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One-pot and Three-Component Synthesis of Isoxazol-5 (4*H*)-one Derivatives in the presence of Citric Acid

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ABSTRACT

In this context, the one-pot three-component synthesis of 3-methyl-4-arylmethylene-isoxazol-5(4*H*)-ones has been performed in the presence of citric acid as catalyst in water. The products have been obtained in high yields (70-90%) and convenient reaction times (5-24 hours).

Keywords: Citric Acid, isoxazol-5(4*H*)-one, one-pot reaction, water, green chemistry.

INTRODUCTION

Isoxazolones and its derivatives have a variety of biological activities. [1] The synthesis of aryl-3-methylisoxazol-5(4*H*)-one derivatives involves a coupling of aromatic aldehydes with ethyl acetoacetate and hydroxylamine. This procedure has been carried out by different reagents and catalysts .[2] Also, multi-component reactions (MCRs) have been used for the synthesis of a variety of natural products and biologically active compounds, because they have many advantages such as excellent functional group compatibility, minimization of waste, versatility, atom economy, environmentally friendly, and easy work-up[3]. In this context we have done a convenient and environmentally benign procedure by citric acid as the catalyst for the synthesis of 4-arylmethylidene-3-substituted-isoxazol-5(4*H*)-ones. Thus, the synthesis of 4-arylmethylidene-3-methyl-isoxazol-5(4*H*)-ones was attempted by using equimolecular quantities of ethyl acetoacetate, hydroxylamine hydrochloride, and a variety of aromatic aldehydes in the presence of citric acid as catalyst in water as shown in scheme 1.

RESULTS AND DISCUSSION

We conceived the preparation of diverse arylmethylidene-isoxazole-5(4*H*)-ones from the reaction between an aromatic aldehyde, hydroxylamine hydrochloride, and ethyl acetoacetate (EAA) catalyzed by citric acid. For determine the optimal reaction conditions, we screened different amounts of citric acid (0-2 mmol) (Table 1) using benzaldehyde as a model compound. Consequently, the amount of 1 mmol for citric acid

was selected as the optimized amount of the catalyst for this procedure. The efficiency of this protocol was examined by the reaction of a variety of aldehydes. all reactions were completed in appropriate times within 5-24 hours in good yields (70-90%) (Table 2). The products were characterized by ^{1}H-NMR spectroscopy, FT-IR spectrum and melting points of the products (Table 2, column 6) were measured and compared with the literature for the known compounds[2]. Characterization and comparison of the formed products with suitable references [**2k** and **2l**] supports the selectivity for the formation of the (*Z*)-isomer. Therefore, the products are assumed to have the double bond with the (*Z*) geometry.

Two proposed mechanism for the formation of the products and the influences of citric acid are shown in Schemes 2.

EXPERIMENTAL

General

All substrates and reagents were purchased from commercially sources (Merck and Sigma-Aldrich). FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectra were recorded on PerkinElmer FT-IR RXI and 300 MHz Bruker spectrometers, respectively. The products were characterized by their FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectra and comparison with authentic samples. Organic layers were dried over anhydrous sodium sulfate. All yields referred to isolated pure products. The purity of products was determinate by ^{1}H NMR. Also, reactions were monitored over silica gel 60 F_{254} aluminum sheet.

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

In a round-bottomed flask (25 mL) equipped with a magnetic stirrer, a mixture of ethyl acetoacetate (1.30 g, 10 mmol), hydroxylamine hydrochloride (0.7 g, 10 mmol), aromatic aldehyde (10 mmol), and citric acid (1.9 g, 10 mmol) in 25 mL of distilled water was prepared and stirred at room temperature for mentioned time in Table 2. After completion of reaction (monitored by TLC), the precipitate was filtered off and washed with cold distilled water. Then products were recrystallized from ethanol or acetone as mentioned in Table 2. Pure (*Z*)-4-arylmethylene-3-methyl-isoxazol-5(4*H*)-ones were obtained as solids after recrystallization from ethanol or acetone and were characterized by ^{1}H-NMR, ^{13}C-NMR, and FT-IR spectroscopy.

Spectral data for prepared compounds

(Z)-4-benzylidene-3-methylisoxazol-5(4H)-one (1)

Yellow crystal: mp 140-142°C (Lit [2k] mp 142-144°C);^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3), 7.44 (s, 1H, ArCH=), 7.49-7.59 (m, 3H, Ar), 8.35 (dd, J = 1.3, 7.4 Hz, 2H, Ar); ^{13}C-NMR (300 MHz, $CDCl_3$): δ 11.63 (CH_3), 119.65 (C=, inside of isoxazolone ring), 129.03 (Ar), 130.47 (Ar), 132.29 (Ar), 134.01 (Ar), 149.98 (ArCH=), 161.16 (C=N), 167.88 (C=O); IR (KBr) ν: 1732 (C=O), 1620, 1100, 1216, 879, 763 cm^{-1}.

(Z)-4-(4-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (2)

Yellow crystal: mp 177-179°C (Lit [2k] mp 177-178°C);^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.34 (s, 1H, ArCH=), 7.00 (d, J = 8.7 Hz, 2H, Ar), 8.44 (d, J = 8.7 Hz, 2H, Ar); ^{13}C-NMR (300 MHz, $CDCl_3$): δ 11.63 (CH_3), 55.70 (OCH_3), 114.64 (C=, inside of isoxazolone ring), 116.31 (Ar), 125.82 (Ar), 136.96 (Ar), 149.35 (ArCH=), 161.29 (Ar-O), 164.60 (C=N), 168,77 (C=O); IR (KBr) ν: 1730 (C=O), 1590, 1267, 1018, 875, 775 cm^{-1}.

(Z)-4-(2-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (3)

Yellow crystal: mp 159-160°C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 6.96 (d, J = 8.4 Hz, 1H, Ar), 7.09 (t, J = 7.8 Hz, 1H, Ar), 7.56 (t, J = 7.05 Hz, 1H, Ar), 8.06 (s, 1H, ArCH=), 8.92 (d, J = 8.1 Hz, 1H, Ar); ^{13}C-NMR (300 MHz, $CDCl_3$): δ 11.67 (CH_3), 55.47 (OCH_3), 110.70 (C=, inside of isoxazolone ring), 118.32 (Ar), 120.84 (Ar), 121.20 (Ar), 133.37 (Ar), 136.27 (Ar), 143.98 (ArCH=), 159.82 (C=N), 161.52 (C=O); IR (KBr) ν: 1732 (C=O), 1590, 1256, 1103, 887, 765 cm^{-1}. IR (KBr) ν: 1732 (C=O), 1590, 1256, 1103, 887, 765 cm^{-1}.

(Z)-3-methyl-4-(3-phenylallylidene)isoxazol-5(4H)-one (4)

Yellow crystal: mp 180-182°C (Lit [2k] mp 179-181°C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, CH_3), 7.28-7.36 (m, 2H, CH=CH), 7.36-7.47

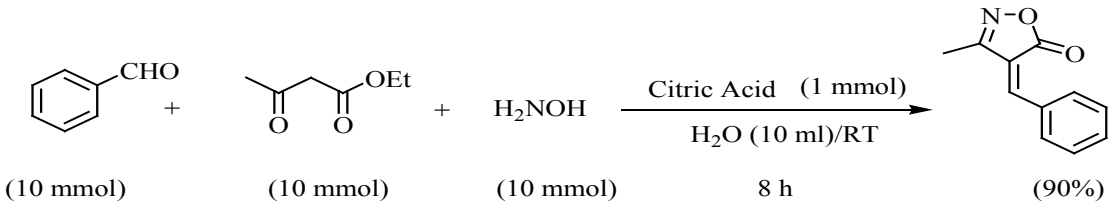
(m, Ar (2H) & ArCH= (1H)), 7.64-7,66 (m, 2H, Ar), 8.26-8.35 (m, 1H, Ar); ^{13}C-NMR (300 MHz, $CDCl_3$): δ 11.19 (CH_3), 117.86 (C=, inside of isoxazolone ring), 121.34 (Ar), 122.38 (Ar), 129.31 (Ar), 131.53 (C=C), 134.96 (C=C), 147.53 (Ar), 151.45 (ArCH=), 159.89 (C=N), 168.99 (C=O); IR (KBr) ν: 1733 (C=O), 1542, 1103, 993, 848, 753 cm^{-1}.

(Z)-4-(3-bromobenzylidene)-3-methylisoxazol-5(4H)-one (5)

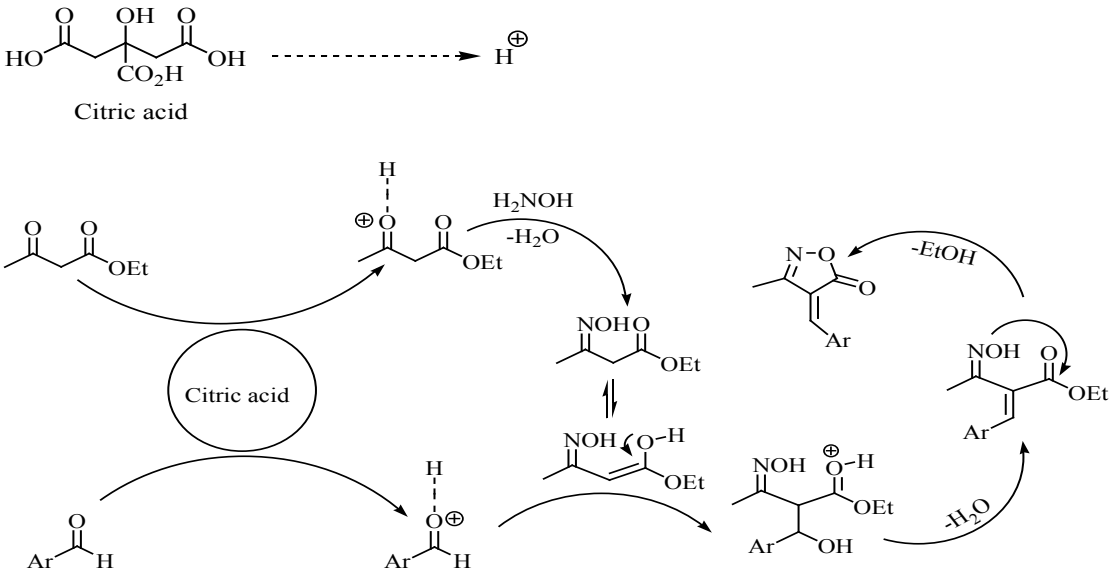
Yellow crystal: mp 141-143 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3), 7.35 (s, 1H, ArCH=), 7.41 (t, J = 8.1 Hz, 1H, Ar), 7.71 (d, J = 7.80 Hz, 1H, Ar), 8.34 (d, J = 7.8 Hz, 1H, Ar), 8.46 (s, 1H, Ar); ^{13}C-NMR (300 MHz, $CDCl_3$): δ 11.60 (CH_3), 121.12 (Ar-Br), 122.89 (C=, inside of isoxazolone ring), 130.48 (Ar), 131.90 (Ar), 133.87 (Ar), 136.03 (Ar), 136.50 (Ar), 147.71 (ArCH=), 160.86 (C=N), 167.45 (C=O); IR (KBr) ν: 1729 (C=O), 1544, 1217, 1123, 871, 775 cm^{-1}.

(Z)-4-(4-methylbenzylidene)-3-methylisoxazol-5(4H)-one (6)

Lemon crystal: mp 129-131°C (Lit [2j] mp 126-127°C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.32 (d, J = 7.8 Hz, 2H, Ar), 7.40 (s, 1H, ArCH=), 8.29 (d, J = 7.8 Hz, 2H, Ar); ^{13}C-NMR (300 MHz, $CDCl_3$): δ 11.65 (CH_3), 22.07 (CH_3), 118.40 (C=, inside of isoxazolone ring), 129.88 (Ar), 134.14 (Ar), 145.73 (Ar), 149.96



Scheme 1: The synthesis of (*Z*)-3-methyl-4-benzylmethylene-isoxazol-5(4*H*)-ones in the presence of citric acid



Scheme 2: The proposed mechanism for the synthesis of (*Z*)-3-methyl-4-arylmethylene-isoxazol-5(4*H*)-ones in the presence of citric acid

Table 1: Optimization reaction condition for the synthesis of (*Z*)-4-benzylidene-3-methylisoxazol-5(4*H*)-one (5a) from benzaldehyde (10 mmol), ethyl acetoacetate (10 mmol) and $NH_2OH.HCl$ (10 mmol) in H_2O (10 ml) in the presence of Citric Acid as shown in scheme 1

Entry	Citric Acid (g)	time (min)	conversion (%)[a]	yield (%)[b]
1	0	10	100<	30
2	0.25	10	100<	50
3	0.5	10	100<	70
4	1	8	100	90
5	2	7	100	90

[a] Conversion refers to TLC monitoring. [b] Yield refers to isolated pure product.

Table 2: Synthesis of (*Z*)-4-arylmethylidene -3-methyl-isoxazol-5(4*H*)-ones with Citric Acid/H_2O

Entry	Product	time (h)	yield (%) [a]	mp (°C) [b]
1	Ph	8	90	140-142
2	4-MeO-Ph	5	90	177-179
3	2-MeO-Ph	5	85	159-160
4	Ph-CH=CH	6	96	180-182
5	3-Br-Ph	24	70	141-143
6	4-Me_2N-Ph	5	90	206-209
7	4-Me-Ph	6	80	129-131

[a] Yields refer to isolated pure products after recrystallization inappropriate solvent. [b] The melting points have been compared with the literatures

(ArCH=), 161.22 (C=N), 168.21(C=O); IR (KBr) ν: 1731 (C=O), 1594, 1114, 873, 777 cm^{-1}.

(Z)-4-(4-(dimethylamino)benzylidene)-3-methylisoxazol-5(4H)-one (7)

Red crystal: mp 206-209°C (Lit [2k] mp 206-207°C); ^{1}H-NMR (300 MHz, $CDC1_3$): δ 2.23 (s, 3H, CH_3), 3.15 (s, 6H, $N(CH_3)_2$), 6.71 (d, J = 9 Hz, 2H, Ar), 7.27 (s, 1H, ArCH=), 8.39 (d, J = 9 Hz, 2H, Ar); ^{13}C-NMR (300 MHz, $CDCl_3$): δ 11.71 (CH_3), 40.10 (($CH_3)_2$N), 111.07 (Ar), 111.50 (C=, inside of isoxazolone ring), 121.51 (Ar), 137.62 (Ar), 149.26 (Ar), 154.22 (ArCH=), 161.59 (C=N), 170.12 (C=O); IR (KBr) ν: 1714 (C=O), 1557, 1380, 1196, 1095, 867, 765 cm^{-1}.

CONCLUSION

In conclusion, we have shown that citric acid in water is a convenient catalyst for the preparation of a variety of alkylidene isoxazol-5(4*H*)-ones, using aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride precursors in one-pot, three-component condensation reaction at room temperature in excellent yields. High efficiency, convenient reaction times, easy work-up, mild reaction conditions, and using of water as a green solvent make to this new protocol attractive for the synthesis of these heterocycles.

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