Indian Journal of Advances in Chemical Science

Research Article

H_2O_2:HCl Catalyzed Simple and Efficient Synthesis of 3-Methyl-4-Arylmethylene Isoxazol-5(4*H*)-One in Aqueous Medium

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ABSTRACT

A simple and efficient method for the synthesis of 3-methyl-4-arylmethylene isoxazol-5(4*H*)-one has been accomplished through Knoevenagel condensation using various aromatic aldehyde, ethyl acetoacetate, and hydroxylamine hydrochloride with H_2O_2:HCl in aqueous medium. In this methodology, H_2O_2:HCl used as catalyst and water as green reaction solvent, which gives one-pot synthesis of 3-methyl-4-arylmethylene isoxazol-5(4*H*)-one with excellent yields (88–93%). All products were characterized by using ^{1}H NMR, ^{13}C NMR, Fourier transform infrared spectroscopy, and mass spectrometry.

Key words: 3-methyl-4-arylmethylene isoxazol-5(4*H*)-one, H_2O_2:HCl catalyst system, Hypochlorous acid, Knoevenagel condensation, Water.

1. INTRODUCTION

Heterocyclic compounds have key role in chemical as well as in pharmaceutical industries, due to their potential biological importance [1,2]. Among them, nitrogen and oxygen contain heterocyclic compounds such as isoxazole and its derivatives having a potent pharmacophore, which plays major role in medicinal chemistry for building blocks of various drugs [3-5]. Several substituted isoxazoles have been shown a variety of biological activities including immunosuppressive [6], β-adrenergic receptor antagonists [7], androgen antagonists [8], histone deacetylase inhibitors [9], anti-inflammatory [10], anti-bacterial [11], anti-viral [12], antiprotozoal [13], anti-tubercular [14], anti-fungal [15], anti-HIV [16,17], anticancer [18,19], and antioxidant activity [20]. In addition to these, several substituted 3-methyl-4-arylmethylene isoxazol-5(4*H*)-ones are used in development of optical storage devices, optical storage, and non-linear optical research [21,22], filter dyes in photographic films [23], and light conversion in molecular devices [24].

In viewpoint of the potential biological activities of 3-methyl-4-arylmethylene isoxazol-5(4*H*)-one, various methods have been developed for their synthesis including several reagents, catalysts, and strategies. Among them, some methods were carried out using different catalysts including organo-catalysts [25-29], basic catalyst [30-33], heterogeneous Brønsted acids [34-36], heterogeneous [37-40] as well as homogeneous [41,42] Lewis acids, and enzyme catalysts [43,44]. Furthermore, many bio-based solvents [45-47], deep eutectic solvents [48-50], ionic liquids [51], ion exchange resins [52,53], and crown ethers [54] were also used. In similar way, some of the newest non-conventional methods such as ultrasound irradiation [55-57], microwave irradiation [58,59], concentrated solar radiations [60], and visible light [61] were reported. However, some of these methods suffer from one or two drawbacks such as harsh reaction conditions, use of harmful solvents, expensive catalysts, tedious workup, and extended reaction time with low yields. Therefore, the development of environmental benign alternative method for synthesis of 3-methyl-4-arylmethylene isoxazol-5(4*H*)-one is high demand in the research fields for organic chemists.

A recent year, combination of hydrogen peroxide (H_2O_2) and hydrochloric acid (HCl) produced green halogenating agent, hypochlorous acid (HOCl) which is used as catalyst in development of various environmental benign green methodologies [62-65]. HOCl is a weak acid, which forms when H_2O_2 reacts with HCl or chlorine dissolves in water (H_2O) and it cannot be isolated from these solutions due to rapid equilibrium with its conjugate acid or base.

As part of our ongoing research, to develop novel and green methodology using alternative procedures [66-70], and by considering the potential biological importance of 3-methyl-4-arylmethylene isoxazol-5(4*H*)-one, herein we wish to report, H_2O_2:HCl catalyzed simple and efficient synthesis of 3-methyl-4-arylmethylene isoxazol-5(4*H*)-one in aqueous medium.

2. EXPERIMENTAL

2.1. General Information

Solvents and reagents were purchased from commercial sources and used without any purification. ^{1}H and ^{13}C NMR spectra were recorded on Gemini-300 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Bruker Fourier transform IR (FTIR) spectrophotometer using neat or KBr disk and mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer with operating at 70 eV. Melting points were recorded on the Buchi R-535 apparatus and are uncorrected.

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ISSN NO: 2320-0898 (p); 2320-0928 (e)
DOI: 10.22607/IJACS.2025.1301003

Received: 25th December 2024;
Revised: 05th January 2025;
Accepted: 06th January 2025;
Published: 02th February 2025

2.2. General Procedure for Synthesis of 3-Methyl-4-Arylmethylene Isoxazol-5(4H)-One

A mixture of aromatic aldehyde (1 mmol), ethyl acetoacetate (1 mmol), and aqueous solution of 30% H_2O_2: 37% HCl (6:3 mmol) were stirred in H_2O (5 mL). After stirring reaction mixture for 10 min, hydroxylamine hydrochloride was added and continuously stirred for 90–120 min at 100°C. Completion of reaction was monitored by thin layer chromatography (ethyl acetate: hexane 2:8), and reaction mixture was quenched by adding saturated $NaHCO_3$. The reaction mixture was extracted with ethyl acetate, dried over sodium sulfate, and the concentrated under vacuum to obtained the crude solid product which was purified by crystallization from ethanol. All the pure products were confirmed by comparing their melting points and spectroscopy data.

2.3. Spectral Data for Synthesized Compounds

2.3.1. (Z)-4-benzylidene-3-methylisoxazol-5(4H)-one (4a)

Pale yellow solid (92%) m.p. 140–142°C ([Lit[27]]142–144°C). IR (KBr): ν 3224, 2372, 1740, 1635, 1210, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H, $-CH_3$), 7.35 (s, 1H, Ar-CH=C), 7.50–7.60 (m, 3H, Ar-H), 7.90 (d, J = 8.8 Hz, 2H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 126.0, 127.4, 127.5, 127.8, 133.1, 152.1, 164.9, 175.7 ppm; ESIMS: *m/z* 188 $[M+1]^+$.

2.3.2. (Z)-3-methyl-4-(4-methylbenzylidene)isoxazol-5(4H)-one (4b)

Pale yellow solid (92%). m.p. 130–132°C ([Lit[27]] 132–134°C). IR (KBr): ν 3055, 2940, 2865, 1735, 1612, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, $-CH_3$), 2.48 (s, 3H, $-CH_3$), 7.36 (d, J = 8.1Hz, 2H, Ar-H) 7.48 (s, 1H, Ar-CH=C), 7.92 (d, J = 8.2 Hz, 2H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8, 22.8, 120.3, 126.0, 127.9, 130.5, 136.0, 150.3, 163.7, 172.4 ppm; ESIMS: *m/z* 201 $[M]^+$.

2.3.3. (Z)-4-(4-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one (4c)

Yellow Solid (93%). m.p. 212–214°C ([Lit[27]] 210–212°C). IR (KBr): ν 3460, 3080, 2940, 1745, 1615, 1220, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ*: 3.00 (s, 3H, $-CH_3$), 7.38 (s, 1H, Ar-CH=C), 7.60 (d, J = 8.2 Hz, 2H, Ar-H), 8.42 (d, J = 8.8 Hz, 2H, Ar-H), 10.70 (s, 1H, -OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.4, 115.5, 123.4, 125.4, 130.8, 149.7, 157.2, 164.5, 174.7 ppm; ESIMS: *m/z* 226 $[M+23]^+$, 203 $[M]^+$.

2.3.4. (Z)-4-(4-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (4d)

Yellow Solid (92%). m.p. 178-180°C ([Lit[27]] 176–178°C). IR (KBr) ν 3080, 2980, 2815, 1736, 1605, 1270, 1025 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H, $-CH_3$), 3.85 (s, 3H, $-OCH_3$), 6.98 (d, J = 8.1 Hz, 2H, Ar-H), 7.42 (s, 1H, Ar-CH=C), 8.10 (d, J = 8.8 Hz, 2H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.3, 54.9, 114.1, 125.8, 130.8, 149.7, 160.6, 163.9, 174.4 ppm. ESIMS: *m/z* 218 $[M+1]^+$.

2.3.5. (Z)-4-(4-hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (4e)

Pale yellow solid (93%). m.p. 210–212°C ([Lit[27]] 210–212°C). IR (KBr): ν 3445, 3136, 2940, 1735, 1642, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, $-CH_3$), 3.42 (s, 3H, $-OCH_3$), 6.86 (d, J = 8.1Hz 1H, Ar-H), 7.24–7.16 (m, 2H, Ar-H), 7.50 (s, 1H, Ar-CH=C), 10.72 (s, 1H, -OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.3, 56.0, 111.6, 116.5, 122.8, 125.4, 129.3, 148.3, 149.7, 151.2, 163.9, 174.7 ppm. ESIMS: *m/z* 251 $[M+18]^+$.

2.3.6. (Z)-4-(3,4-dimethoxybenzylidene)-3-methylisoxazol-5(4H)-one (4f)

Yellow solid (92%). m.p.132–134°C ([Lit[27]] 134–136°C). IR (KBr): ν 3092, 2935, 2830, 2355, 1730, 1565, 1266 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H, $-CH_3$), 3.83 (s, 6H, 2-CH_3), 6.90 (d, J = 8.1Hz, 1H, Ar-H), 7.320-7.28 (m, 2H, Ar-H), 7.50 (s, 1H, Ar-CH=C) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.4, 56.2, 111.1, 111.6, 122.6, 126.0, 127.9, 147.7, 149.4, 150.3, 167.6, 175.1 ppm; ESIMS: *m/z* 248 $[M+1]^+$.

2.3.7. (Z)-4-(3,4,5,-trimethoxybenzylidene)-3-methylisoxazol-5(4H)-one (4g)

Yellow solid (92%). m.p.128-130°C ([Lit[27]] 128–130°C). IR (KBr): ν 3130, 2945, 1740, 1560, 1278, 1042, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H, $-CH_3$), 3.78 (s, 9H, 3-OCH_3), 7.08 (d, J = 8.8, 2H, Ar-H), 7.40 (s, 1H, Ar-CH=C) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.5, 56.3, 60.5, 103.7, 125.1, 129.7, 138.0, 150.3, 153.0, 164.5, 174.4 ppm; ESIMS: *m/z* 278 $[M+1]^+$, 277 $[M]^+$.

2.3.8. (Z)-4-(4-(dimethylamino)benzylidene)-3-methylisoxazol-5(4H)-one (4h)

Pale red solid (90%). m.p. 215–217°C ([Lit[27]] 212–214°C). IR (KBr): ν 1730, 1625, 1552, 1505, 1436 , 1312 1245, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, $-CH_3$), 3.10 (s, 6H, $-N(CH_3)_2$), 6.71 (d, J = 9.2 Hz, 2H, Ar-H), 7.34 (s, 1H, Ar-CH=C), 8.42 (d, J = 8.5 Hz, 2H, Ar-H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.0, 41.7, 111.6, 120.2, 122.6, 138.1, 149.3, 153.5, 162.4, 172.2 ppm; ESIMS: *m/z* 248 $[M+18]^+$, 230 $[M]^+$.

2.3.9. (Z)-3-methyl-4-(thiophen-2-ylmethylene)isoxazol-5(4H)-one (4i)

Pale yellow solid (92%). m.p.146–148°C ([Lit[25]] 147–148°C). IR (KBr): ν 2930, 1736, 1695, 1510, 1330, 1145 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, $-CH_3$), 7.35 (t, J = 4.8 Hz, 1H, Ar-H), 7.60 (s, 1H, Ar-CH=C), 7.92 (d, J = 4.8 Hz, 1H, Ar-H), 8.15 (d, J = 3.6 Hz, 1H, Ar-H), ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.9, 114.9, 128.5, 136.8, 140.0, 140.7, 141.5, 160.6, 168.8 ppm; ESIMS: *m/z* 193 $[M]^+$.

2.3.10. (Z)-4-(4-chlorobenzylidene)-3-methylisoxazol-5(4H)-one (4j)

White solid (90%), m.p.118–120°C ([Lit[25]] 118–120°C). IR (KBr): ν 3015, 1705, 1632, 1552, 1480 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 3.10 (s, 3H, $-CH_3$), 7.12 (s, 1H, Ar-CH=C), 7.42 (d, J = 7.2 Hz, 2H, Ar-H), 7.66 (d, J = 7.2 Hz, 2H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.0, 125.8, 127.3, 128.3, 130.9, 132.9, 133.2, 141.4, 160.2, 171.3 ppm.

2.3.11. (Z)-3-methyl-4-(4-nitrobenzylidene)isoxazol-5(4H)-one (4k)

Pale red solid (88%), m.p. 140–142°C ([Lit[25]] 142–144°C). IR (KBr): ν 3010, 1690, 1525, 1330, 1085 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3H, $-CH_3$), 7.11 (d, J = 8.2Hz, 2H, Ar-H), 7.50 (s, 1H, Ar-CH=C), 8.42 (d, J = 8.2Hz, 2H, Ar-H)ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.8, 123.2, 125.8, 132.9, 139.1, 142.2, 151.0, 160.6, 171.4 ppm.

3. RESULTS AND DISCUSSION

In continuation our research interest in the development of green synthetic methodologies, we decided to explore the use of H_2O_2: HCl catalyst system for the synthesis of 3-methyl-4-arylmethylene isoxazol-5(4*H*)-one in aqueous medium (Scheme 1).

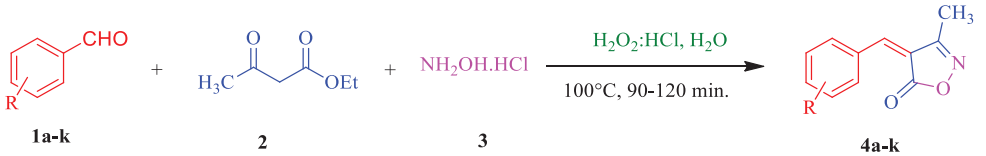
To optimize the catalyst and reaction conditions, equimolar mixture of benzaldehyde (1a) (1 mmol), ethyl acetoacetate (2) (1 mmol), and hydroxylamine hydrochloride (3) (1 mmol) was stirred with H_2O_2:HCl catalyst system in H_2O to obtain (*Z*)-4-benzylidene-3-methylisoxazol-5(4*H*)-one (4a). Initially, the reaction was carried out using catalyst-free condition at room temperature as well as at 100°C for extended time (120 min) which led to the formation of desired product with only 20 and 32 % yields, respectively.

After that, we decided to use of H_2O_2: HCl as catalyst for the investigation of its efficacy. The reaction was started with 2:1 mmol of H_2O_2:HCl catalyst system at room temperature for 120 min to obtained

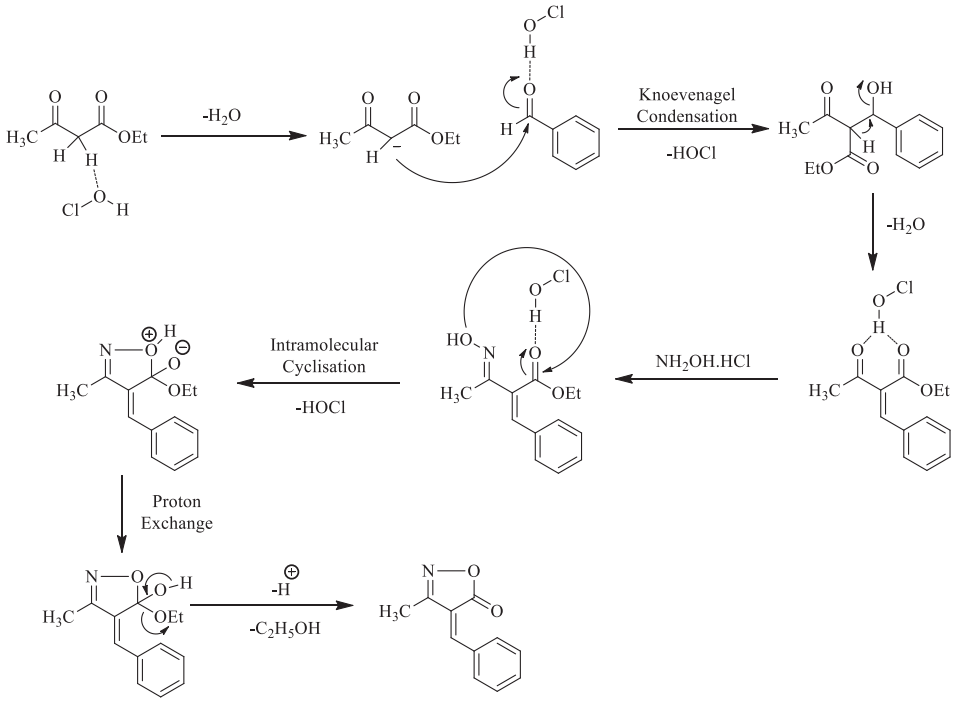
little improved product yield with 45%. By considering this result, we moved to increase in the reaction temperature by 50, 70, 80, and 100°C for 120 min then considerably increased product yield with 54, 62, 70, and 78%, respectively.

After optimization of temperature, we moved to explore the effect of different molar ratios of the H_2O_2:HCl catalyst system from 4:2 mmol to 8:4 mmol. When the molar ratio of the catalyst was increased from 4:2 mmol to 6:3 mmol, an increase in the yield of product was observed. Interestingly, when the reaction was carried out using 6:3 mmol of catalyst at 100°C, reaction was completed within 90 min with 92% yield. A further increase in the mole ratio of catalyst (8:4 mmol) led to no increment in the yield. The observation shows that 6:3 mmol equivalent of H_2O_2:HCl catalyst system is sufficient for the completion of the reaction within 90 min at 100°C. All the results are summarized in Table 1.

With the optimized catalyst and reaction conditions in hand, the scope of the reaction was explored in details (Table 2). Variety of aromatic and heterocyclic aldehydes were reacted with ethyl acetoacetate and hydroxylamine hydrochloride for the synthesis of 3-methyl-4-arylmethylene isoxazol-5(4*H*)-one derivatives (Table 2, entry 4a-4k) to demonstrate the scope of H_2O_2:HCl as catalyst. All results are summarized in Table 2.



Scheme 1: H_2O_2:HCl catalyzed synthesis of 3-methyl-4-arylmethylene isoxazol-5(4*H*)-one.



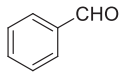
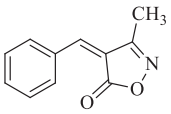
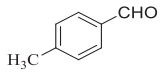
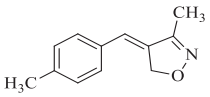
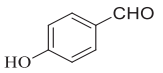
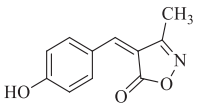
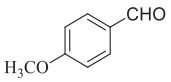
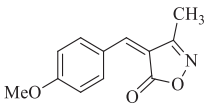
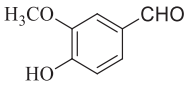
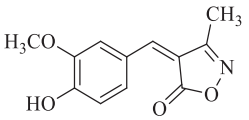
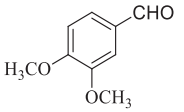
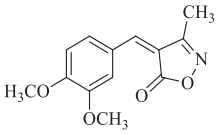
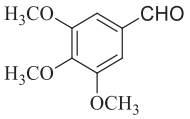
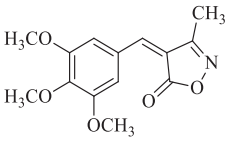
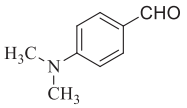
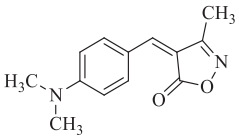
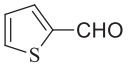
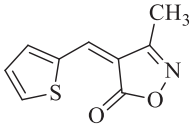
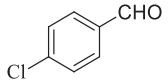
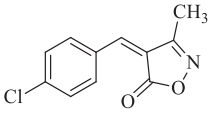
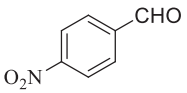
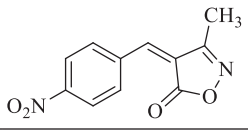
Scheme 2: Possible reaction mechanism of 3-methyl-4-arylmethylene isoxazol-5(4H)-one.

Table 1: Optimization of H_2O_2:HCl catalyst system in water at different conditions

S. No.	Catalyst system	Ratio (mmol)	Temperature (°C)	Time (min.)	Isolated yields (%)
1	Catalyst-free	--	RT[a]	120	20
2	Catalyst-free	--	100	120	32
3	H_2O_2:HCl	2:1	RT[a]	120	45
4	H_2O_2:HCl	2:1	50	120	54
5	H_2O_2:HCl	2:1	70	120	62
6	H_2O_2:HCl	2:1	80	120	70
7	H_2O_2:HCl	2:1	100	120	78
8	H_2O_2:HCl	4:2	100	120	84
9	H_2O_2:HCl	6:3	100	90	92
10	H_2O_2:HCl	8:4	100	90	92

RT[a]: Room temperature

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

S. No.	Aldehyde	Product	Reaction time (min.)	Isolated yield (%)	M.P. °C [Lit. M.P.][Ref]
a			90	92	140–142 [142–144] [27]
b			90	92	130–132 [132–134] [27]
c			90	93	212–214 [210–212] [27]
d			90	92	178–180 [176–178] [27]
e			90	93	210–212 [210–212] [27]
f			90	92	132–134 [134–136] [27]
g			90	92	128–130 [128–130] [27]
h			90	90	215–217 [212–214] [27]
i			90	92	146–148 [147–148] [25]
j			90	90	118–120 [118–120] [25]
k			90	88	140–142 [142–144] [25]

3.1. Possible Reaction Mechanism

Formation of the product can be explained by possible reaction mechanism as shown in Scheme 2. Initially, HOCl was formed by the reaction of H_2O_2 with HCl which abstract the proton from active methylene compound to generate carbanion. Then, generated carbanion reacts with preactivated carbonyl carbon of aldehyde followed by dehydration to obtained Knoevenagel product which was reacted with hydroxylamine hydrochloride to formed imine product. This product was cyclized followed by proton exchange to formed desired product. In this mechanism, active methylene compound and electrophilicity of carbonyl groups are increased by HOCl due to inter molecular hydrogen bonding between them.

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

4. CONCLUSION

In summary, we have demonstrated a simple, efficient, and novel method for synthesis of 3-methyl-4-arylmethylene isoxazol-5(4*H*)-one derivatives using various aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride with H_2O_2:HCl catalyst system in aqueous medium. The present method highlights the valuable advantages such as use of H_2O as the solvent, metal-free catalyst, easy work-up, one-pot synthesis with excellent yields, and elimination of toxic organic solvent as well as byproducts. All synthesized compounds were analyzed by ^{1}H NMR, ^{13}C NMR, FTIR spectroscopy, and mass spectrometry.

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