An Efficient Synthesis of 4-Arylmethylidene-3-substituted-Isoxazol-5(4*H*)-ones in Aqueous Medium

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INTRODUCTION

Increased environmental awareness within the synthetic chemistry community has lately pushed green chemistry technologies to the fore. Since the last decade, the development of non-hazardous alternatives is not only due to the increased regulatory pressure focusing on organic solvents but also for sustainability benefits. Viewed in this light, water is uniquely advantageous as a solvent [1–10].

Isoxazolone is a class of heterocyclic compounds having a remarkable number of pharmaceutical [11-14] applications and have been demonstrated to be versatile building blocks in the synthesis of natural products [15–18], in optical recording, and nonlinear optical research [19,20]. 4-(Arylmethylene)-isoxazol-5-ones are known to be useful building blocks for the preparation of fused heterocycles [21-24]. The synthesis of 4-arylmethylidene-3-methylisoxazol-5(4H)-one derivatives involves a coupling of ethyl acetoacetate, hydroxylamine hydrochloride, and aromatic aldehydes catalyzed in basic medium [25,26]. Literature enumerates different reagents, catalysts, and/or reaction medium viz pyridine [27], sodium benzoate [28], sodium silicate [29], sodium sulfide [30], sodium ascorbate [31], sodium tartraborate [32], boric acid [33], sodium azide [34], sodium saccharin [35], and sodium citrate [36] in the presence of organic solvents and/or water. Literature also revealed that the methods indicated previously requires high temperature [37], long reaction time [37,38], reagent in stoichiometric amount [27,38], and the reaction conditions like grinding or use of ultrasound irradiation [38], or visible light [39]. Recently, we have reported [40-42] the synthesis of β-hydroxyester, 4-aryl/ alkylaminocoumarins under solvent-free condition using microwave irradiation and synthesis of xanthene derivatives in aqueous medium. The success of these reactions encouraged us to probe the development of efficient and environmentally benign method for the synthesis of 4-arylmethylidene-3substituted-isoxazol-5(4*H*)-one derivatives. Thus, the synthesis of 4-arylmethylidene-3-methyl-isoxazol-5(4*H*)-one was attempted using equimolecular quantities of β -ketoesters, hydroxylamine hydrochloride, and an aromatic aldehyde in an aqueous medium (Scheme 1).

RESULTS AND DISCUSSION

In the beginning, the synthesis of 4-(4-methoxyphenyl)-3-methyl-5(4*H*)-isoxazolone (4a) was carried out by reacting ethyl 3-oxobutanoate, 1a and hydroxylamine hydrochloride (2), and 4-methoxybenzaldehyde (3a) in water. It was observed that the reaction proceeded effectively without any catalyst in 91% yield (Scheme 2).

It is known that the Knöevenagel type reactions are solvent-dependent and that usually dipolar aprotic solvents, like DMF, are especially useful in this condensation. This is because the second step, viz 1,2-elimination, is inhibited by protic solvents [25]. The effects of various solvents with different properties, like polarity and proticity, were employed in the model reaction (Scheme 2) to optimize the reaction conditions. The representative results are summarized in Table 1, which showed that the reaction works well in water (Table 1, entry 7).

The Knöevenagel condensation reaction proceeds smoothly in water to afford the desired product 4a in 91% yield (Table 1, entry 7). The enhanced reactivity in aqueous medium observed in some reactions was rationalized by various researchers [5] as a consequence of hydrophobic effects and enforced hydrophobic interactions. The protic solvents are favorable over the usual DMSO or DMF, which are toxic, teratogenic, and suspected carcinogenic solvents. Further, this model reaction occurs with moderate yield in ethanol (81%), methanol (79%), and isopropanol (74%) (Table 1, entries 4–6, respectively).

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Scheme 1. Synthesis of 4-arylmethylidene-3-methyl-isoxazol-5(4H)-one.

Ar-CHO +
$$R_1$$
 O O
 OR_2 + $NH_2OH.HC1$ $Water$ R_1 N_0 O
 $R_1 = H, Cl; R_2 = CH_3, CH_2CH_3$

Scheme 2. Synthesis of 4-(4-methoxyphenyl)-3-methyl-5(4H)-isoxazolone (4a).



 Table 1

 Solvent effect on the yield of model reaction (Scheme 2).

	•	· · · · · · · · · · · · · · · · · · ·
Entry	Solvent ^a	Yield ^b (%)
1	None	20
2	DMF	88
3	DMSO	75
4	EtOH	81
5	MeOH	79
6	IPA	74
7	H_2O	91

^aThe reaction was carried out in solvents (5 mL) for 2 h. ^bIsolated yield.

The moderate yields were obtained in alcoholic medium that suggest the hydrophobic effect of polar protic solvents.

Because the reaction easily occurs in non-basic aqueous medium, glass catalyzed processes were excluded by carrying out the reaction in a polyethylene vessel, which gave 85% yields.

The investigation was further extended by substituting ethyl 3-oxobutanoate with methyl 3-oxobutanoate, and it was observed that the yield of the product was increased up to 17%. This may be due to the easier substitution of $-OCH_3$ group of methyl 3-oxobutanoate compared to $-OC_2H_5$ group of ethyl 3-oxobutanoate (Table 2).

It was found that aldehydes having a wide range of substituents undergo MCP to afford the desired product in good yield (Table 2). The reaction of aromatic aldehydes bearing electron donating groups at para (Table 2, compounds **4a**, **4c**, **4d**, **4g**, **4h**, **4i**, and **4k**) and meta (Table 2, compounds **4f** and **4j**) position provided a higher yield, while an electron donating group at ortho (Table 2, compounds **4b** and **4e**) resulted in lower yield. It is important to note that α , β unsaturated aldehyde and heterocyclic aldehyde (Table 2, compounds **4m** and **4n**) underwent reaction gave good yields of the corresponding products under the same reaction condition. However, aromatic aldehydes with an electron-withdrawing group like chloride, nitro, failed to give the desired product.

 Table 2

 Synthesis of 4-arylmethylidene-3-methyl-isoxazol-5(4H)-one in aqueous medium.

H ₃ C OR ⁺	NH ₂ OH.HCl +	Ar-CHO Water	→ H ₃ C N ₀ Ar
1a	2	3a-n	4 a-n

Product	Ar	$R = CH_3$		$R = C_2 H_5$	
Tioudet		Time (min)	Yield ^a (%)	Time (min)	Yield ^a (%)
4a	4 H ₃ CO-Ph	30	97	30	88
4b	2 H ₃ CO-Ph	45	77	45	60
4c	4 H ₅ C ₂ O-Ph	30	90	30	85
4d	3,4 OCH ₂ O Ph	30	88	30	82
4e	2 HO-Ph	75	70	75	45
4f	3 HO-Ph	45	79	75	60
4g	4 HO-Ph	20	90	20	88
4h	4 Me ₂ N-Ph	30	95	30	84
4i	4 H ₃ C-Ph	60	80	60	75
4j	3-F-Ph	30	90	30	80
4k	4-F-Ph	20	98	20	90
41	Ph	30	80	55	72
4m	Ph-CH=CH-	30	90	30	86
4n	3-Indole	30	92	30	73

^aIsolated yield.

Finally, the method was scaled up to generate multigram quantities of 4-arylmethylidene-3-methyl-isoxazol-5(4*H*)one without any significant loss in yields. Isoxazolone derivatives constitute an important and privileged structural motif in the context of medicinal chemistry applications [43–47]. In order to access these valuable isoxazolone derivatives, we have evaluated the reaction of ethyl 4chloro-3-oxobutanoate (**1b**) with substituted aldehydes and hydroxylamine hydrochloride under aqueous condition. The reactions afforded a number of 3-chloromethyl-5(4H)-isoxazolone in excellent yields under the optimal reaction conditions (Table 3).

 Table 3

 Synthesis of 4-arylmethylidene-3-chloromethylene-isoxazol-5(4H)-one in aqueous medium.

Ar-CHO + 3a-j	CIH ₂ C OC ₂ H ₅ +	NH ₂ OH.HCl Water	ClH ₂ C Ar N _O 5a-j
Product	Ar	Time (min)	Yield ^a (%)
5a	4 H ₃ CO-Ph	40	92
5b	4 H ₅ C ₂ O-Ph	40	90
5c	3 HO-Ph	45	85
5d	4 HO-Ph	30	88
5e	3,4 OCH ₂ O-Ph	30	90
5f	3 H ₃ CO,4 OH-Ph	30	88
5g	4 Me ₂ N-Ph	30	90
5h	4 H ₃ CCOHN-Ph	45	79
5i	4 H ₃ C-Ph	50	80
5j	Ph	40	90
5k	Ph-CH=CH-	50	75
51	3-Indole	50	85

^aIsolated yield.

CONCLUSIONS

We have demonstrated a convenient, practical, and an efficient method for the synthesis of 4-arylmethylidene-3-substituted-isoxazol-5(4H)-ones in aqueous medium. This operationally simple procedure is less laborious and provides a better scope and chemo-selectivity than previously reported procedures.

EXPERIMENTAL

All common reagents and solvents were used and obtained from commercial supplies without further purification. All reactions were monitored, and purity of the products was checked by TLC. TLC was performed on Merck 60 F-254 (India) silica gel plates with visualization by UV-light. Melting points were determined in capillary tubes in silicon oil bath using a Veego melting point apparatus (MP-DS, India) and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded on Varian mercury XL-300 (California, USA) or Bruker spectrometer (Switzerland) instruments. Chemical shifts are reported from internal tetramethyl silane as a standard and are given in δ units. Infrared spectra were taken on Shimadzu FTIR – 408 (Singapore) in KBr. Electron impact HR mass spectra were obtained using Q-Tof Micromass mass spectrometer (Waters, UK) using an ionizing voltage of 70 eV.

General procedure 4-arylmethylidene-3-methyl-isoxazol-5(4H)-one (4a–n and 5a–l). A mixture of ethyl 3oxobutanoate (1a, 0.25 g, 1.92 mmol) and hydroxylamine hydrochloride (2, 0.13 g, 1.92 mmol) in water (5 mL) was stirred in ice bath (5 °C) for 15 min. After the color of the mixture changed to pale yellow, the aromatic aldehyde (3a–n, 1.92 mmol) was slowly added to the reaction mixture; the solid product was formed immediately. The resulting threecomponent mixture was further stirred till completion of the reaction (monitored by TLC). The solid material was filtered, and washed with water $(2 \times 5 \text{ mL})$ to furnish pure product **4a–n**. If necessary, the products were further purified by crystallization from aqueous ethanol. The same procedure was applied for the synthesis of **4a–n** and **5a–l** using methyl 3-oxobutanoate (**1b**) and ethyl 4-chloro-3-oxobutanoate (**1c**), respectively. The practical yield is presented in Tables 2 and 3. The ¹H and ¹³C NMR data of the known compounds are in good agreement with those reported in the literature. ¹H, ¹³C NMR, and HRMS data for only new products are given in what follows, while the spectral data for known products matched with the previously reported literature data [25–36].

4-(4-Ethoxybenzylidene)-3-methyl-isoxazol-5(4H)-one (Table 2, entry 4c). mp 150–152 °C; IR (KBr) 1735, 1586, 1564, 1518,1432, 1265,890 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.33 (t, J=7.2 Hz, 3H, <u>H</u>₃C-CH₂), 2.28 (s, 3H, <u>H</u>₃C-isoxazol), 4.16 (q, J=7.2 Hz, 2H, H₃C-CH₂-O), 6.70 (d, J=8.6 Hz, 2H, Ar-H), 7.34 (s, 1H, =C<u>H</u>), 8.44 (d, J=8.6 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃) δ 14.8, 22.1, 64.7, 118.2, 129.8, 129.9, 134.2, 145.8, 150.2, 161.4, 168.3; HRMS (*m*/*z*): 232.0961 (M + H)⁺.

4-(3-Fluorobenzylidene)-3-methyl-isoxazol-5(4H)-one (Table 2, entry 4j). mp 142–144 °C; IR (KBr) 1730, 1686, 1594, 1520, 1427, 1250, 870 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.33 (s, 3H, <u>H</u>₃C-isoxazol), 7.19 (m, 1H, Ar-H), 7.32 (t, J=7.6 Hz, 1H, Ar-H), 7.60 (m, 1H, Ar-H), 7.39 (s, 1H, =C<u>H</u>), 9.00 (m, 1H, Ar-H); ¹³C NMR (75 MHz, CDCl₃) δ 22.1, 111.3, 114.7, 122.2, 125.0, 132.0, 137.8, 150.9, 162.2, 165.9, 170.0; HRMS (*m*/*z*): 206.0617 (M+H)⁺.

4-(4-Methoxybenzylidene)-3-(chloromethyl)isoxazol-5(4H)one (Table 3, entry 5a). mp 138–140 °C; IR (KBr) 1751, 1550, 1455, 1423, 1181, 1084, 922 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.94 (s, 3H, <u>H</u>₃C-O) 4.55 (s, 2H, Cl-C<u>H</u>₂-isoxazol) 7.04 (d, J=8.7 Hz, 2H, Ar-H), 7.68 (S, 1H, =CH), 8.49 (d, J=8.7 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCL₃) δ 35.2, 55.8, 112.5, 114.8, 125.6, 137.5, 151.1, 160.3, 165.2, 168.2; HRMS (m/z): 252.0439 (M+H)⁺.

4-(4-Ethoxybenzylidene)-3-(chloromethyl)isoxazol-5(4H)one (Table 3, entry 5b). mp 150–152 °C IR (KBr) 1749, 1555, 1461, 1427, 1177, 1085, 928 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.45 (t, J=7.2 Hz, 3H, <u>H</u>₃C-CH₂), 4.16 (q, J=7.2 Hz, 2H, H₃C-C<u>H</u>₂-O), 4.52 (s, 2H, Cl-C<u>H</u>₂-isoxazol) 7.02 (d, J=8.7 Hz, 2H, Ar-H), 7.70 (s, 1H, =CH), 8.50 (d, J=8.7 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCL₃) δ 17.9, 35.3, 57.8, 114.3, 115.7, 125.5, 137.8, 151.2, 160.1, 165.0, 168.0; HRMS (*m*/*z*): 232.0961 (M+H)⁺.

4-(3-Hydroxybenzylidene)-3-(chloromethyl)isoxazol-5(4H)one (Table 3, entry 5c). mp 188–190 °C; ¹H NMR (300 MHz, DMSO- d_6) δ 4.80 (s, 2H, -CH₂-isoxazol), 7.06 (dd, J=7.6 and 1.72 Hz, 1H, Ar-H), 7.39 (t, J=8.0 Hz, 1H, Ar-H), 7.79 (d, J=7.6 Hz, 1H, Ar-H), 7.86 (s, 1H, =CH), 8.01 (s, 1H, Ar-H), 9.90 (bs, 1H, Ar-O<u>H</u>). ¹³C NMR (75 MHz, DMSO- d_6) δ 35.0, 112.2, 115.2, 119.0, 125.5, 130.8, 136.6, 152.4, 157.6, 165.2, 169.0; HRMS (m/z): 238.0266 (M+H)⁺.

4-(4-Hydroxybenzylidene)-3-(chloromethyl)isoxazol-5(4H)one (Table 3, entry 5d). mp 190–192 °C; IR (KBr) 3159,1746,1552,1446, 1258,1176,1084,933 cm⁻¹; ¹H NMR (300 MHz, DMSO- d_6) δ 4.88 (s, 2H, Cl-CH₂-isoxazol), 7.00 (d, J=9.1 Hz, 2H, Ar-H), 8.02 (s, 1H, =CH), 8.46 (d, J=9.1 Hz, 2H, Ar-H); 11.26 (bs, 1H, Ar-OH). ¹³C NMR (75 MHz, CDCl₃) δ 35.3, 111.5, 113.8, 126.7, 138.9, 151.0, 161.6, 163.9, 169.5; HRMS (m/z): 238.0285 (M+H)⁺. 4-((Benzo[d][1,3]dioxol-5-yl)methylene)-3-(chloromethyl) isoxazol-5(4H)-one (Table 3, entry 5e). mp 184–186 °C; IR (KBr) 1730, 1589, 1530, 1429, 1220, 1102, 878 cm⁻¹; ¹H NMR (400 MHz, DMSO- d_6) δ 4.84 (s, 2H, Cl-CH₂-isoxazol), 6.22 (s, 2H, O-CH₂-O), 7.14 (d, J=8.2 Hz, 1H, Ar-H), 7.87 (dd, J=8.32 and 1.72 Hz, 1H, Ar-H), 8.02 (s, 1H, =CH), 8.40 (d, J=1.72 Hz, 1H, Ar-H); ¹³C NMR (100 MHz, DMSO- d_6) δ 34.9, 102.8, 108.9, 111.4, 112.1, 127.2, 134.3, 148.0, 152.4, 153.5, 161.5, 168.0; HRMS (m/z): 266.0232 (M + H).⁺

4-(4-Hydroxy-3-methoxybenzylidene)-3-(chloromethyl)isoxazol-5(4H)-one (Table 3, entry 5f). mp 184–186 °C; IR (KBr) 3350, 1748, 1555, 1451, 1418, 1174, 1079, 930 cm⁻¹; ¹H NMR (400 MHz, DMSO- d_6) δ 3.88 (s, 3H, H₃C–O), 4.77 (s, 2H, Cl-CH₂-isoxazol), 6.95 (d, J=8.8 Hz, 1H, Ar-H), 7.80 (dd, J=8.8 and 2 Hz, 1H, Ar-H), 7.90 (s, 1H, =CH), 8.55 (d, J=2 Hz, 1H, Ar-H) 10.83 (bs, 1H, Ar-OH); ¹³C NMR (100 MHz, DMSO- d_6) δ 34.9, 55.5, 110.0, 115.8, 116.5, 124.9, 132.5, 147.5, 152.7, 154.7, 161.3, 168.5; HRMS (m/z): 268.0377 (M + H)⁺.

4-(4-(Dimethylamino)benzylidene)-3-(chloromethyl)isoxazol-5(4H)-one (Table 3, entry 5g). mp 178–180 °C; IR (KBr) 1734, 1589, 1530, 1429, 1180, 1096, 870 cm^{-1} ; ¹H NMR (400 MHz, DMSO- d_6) δ 3.19 (s, 6H, (<u>H</u>₃C)₂N-), 4.72 (s, 2H, Cl-C<u>H</u>₂-isoxazol), 6.83 (d, J=8.2 Hz, 2H, Ar-H), 7.72 (s, 1H, =CH), 8.46 (d, J=8.2 Hz, 2H, Ar-H); ¹³C NMR (100 MHz, DMSO- d_6) δ 35.2, 39.3, 105.4, 111.5, 121.0, 138.0, 150.8, 154.6, 161.1, 169.4; HRMS (*m*/*z*): 265.0717 (M+H)⁺

N-(*4*-((*3*-(*Chloromethyl*)-*5*-oxoisoxazol-4(5H)-ylidene)methyl) phenyl)acetamide (Table 3, entry 5 h). mp 182–184 °C; IR (KBr) 3333, 3196, 1735, 1600, 1512, 1105, 1010, 956 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.26 (s, 3H, <u>H</u>₃CCO), 4.56 (s, 2H, Cl-C<u>H</u>₂-isoxazol), 7.45 (d, *J*=8.8 Hz, 2H, Ar-H), 7.54 (bs, 1H, NH), 7.72 (s, 1H, =CH), 8.45 (d, *J*=8.8 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃) δ 29.7, 35.1, 113.6, 115.2, 125.1, 137.1, 151.4, 160.9, 165.7, 169.0; HRMS (*m*/*z*): 279.0536 (M+H).⁺

4-(4-Methylbenzylidene)-3-(chloromethyl)isoxazol-5(4H)-one (Table 3, entry 5i). mp 178–180 °C; IR (KBr) 1741, 1593, 1522, 1435, 1188, 1091, 877 cm^{-1} ;¹H NMR (300 MHz, CDCl₃) δ 2.47 (s, 3H, <u>H</u>₃C-Ar), 4.56 (s, 2H, Cl-C<u>H</u>₂-isoxazol), 7.35 (d, J=8.2 Hz, 2H, Ar-H), 7.72 (s, 1H, =CH), 8.32 (d, J=8.2 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃) δ 22.3, 35.1, 118.1, 128.8, 129.9, 134.9, 145.8, 150.4, 161.7, 236.0; MS (*m*/*z*): 236.0493 (M+H)⁺.

4-Benzylidene-3-(chloromethyl)isoxazol-5(4H)-one (Table 3, entry 5j). mp 184–186 °C; IR (KBr) 1761, 1601, 1552, 1323, 1170, 1085, 922, cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.50 (s, 2H, Cl-CH₂-isoxazol), 7.18–7.28 (m, 3H, Ar-H), 7.32 (s, 1H, =CH), 7.70 (m, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃) δ 34.6, 125.2, 126.8, 128.9, 129.4, 135.1, 151.6, 166.5, 169.0; HRMS (m/z): 221.0244 (M+H)⁺.

4-((*E*)-3-Phenylallylidene)-3-(chloromethyl)isoxazol-5(4H)one (Table 3, entry 5k). mp 186–188 °C; IR (KBr) 1757, 1599, 1546, 1315, 1176, 1096, 868 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.52 (s, 2H, Cl-CH₂-isoxazol) 7.40 (d, *J*=15.8 Hz, 1H, =CH), 7.44 (m, 3H, Ar-H), 7.61 (d, *J*=15.8 Hz, 1H, =CH), 7.66–7.69 (m, 2H, Ar-H), 8.33 (dd, *J*=15.8 and 15.8 Hz, 1H, =CH); ¹³C NMR (75 MHz, CDCl₃) δ 34.8, 113.6, 121.8, 128.3, 128.9, 131.6, 134.7, 150.7, 153.3, 159.8, 168.0; HRMS (*m*/*z*): 248.0465 (M + H)⁺.

4-((1H-Indol-3-yl)methylene)-3-(chloromethyl)isoxazol-5(4H)one (Table 3, entry 5l). mp 240–242 °C; IR(KBr) 1757, 1599, 1546, 1315, 1176, 1096, 868 cm⁻¹; ¹H NMR (300 MHz, DMSO- d_6) δ 5.01 (s, 2H, Cl-CH₂-isoxazol), 7.37–7.39 (m, 2H, Ar-H), 7.62–7.65 (m, 1H, Ar-H), 8.14–8.17 (m, 1H, Ar-H), 8.46 (s, 1H, =CH), 9.56 (d, J=3.0 Hz, 1H, indole-H), 13.03 (bs, 1H, HN–); ¹³C NMR (75 MHz, DMSO- d_6) δ 35.5, 108.3, 112.3, 112.7, 118.4, 122.1, 123.5, 127.5, 135.9, 138.0, 140.0, 161.2, 169.9; HRMS (m/z): 261.0447 (M+H)⁺.

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