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Tomato fruit extract: an environmentally benign catalytic medium for the synthesis of isoxazoles derivatives

Bhushan B Popatkar*, Ankita A Mane & Gangadhar A Meshram

Department of Chemistry, University of Mumbai, Vidyanagari, Kalina, Santacruz (E), Mumbai 400 098, India

E-mail: bpopatkar@chemistry.mu.ac.in

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One-pot multicomponent reaction between aromatic aldehyde, hydroxylamine hydrochloride and ethyl acetoacetate/ methyl acetoacetate for the synthesis of isoxazoles derivatives by employing tomato fruit extract as a catalytic medium has been developed. Tomato fruit extract was found to be a favorable catalytic medium for the synthesis of titled compounds. Mild reaction condition, ease of separation, moderate to high yield of the product, and short reaction time makes this method more attractive over earlier reported methods for the synthesis of isoxazoles derivatives.

Keywords: Tomato fruit extract, isoxazoles, aldehydes, ethyl acetoacetate, methyl acetoacetate, hydroxylamine hydrochloride

Now a days, there has been increasing much attention on development of green synthetic pathways and processes[1]. For the model synthesis, multicomponent reactions (MCRs) remained an important tool of synthetic organic chemistry, which includes atom economy, less time, one-pot, energy saving, eco-friendly and leads to a targeted and diversely oriented synthesis[2]. Hence, the development of new MCRs by the approach of green chemistry has been given a great consideration, especially in the areas such as organic synthesis, drug manufacturing, and material science[3].

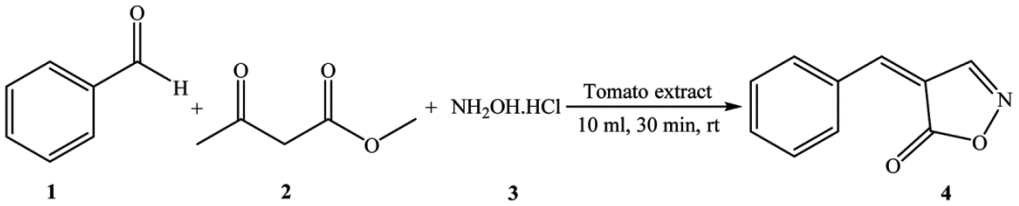
Isoxazoles are classified as a heterocyclic compounds, isoxazole moiety has been used in many synthetic products of day-to-day life[4]. The presence of isoxazole motif in the drug molecule may enhance the efficacy, reduces toxicity, and improved pharmacological potency in a positive direction[5-7]. The presence of isoxazole scaffold in the molecule exhibits broad biological activities[8] which includes anti-cancer[9], anti-microbial[10], anti-fungal[11], anti-viral[12], anti-bacterial[13], anti-tuberculosis[14], anti-inflammatory[15], *etc*.

In the recent years, good number of methods for the synthesis of isoxazole and its related compounds have been reported in the literature. Although their potential ability some of these methods suffer from one or more defects like extensive use of transition metals based catalysts[16-19], organic solvents[20-22], harsh reaction conditions[23-26]. Some methods used $Na_2S.9H_2O$[27], sulphated polyborate[28], PPTS[29], *etc*. Similarly, an edible fruit juice or extract have also been used in many reactions for the synthesis of heterocyclic compounds[30-33].

In continuation of our work on the synthesis of heterocyclic compounds, we wish to report the simple, mild and environmental benign method for the synthesis of isoxazoles and their analogues by the use of tomato fruit extract which either acts as a natural catalyst or it may provide favorable catalytic medium for the reaction and followed most of the principles of green chemistry. Tomato (*Lycopersicone sculentum*) is an edible, red color fruit used in many dishes, sauces, salads and drinks. The composition of tomato extract varies with geographical coordinates and growing conditions. It mainly composes of water, also contains weak acid (32%) such as citric acid, malic acid, ascorbic acid, succinic acid, *etc*. and other components consists of total soluble solids (6.1%), sugars (22.64%)[34]. Upon analysis the *p*H of our fruit extract was found to be (*p*H=5.2). This low *p*H indicates the presence of acidic components that may facilitate the reaction in forward direction. HPLC and LC-MS: study also confirmed the presence of acid contents in the tomato fruit extract.

Result and Discussion

Preliminary, a model reaction between benzaldehyde **(1)**, methyl acetoacetate **(2)**, and hydroxylamine hydrochloride **(3)**, in 10 mL tomato fruit extract was performed (Scheme I). The progress



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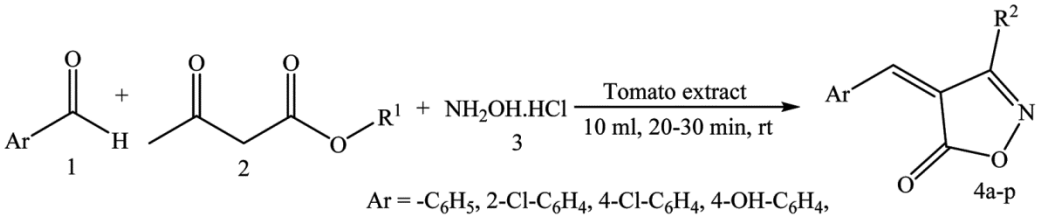
Scheme I — Tomato extract catalyzedsynthesis of (Z)-4-benzylideneisoxazol-5(4*H*)-one



Ar = -C_6H_5, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 4-OH-C_6H_4, 4-OCH_3-C_6H_4, 2,4-Cl-C_6H_3, etc.

R^1 = Et, Me

R^2 = H, CH_3

Scheme II — Synthesis of isoxazoles derivatives

of reaction was monitored by TLC. Here, tooptimize the reaction condition we have checked out an effect of different amount of tomato, pine apple, and orange fruit extract on reaction time as well as on % yield of the product **(**Table I entry 1-9). These fruit extracts were catalyzed the reaction and resulted into (Z)-4-benzylideneisoxazol-5(4*H*)-one **4** (Scheme II). Tomato fruit extract was found to be more efficient than the other used fruit extracts for this conversion (Table I, entry 5). Therefore, we choosetomato fruit extract as a catalyst or catalytic medium for the synthesis of isoxazoles derivatives.

To explore the substrate scope, and to generalize this protocol. We employed various substituted aromatic aldehydes, hydroxylamine hydrochloride and ethyl acetoacetate/methyl acetoacetate.The selected aromatic aldehydes having electron withdrawing and donating groups reacted smoothly under the similar reaction condition, and resulted in moderate to high yield of the product (Table II, entry 1-16).

Here, we have observed that, the chloro-substituted aldehydes reacts slowly hence resulted into small drop in chemical yield. This may be due to the electron withdrawing ability of chlorine **(4b, 4c, 4f, 4g, 4j, 4l,** and **4n,** Scheme III). Contrary, hydroxyl, methoxy and dimethyl amino substituted aldehydes reacts faster and proceeds into relatively moderate to high % yield of the product (**4d, 4e, 4h, 4i, 4k, 4m, 4o** and **4p,** Scheme III) that may be because of electron donating ability of the substituted groups on aldehydes (Scheme IV).

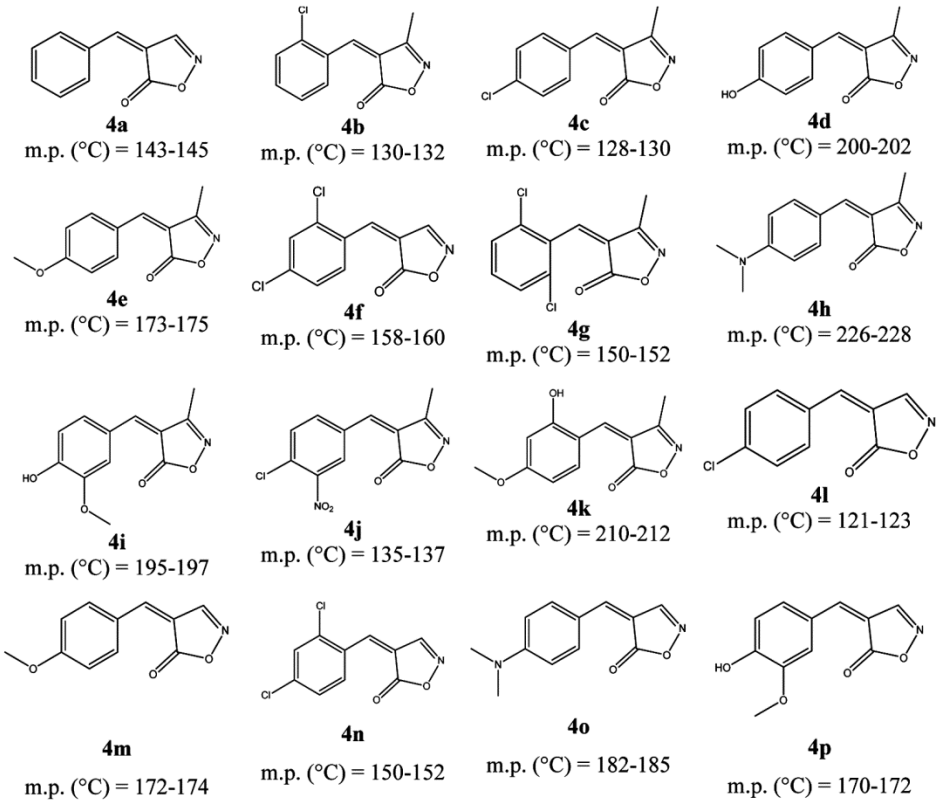
Table I — Reaction time and yield under different conditions for the formation of 4-benzylideneisoxazol 5(4*H*)-one[a]

Entry	Fruit Extracts	Volume of Fruit extract (mL)	Time (min)	Yield[b] (%)
1	Pine apple	5	80	40
2	Pine apple	10	70	50
3	Pine apple	15	70	55
4	Tomato	5	60	75
5	Tomato	10	30	85
6	Tomato	15	30	85
7	Orange	5	90	45
8	Orange	10	70	55
9	Orange	15	65	60

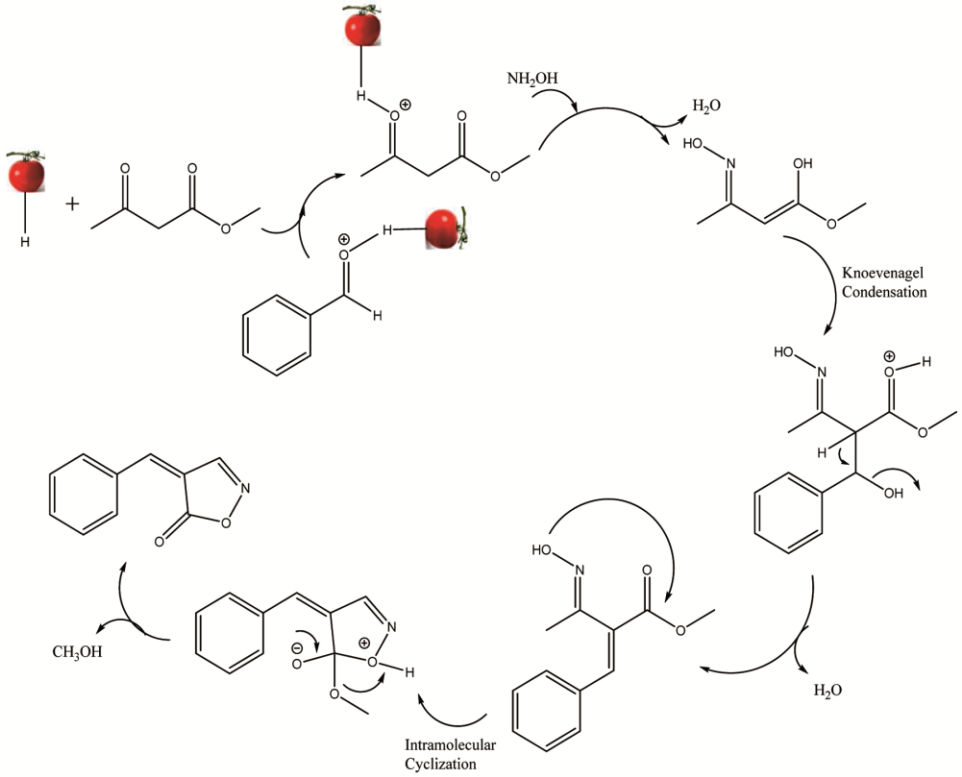
[a]Reaction condition: benzaldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol), methyl acetoacetate (1 mmol).
[b]Isolated yield.

Experimental Section

All the required chemicals were purchased from Sigma Aldrich and used without further purification. The tomatoes were purchased from local market. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker 300 MHz Ultra shield, Avance II model NMR spectrometer using tetramethylsilane (TMS) as an internal standard and DMSO-d_6/$CDCl_3$ as a solvent. Melting points were recorded by an open glass capillary sealed at one end melting point tube and are uncorrected. Fourier Transform Infrared (FT-IR) spectra of the synthesized products were recorded on a Perkin-Elmer GX FT-IRspectrometer. Mass spectra were recorded on AB SCIEX QTRAP 3200 model LC-MS:



Scheme III — Structures of synthesized compounds **4a-p**



Scheme IV — Plausible mechanism for tomato fruit extract catalyzed synthesis of (Z)-4-benzylideneisoxazol-5(4*H*)-one

spectrophotometer. The purity determination of the starting materials and reaction monitoring was accomplished by thin-layer chromatography (TLC) on Merck silica gel 60 F_{254} plates also by exposing to iodine chamber.

Preparation of tomato fruit extract

One average size red color ripened tomato was weighed 93 gm, washed with distilled water and cut by knife into two equal half. The tomato was squeezed over the filter paper kept on the funnel, and collected the fresh extract in the beaker which appears colorless, transparent, watery, non-viscus liquid. This 10 mL of extract (*p*H=5.2) was used directly as a catalyst for the reaction.

General procedure for the synthesis of isoxazoles derivatives, 4a-p

In an oven dried 50 mL round bottomed flask, an equimolar mixture of aromatic aldehyde (1 mmol), ethyl acetoacetate/methyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol) and 10 mL tomato fruit extract were added and stirred at RT for about 30 min (clear solution). After the given time (Table I) the reaction mixture turned into precipitate, this precipitate washed with water (3 × 5 mL), and checked for TLC, the single spot obtained in hexane: ethyl acetate system (80:20). The product was dried under vacuum and further recrystallized from ethanol to afford the pure product.

Spectral data of representative compounds

(Z)-4-Benzylideneisoxazol-5(4*H*)-one, 4a: Yellow solid. m.p.143-145°C; IR: 3251, 1774, 1658, 1557, 1427, 1093, 981, 777, 644 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (m, 2H), 7.38 (m, 4H), 8.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6): δ 128.58, 129.45, 130.00, 134.49, 144.93; LC-MS: *m/z* (M + 1) 174.2. Anal. Calcd for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.30; H, 4.01; N, 8.03%.

(Z)-3-Methyl-4-(4-methylbenzylidene)isoxazol-5(4*H*)-one, 4c: Yellow solid. m.p.128-130°C; IR: 3261, 3084, 2997, 2856, 1660, 1491, 1086, 1204, 967, 821, 682, 499 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.90 (s, 3H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 8.5, Hz 1H), 8.14 (s, 1H);^{13}C NMR (75 MHz, DMSO-d_6): δ 10.84, 127.96, 128.12, 128.70, 129.57, 131.07, 131.94, 133.70, 147.08, 161.33, 171.24; LC-MS: *m/z* (M + 1) 222.1;Anal. Calcd for: $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; Cl, 15.99; N, 6.32. Found: C, 59.53; H, 3.59; Cl, 15.81; N, 6.21%.

(Z)-4-(4-Hydroxybenzylidene)-3-methylisoxazol-5(4*H*)-one, 4d: Yellow solid. m.p.200-202°C; IR: 3364, 3076, 2772, 2626, 1725, 1606, 1585, 1511, 1103, 819, 518 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (s, 3H), 6.08 (d, *J* = 8.4 Hz, 1H), 6.24 (d, *J* = 8.6 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.97-7.04 (m, 1H), 7.74 (d, *J* = 8.6 Hz, 1H), 9.18 (s, 1H); LC-MS: *m/z* (M + 1) 204.1. Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.91; H, 4.39; N, 6.80%.

(Z)-4-(4-Methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one, 4e: Yellow solid. m.p.173-175°C; IR: 2977, 2935, 2823, 1725, 1586, 1428, 1262, 842, 773, 515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H), 3.92 (s, 3H), 7.01 (d, *J* = 8.9 Hz, 2H), 7.31 (s, 1H), 8.44 (d, *J* = 8.9 Hz, 2H); LC-MS: *m/z* (M + 1) 218.0. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.25; H, 5.99; N, 6.39%.

(Z)-4-(2,4-Dichlorobenzylidene)isoxazol-5(4*H*)-one, 4f: Yellow solid. m.p.158-160°C; IR: 3240, 3087, 3016, 2925, 1685, 1556, 1387, 1050, 974, 815 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, *J* = 6.6 Hz, 2H), 7.41 (s, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 8.50 (s, 1H); ^{13}C NMR (75 MHz, CDCl3/DMSO-d_6): δ 127.28, 127.62, 129.02, 129.23, 129.43, 133.46, 134.97, 144.20, 160.97, 171.72. Anal. Calcd for: $C_{10}H_5Cl_2NO_2$: C, 49.62; H, 2.08; Cl, 29.29; N, 5.79. Found: C, 49.53; H, 2.01; Cl, 29.18; N, 5.71%.

(Z)-4-(2,6-Dichlorobenzylidene)-3-methylisoxazol-5(4*H*)-one, 4g: Yellow solid. m.p.150-152°C; IR: 3269, 2888, 1775, 1558, 1435, 1186, 1094, 982, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.06 (s, 3H), 6.86 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.88-8.05 (m, 1H), 8.53 (d, *J* = 8.6 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 29.70, 128.35, 128.85, 129.76, 131.64, 133.59, 136.86, 142.54, 145.98, 158.23, 188.84; LC-MS: *m/z* (M + 1) 256.0. Anal. Calcd for: $C_{11}H_7Cl_2NO_2$: C, 51.59; H, 2.76; Cl, 27.69; N, 5.47. Found: C, 51.49; H, 2.69; Cl, 27.61; N, 5.41%.

(Z)-4-(4-(Dimethylamino)benzylidene)-3-methylisoxazol-5(4*H*)-one, 4h: Yellow solid. m.p.226-228°C; IR: 3087, 2909, 2797, 2212, 1709, 1522, 1367, 1163, 948, 809, 506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H), 3.16 (s, 6H), 6.70 (t, *J* = 9.6 Hz, 1H), 7.22 (s, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 8.05 (s, 1H), 8.41 d, *J* = 8.5 Hz, 1H); LC-MS: *m/z* (M + 1) 231.1. Anal. Calcd for: $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.70; H, 6.01; N, 12.11%.

Table II — Synthesis of isoxazoles derivatives as per the Scheme II

Entry	Ar	R^1	R^2	Product	Time (min)	Yield[b] (%)
1	C_6H_5	Me	H	4a	30	85
2	2-Cl-C_6H_4	Et	Me	4b	33	74
3	4-Cl-C_6H_4	Et	Me	4c	32	75
4	4-OH-C_6H_4	Et	Me	4d	28	87
5	4-OCH_3-C_6H_4	Et	Me	4e	25	88
6	2,4-Cl-C_6H_3	Me	H	4f	35	70
7	2,6-Cl-C_6H_3	Et	Me	4g	35	68
8	4-$N(CH_3)_2$-C_6H_4	Et	Me	4h	30	80
9	4-OH-3-OCH_3-C_6H_3	Et	Me	4i	25	87
10	4-Cl-3-NO_2-C_6H_3	Et	Me	4j	32	65
11	2-OH-4-OCH_3-C_6H_3	Et	Me	4k	28	87
12	4-Cl-C_6H_4	Me	H	4l	32	75
13	4-OCH_3-C_6H_4	Me	H	4m	25	88
14	2,4-Cl-C_6H_3	Me	H	4n	35	70
15	4-$N(CH_3)2$-C_6H_4	Me	H	4o	30	80
16	4-OH-3-OCH_3-C_6H_3	Me	H	4p	25	88

[a]Reaction condition: benzaldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol), methyl acetoacetate (1 mmol).[b]Isolated yield.

(Z)-4-(4-Hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one, 4i: Yellow solid. m.p.195-197°C; IR: 3212, 3004, 2940, 2842, 1730, 1567, 1509, 1268, 1028, 939, 560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.06 (s, 3H), 3.87 (s, 3H), 6.85 (d, *J* = 8.1 Hz, 1H), 7.04 (t, *J* = 8.4 Hz, 1H), 7.83 (m, 1H), 8.04 (s, 1H), 10.00 (s, 1H); LC-MS: *m/z* (M + 1) 234.1. Anal. Calcd for: $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.71; H, 4.67; N, 5.95%.

(Z)-4-(4-Chloro-3-nitrobenzylidene)-3-methylisoxazol-5(4*H*)-one, 4j: Yellow solid. m.p.133-135°C; IR: 3294, 3099, 1747, 1596, 1531, 1350, 1136, 1050, 977, 663 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.80 (s, 3H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.51-8.34(m, 2H), 8.69 (d, *J* = 16.5 Hz, 1H);^{13}C NMR (75 MHz, DMSO-d_6): δ 11.48, 123.82, 126.76, 130.33, 131.78, 132.98, 134.93, 138.32, 146.84, 162.60, 190.53; LC-MS: *m/z* (M + 1) 267.1. Anal. Calcd for: $C_{11}H_7ClNO_4$: C, 49.55; H, 2.65; Cl, 13.30; N, 10.51. Found: C, 49.47; H, 2.59; Cl, 13.21; N, 10.41%.

(Z)-4-(2-Hydroxy-4-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one, 4k: Yellow solid. m.p.210-212°C; IR: 3381, 3076, 1692, 1566, 1441, 1386, 1276, 1204, 960, 843, 562 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.20 (s, 3H), 3.72 (s, 3H), 6.61-6.41(m, 2H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.95 (s, 1H), 8.99 (d, *J* = 9.1 Hz, 1H), 10.7 (s, 1H);^{13}C NMR (75 MHz, DMSO-d_6): δ 11.09, 55.59, 101.00, 107.37, 112.13, 113.85, 129.47, 134.61, 148.21, 157.65, 162.13, 166.77, 169.11; LC-MS: *m/z* (M + 1) 234.1. Anal. Calcd for: $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.73; H, 4.69; N, 5.93%.

Conclusion

In conclusion, we have successfully developed a simple, highly efficient, environmental benign, and comparatively greener method for the synthesis of (Z)-4-benzylideneisoxazol-5(4*H*)-oneand their derivatives (Table II, entry 1-16). The tomato fruit extract used as a natural catalyst which provided acidic catalytic medium for the synthesis of titled compounds. This method excludes the reaction work up and column chromatography step for the separation and purification of the product. Easy availability of the catalyst, relatively less reaction time and ease of separation of product makes this procedure better than the earlier reported methods in the literature.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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