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Green synthesis of 3,4-disubstituted isoxazol-5(4*H*)-one using Gluconic acid aqueous solution as an efficient recyclable medium

Ganesh V. Shitre [1], Anisha R. Patel [2] and Ramesh S. Ghogare [2*]

[1]*Department of Chemistry, Vaishnavi Mahavidyalaya,Wadwani, Dist-Beed- 431144, India*

[2]*Department of Chemistry*, B. *N. N. College Bhiwandi, Dist-Thane-421305, India*

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Abstract: Green synthesis of 3,4-disubstituted isoxazol-5(*4H*)-ones has been achieved via Knoevenagel condensation using three-component coupling reaction of aromatic aldehyde, ethyl acetoacetate and hydroxylamine hydrochloride in Gluconic acid aqueous solution (50 wt % GAAS). In this methodology, Gluconic acid aqueous solution used as reaction medium as well as catalyst and it can be recycled and reused several times without loss of its a significant efficacy. All compounds have been confirmed by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and mass spectrometry.

Keywords: Green synthesis; gluconic acid aqueous solution; bio-based green solvent; Knoevenagel condensation; 3,4-disubstituted isoxazol-5(*4H*)-ones.

1. Introduction

Nowdays, environmental benign green synthesis is important perspective in chemical and pharmaceutical productions, because uses of conventional organic solvents as well as reagents are harmful and toxic to environments[1-2]. In addition, some other organic solvents are also responsible to depletion of ozone layer. Therefore, use of secure and less toxic chemicals as the solvent is one of the most important criterions among the green chemistry principles. The purpose of using "green reaction medium" is to reduce or eliminate the toxic and harmful effects of chemicals on the environment. Hence, emerging interest in the development of novel methodologies in organic synthesis, researchers have need to find out an alternative non-polluting as well as bio-degradable green reaction medium[3-10] for organic transformations. Recently, Gluconic acid aqueous solution (50 wt % GAAS) is used as bio-based green solvent for the organic syntheses[11-16]. This solvent shows various characteristics like non-volatility, bio-degradability, recyclability, eco-friendly and cost-effective organic acid solvent. Present work has performed using Gluconic acid aqueous solution as reaction medium, which has been recycled and reused several times.

Isoxazole and its derivatives are significant class of heterocyclic compounds containing a potent pharmacophore and these pharmacophore plays important role in medicinal chemistry for building blocks of drugs[17-19]. Several substituted isoxazoles have been shown a broad range of biological activities such as anti-inflammatory[20], immunosuppressive[21], β-Adrenergic receptor antagonists[22], Androgen antagonists[23], anti-viral[24], anti-HIV[25-26], antiprotozoal[27], HDAC inhibitors[28], anti-tubercular[29],

* Corresponding author: E-mail*:* rsghogare05@gmail.com

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anti-bacterial[30], anti-fungal[31], anticancer [32-33] and antioxidant activity[34]. Some of isoxazoles are also used as fungicidal in agricultural field[35]. In addition to these, many 3,4-disubstituted isoxazol-5(4*H*)-ones are used in development of optical storage devices, optical storage and nonlinear optical research[36-37], filter dyes in photographic films[38] and light conversion in molecular devices[39].

In view of the emerging importance of 3,4-disubstituted isoxazol-5(4*H*)-ones, various modified methods were developed for their synthesis using several reagents, catalysts and strategies. Amongst them, some methods were carried out using different catalysts like acidic catalyst[40-50], basic catalyst[51-68], nano materials[69-75] and Synthetic enzyme[76]. Additionally, various bio-based solvents[77-80], deep eutectic solvents[81-82], ion exchange resins[83-84], ionic liquids[85-86] as well as metal and its complexes[87-89] were also used. In similar manner, some of the newest techniques such as microwave irradiation[90-92] ultrasound irradiation[93-94] and visible light[95] have been reported. However, several of these reported methods suffer from one or two drawbacks such as harsh reaction conditions, expensive catalysts, toxic solvents, prolonged reaction time, poor yields and tedious workup process. Thus, the need for the development of an alternate route to synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones is in high demand.

During our recent studies directed towards the development of novel methodology using alternative procedures[96-98] and by considering the significance of 3,4-disubstituted isoxazol-5(4*H*)-ones, herein we wish to report, a green approach for the catalyst-free synthesis of 3,4-disubstituted isoxazol-5(4*H*)-one using Gluconic acid aqueous solution as an efficient recyclable medium.

2. Experimental

2.1. General Methods

Solvents and reagents were purchased from commercially and used without purification. Melting points were recorded on the Buchi R-535 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Gemini-300 spectrometer in $CDCl_3$ using TMS as an internal standard. IR spectra were recorded on a Bruker FT-IR spectrophotometer using neat or KBr disk and mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer with operating at 70 eV.

2.2. General Procedure

A mixture of benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and hydroxylamine hydrochoride (1 mmol) were stirred in gluconic acid aqueous solution (GAAS) (5 mL) at 70 °C. The progress of the reaction was monitored by thin layer chromatography (TLC) and the reaction was completed within 45 minutes. Then, the reaction mixture was cooled and extracted with ethyl acetate. The extracted ethyl acetate was concentrated under reduced pressure to obtained crude solid product, which was purified by crystallization from ethanol. All the pure products were confirmed by comparing their physical and spectral data.

2.3. Spectral Data for Compounds

(Z)-4-benzylidene-3-methylisoxazol-5(4H)-one (***4a***): Pale yellow solid (90 %). m.p. 143-145^{o}C. IR (KBr): ν_{max} = 3225, 2370, 1740, 1635, 1215, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.8 Hz, 2H), 7.49-7.61 (m, 3H), 7.36 (s, 1H), 2.40 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 175.7, 164.9, 152.1, 133.1, 127.8, 127.5, 127.4, 126.0, 17.4 ppm; ESIMS: *m/z* 188 $[M+1]^+$.

(Z)-3-methyl-4-(4-methylbenzylidene)isoxazol-5(4H)-one (***4b***): Pale yellow solid (90%). m.p. 128-130^{o}C. IR (KBr): ν_{max} = 3055, 2940, 2865, 1735, 1612, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, *J*=8.2 Hz, 2H); 7.48 (s, 1H); 7.36 (d, *J*=8.1Hz, 2H); 2.48 (s, 3H); 2.30 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 163.7, 150.3, 136.0, 130.5, 127.9, 126.0, 120.3, 22.8, 17.8 ppm; ESIMS: *m/z* 201 $[M]^+$.

(Z)-4-(4-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one (***4c***): Yellow Solid (92%). m.p. 214-216 ^{o}C. IR (KBr): ν_{max} = 3460, 3080, 2940, 1745, 1615, 1220, cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 10.70 (s, 1H), 8.42 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.38 (s, 1H), 3.00 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 164.5, 157.2, 149.7, 130.8, 125.4, 123.4, 115.5, 17.4 ppm; ESIMS: *m/z* 226 $[M+23]^+$, 203 $[M]^+$.

*(Z)-4-(4-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (**4d**)*: Yellow Solid (90%). m.p. 180-182 ^{o}C. IR (KBr) ν_{max} = 3080, 2980, 2815, 1736, 1605, 1270, 1025 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, *J*= 8.8 Hz, 2H); 7.42 (s, 1H), 6.98 (d, *J*= 8.1 Hz, 2H), 3.85 (s, 3H), 2.40 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4, 163.9, 160.6, 149.7, 130.8, 125.8, 114.1, 54.9, 17.3 ppm. ESIMS: *m/z* 218 $[M+1]^+$.

(Z)-4-(4-hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (***4e***): Pale yellow solid (92%). m.p.214-216^{o}C. IR (KBr): ν_{max} = 3445, 3136, 2940, 1735, 1642, 1270 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.72 (s, 1H), 7.50 (s, 1H), 7.24-7.16 (m, 2H),6.86 (d, *J*=8.1Hz 1H), 3.42 (s, 3H), 2.31 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 163.9, 151.2, 149.7, 148.3, 129.3, 125.4, 122.8, 116.5, 111.6, 56.0, 17.3 ppm. ESIMS: *m/z* 251 $[M+18]^+$.

(Z)-4-(3,4-dimethoxybenzylidene)-3-methylisoxazol-5(4H)-one (***4f***): Yellow solid (92%). m.p.130-132^{o}C. IR (KBr): ν_{max} = 3092, 2935, 2830, 2355, 1730,1565, 1266 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.320-7.28 (m, 2H), 6.90 (d, *J*=8.1Hz, 1H) 3.83 (s, 6H), 2.44 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 167.6), 150.3, 149.4, 147.7, 127.9, 126.0, 122.6, 111.6, 111.1, 56.2, 17.4) ppm; ESIMS: *m/z* 248 $[M+1]^+$.

(Z)-4-(3,4,5,-trimethoxybenzylidene)-3-methylisoxazol-5(4H)-one **(4g):** Yellow solid (94%). m.p.138-140^{o}C. IR (KBr): ν_{max} = 3130, 2945, 1740, 1560, 1278, 1042, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (s, 1H), 7.08 (d, *J*= 8.8, 2H), 3.78 (s, 9H), 2.43 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4, 164.5, 153.0, 150.3, 138.0, 129.7, 125.1, 103.7, 60.5, 56.3, 17.5 ppm; ESIMS: *m/z* 278 $[M+1]^+$, 277 $[M]^+$.

(Z)-4-(4-(dimethylamino)benzylidene)-3-methylisoxazol-5(4H)-one (***4h***): pale red solid (90%). m.p. 212-214^{o}C. IR (KBr): ν_{max} = 1730, 1625, 1552,1505, 1436 , 1312 1245, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (d, *J*= 8.5 Hz, 2H), 7.34 (s, 1H), 6.71 (d, *J*=9.2 Hz, 2H), 3.10 (s, 6H), 2.26 (s, 3H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 162.4, 153.5, 149.3, 138.1, 122.6, 120.2, 111.6, 41.7, 13.0 ppm; ESIMS: *m/z* 248 $[M+18]^+$, 230 $[M]^+$.

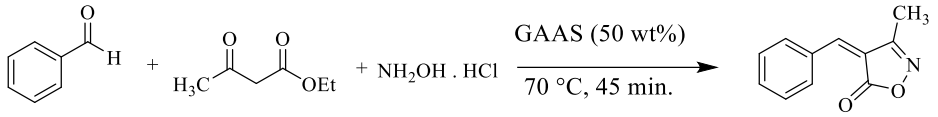
(Z)-3-methyl-4-(thiophen-2-ylmethylene)isoxazol-5(4H)-one (***4i***): Pale yellow solid (88%). m.p.144-146^{o}C. IR (KBr): ν_{max} = 2930, 1736, 1695, 1510, 1330, 1145 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, *J*= 3.6 Hz, 1H), 7.92 (d, *J*= 4.8 Hz, 1H), 7.60 (s, 1H), 7.35 (t, *J*= 4.8 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 160.6, 141.5, 140.7, 140.0, 136.8, 128.5, 114.9, 12.9 ppm; ESIMS: *m/z* 193 $[M]^+$.

3. Results and Discussion

In continuation our research interest in the development of green synthetic methodologies, we decided to explore the use of Gluconic acid aqueous solution (50 wt% GAAS) as reaction medium for the synthesis of 3,4-disubstituted isoxazol-5(4*H*)-one.

In viewpoint of green chemistry, the model reaction was carried out between benzaldehyde (**1**) (1.0 mmol), ethyl acetoacetate (**2**) (1.0 mmol) and hydroxylamine hydrochloride (**3**) (1.0 mmol) under various solvents conditions using different reaction temperature. The results are shown in Table 1. Initially, the reaction was carried out under solvent free condition at room temperature as well as higher temperature (100 ^{o}C) for prolonged reaction time (120 minutes) but formation of the desired product was not observed (Table 1, entry 1-2). After that, we chose water as a green solvent and reaction was carried out at different temperatures for 120 minutes. Amongst them, reflux condition progresses towards the desired product up to 30 % yield (Table 1, entry 3-4).

Green synthesis of 3,4-disubstituted isoxazol-5(4*H*)-one



Scheme 1. Gluconic acid aqueous solution catalyzed synthesis of 3,4-disubstituted isoxazol-5(4*H*)-one

With these obtained results in hand, our next goal was to improve the product yield with reducing the reaction time. It has needed to use an appropriate catalyst which acts green catalyst as well as recyclable reaction medium and increases the product yield with reducing the reaction time. Here, we decided to explore the use of Gluconic acid aqueous solution (50 wt % GAAS) system as bio-based reaction medium and catalyst for this reaction. Because, Gluconic acid aqueous solution (GAAS) has hydrophobic nature with organic substrate which induce favorable aggregation of organic substrates in water to leads the fast collisions of the reactants and formation of desired product in short reaction times.

Initially, the reaction was performed at room temperature using various concentrations of GAAS system from 3 mL to 6 mL for 120 minutes (Table 1, entry 5-8**).** The yield of product gradually increases with increasing the volume of solvent till 5 mL, and further increasing the volume of reaction medium, no improvement occurred in terms of product yield. Thus, the observation shows that a 5 mL volume of GAAS system was enough for obtaining moderate yield of product at the room temperature. After these results, the effects of temperature were studied, by carrying out the model reaction at different temperatures from 40 to 80 °C. In this optimization of reaction, increasing the reaction temperature from 40 to 70 °C, the product yield increases with gradually decreasing reaction time (Table 1, entry 9-12). Further increasing the reaction temperature up to 80 °C, but yield of the product was not improved (Table 1, entry 13). The observation shows that reaction condition at 70 °C is sufficient for the completion of reaction within 45 minutes with excellent yield.

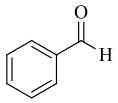
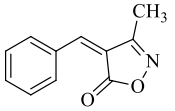
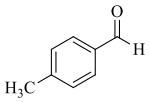
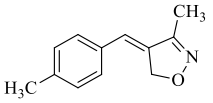
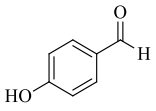
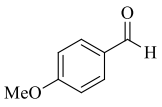
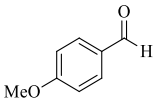
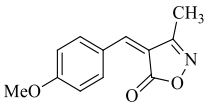
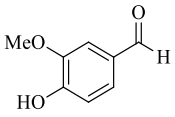
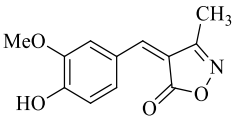
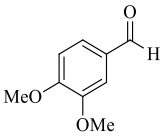
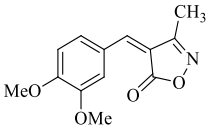
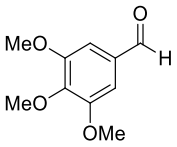
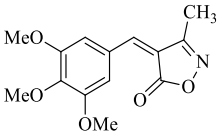
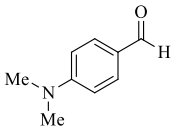
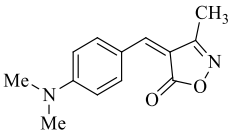
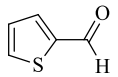
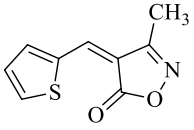
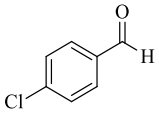
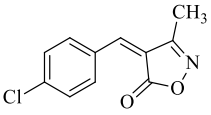
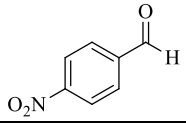
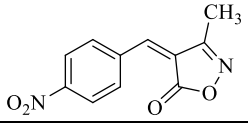
Table 1. Optimization of reaction solvent and GAAS (50 wt%) at different conditions

Sr. No.	Solvent	Quantity Solvent (mL)	Temperature (°C)	Time (min.)	Isolated Yields (%)
1	Solvent-free	--	RT[a]	120	NR[b]
2	Solvent-free	--	100	120	NR[b]
3	H_2O	5	RT[a]	120	Trace
4	H_2O	5	Reflux	120	30
5	GAAS	3	RT[a]	120	40
6	GAAS	4	RT[a]	120	54
7	GAAS	5	RT[a]	120	60
8	GAAS	6	RT[a]	120	60
9	GAAS	5	50	70	72
10	GAAS	5	60	60	85
11	GAAS	**5**	**70**	**45**	**92**
12	GAAS	5	80	45	92

RT[a] = Room Temperature, NR[b]= No Reaction (Product not formed).

Based on the optimized reaction conditions, various aromatic and heterocyclic aldehydes were reacted with ethyl acetoacetate and hydroxylamine hydrochloride for the synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones (Table 2, **4a**-**4k**) to demonstrate the scope of GAAS as catalyst as well as reaction medium. All results are summarized in table 2.

Table 2. Synthesis of the 3-Methyl-4-arylmethylene isoxazol-5(4*H*)-one

Sr No	Aldehyde	Product	Reaction Time (min.)	Isolated Yield (%)	M.P. ºC [Lit. M.P.]Ref
a			45	92	143-145 [142-144][50]
b			45	90	128-130 [132-134] [50]
c			45	92	214-216 [210-212] [50]
d			45	90	180-182 [176-178] [50]
e			45	92	214-216 [210-212] [50]
f			45	92	130-132 [134-136] [50]
g			45	94	138-140 [134-136] [50]
h			45	90	212-214 [206-209] [50]
i			45	90	144-146 [146-147] [66]
j			120	00	--
k			120	00	--

NR*= No Reaction

Various effects of substituents present on the aromatic aldehyde were examined by using different electron donating and withdrawing functional groups. The aromatic aldehyde having electron donating groups reacted in appropriate time to achieve desired products with excellent yields, while electron withdrawing groups failed to obtain the required product even increasing reaction time. In general, it observed that the nature of the functional group on aromatic aldehyde have a various effect on this reaction.

For the investigation of reusability of the reaction medium, reaction was carried out using model reaction (Scheme 1). After the completion of the reaction, the reaction mixture was cooled and the formed product extracted with ethyl acetate from the GAAS phase.

Table 3. Recyclability study of the GAAS (50 wt %)

Sr. No.	Cycle	Reaction Time (min.)	Isolated Yields (%)
1	1	45	92
2	2	45	90
3	3	50	85
4	4	60	82

The immiscibility of Gluconic acid aqueous solution (GAAS) with ethyl acetate, it's easy to separate out and reused up to four times for further reactions without loss of its a significant efficacy (Table 3).

After that, GAAS solvent system has also compared with some previously reported green catalysts or reaction mediums used for synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones (Table 4). The results show that the present method has more advantages from the viewpoint of product yield and reaction time.

Table 4. Comparison for different green catalysts or reaction mediums used for synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones

Sr. No.	Catalyst	Solvent	Temperature (°C)	Time (min)	Yield (%)	Ref
1	DL-Tartaric acid (10 mole %)	H_2O	RT	100	88	41
2	Citric acid (1 mmol)	H_2O	RT	480	90	43
3	Pyruvic acid	H_2O	100	60	85-92	49
4	Succinic acid (15 mol %)	H_2O	RT	90	92	50
5	Lemon juice (1 mL)	H_2O:EtOH	90	55-60	94	77
6	Starch solution (4 mL)	--	90	50-60	80-86	78
7	Fruit juice (10 mL)	H_2O:EtOH	RT	240-420	90-95	80
8	**Gluconic acid aqueous solution (50 wt % GAAS)**	**--**	**70**	**45**	**70-92**	**Present work**

In general, all the reactions were very neat in terms of conversion as well as isolation of products. All the products were characterized by their spectroscopy analysis such as ^{1}H, ^{13}C NMR, IR spectroscopy and mass spectrometry.

4. Conclusion

In summary, we have represented a simple, inexpensive and novel one pot three-component methodology for the green synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones derivatives using various aromatic aldehydes, ethyl acetoacetate and hydroxylamine hydrochloride in Gluconic acid aqueous solution. Gluconic acid aqueous solution is recycled and reused several times without loss of its effectiveness. The present method offers significant advantages such as economical, nontoxic, shorter reaction time, catalyst-free condition and use of green reaction medium. All synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, FT-IR spectroscopy, and mass spectrometry.

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Supporting Information

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ORCID
Ganesh V. Shitre 0009-0004-4882-7928
Anisha Patel: 0009-0006-6074-9146
Ramesh S. Ghogare: 0000-0003-0810-9636

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