8, 150.2, 161.4, 168.3.

3-Methyl-4-thiophen-2-ylmethylene-4*H*-isoxazol-5-one (4f), yellow solid, ^{1}H NMR (400 MHz, $CDC1_3$): δ 2.32 (s, 3H), 7.29 (t, *J* = 4.8 Hz, 1H), 7.64 (s, 1H), 7.95 (d, *J* = 4.8 Hz, 1H), 8.13 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDC1_3$): δ 11.5, 114.6, 128.9, 136.5, 139.2, 139.6, 141.5, 160. 7, 168.7.

3-Methyl-3-thiophen-2-ylmethylene-4*H*-isoxazol-5-one (4g), yellow solid, ^{1}H NMR (400 MHz, $CDC1_3$): δ 2.29 (s, 3H), 7.42 (dd, *J* = 5.2, 2.8 Hz, 1H), 7.49 (s, 1H), 7.95 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.99 (dd, *J* = 2.8, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDC1_3$): δ 11.6, 117.0, 126.8, 131.5, 135.2, 139.4, 140.9, 161.3, 168.5.

4-(3-Hydroxybenzylidene)-3-methyl-4*H*-isoxazol-5-one (4i), yellow solid, ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.85 (s, 1H), 7.95 (s, 1H), 9.96 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.7, 118.9, 119.9, 121.8, 125.8, 130.2, 134.1, 152.3, 157.8, 162.6, 168.2.

4-(4-Dimethylaminobenzylidene)-3-methyl-4*H*-isoxazol-5-one (4k), red solid, ^{1}H NMR (400 MHz, $CDC1_3$): δ 2.27 (s, 3H), 3.19 (s, 6H), 7.24 (s, 1H), 6.75 (dd, *J* = 8.4, 1.2 Hz, 2H), 8.43(d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDC1_3$): δ 11.7, 40.1, 110.9, 111.5, 121.5, 137.7, 149.3, 154.2, 161.7, 170.2.

4-(4-Hydroxy-3-nitrobenzylidene)-3-methyl-4*H*-isoxazol-5-one (4m), yellow solid, ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.92 (s, 1H), 8.20 (s, 1H), 8.62 (d, *J* = 9.2 Hz, 1H), 9.2 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO-d_6): δ 11.7, 117.8, 119.9, 124.5, 132.3, 137.2, 140.5, 149.6, 157.0, 162.3, 168.7.

CONCLUSION

In summary, a facile, efficient, green, and safe protocol has been developed for the one-pot three-component preparation of 4*H*-isoxazol-5-one derivatives. Also 4*H*-isoxazol-5-ones were synthesized in high to excellent yields from readily available substrates. Utilizing of water and sodium ascorbate system overcome the some limitations such as long reaction time, low yield, reflux and ultrasound irradiation[7].

ACKNOWLEDGEMENT

The author is thankful Research Council of the Damghan University.

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