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# An efficient solvent-free synthesis of 3,4-disubstituted isoxazole-*5(4H)*-ones using microwave irradiation

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ABSTRACT

I have reported one-pot and three-component synthesis of 3-mehyl-4-arylmethyleneisoxazol-5(*4H*)-ones using microwave radiation under the solvent-free conditions, in the presence of potassium bromide as the catalyst. The method has given the products in high yields and short reaction times with an easy work-up process. The present method provides an easy and efficient approach for the synthesis of this class of compounds, because of its clean reaction profile and operational simplicity.

## 1. Introduction

Isoxazoles, a privileged class of five-member nitrogen and oxygen-containing heterocycles, conquer reputation in organic chemistry for their wide applications in pharmaceuticals, biologically active molecules, advanced organic materials, and as intermediates in organic synthesis [1]. Isoxazole-5(*4H*)-one showed important biological activity; such as anti-obesity [2], antimycobacterial [3], anti-osteoporotic [4], anticancer [5], antimicrobial and larvicidal [6], cytotoxic [7], nematicidal agents [8], carbonic anhydrase inhibitor [9], and antiprotozoal activities [10]. Isoxazolone compounds have applications in the material sciences. They are used for the design of materials such as liquid crystals [11], and photochromic components [12]. An isoxazolone nucleus is a virtuous proaromatic acceptor, when linked to aromatic donors, for conjugated donor-acceptor (D-Π-A) merocyanine dyes. Isoxazolone nucleus is a good proaromatic acceptor because of its good molar extinction coefficients tunable absorption spectra and large first molecular hyper-polarizabilities. Merocyanine dyes with an isoxazolone nucleus have used for optical recording and nonlinear optical research [13]. 4-(Arylmethylene) isoxazol-5-ones intermediates in synthetic organic chemistry for the synthesis of β-branched carbonyl compounds [14], 3, 4-disubstituted 2*H*-isoxazol-5-ones [15], methyl 5-aminopyrrole-3-carboxylates via cyanide Michael addition, methylation and reductive isoxazole-pyrrole [16], in the synthesis of heterocycle and terminal alkynes [17]. The isoxazole core is a backbone and a structural component of a variety of natural products such as muscimol [18], pantherine [19], ibotenic acid and isoxazol-4-carboxylic acid [20]. Multiple synthetic protocols have been described in the literature for the synthesis of isoxazole derivatives and their analogs. A Literature study displays that many catalyzed methods reported for the synthesis of various isoxazole derivatives. To state a few, such protocols potassium phthalimide [21], antimony chloride [22], ZnO@$Fe_3O_4$ core-shell nanocatalyst in water [23], pyridinium *p*-toluenesulfonate [24], Boric acid [25], phthalimide-*N*-oxyl salts [26], starch solution [27], sodium benzoate [28], 2-hydroxy-5-sulfobenzoic acid [29], *N*-bromosuccinimide [30], nano-MgO [31], modified mesolite [32], sulfonated graphene-oxide [33], nanocrystalline hydroxyapatite [34], 6-methylguanamine-supported $CoFe_2O_4$ [35], nano-$SiO_2$- $H_2SO_4$ [36], salicylic acid [37], KI [38], sulfated polyborate [39], and sulfanilic acid [40]. Furthermore, different conditions and techniques such as using sonochemical condition using amine-modified [41], visible light in the presence of sodium acetate in aqueous ethanol [42], Fruit juice [43], Microwave irradiation in the presence of potassium fluoride on alumina [44], and ionic liquid [45]. However, most of the above stated procedures for the synthesis of these compounds suffer from disadvantages, including the use of toxic or odorous, expensive catalysts, catalyst preparation required, strong acid or base catalysts, use of organic solvent, tedious work-up procedures, troublesome waste discarding, two step procedure, long reaction times, and low yields. Thus, preclusion of these limitations is crucial to improve more efficient and green synthesis of 3-methyl-4-(arylmethylene) isoxazole-5(*4H*)-one derivatives. Hence, we here report the preparation of 3-methyl-4-(arylmethylene)-isoxazole-5(*4H*)-one by one-pot three--component condensation of aryl aldehydes (1), hydroxylamine hydrochloride (2), and ethyl acetoacetate (3), using microwave irradiation under solvent free condition.

Microwave irradiation (MWI) provides an alternative source of

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energy to the conventional energy for heating into the organic synthesis. This method has been utilizes the capacity of mobile electric charges existing in liquid or conducting ions in solid to transform electromagnetic energy into heat. The reactions have performed by the microwave-assisted irradiation is fast, clean, economical and environmentally benign. This method has been suggested as the 'technology of future' as various merits has been found [46].

## 2. Experimental

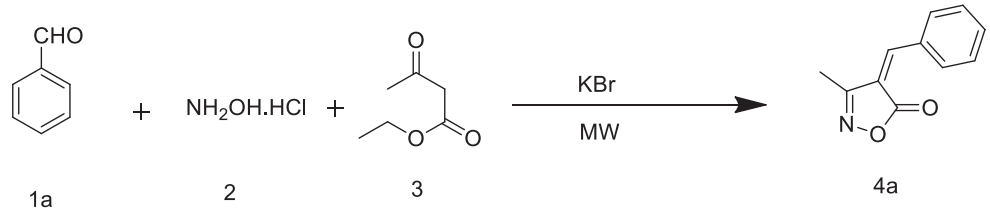
Melting points were measured using an open capillary method and are uncorrected. IR spectra were recorded on alpha T BRUKER model. $^1$H NMR and $^{13}$C NMR spectra were recorded at ambient temperature on a BRUKER AVANCE DRX-300 MHz spectrophotometer using $CDCl_3$ or DMSO-D6 as the solvent and TMS as an internal standard. The elemental analysis were recorded on Thermo Scientific (FLASH 2000) Elemental Analyser. The purity of newly synthesized compounds and the development of the reaction was monitored by thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F254 aluminium sheets, visualized by UV light.

General procedure for preparation of 3,4-disubstituted isoxazole-5(*4H*)-ones.

A mixture of ethyl acetoacetate (1 mmol, 1.30 g), hydroxylamine hydrochloride (1.5 mmol, 1.042 g), and substituted aromatic aldehyde (1 mmol) and potassium bromide (0.2 mmol, 0.0238 g) was taken in a 50 mL beaker. The beaker was irradiated at 200 W in the microwave oven for the respective time given in Table 3. The progress of the reaction mixture was monitored by TLC. After completion of the reaction, the reaction mass was cooled at room temperature. The reaction mass was diluted with 20 mL chloroform and the catalyst was precipitated as solid. The catalyst was separated by a filtration method and the product was found in the filtrate. After evaporating, the organic layer gets crude product in solid form. The product was purified by recrystallization in the ethanol.

### 2.1. Spectral data of synthesized compounds

1. (*4Z*)-*4-Benzylidene-3-methylisoxazol-5(4H)-one* **(4a):** Yield 95%, m. p. 140-141 °C (Lit. 141-143 °C). IR$\nu_{max}$ cm$^{-1}$: 3072 (C–H stretching), 1660 (C═O stretching), 1543 (C═C stretching), 1470 (N–O stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): 1.75 (s, 3H), 6.97 (s, 1H), 7.23–7.17 (m, 3H), 7.30–7.26 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 29.3, 126.2, 128.4, 129.3, 140.2, 162.1, 171.8. HRMS ESI (*m/z*): 187.04 ($M^+$), 188.10 $(M+1)^+$. Anal. Calcd. for $C_{11}H_9NO_2$: C 70.58, H 4.85 and N 7.48%; found C 70.40, H 4.82, and N 7.36%.
2. (*4Z*)-*4-(2-chloroBenzylidene)-3-methylisoxazol-5(4H)-one* **(4b):** Yield 70%, m. p. 163–165 °C. IR$\nu_{max}$ cm$^{-1}$: 3055 (C–H stretching), 1663 (C═O stretching), 1547 (C═C stretching), 1475 (N–O stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): 1.76 (s, 3H), 7.03 (s, 1H), 7.10 (m, 1H), 7.14 (m, 1H), 7.23 (m, 1H), 7.29 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 29.5, 124.6, 127.2, 128.6, 129.7, 130.8, 132.1, 134.5, 161.2, 172. HRMS ESI (*m/z*): 221.56 ($M^+$), 222.43 $(M+1)^+$. Anal. Calcd. for $C_{11}H_8ClNO_2$: C 59.61, H 3.64, and N 6.32%; found C 59.35, H 3.54, and N 6.20%.
3. *(4Z)-4-(3-nitrobenzylidene)-3-methylisoxazol-5(4H)-one* (**4c**): Yield 91%, m. p. 143–144 °C (Lit. 144-145 °C). IR$\nu_{max}$ cm$^{-1}$: 3040 (C–H stretching), 1667 (C═O stretching), 1330 (N–O stretching) and 1088 (C–N stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm)): 1.79 (s, 3H), 7.26 (s, 1H), 7.60–7.57 (m, 1H), 8.00–7.90 (m, 1H), 8.25–8.22 (m, 1H), 8.44–8.43 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 29.7, 121.8, 124.4, 129.8, 132.5, 133.8, 148.2, 148.5, 170.5. HRMS ESI (*m/z*): 232.10 ($M^+$), 233.03 $(M+1)^+$. Anal. Calcd. for $C_{11}H_8N_2O_4$: C 56.90, H 3.47, and N 12.06%; found C 56.74, H 3.31, and N 12.02%.
4. *(4Z)-4-(4-chlorobenzylidene)-3-methylisoxazol-5(4H)-one* (**4d**): Yield 94%, m. p. 117–119 °C (Lit. 118–119 °C). IR$\nu_{max}$ cm$^{-1}$: 3010 (C–H stretches), 1653 (C═O is stretching), 1552 (C═C stretching), 1482 (N–O is stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): 1.89 (s, 3H), 7.14 (s, 1H), 7.26–7.23 (d, $J = 7.2$ Hz, 2H), 7.45–7.41 (d, $J = 7.2$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 31.9, 126.8, 127.4, 128.2, 130.1, 130.9, 133.3, 142.4, 161.1, 171.9. HRMS ESI (*m/z*): 221.43 ($M^+$), 222.12 $(M+1)^+$. Anal. Calcd. for $C_{11}H_8ClNO_2$: C 59.61, H 3.64, and N 6.32%; found C 59.57, H 3.59, and N 6.30%.
5. *(4Z)-4-(4-bromobenzylidene)-3-methylisoxazol-5(4H)-one* (**4e**): Yield 92%, m. p. 123–124 °C (Lit. 124–126 °C). IR$\nu_{max}$ cm$^{-1}$: 3005 (C–H stretching), 1656 (C═O stretching), 1545 (C═C stretching), 1475 (N–O stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): 1.84 (s, 3H), 7.10 (s, 1H), 7.20–7.16 (d, $J = 7.6$Hz, 2H), 7.38–7.34 (d, $J = 7.6$Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 31.3, 125.4, 128.2, 128.9, 131.3, 133.1, 143.2, 160.4, 171.2. HRMS ESI (*m/z*): 264.85 ($M^+$), 265.93 $(M+1)^+$. Anal. Calcd. for $C_{11}H_8BrNO_2$: C 49.65, H 3.03, and N 5.26%; found C 49.62, H 3.02, and N 5.21%.
6. *(4Z)-3-methyl-4-(3-phenylallylidene)isoxazole-5(4H)-one* (**4f**): Yield 89%, m. p. 174–175 °C (Lit. 175–176 °C). IR$\nu_{max}$ cm$^{-1}$: 3015 (C–H stretches), 1649 (C═O is stretching), 1560 (C═C stretching), 1468 (N–O is stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): 1.82 (s, 3H), 7.05–6.97 (m, 4H), 7.51–7.47 (d, $J = 6.9$ Hz, 2H), 7.95 (s, 1H), 8.50–8.35 (d, $J = 6.9$Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 30.6, 117.2, 117.9, 120.1, 120.7, 125.6, 132.8, 137.4, 146.8, 160.1, 162.8, 169.6. HRMS ESI (*m/z*): 213.18 ($M^+$), 214.24 $(M+1)^+$. Anal. Calced. for $C_{13}H_{11}NO_2$: C 73.23, H 5.20, and N 6.57%; found C 73.22, H 5.17, and N 6.54%.
7. *(4Z)-4-(4-mthylbenzylidene)-3-methylisoxazol-5(4H)-one* (**4g**): Yield 96%, m. p. 136–137 °C (Lit. 135–136 °C). IR$\nu_{max}$ cm$^{-1}$: 2998 (C–H stretching), 1652(C═O stretching), 1538 (C═C stretching), 1376 (N–O stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): 1.78 (s, 3H), 2.38 (s, 3H), 7.19–7.14 (d, $J = 8.3$Hz, 2H), 7.34 (s, 1H), 7.72–7.68 (d, $J = 8.3$ Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 28.3 34.5, 115.8, 120.6, 129.3, 130.1, 136.8, 151.8, 162.4, 169.1. HRMS ESI (*m/z*): 201.08 ($M^+$), 202.10 $(M+1)^+$. Anal. Calcd. for $C_{12}H_{11}NO_2$: C 71.63, H 5.51, and N 6.96%; found C 71.59, H 5.50, and N 6.90%.
8. *(4Z)-4-(3,4-dimethoxybenzylidene)-3-methylisoxazol-5(4H)-one* (**4h**): Yield 91%, m. p. 128–130 °C (Lit. 129–131 °C). IR$\nu_{max}$ cm$^{-1}$: 3016 (C–H stretching), 1640(C═O stretching), 1556 (C═C stretching), 1371 (N–O stretching), 1282 (O–$CH_3$ stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): $\delta$ 2.26 (s, 3H), 3.97 (s, 3H), 3.98 (s, 3H), 6.92–6.94 (m, 1H), 7.31 (s, 1H), 7.57–7.59 (m, 1H), 8.72 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 11.6, 56.1, 110.7, 115.0, 116.2, 126.3, 131.2, 149.0, 149.8, 154.5, 161.3, 169.0. HRMS ESI (*m/z*): 247.15 ($M^+$), 248.15 $(M+1)^+$. Anal. Calcd. for $C_{13}H_{13}NO_4$: C 63.15, H 5.30, and N 5.67%; found C 63.14, H 5.27, and N 5.63%.
9. *(4Z)-4-(2,4,6-trimethoxybenzylidene)-3-methylisoxazol-5(4H)-one* (**4i**): Yield 83%, m. p. 230-231 °C (Lit. 231–233 °C). IR$\nu_{max}$ cm$^{-1}$: 3020 (C–H stretching), 1638(C═O stretching), 1549 (C═C stretching), 1376 (N–O stretching), 1276 (O–$CH_3$ stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): $\delta$ 2.22 (s, 3H), 3.97 (s, 3H), 3.98 (s, 6H), 6.45–6.47 (s, 2H), 7.13 (s, 1H); $^{13}$CNMR (75 MHz, $CDCl_3$, $\delta$ ppm): 11.7, 56.2, 56.8, 100.8, 105.3, 124.7, 151.2, 159.8, 162.3, 164.6, 169.9. HRMS ESI (*m/z*): 277.25 ($M^+$), 278.21 $(M+1)^+$. Anal. Calcd. for $C_{14}H_{15}NO_5$: C 60.64, H 5.45, and N 5.05%; found C 60.59, H 5.44, and N 5.02%.
10. *(4Z)-4-(2,4-dimethoxybenzylidene)-3-methylisoxazol-5(4H)-one* (**4j**): Yield 86%, m. p. 177-178 °C (Lit. 176–179 °C). IR$\nu_{max}$ cm$^{-1}$: 3012 (C–H stretching), 1649(C═O stretching), 1557 (C═C stretching), 1374 (N–O stretching), 1280 (O–$CH_3$ stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): $\delta$ 2.16 (s, 3H), 3.95 (s, 3H), 3.99 (s, 3H), 6.32–6.29 (d, $J = 1.8$ Hz, 1H), 6.39–6.36 (dd, $J = 1.8$




**Scheme 1.** Model Reaction for optimization of reaction conditions.

**Table 1**
Screening of catalysts.[a].

| Sr. No | Catalyst | Amount of catalyst loaded in gm | Product 4a | Time in Sec | % yield[b] |
|---|---|---|---|---|---|
| 1 | KCl | 0.0149 | 4a | 110 | 88 |
| 2 | KBr | 0.0238 | 4a | 80 | 95 |
| 3 | NaOAC | 0.0164 | 4a | 140 | 81 |
| 4 | Sodium oxalate | 0.0268 | 4a | 180 | 84 |
| 5 | $CaCl_2$ | 0.0221 | 4a | 210 | 88 |
| 6 | KOAc | 0.0196 | 4a | 160 | 85 |
| 7 | $MgBr_2$ | 0.0368 | 4a | 90 | 89 |
| 8 | $MgCl_2$ | 0.0190 | 4a | 120 | 87 |
| 9 | $KNO_3$ | 0.0202 | 4a | 900 | Unidentified product |
| 10 | Potassium oxalate | 0.0332 | 4a | 120 | 78 |

[a] Reaction conditions are: 1 mmol of ethyl acetoacetate, 1.5 mmol of hydroxylamine hydrochloride, 1 mmol benzaldehdye and 0.2 mmol of catalyst in a 50 mL beaker in microwave oven.
[b] Isolated yield after purification.

Hz, 8.2 Hz, 1H), 6.98–6.95 (d, $J$ = 8.2 Hz, 1H), 7.07 (s, 1H);$^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 11.9, 55.9, 56.3, 101.8, 107.3, 109.1, 126.3, 129.2, 150.5, 159.3, 161.4, 165.2, 170.2. HRMS ESI ($m/z$): 247.17 ($M^+$), 248.25 $(M+1)^+$. Anal. Calcd. for $C_{13}H_{13}NO_4$: C 63.15, H 5.30, and N 5.67%; found C 63.14, H 5.28, and N 5.64%.

11. *(4Z)-4-(2-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one* (**4k**): Yield 78%, m. p. 201-202 °C (Lit. 202–204 °C). IR$\nu_{max}$ cm$^{-1}$: 3420 (OH stretching) 3034 (C–H stretching), 1694 (C═O stretching), 1534 (C═C stretching), 1381 (N–O stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): $\delta$ 2.0 (s, 3H), 6.99–6.96 (m, 2H), 7.50–7.44 (m, 1H), 7.83 (s, 1H), 8.04–7.99 (m, 1H), 10.75 (s, 1H);$^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 24.7, 117.1, 117.9, 119.8, 120.5, 132.1, 137.8, 145.7, 160.1, 163.4, 169.3. HRMS ESI ($m/z$): 203.18 ($M^+$), 204.31 $(M+1)^+$. Anal. Calcd. for $C_{11}H_9NO_3$: C 65.02, H 4.46, and N 6.89%; found C 65.01, H 4.44, and N 6.87%.
12. *(4Z)-4-(4-(diethylamino)-2-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one* (**4l**): Yield 78%, m. p. 256-260 °C (Lit. 258-261 °C).

**Table 2**
Effect of Power on synthesis of synthesis of 3,4-disubstituted isoxazole-5(*4H*)-ones.[a].

| Entry | Power Watt | Product (4a) | Time in Seconds | % Yield[b] |
|---|---|---|---|---|
| 1 | 100 | **4a** | 120 | 87 |
| 2 | 200 | **4a** | 80 | 95 |
| 3 | 300 | **4a** | 80 | 95 |
| 4 | 400 | **4a** | 75 | 90 |
| 5 | 600 | **4a** | 20 | Decomposed |
| 6 | 800 | **4a** | 20 | Decomposed |
| 7 | 1200 | **4a** | 20 | Decomposed |

[a] Reaction conditions are: 1 mmol of ethyl acetoacetate, 1.5 mmol of hydroxylamine hydrochloride, 1 mmol benzaldehdye and 0.2 mmol of catalyst in a 50 mL beaker in microwave oven.
[b] Isolated yield after purification.

IR$\nu_{max}$ cm$^{-1}$: 3450 (OH stretching) 3002 (C–H stretching), 1645 (C═O stretching), 1547 (C═C stretching), 1365 (N–O stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): $\delta$ 1.14 (t, $J$ = 6.7z, 6H), 1.97 (s, 3H), 3.32 (q, $J$ = 6.7 Hz, 4H) 6.10–6.05 (d, $J$ = 2 Hz, 1H), 6.25–6.22 (dd, $J$ = 2 Hz, 8 Hz, 1H), 6.83–6.78 (d, $J$ = 8 Hz, 1H), 7.02 (s, 1H), 10.67 (s, 1H);$^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 14.6, 27.4, 45.3, 101.1, 106.7, 107.4, 125.8, 129.3, 149.9, 150.8, 160.8, 165.2, 170.1. HRMS ESI ($m/z$): 274.24 ($M^+$), 275.17 $(M+1)^+$. Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C 65.68, H 6.61, and N 10.21%; found C 65.67, H 6.57, and N 10.14%.

13. *(4Z)-4-(2-nitrobenzylidene)-3-methylisoxazol-5(4H)-one* (**4m**): The product was not formed.
14. *(4Z)-4-(4-(dimethylamino)benzylidene)-3-methylisoxazol-5(4H)-one* (**4n**): Yield 87%, m. p. 226–227 °C (Lit. 225–227 °C). IR$\nu_{max}$ cm$^{-1}$: 3010 (C–H stretching), 1663(C═O stretching), 1533 (C═C stretching), 1368 (N–O stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): 1.83 (s, 3H), 3.23 (s, 3H), 3.36 (s, 3H), 6.79–6.75 (d, $J$ = 8.6 Hz, 2H), 7.27 (s, 1H), 7.85–7.8 (d, $J$ = 8.6Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 25.8, 53.4, 54.1, 108.9, 112.2, 121.4, 135.1, 150.4, 154.2, 162.5, 169.8. HRMS ESI ($m/z$): 230.22 ($M^+$), 231.26 $(M+1)^+$. Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C 67.81, H 6.13, and N 12.17%; found C 67.79, H 6.12, and N 12.16%.
15. *(4Z)-4-(2,3-dichlorobenzylidene)-3-methylisoxazol-5(4H)-one* (**4o**): Yield 73%, m. p. 174–177 °C. IR$\nu_{max}$ cm$^{-1}$: 3013 (C–H stretching), 1671 (C═O stretching), 1545 (C═C stretching), 1376 (N–O stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): 1.92 (s, 3H), 7.05–7.09 (m, 2H), 7.15–7.11 (m, 1H), 7.20 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 28.4, 125.2, 126.3, 127.9, 128.4, 129.7, 133.9, 134.4, 151.3, 164.7, 170.2. HRMS ESI ($m/z$): 256.06 ($M^+$), 257.12 $(M+1)^+$. Anal. Calcd. for $C_{11}H_7Cl_2NO_2$: C 51.59, H 2.76, and N 5.47%; found C 51.56, H 2.75, and N 5.47%.
16. *(4Z)-4-(4-nitrobenzylidene)-3-methylisoxazol-5(4H)-one* (**4p**): Yield 92%, m. p. 145 °C (Lit. 148–150 °C). IR$\nu_{max}$ cm$^{-1}$: 3030 (C–H stretching), 1676 (C═O stretching), 1520 (C═C stretching), 1328 (N–O stretching) and 1083 (C–N stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): 2.23 (s, 3H), 7.13–7.08 (d, $J$ = 8.2Hz, 2H), 7.52 (s, 1H), 8.43–8.38 (d, $J$ = 8.2Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 34.4, 123.4, 125.7, 133.2, 139.1, 142.8, 151.1, 163.6, 171.4. HRMS ESI ($m/z$): 232.08 ($M^+$), 233.10 $(M+1)^+$. Anal. Calcd. for $C_{11}H_8N_2O_4$: C 56.90, H 3.47, and N 12.06%; found C 56.89, H 3.48, and N 12.04%.
17. *(4Z)-4-(4-methoxybenzylidene)-3-methylisoxazol-5(4H)-one* (**4q**): Yield 90%, m. p. 177–179 °C (Lit. 178–180 °C). IR$\nu_{max}$ cm$^{-1}$: 3040 (C–H stretching), 1670 (C═O stretching), 1543 (C═C stretching), 1367 (N–O stretching) and 1267 (O–$CH_3$ stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): 1.97 (s, 3H), 3.89 (s, 3H), 6.88–6.84 (d, $J$ = 8.6 Hz, 2H), 7.32 (s, 1H), 7.94–7.91 (d, $J$ = 8.6 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 18.4, 56.3, 114.1, 116.2, 117.3, 125.5, 132.1, 148.2, 152.3, 154.4, 163.2, 169.4. HRMS ESI ($m/z$): 217.19 ($M^+$), 218.21 $(M+1)^+$. Anal. Calcd. for $C_{12}H_{11}NO_3$: C 66.35, H 5.10, and N 6.45%; found C 66.37, H 5.09, and N 6.43%.
18. *(4Z)-4-((furan-2-yl)methylene-3-methylisoxazol-5(4H)-one* (**4r**): Yield 84%, m. p. 242–243 °C (Lit. 240–243 °C). IR$\nu_{max}$ cm$^{-1}$: 3050 (C–H stretching), 1685 (C═O stretching), 1565 (C═C stretching), 1371 (N–O stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): 1.93 (s,

**Table 3**
Synthesis of arylmethylene-isoxazole-5(*4H*)-ones (4) catalyzed by potassium bromide hexahydrate using Microwave irradiation.[a].

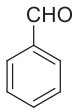
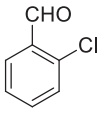
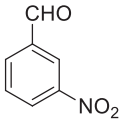
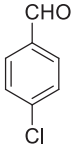
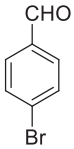
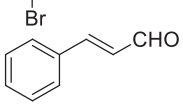
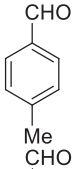
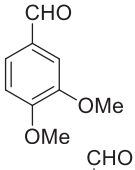
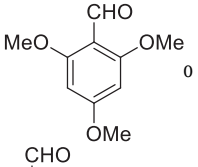
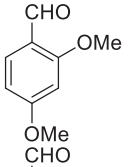
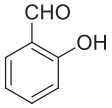
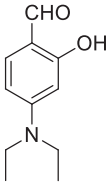
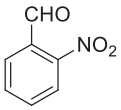
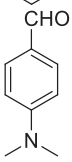
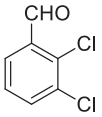
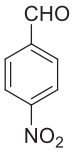
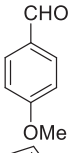
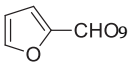
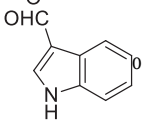
| Entry | Ar-Aldehyde | Product (4) | Time Sec | % Yield[a] | M. P. °C [Ref] |
|---|---|---|---|---|---|
| 1 |  | **4a** | 80 | 95 | 140-141 [33] |
| 2 |  | **4b** | 65 | 70 | 163 |
| 3 |  | **4c** | 70 | 91 | 143-144 [33] |
| 4 |  | **4d** | 55 | 94 | 117-119 [33] |
| 5 |  | **4e** | 50 | 92 | 123-124 [33] |
| 6 |  | **4f** | 90 | 89 | 174-175 [33] |
| 7 |  | **4g** | 60 | 96 | 136-137 [33] |
| 8 |  | **4h** | 85 | 91 | 128-130 [22] |
| 9 |  | **4i** | 120 | 83 | 230-231 [47] |
| 10 |  | **4j** | 115 | 86 | 177-178 [35] |
| 11 |  | **4k** | 150 | 78 | 201-202 [33] |
| 12 |  | **4l** | 90 | 78 | 256-260 [37] |
| 13 | | **4m** | 900 | NR | – |

**Table 3** (*continued*)

| Entry | Ar-Aldehyde | Product (4) | Time Sec | % Yield[a] | M. P. °C [Ref] |
|---|---|---|---|---|---|
| |  | | | | |
| 14 |  | **4n** | 75 | 87 | 226-227 [33] |
| 15 |  | **4o** | 130 | 73 | 174–177 |
| 16 |  | **4p** | 55 | 92 | 145 [48] |
| 17 |  | **4q** | 70 | 90 | 177-179 [33] |
| 18 |  | **4r** | 65 | 84 | 242-243 [33] |
| 19 |  | **4s** | 80 | 82 | 244-245 [33] |

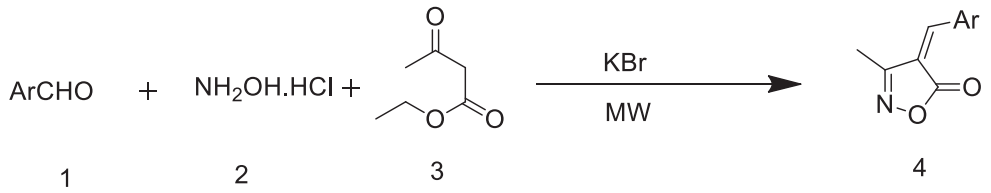
[a] Reaction conditions: Ethyl acetoacetate (1 mmol), aromatic aldehyde (1 mmol), hydroxylamine hydrochloride (1.5 mmol) in microwave oven. [b]All yields are of pure products after filtrated and recrystallization from ethanol.

3H), 6.93–6.90 (d, $J = 8.3$ Hz, 2H), 7.06 (s, 1H), 7.99–7.96 (d, $J = 8.3$ Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 23.4, 114.3, 116.5, 125.1, 137.8, 151.7, 162.6, 164.1, 169.8. HRMS ESI (*m/z*): 177.14 ($M^+$), 178.20 $(M+1)^+$. Anal. Calcd. for $C_9H_7NO_3$: C 61.02, H 3.98, and N 7.91%; found C 61.01, H 3.99, and N 7.90%.

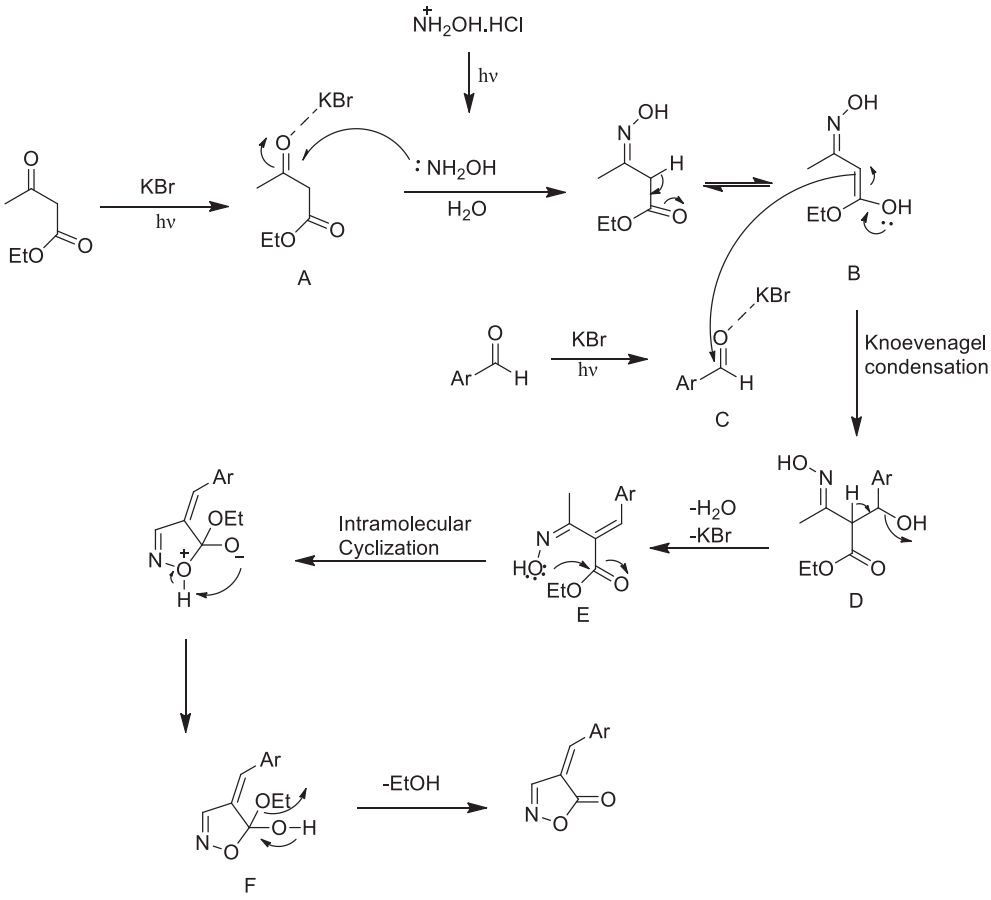
19. *(4Z)-4-((1H-indol-3-ylmethylene)-3-methylisoxazol-5(4H)-one* (**4s**)): Yield 82%, m. p. 244–245 °C (Lit. 243–246 °C). IR$\nu_{max}$ $cm^{-1}$: 3350 (-NH stretching), 3045 (C–H stretching), 1665 (C═O stretching), 1528 (C═C stretching), 1366 (N–O stretching). $^1$HNMR (300 MHz, $CDCl_3$, $\delta$ ppm): 1.85 (s, 3H), 7.35–7.32 (m, 2H), 7.57–7.54 (s, 1H), 7.67–7.63 (s, 1H), 7.94–7.90 (m, 2H), 11.76 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 27.4, 109.4, 113.2, 113.6, 119.4, 123.0, 124.5, 128.7, 136.7, 138.6, 141.2, 162.3, 170.6. HRMS ESI (*m/z*): 226.21 ($M^+$), 227.08 $(M+1)^+$. Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C 69.02, H 4.46, and N 12.38%; found C 69.01, H 4.44, and N 12.37%.

## 3. Results and discussion

The condensation of ethyl acetoacetate, hydroxylamine hydrochloride and benzaldehyde was selected as a model reaction (Scheme 1). Initially we have various metal salts such as potassium chloride, potassium bromide, sodium acetate, sodium oxalate, calcium chloride, potassium acetate, magnesium bromide hexahydrate, magnesium chloride, magnesium nitrate, potassium nitrate, and potassium oxalate as catalyst for the condensation reaction under microwave irradiation and results are summarized in table (Table 1). The model reaction is performed in 50 mL beaker using 1 mmol of ethyl acetoacetate, 1.5 mmol of




**Scheme 2.** Synthesis of various 3,4-disubstituted isoxazole-*5(4H)*-ones under microwave condition.




**Scheme 3.** A plausible mechanism for the synthesis of 3,4–disubstituted isoxazol–5(4H)–ones catalyzed by potassium bromide.

hydroxylamine hydrochloride, 1 mmol of benzaldehyde and 0.2 mmol of catalyst irradiated in a household microwave oven. From Table 1 it was observed that potassium bromide was found an efficient catalyst for synthesis of 4-aryl-3-methyl isoxazole with 95% yield. However, potassium nitrate did not afford the desired product.

To study the effect of power watt on the reaction was used the model reaction of 1 mmol of ethyl acetoacetate, 1.5 mmol of hydroxylamine hydrochloride, 1 mmol of benzaldehyde and 0.2 mmol of potassium bromide. The reaction was irradiated at 100W, 200W, 300W, 400W, 600W, 800W and 1200W. The results of the study are tabulated in Table 2 and the reaction well proceeded at 200W. The reaction was decomposed at high power 600W, 800W and 1200W. Hence, all the reactions were performed at 200W in microwave oven.

With the above-optimized reaction conditions in hand, the convenience of this method was well evaluated using a variety of aromatic aldehydes and a series of compounds **4** were synthesized with this simple approach (Scheme 2). The results are summarized in Table 3. The nature and position of the functional groups on the phenyl ring affected the reaction time and yields of the product. The results indicated that aromatic aldehydes bearing electron-donating groups such as $–OCH_3$, $–CH_3$, –OH, as well as electron-withdrawing group such as $NO_2$ reacts with ethyl acetoacetate and hydroxylamine hydrochloride to afford high yields of products. 2-Hydroxybenzaldehyde derivative yielded the corresponding isoxazol-5(*4H*)-one derivative in moderate yield of the desired product presumably due to its higher crowded steric effect. 2-Nitrobenzaldehyde on reaction with ethyl acetoacetate and hydroxylamine does not afford the corresponding isoxazol-5(*4H*)-one derivative due to bulky size, -E as well as –M effect of the nitro group, destabilize the transition state. In the compound 4c, nitro group present at meta position. The meta position does not participate in mesomeric effect, but only electronic effect is operate. Hence the compound 4c, has obtained in good yield. The product 4d and 4e has chloro and bromo group at para position. The mesomeric effect in these compounds have not effective due to overlapping between two different energy level orbitals viz, 2p orbitals of carbon and 3p and 4p orbitals of chlorine and bromine respectively. Hence, this effect have not strongly operative. Therefore, 4d and 4e, have got in higher yields.

A plausible mechanism for the synthesis of 3,4-disubstituted isoxazole-54H-one was shown here 9Scheme 3 using potassium bromide. The mechanism is based on the Knoevenagel condensation

**Table 4**
Comparison of the results of the reaction of benzyaldehyde (1a), with hydroxylamine hydrochloride (2) and ethyl acetoacetate (3), using microwave irradiation with some reported methods.

| Entry | Catalysts/conditions | Catalyst amount | Time | % Yield | Comment | Ref |
|---|---|---|---|---|---|---|
| 1 | PPI/$H_2O$/r.t. | 10 mol% | 70min | 90 | Amount of catalyst high | [21] |
| 2 | Nano-$SiO_2$-$H_2SO_4$ | 0.05 gm | 30min | 89 | Highly acidic and corrosive catalyst | [36] |
| 3 | Graphene Oxide | 0.025 gm | 1hr | 90 | Catalyst preparation has a drastic reaction condition | [33] |
| 4 | ZnO@$Fe_3O_4$ | 0.005 gm | 70min | 93 | Catalyst preparation required | [23] |
| 5 | $SbCl_3$ | 0.05 gm | 120min | 90 | Toxic metals, liberated HCl on decomposition, highly acidic condition | [22] |
| 6 | 6-Methylguanamine-supported $CoFe_2O_4$ | 0.03 gm | 3min | 94 | Two steps catalyst preparation, expensive reagent required | [35] |
| 7 | Pyridinium *p*-toluenesulfonate | 5mol% | 3h | 63 | Reaction was carried out at reflux condition, long reaction time | [24] |
| 8 | Salicylic acid | 15mol% | 120min | 85 | The work up is a tedious process | [37] |
| 9 | Boric acid | 10mol% | 100min | 90 | Inexpensive and easily available catalyst | [25] |
| 10 | 2-hydroxy-5-sulfobenzoic acid | 15mol% | 70min | 96 | High yield, | [29] |
| 11 | KBr/Microwave Oven | 0.0238 | 80s | 95 | Simple reaction condition, easily available and inexpensive catalyst | This work |

reaction. in this reaction, initially the potassium bromide coordinated with oxygen of the carbonyl group of ethyl acetoacetate A then the lone pair of nitrogen attacks to the carbonyl carbon and water is eliminated to form B. Then, *keto-enol* tautomerism results to form the intermediate C, after which nucleophilic addition of aldehyde is coordinated with potassium bromide to form intermediate D. Further removal of water molecules leads to the formation of an intermediate E, which eventually undergoes cyclization to form the intermediate F that removes the ethanol molecule to obtain the target molecule.

The efficiency of the method has compared with some other reported method and comparison is given in Table 4.

## 4. Conclusions

Here, I developed an efficient synthesis of arylmethylene-isoxazol-5(*4H*)-ones using desktop solid potassium bromide as catalyst in microwave oven under solvent-free condition. The efficiency of the method has been demonstrated by synthesizing various substituted isoxazole derivatives. Some advantages of this method are high yield, short reaction time, avoiding the use of hazardous chemicals and solvents, inexpensive and easily available catalysts, use of non-conventional energy source and eco-friendly method.

## Declaration of competing interest

The author declares have no Conflict of Interest.

## Acknowledgement

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jics.2021.100013.

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