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REGULAR ARTICLE

Potassium iodate (KIO_3) as a novel reagent for the synthesis of isoxazolines: evaluation of antimicrobial activity of the products

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Abstract. A novel reagent for the synthesis of isoxazolines has been reported. Aryl aldoximes were made to react with alkenes in the presence of KIO_3 as the oxidising agent. This new reagent has been useful as an oxidant in the synthesis of isoxazoline and its function is attributed to the generation of nitrile oxide, which is an important intermediate for the synthesis of the valuable heterocycle like isoxazoline.

Keywords. KIO_3; oxidation; isoxazolines; antimicrobial.

1. Introduction

Among the various five-membered heterocycles, 2-isoxazolines have gained much attention as structural units of biologically potent compounds. They have remarkable applications as intermediates in the synthesis of numerous organic scaffolds. On the other hand, these important synthetic intermediates can be easily synthesized by 1,3-dipolar cycloaddition reaction of alkenes with nitrile oxides generated *in situ*;[1] this pericyclic reaction is a versatile and effective tool for the synthesis of isoxazolines from the chemically different compounds. Isoxazolines have found applications as antituberculosis agents,[2] antibacterial agents, antifungal agents,[3] anticancer agents,[4] anti-inflammatory agents and COX-2 inhibitors. They are also found to possess mesogenic core exhibiting liquid crystalline properties.[5,6] These varied applications have attracted more interest in isoxazolines and their synthetic routes. Various methods have been reported in the literature. These include (i) condensation of ethyl benzoylacetate, aromatic aldehydes and hydroxylamine under reflux condition in ethanol using DABCO,[7] (ii) cyclization of *N*-alkenylamides catalyzed by iodoarenes under oxidative conditions,[8] (iii) $Cu(OAc)_2$-catalyzed oxidation of unsaturated alkenes,[9] (iv) use of DMTMM (4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride) as the dehydrating agent in the presence of DMAP in acetonitrile,[10] (v) treatment of aldoximes with magtrieve (CrO_2) at 80 °C,[11] (vi) β, γ-unsaturated ketoximes reacted with 2-arylphenyl isonitriles in the presence of *t*-BuOOH and *n*-Bu_4NI,[12] (vii) reaction of aldoximes with alkenes in presence of CAT,[13] (viii) use of *tert*-butyl hypoiodite (*t*-BuOI) in dioxane in the presence of 2,6- lutidine,[14] (ix) reaction of aldehydes with hydroxylamine sulphate to obtain aldoximes and then the formation of isoxazoline by the *in situ* generated hypervalent iodine compound,[15] (x) iodobenzene diacetate for the formation of nitrile oxides,[16] (xi) use of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO)-mediated Cope-like elimination,[17] and (xii) oxidation of allyloximes by 2,2,2-trifluoroacetophenone in the presence of H_2O_2.[18] In view of the wide applications of isoxazoline, a literature survey revealed that KIO_3/KI in acetic acid can be used as an iodination agent at 110 °C.[19] A polyol process was reported for the synthesis of water dispersible anatase TiO_2 nanoparticles by using KIO_3.[20] It is also reported as a catalyst for the α-sulfenylation of enaminones.[21] These reports prompted us to use KIO_3, which turned out as a novel oxidising agent for the synthesis of isoxazolines. This metal-free process is less time consuming; in addition, the easy availability and stability of KIO_3 and effortless purification of the product makes it a versatile reagent for the synthesis of isoxazolines.

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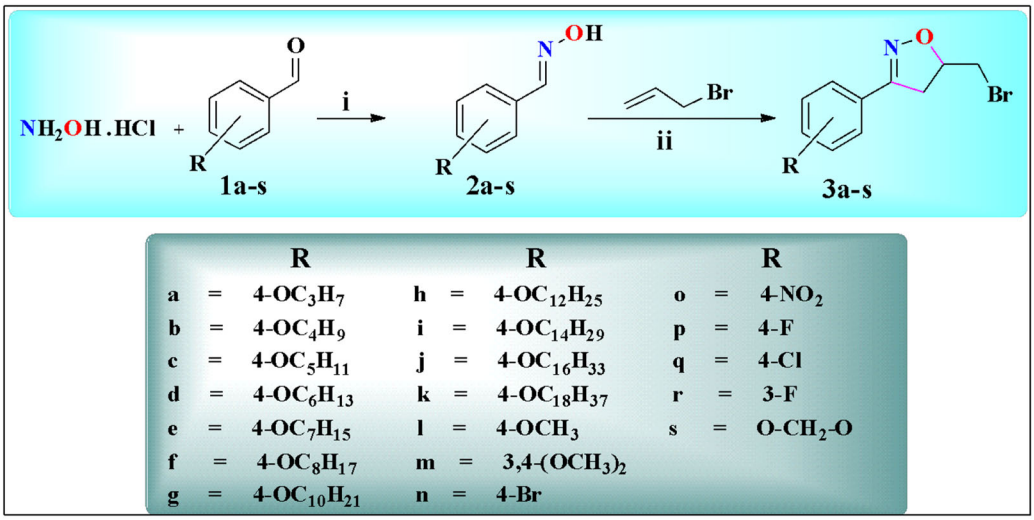


(i): NaOAc in EtOH (ii) KIO_3, Acetic acid

Scheme 1. Scheme of synthesis

Typically, cycloaddition reaction is carried out by heating an equimolar mixture of allyl bromide, aldoxime, potassium iodate and acetic acid in ethanol under reflux for 4–6 h. Among the synthesized compounds, known compounds exhibited identical ^{1}H and ^{13}C NMR spectra, LC-MS, mixed MPs and TLC behaviour with those of authentic samples. The plan of synthesis is reported in Scheme 1.

2. Experimental

2.1 *Materials and methods*

The NMR analysis of the synthesized intermediates and final compounds was carried out in AGILENT (400 MHz) NMR spectrometer using deuterated chloroform as the solvent. LC-MS of synthesized final products were obtained using WATERS SynaptG2 model spectrometer. The completion of the reaction was monitored by thin layer chromatography (TLC) performed on aluminium sheets coated with silica gel obtained from Merck Kieselgel. All the chemicals were commercially obtained and were used without further purification.

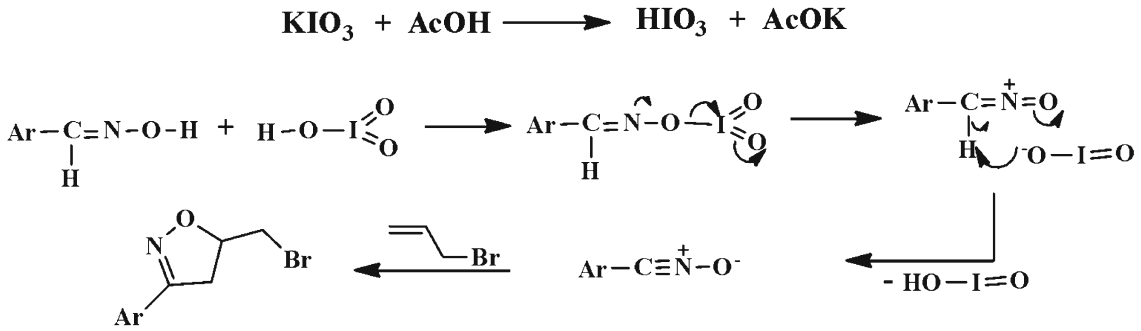
Antibacterial activity of the synthesized compounds was assessed by agar well diffusion method. The bacterial strains used in this study were gram-negative bacteria such as *Klebsiella pneumonia* (MTCC 661), *Escherichia coli* (MTCC 1698), gram-positive bacteria such as *Bacillus subtilus* (MTCC 121), *Staphylococcus aureus* (MTCC 6908). 100 mL of Nutrient Agar was prepared and sterilized. 20 mL agar was poured in each clean petri dish and was placed in a laminar airflow chamber. After solidification, 0.1 mL of the human pathogenic bacteria was spread in the nutrient agar plate using the cotton swabs. Well of 10 mm diameter was formed in the agar plates using well puncture apparatus. The prepared compounds were poured into the well with 100 µg/mL concentration, and the sample volume being 75 µL. The plates were kept for incubation at 37 °C for 24 h. After incubation, the zone of inhibition was measured. DMSO (solvent) which acts as a negative control was added in one well and in the other well, gentamicin sulphate obtained from HIMEDIA was added as a positive control.

2.2 *Probable mechanistic pathway*

The probable mechanistic pathway is given in Scheme 2. Generation of nitrile oxide involves the reaction of oxime with iodic acid obtained from potassium iodate and acetic acid to form oximino iodate. This undergoes disproportionation to yield the nitrile oxide, which then underwent cycloaddition with alkenes to form the required isoxazolines in almost quantitative yield.

2.3 *Synthesis of isoxazolines*

Alkylated benzaldehydes (1 mmol) and aldoximes (1 mmol) were prepared by reported methods.[6] In a typical procedure, *p*-propoxy- benzaldoxime and allyl bromide were made to react with KIO_3 (1.2 mmol) for the generation of nitrile oxide *in situ* under reflux conditions for 4–6 h in the presence of acetic acid in catalytic amount and ethanol as solvent. The completion of the reaction was monitored by TLC. After completion, the residue was extracted with ether (25 mL × 3), the extract was washed successively with water (15 mL × 2), 10% NaOH (15 mL × 2), and saturated brine solution (10 mL). The organic layer was dried over anhydrous Na_2SO_4. The crude product was purified by recrystallization using methanol. The TLC and NMR spectra were compared with the standard compounds prepared using Chloramine-T and were found to be the same.



Scheme 2. Probable mechanism

2.3a *5-(bromomethyl)-3-(4-propoxyphenyl)-4,5-dihydroisoxazole (**3a**)*: Prepared from **2a** and **ii** (allyl bromide). White solid, Yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 2H, ArH, J = 8.4 Hz), 6.90 (d, 2H, ArH, J = 8.4 Hz), 4.96 (m, 1H, OCH), 3.94 (t, 2H, OCH_2, J = 6.4 Hz), 3.58–3.26 (m, 4H, CH_2), 1.84–1.56 (m, 2H, CH_2), 1.03 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.88, 155.62, 128.29, 121.62, 121.30, 114.70, 114.59, 79.43, 69.63, 39.86, 33.16, 22.47, 10.42. Anal. Calcd for $C_{13}H_{16}BrNO_2$: C - 52.36; H - 5.41; N - 4.70%; Found: C - 52.18; H - 5.01; N - 4.03%. LCMS [M+1]: Calcd for $C13H_{16}BrNO_2$: 298.1, Found:298.1.

2.3b *5-(bromomethyl)-3-(4-butoxyphenyl)-4,5-dihydroisoxazole (**3b**)*: Prepared from **2b** and **ii** (allyl bromide). White solid; Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, 2H, ArH, J= 8.4 Hz), 6.97 (d, 2H, ArH, J = 8.4 Hz), 4.88 (m, 1H, OCH), 3.97 (t, 2H, OCH2, J = 6.4 Hz), 3.51–3.36 (m, 4H, CH_2), 1.86–1.44 (m, 4H, CH_2), 1.01 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.79, 154.82, 128.34, 121.29, 121.18, 114.69, 114.62, 79.34, 69.54, 39.26, 33.25, 29.69, 22.31, 10.51. Anal. Calcd for $C_{14}H_{18}BrNO_2$: C - 53.86; H - 5.81; N - 4.49; Found: C - 53.32; H - 5.53; N - 4.14; LCMS [M+1]: Calcd for $C_{14}H_{18}BrNO_2$: 312.2, Found: 312.1.

2.3c *5-(bromomethyl)-3-(4-(pentyloxy)phenyl)-4,5-dihydroisoxazole (**3c**)*: Prepared from **2c** and **ii** (allyl bromide).White solid; Yield: 69%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, 2H, ArH, J = 8.4 Hz), 6.91 (d, 2H, ArH, J= 8.4 Hz), 4.78 (m, 1H, OCH), 3.99 (t, 2H, OCH_2, J = 6.4 Hz), 3.54–3.38 (m, 4H, CH_2), 1.88–1.47 (m, 6H, CH_2), 1.07 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.45, 155.25, 128.34, 121.25, 121.20, 114.59, 114.47, 79.43, 69.54, 39.71, 33.14, 29.48, 24.41, 22.39, 10.27. Anal. Calcd for $C_{15}H_{20}BrNO_2$: C – 55.83; H – 6.18; N – 4.29; Found: C - 54.82; H - 5.83; N - 4.04. LCMS [M+1]: Calcd for $C_{15}H_{20}BrNO_2$: 326.2, Found: 326.1.

2.3d *5-(bromomethyl)-3-(4-(hexyloxy)phenyl)-4,5-dihydroisoxazole (**3d**)*: Prepared from **2d** and **ii** (allyl bromide).White solid; Yield: 73%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, 2H, ArH, J = 8.4 Hz), 6.94 (d, 2H, ArH, J = 8.4 Hz), 4.81 (m, 1H, OCH), 3.91 (t, 2H, OCH_2, J = 6.4 Hz), 3.56–3.41 (m, 4H, CH2), 1.87–1.37 (m, 8H, CH_2), 1.05 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.87, 155.62, 128.29, 121.29, 121.21, 114.69, 114.52, 79.42, 68.15, 39.85, 33.22, 31.53, 29.10, 25.64, 22.56, 13.99. Anal. Calcd for $C_{16}H_{22}BrNO_2$: C – 56.48; H – 6.52; N – 4.12; Found: C - 56.13; H - 6.23; N - 3.91. LCMS [M+1]: Calcd for $C_{16}H_{22}BrNO_2$: 340.2, Found: 340.1.

2.3e *5-(bromomethyl)-3-(4-(heptyloxy)phenyl)-4,5-dihydroisoxazole (**3e**)*: Prepared from **2e** and **ii** (allyl bromide). White solid; Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, 2H, ArH, J = 8.4 Hz), 6.94 (d, 2H, ArH, J= 8.4 Hz), 4.72 (m, 1H, OCH), 3.96 (t, 2H, OCH_2, J = 6.4 Hz), 3.58–3.34 (m, 4H, CH_2), 1.89–1.49 (m, 10H, CH_2), 1.04 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.87, 155.41, 128.34, 121.28, 121.19, 114.64, 114.43, 79.28, 69.57, 39.64, 33.58, 29.34, 28.52, 27.26, 24.51, 22.37, 10.46. Anal. Calcd for $C_{17}H_{24}BrNO_2$: C - 57.63; H - 6.83; N - 3.95; Found: C - 56.82; H - 6.01; N - 3.54. LCMS [M+1]: Calcd for $C_{17}H_{24}BrNO_2$: 354.2, Found: 354.1.

2.3f *5-(bromomethyl)-3-(4-(octyloxy)phenyl)-4,5-dihydroisoxazole (**3f**)*: Prepared from **2f** and **ii** (allyl bromide). White solid; Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, 2H, ArH, J = 8.4 Hz), 6.90 (d, 2H, ArH, J = 8.4 Hz), 4.95 (m, 1H, OCH), 3.97 (t, 2H, OCH_2, J = 6.4 Hz), 3.58–3.26 (m, 4H, CH_2), 1.81–1.30 (m, 12H, CH_2), 0.87 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.87, 155.63, 128.29, 128.19, 121.27, 114.69, 114.34, 79.42, 68.15, 39.86, 33.21, 29.53, 29.31, 29.20, 29.13, 25.97, 22.63, 14.06. Anal. Calcd for $C_{18}H_{26}BrNO_2$: C - 58.70; H – 7.12; N - 3.80; Found: C - 58.42; H - 6.91; N - 3.54. LCMS [M+2]: Calcd for $C_{18}H_{26}BrNO_2$: 370.1, Found: 370.2.

2.3g *5-(bromomethyl)-3-(4-(decyloxy)phenyl)-4,5-dihydroisoxazole (**3g**)*: Prepared from **2g** and **ii** (allyl bromide). White solid; Yield: 70%;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, 2H, ArH, J = 8.4 Hz), 6.90 (d, 2H, ArH, J = 8.4 Hz), 4.94 (m, 1H, OCH), 3.96 (t, 2H, OCH_2, J = 6.4 Hz), 3.58–3.27 (m, 4H, CH_2), 1.79–1.43 (m, 16H, CH_2), 0.86 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.87, 155.62, 128.29, 121.28, 114.68, 79.42, 77.37, 77.06, 68.15, 39.85, 33.24, 31.87, 29.54, 29.35, 29.29, 29.20, 29.14,

25.98, 22.66, 14.09. Anal. Calcd for $C_{20}H_{30}BrNO_2$: C - 60.60; H – 7.63; N - 3.53; Found: C - 60.01; H - 7.01; N - 3.41. LCMS [M+2]: Calcd for $C_{20}H_{30}BrNO_2$:398.3, Found: 398.2.

2.3h *5-(bromomethyl)-3-(4-(dodecyloxy)phenyl)-4, 5-dihydroisoxazole (**3h**)*: Prepared from **2h** and **ii** (allyl bromide). White solid; Yield: 74%; ^{1}H NMR(400 MHz, $CDCl_3$): δ 7.58 (d, 2H, ArH, J = 8.4 Hz), 6.90 (d, 2H, ArH, J = 8.4 Hz), 4.95 (m, 1H, OCH), 3.97 (t, 2H, OCH_2, J = 6.4 Hz), 3.57–3.26 (m, 4H, CH_2), 1.81–1.25 (m, 20H, CH_2), 0.86 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.89, 155.60, 128.28, 121.30, 114.71, 79.43, 77.29, 76.98, 76.66, 68.17, 39.86, 33.14, 31.87, 29.59, 29.54, 29.43, 29.32, 29.30, 29.13, 25.96, 22.64, 14.05. Anal. Calcd for $C_{22}H_{34}BrNO_2$: C - 62.26; H – 8.09; N - 3.30; Found: C - 62.06; H - 7.99; N - 3.24. LCMS [M+1]: Calcd for $C_{22}H_{34}BrNO_2$: 424.4, Found: 424.1.

2.3i *5-(bromomethyl)-3-(4-(tetradecyloxy)phenyl)-4, 5-dihydroisoxazole (**3i**)*: Prepared from **2i** and **ii** (allyl bromide). White solid; Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, 2H, ArH, J= 8.4 Hz), 6.90 (d, 2H, ArH, J = 8.4 Hz), 4.96 (m, 1H, OCH), 3.78 (t, 2H, OCH_2, J = 6.4 Hz), 3.57–3.26 (m, 4H, CH_2), 1.81–1.25 (m, 24H, CH_2), 0.86 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.89, 155.62, 129.29, 121.25, 121.18, 114.45, 114.37, 79.42, 68.26, 40.24, 39.85, 33.24, 31.87, 29.74, 29.54, 29.35, 29.29, 29.14, 28.16, 27.49, 27.14, 25.98, 22.66, 14.07. Anal. Calcd for $C_{24}H_{38}BrNO_2$: C - 63.71; H - 8.47; N – 3.10; Found: C - 63.12; H - 8.19; N - 2.99. Calcd for $C_{24}H_{38}BrNO_2$: 452.4, Found: 452.1.

2.3j *5-(bromomethyl)-3-(4-(hexadecyloxy)phenyl)-4, 5-dihydroisoxazole (**3j**)*: Prepared from **2j** and **ii** (allyl bromide). White solid; Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, 2H, ArH, J= 8.4 Hz), 6.90 (d, 2H, ArH, J = 8.4 Hz), 4.95 (m, 1H, OCH), 3.97 (t, 2H, OCH_2, J = 6.4 Hz), 3.57–3.26 (m, 4H, CH_2), 1.81–1.25 (m, 28H, CH_2), 0.87 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.88, 155.62, 128.29, 121.27, 114.69, 79.43, 77.32, 77.01, 76.69, 68.16, 39.87, 33.19, 31.90, 29.66, 29.55, 29.35, 29.29, 29.20, 29.14, 28.69, 28.51, 28.19, 27.14, 25.98, 22.67, 14.09. Anal. Calcd for $C_{26}H_{42}BrNO_2$: C - 64.99; H – 8.81; N - 2.91; Found: C - 64.08; H - 8.19; N - 2.28. LCMS [M+1]: Calcd for $C_{26}H_{42}BrNO_2$: 480.5, Found: 480.1.

2.3k *5-(bromomethyl)-3-(4-(octadecyloxy)phenyl)-4, 5-dihydroisoxazole (**3k**)*: Prepared from **2k** and **ii** (allyl bromide). White solid; Yield: 72%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, 2H, ArH, J= 8.4 Hz), 6.90 (d, 2H, ArH, J = 8.4 Hz), 4.96 (m, 1H, OCH), 3.97 (t, 2H, OCH_2, J = 6.4 Hz), 3.57–3.26 (m, 4H, CH_2), 1.81–1.25 (m, 32H, CH_2), 0.88 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.79, 155.67, 128.18, 129.04, 121.24, 114.29, 114.21, 79.57, 68.02, 40.08, 39.79, 33.08, 31.87, 29.57, 29.51, 29.47, 29.40, 29.38, 29.31, 29.27, 29.24, 28.57, 28.48, 28.38, 27.34, 25.87, 22.75, 14.12. Anal. Calcd for $C_{28}H_{46}BrNO_2$: C - 66.13; H - 9.12; N - 2.75; Found: C - 66.02; H - 9.02; N - 2.19. LCMS [M+1]: Calcd for $C_{28}H_{46}BrNO_2$: 508.5, Found: 508.1.

2.3l *5-(bromomethyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (**3l**)*: Prepared from **2l** and **ii** (allyl bromide).White solid; Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 2H, ArH, J= 8.4 Hz), 6.90 (d, 2H, ArH, J = 8.4 Hz), 4.39 (m, 1H, OCH), 3.57 (s, 3H, OCH_3), 3.56–3.25 (m, 4H, $ArCH_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.74, 155.56, 128.19, 121.37, 121.24, 114.59, 114.46, 79.35, 69.38, 39.79, 33.17. Anal. Calcd for $C_{11}H_{12}BrNO_2$: C - 48.91; H - 4.48; N - 5.19; Found: C - 48.18; H - 4.01; N - 5.03. LCMS [M+1]: Calcd for $C_{11}H_{12}BrNO_2$: 270.1, Found: 270.1.

2.3m *5-(bromomethyl)-3-(3,4-dimethoxyphenyl)-4,5-dihydroisoxazole (**3m**)*: Prepared from **2m** and **ii** (allyl bromide). White solid; Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 2H, ArH, J = 8.4 Hz), 6.91 (d, 1H, ArH, J = 8.4 Hz), 4.39 (m, 1H, OCH), 3.58 (s, 6H, OCH_3), 3.57–3.26 (m, 4H, $ArCH_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.86, 155.59, 128.34, 121.27, 121.59, 114.64, 114.48, 79.39, 69.57, 69.49, 39.59, 33.1. Anal. Calcd for $C_{12}H_{14}BrNO_3$: C - 48.02; H - 4.70; N - 4.67; Found: C - 47.81; H - 4.43; N - 4.43. LCMS [M+1]: Calcd for $C_{12}H_{14}BrNO_3$: 300.1, Found: 300.1.

2.3n *5-(bromomethyl)-3-(4-bromophenyl)-4,5-dihydroisoxazole (**3n**)*: Prepared from **2n** and **ii** (allyl bromide). White solid; Yield: 74%;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, 2H, ArH, J = 8.4 Hz), 7.38 (d, 2H, ArH, J = 8.4 Hz), 4.99 (m, 1H, OCH), 3.57–3.26 (m, 4H, $ArCH_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.82, 155.61, 128.24, 121.86, 121.72, 114.97, 114.78, 79.51, 39.98, 33.49. Anal. Calcd for $C_{10}H_9Br_2NO$: C - 37.65; H - 2.84; N - 4.39; Found: C - 37.43; H - 2.73; N - 4.25. LCMS [M+1]: Calcd for $C_{10}H_9Br_2NO$: 318.9, Found: 318.3.

2.3o *5-(bromomethyl)-3-(4-nitrophenyl)-4,5-dihydroisoxazole (**3o**)*: Yield: 72%; Prepared from **2o** and **ii** (allyl bromide). Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, 2H, ArH, J = 8.4 Hz), 7.37 (d, 2H, ArH, J = 8.4 Hz), 4.98 (m, 1H, OCH), 3.58–3.26 (m, 4H, $ArCH_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.81, 155.54, 128.31, 121.67, 121.32, 114.48, 114.43, 79.69, 39.43, 33.32. Anal. Calcd for $C_{10}H_9BrN_2O_3$: C - 42.13; H - 3.18; N - 9.83; Found: C - 42.04; H - 3.08; N - 9.47. LCMS [M+1]: Calcd for $C_{10}H_9BrN_2O_3$: 286.1, Found: 286.1.

2.3p *5-(bromomethyl)-3-(4-fluorophenyl)-4,5-dihydroisoxazole (**3p**)*: Prepared from **2p** and **ii** (allyl bromide).White solid; Yield: 70%;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, 2H, ArH, J = 8.4 Hz), 7.38 (d, 2H, ArH, J = 8.4 Hz), 4.99 (m, 1H, OCH), 3.57–3.26 (m, 4H, $ArCH_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.82, 155.61, 128.24, 121.86, 121.72, 114.97, 114.78, 79.51, 39.98, 33.49. Anal. Calcd for $C_{10}H_9BrFNO$: C - 46.54; H - 3.51; N - 5.43; Found: C - 46.31; H - 3.23; N - 5.16. LCMS [M+1]: Calcd for $C_{10}H_9BrFNO$: 257.1, Found: 257.1.

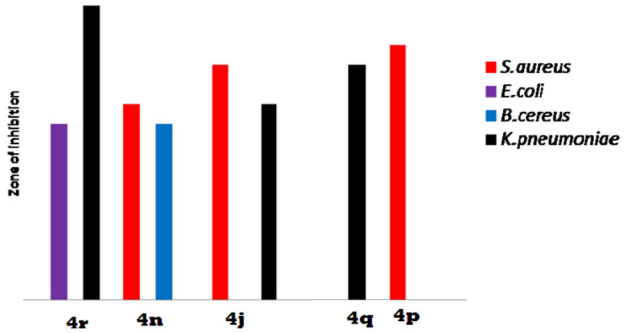


Figure 1. Graphical representation of the zone of inhibition exhibited by the synthesized compounds.

2.3q *5-(bromomethyl)-3-(4-chlorophenyl)-4,5-dihydroisoxazole (**3q**)*: Prepared from **2q** and **ii** (allyl bromide). White solid; Yield: 72%;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, 2H, ArH, J = 8.4 Hz), 7.36 (d, 2H, ArH, J = 8.4 Hz), 4.99 (m, 1H, OCH), 3.57–3.24 (m, 4H, $ArCH_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.84, 155.57, 128.31, 121.28, 121.58, 114.65, 114.49, 79.38, 39.54, 33.17. Anal. Calcd for $C_{10}H_9BrClNO$: C - 43.75; H - 3.30; N - 5.10; Found: C - 43.17; H - 3.21; N - 5.03. LCMS [M+1]: Calcd for $C_{10}H_9BrClNO$: 275.5, Found: 275.4.

2.3r *5-(bromomethyl)-3-(3-fluorophenyl)-4,5-dihydroisoxazole (**3r**)*: Prepared from **2r** and **ii** (allyl bromide). White solid; Yield: 74%;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, 2H, ArH, J= 8.4 Hz), 7.36 (d, 2H, ArH, J = 8.4 Hz), 4.99 (m, 1H, OCH), 3.57–3.24 (m, 4H, $ArCH_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.84, 155.62, 128.34, 121.29, 121.57, 114.46, 114.38, 79.29, 39.57, 33.09. Anal. Calcd for $C_{10}H_9BrFNO$: C - 46.54; H - 3.51; N - 5.43; Found: C - 46.14; H - 3.47; N - 5.21. LCMS [M+1]: Calcd for $C_{10}H_9BrFNO$: 258.1, Found: 258.1.

2.3s *5-(bromomethyl)-3-(1,3-dihydroisobenzofuran-5-yl)-4,5-dihydroisoxazole (**3s**)*: Prepared from **2s** and **ii** (allyl bromide). White solid; Yield: 72%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, 1H, ArH, J = 8.4 Hz), 7.36 (s, 1H, ArH), 6.86 (d, ^{1}H, ArH, J = 8.4 Hz), 6.02 (s, 4H), 4.99 (m, 1H, OCH), 3.58–3.26 (m, 4H, $ArCH_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.79, 155.58, 128.34, 121.87, 121.59, 114.56, 114.54, 79.35, 39.79, 33.24. Anal. Calcd for $C_{12}H_{12}BrNO_2$: C - 51.09; H - 4.29; N - 4.96; Found: C - 51.01; H - 4.21; N - 4.53. LCMS [M+1]: Calcd for $C_{12}H_{12}BrNO_2$: 282.1, Found: 282.1.

2.4 *Biological assay*

The plates were analysed for the zone of inhibition and the results obtained are represented graphically in Figure 1. The appearance of the inhibition zone around the well indicates antimicrobial activity of the synthesized isoxazoline derivatives. However, the mode of action caused by the compounds is not known well, it is believed that the synthesized compounds get adhered on the cell wall of the bacteria, which results in the lysis of the cell thus proving it to be fatal.[22]

Table 1. Determination of the MIC by Resazurin aided microdilution method of synthesized compounds against standard pathogens.

Bacteria	Compounds	MIC reported in this study (mg mL^{-1})
Klebsiella pneumoniae	**4r**	0.75
Escherichia coli	**4r**	0.75
Klebsiella pneumoniae	**4j**	1.25
Staphylococcus aureus	**4j**	1.25
Klebsiella pneumoniae	**4q**	1.25
Staphylococcus aureus	**4p**	1.25
Staphylococcus aureus	**4n**	1.25
Bacillus cereus	**4n**	2.5

From the results obtained, it can be inferred that compound **4r** exhibited excellent inhibitory activity against both gram-negative bacterial strains; this might be attributed to the presence of the F atom in the third position. The presence of halogens usually will increase the inhibitory effect. Compound **4n** was found to exhibit inhibitory activity against both gram-positive bacterial strains, probably due to the presence of Br atom. Compound **4q** exhibited good inhibitory activity against *Klebsiella pneumoniae* and **4p** exhibited appreciable inhibitory activity against *Staphylococcus aureus*. It is evident from the results that halogen substituents do contribute to the inhibition activity may be due to the presence of electron withdrawing nature (Table 1).

3. Conclusions

A novel metal-free benign procedure is reported for the synthesis of isoxazolines. Aryl aldehydes were converted to aldoximes in the presence of hydroxylamine hydrochloride and sodium acetate. Later, they were made to react with alkenes in the presence of the novel reagent – KIO_3 which acts as an oxidising agent. The obtained products are important heterocycles as they can be further used for Suzuki coupling or Heck reactions to obtain pharmaceutically potent drugs. Other applications are under investigation.

Supporting Information (SI)

Detailed Results and Discussion with ^{1}H and ^{13}C NMR, LC-MS and biological assay images are available at www.ias.ac.in/chemsci.

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Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest.

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