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One-pot synthesis of new series 3,4,5-trisubstituted–dihydroisoxazoline derivatives via 1,3-dipolar cycloaddition of nitrile oxides with chalcones

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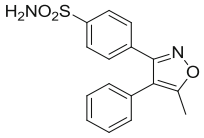
Abstract. We have synthesized a series of novel isoxazolines via 1,3-dipolar cycloaddition reaction. Aromatic aldoximes undergo oxidative–dehydrogenation with chloramine–T to give nitrile oxides, which were reacted with chalcones to afford of 3,4,5-trisubstituted 4,5-dihydroisoxazolines in a good yield.

Keywords. Isoxazoline; 1,3-dipolar cycloaddition; aromatic aldoximes; chalcones.

1. Introduction

Heterocyclic compounds have wide range of application in synthetic organic chemistry. Among them five-membered heterocycles, isoxazolines are of considerable interest due to their versatile application in pharmaceutical and agrochemical agents. Isoxazoline derivatives have been reported to possess antidiabetic,[1] antiinfluenza virus,[2] antifungal,[3] glycoprotein IIb/IIIa receptor antagonists,[4] antiHIV,[5] spermicidal and antiHIV,[6] analgesic and antiinflammatory,[7] and β-adrenergic receptor antagonist,[8] antitumour,[9] antistress[10] and anticancer properties.[11] Isoxazolines also act as an important building block for the synthesis of biologically active molecules.[12] In fact, Valdecoxib is an isoxazoline derivative, now widely used in the market as an antiinflammatory drug.[13]



Valdecoxib

1,3-Dipolar cycloadditions are powerful methods for building a variety of five-membered heterocycles in a convergent manner from simpler molecules which are otherwise accessible only through a difficult synthetic exercise. Cycloaddition of nitrile oxide to olefinic compounds are of synthetic interest, since the resulting isoxazolines are versatile intermediates for the synthesis of bifunctional compounds.[14] Nitrile oxides can be generated by dehydrogenation of aryl aldoximes with mercuric acetate,[15] manganese dioxide,[16] *tert*-butyl hypochlorite,[17] chloramine–T.[18] In 1989 Hassner and Rai have reported the synthesis of isoxazolines via the formation of nitrile oxides from crossponding oxime and the subsequent reaction with olefins and suggested a mechanism for the reaction.[19] Recently, Ganoker *et al.* used chloramine–T for the generation and cycloaddition of α-nitrosoolefin and α-azoalkenes from ketoximes and ketone hydrazones,[20] respectively. Yongjia *et al.* synthesized 3,4,5-trisubstituted isoxazoles from 3,4,5-trisubstituted isoxazolines.[21] With this background, herein we report the cycloaddition reaction of different aldoximes with various chalcones.

2. Experimental

2.1 *General*

The IR spectra (in KBr pellets) were recorded on JASCO FT/IR-460/113257 spectometer (Japan) in the wave number range of 4000–400 cm^{-1}.

Elemental analyses were carried out on an Elementor vairo-EL instrument. ^{1}H–NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured on $CDCl_3$ and tetramethylsilane is used as internal reference. The mass analysis was performed on HP-5989A LC/MS spectrometer. The solvents and reagents were used without further purification.

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2.2 *General procedure for synthesis of chalcones (**1a–g**)*[22]

Acetophenone (0.01 mol) and aromatic aldehyde (0.01 mol) were dissolved in (5 ml, 95%) ethanol. 0.5 ml, 60% solution of sodium hydroxide was added slowly and stirred the mixture until it solidifies and then adding 10 ml of ice water. The solid product was filtered, dried and purified from ethanol.

2.3 *General procedure for synthesis of aromatic aldoximes (**2a–c**)*[23]

Aromatic aldehyde (benzaldehyde or 3-methoxybenzaldehydeor 3,4-dimethoxybenzaldehyde) (0.1 mol) in 15 ml ethanol was added to a solution of hydroxylamine hydrochloride (0.14 mol) and sodium acetate (0.14 mol) the mixture was heated at 80–90°C for 1 h and then left to cool to room temperature. The precipitate was collected and purified by crystallization from ethanol to give compound (**2a–g**).

2.4 *General procedure for synthesis of isoxazoline (**3aa–3gc**)*

A mixture of chalcone (5 mmol), oxime (5 mmol) and chloramine–T (5.2 mmol) in ethanol (20 ml) was refluxed on a water-bath. After 2 h, the reaction was monitored by TLC. After completion, the mixture was cooled to room temperature. Sodium chloride formed was filtered off and washed with ethanol (15 ml). Filtrate and washing were combined and the solvent was evaporated in vacuum. The residue was extracted with ether (25 ml), the extract was washed successively with water (2 × 15 ml), 10% NaOH (2 × 15 ml), and saturated brine solution (10 ml). The organic layer was dried over anhydrous sodium sulphate. The crude product was filtered and purified by column chromatography on silica gel using chloroform–methanol to give the corresponding pure product.

2.4a *Isoxazoline **3aa***: Obtained as brown oil from chalcone **1a** and oxime **2a**, IR (neat, cm^{-1}): 3180, 3074, 2924, 1678, 1616, 1234: 1H–NMR (400 MHz, $CDCl_3$): δ 3.40 (d, 8.2 Hz, 1H, C_4), 5.46 (d, 8.2 Hz, 1H, C_5), 7.27–8.08 (m, 15H, ArH), 10.00 (br, 1H, NH).^{13}C–NMR (100 Hz, $CDCl_3$, rt): 47.13, 83.81, 109.01, 126.76, 127.18, 127.86, 128.60, 128.92, 129.48, 129.95, 131.53, 132.25, 138.17, 141.53, 152.19, 155.28, 196.57, Anal. Calcd. for $C_{22}H_{17}NO_2$: C 80.71, H 5.23, N 4.28, found C 80.90, H 5.20, N 4.39. LC-MS m/z: 328.13 $(M + 1)^+$.

2.4b *Isoxazoline **3ab***: Obtained as yellow oil from chalcone **1a** and oxim **2b**, IR (neat, cm^{-1}): 3210, 3045, 2953, 1680, 1612, 1245, 1173: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 3.76 (s, 3H, OCH_3), 3.49 (d, 8.2 Hz, 1H, C_4), 5.20 (d, 8.2 Hz, 1H, C_5), 6.80–8.08 (m, 14H, ArH), 9.90 (s, 1H, NH). ^{13}C–NMR (100 Hz, $CDCl_3$, rt): 44.31, 57.15, 83.74, 109.23, 119.96, 122.81, 126.65, 127.52, 128.60, 128.94, 134.50, 138.00, 141.74, 153.42, 155.60, 160.57, 197.62. Anal. Calcd. for $C_{23}H_{19}NO_3$: C 77.29, H 5.36, N 3.92, found C 77.50, H 5.49, N 3.99. LC-MS m/z: 358.14 $(M + 1)^+$.

2.4c *Isoxazoline **3ac***: Obtained as pale yellow oil from chalcone **1a** and oxime **2c**, IR (neat, cm^{-1}): 3196, 3071, 2973, 1660, 1610, 1241, 1192, ^{1}H–NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 6H, OCH_3), 3.52 (d, 8.4 Hz, 1H, C_4), 5.39 (d, 8.4 Hz, 1H, C_5), 6.65–8.04 (m, 13H, ArH), 9.75 (br, 1H, NH).^{13}C–NMR (100 Hz, $CDCl_3$, rt): 45.49, 57.13, 84.38, 108.35, 115.46, 121.76, 124.45, 127.11, 127.62, 128.40, 128.63, 131.74, 136.27, 139.91, 146.65, 150.12, 153.50, 155.70, 199.02. Anal. Calcd. for $C_{24}H_{21}NO_4$: C 74.40, H 5.46, N 3.62, found C 74.50, H 5.20, N 3.39. LC-MS m/z: 388.15 $(M + 1)^+$.

2.4d *Isoxazoline **3ba***: Obtained as yellow oil from chalcone **1b** and oxime **2a**, IR (neat, cm^{-1}): 3185, 3035, 2971, 1671, 1618, 1241: ^{1}H–NMR (400 MHz, $CDCl_3$), rt): δ 2.40 (s, 3H, CH_3), 3.51 (d, 8.2 Hz, 1H, C_4), 5.60 (d, 8.2 Hz, 1H, C_5), 7.22–8.05 (d, 14H, ArH), 9.81 (s, 1H, NH). ^{13}C–NMR (100 MHz, $CDCl_3$, rt): 21.19, 43.51, 86.30, 105.96, 126.33, 127.52, 128.33, 128.72, 129.35, 131.21, 131.93, 133.14, 135.65, 136.14, 136.81, 153.43, 155.18, 199.03. Anal. CHN: Calcd. For $C_{23}H_{19}NO_2$: C 80.92, H 5.61, N 4.10, found C 80.76, H 5.87, N 4.01. LC-MS m/z: 342.14 $(M + 1)^+$.

2.4e *Isoxazoline **3bb***: Obtained as yellow oil from chalcone **1b** and oxime **2b**, IR (neat, cm^{-1}): 3205, 3038, 2946, 1675, 1618, 1237: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 2.39 (s, 3H, CH_3), 3.50 (d, 8.2 Hz, 1H, C_4), 3.81 (s, 3H, OCH_3), 5.60 (d, 8.2 Hz, 1H, C_5), 6.80–8.06 (m, 13H, ArH), 9.50 (br, 1H, NH).^{13}C–NMR (100 MHz, $CDCl_3$, rt): 19.75, 45.61, 58.13, 85.14, 106.42, 121.1, 122.62, 125.77, 126.83, 128.61, 130.14, 137.30, 138.10, 140.23, 153.34, 156.43, 165.15, 195.67. Anal. Calcd. for $C_{24}H_{21}NO_3$: C 77.61, H 5.70, N 3.77 found C 77.56, H 5.99, N 3.43. LC-MS m/z: 372.15 $(M + 1)^+$.

2.4f *Isoxazoline* ***3bc***: Obtained as pale brown oil from chalcone **1b** and oxime **2c**, IR (neat, cm^{-1}): 3218, 3036, 2978, 1694, 1628, 1244, 1178: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 2.43 (s, 3H, CH_3), 3.55 (d, 8.4 Hz, 1H, C_4), 3.90 (s, 6H, OCH_3), 5.46 (d, 8.4 Hz, 1H, C_5) 7.26–7.82 (m, 12H, ArH), 10.02 (s, 1H, NH). ^{13}C–NMR (100 MHz, $CDCl_3$, rt): 22.12, 44.45, 57.21, 87.13, 107.66, 114.73, 122.50, 125.61, 126.84, 128.11, 128.65, 132.64, 135.88, 136.16, 139.50, 142.19, 145.11, 153.13, 155.60, 196.82. Anal. CHN: Calcd. for $C_{25}H_{23}NO_4$: C 74.79, H 5.77, N 3.49, found C 74.69, H 5.92, N 3.33. LC-MS m/z: 402.16 $(M + 1)^+$.

2.4g *Isoxazoline* ***3ca***: Obtained as yellow oil from chalcone **1c** and oxime **2a**, IR (neat, cm^{-1}) 3205, 3061, 2927, 1681, 1622, 1253: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 3.61 (d, 8.2 Hz, 1H, C_4), 5.14 (d, 8.2 Hz, 1H, C_5), 7.26–8.02 (m, 14H, ArH), 10.20 (s, 1H, NH). ^{13}C–NMR (100 MHz, $CDCl_3$, rt): 48.07, 86.42, 107.52, 125.54, 127.85, 128.17, 128.38, 128.92, 129.33, 130.19, 132.29, 134.04, 137.56, 138.01, 139.9, 141.10, 153.88, 156.96, 198.20. Anal. Calcd. for $C_{22}H_{16}ClNO_2$: C 73.03, H 4.46, N 3.87, found C 73.20, H 4.33, N 3.95. LC-MS m/z: 363.09 $(M + 2)^+$.

2.4h *Isoxazoline* ***3cb***: Obtained as pale brown oil from chalcone **1c** and oxime **2b**, IR (neat, cm^{-1}): 3183, 3096, 2954, 1678, 1620, 1240, 1197: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 3.52 (d, 8.2 Hz, 1H, C_4), 3.86 (s, 3H, OCH_3), 5.60 (d, 8.2 Hz, 1H, C_5), 6.80–8.01 (m, 13H, ArH), 9.50 (s, 1H, NH). ^{13}C–NMR (100 MHz, $CDCl_3$, rt): 48.12, 57.37, 86.95, 109.21, 124.15, 128.40, 128.57, 129.10, 129.59, 131.30, 132.13, 136.78, 140.66, 152.40, 155.90, 160.18, 198.50. Anal. Calcd. for $C_{23}H_{18}ClNO_3$: C 70.50, H 4.63, N 3.57, found C 70.39, H 4.81, N 3.46. LC-MS m/z: 393.10 $(M + 2)^+$.

2.4i *Isoxazoline* ***3cc***: Obtained as brown oil from chalcone **1c** and oxime **2c**, IR (neat, cm^{-1}): 3192, 3078, 2951, 1680, 1618, 1240, 1186: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 3.74 (d, 8.4 Hz, 1H, C_4), 3.83 (s, 6H, OCH_3), 5.62 (d, 8.4 Hz, 1H, C_5), 6.93–8.02 (m, 12H, ArH), 10.14 (s, 1H, NH).^{13}C–NMR (100 MHz, $CDCl_3$, rt): 45.81, 54.73, 83.45, 108.83, 117.36, 124.82, 126.60, 128.14, 128.61, 130.20, 132.22, 134.50, 135.61, 137.31, 139.18, 148.02, 149.16, 150.34, 156.63, 199,13. Anal. Calcd. for $C_{24}H_{20}ClNO_4$: C 68.33, H 4.78, N 3.32, found C 68.13, H 4.80, N 3.13. LC-MS m/z: 423.11 $(M + 2)^+$.

2.4j *Isoxazoline* ***3da***: Obtained as pale brown oil from chalcone **1d** and oxime **2a**, IR (neat, cm^{-1}): 3211, 3081, 2988, 1671, 1610, 1235: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 3.40 (d, 8.4 Hz, 1H, C_4), 5.71 (d, 8.4 Hz, 1H, C_5), 7.26–8.23 (m, 14H, ArH), 10.10 (br, 1H, NH). ^{13}C–NMR (100 MHz, $CDCl_3$, rt): 48.63, 88.72, 110.10, 122.51, 127.73, 128.15, 128.93, 129.26, 129.88, 131.65, 133.17, 139.08, 145.73, 152.51, 158.16, 193.49. Anal. Calcd. for $C_{22}H_{16}N_2O_4$: C 70.96, H 4.33, N 7.52, found C 70.79, H 4.53, N 7.41. LC-MS m/z: 373.11$(M + 1)^+$.

2.4k *Isoxazoline* ***3db***: Obtained as pale brown oil from chalcone **1d** and oxime **2b**, IR (neat, cm^{-1}): 3178, 3051, 2986, 1691, 1609, 1241: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 3.41 (d, 8.2 Hz, 1H, C_4), 3.76 (s, 3H, OCH_3), 5.47 (d, 8.2 Hz, 1H, C_5), 6.81–7.99 (m, 13H, ArH), 11.21 (s, 1H, NH). ^{13}C–NMR (100 MHz, $CDCl_3$, rt): 47.12, 55.73, 82.67, 110.31, 121.83, 128.71, 129.20, 130.40, 131.32, 139.07, 141.42, 148.13, 152.40, 158.20, 160.03, 198.11. Anal. Calcd. for $C_{23}H_{18}N_2O_5$: C 68.65, H 4.51, N 6.96, found C 68.85, H 4.31, N 6.98. LC-MS m/z: 403.12 $(M + 1)^+$.

2.4l *Isoxazoline* ***3dc***: Obtained as brown oil from chalcone **1d** and oxime **2c**, IR (neat, cm^{-1}): 3183, 3062, 2945, 1684, 1621, 1245, 1190: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 3.43 (d, 8.4 Hz, 1H, C_4), 3.89 (s, 6H, OCH_3), 5.85 (d, 8.4 Hz, 1H, C_5), 6.88–8.31 (m, 12H, ArH), 10.13 (s, 1H, NH).^{13}C–NMR (100 MHz, $CDCl_3$, rt): 45.88, 57.21, 86.20, 110.11, 112.83, 121.15, 122.94, 125.36, 127.82, 128.01, 133.75, 135.19, 145.07, 147.44, 149.65, 150.50, 152.70, 156.06, 193.76. Anal. Calcd. for $C_{24}H_{20}N_2O_6$: C 66.66, H 4.66, N 6.48, found C 66.87, H 4.55, N 6.69. LC-MS m/z: 433.13 $(M + 1)^+$.

2.4m *Isoxazoline* ***3ea***: Obtained as brown oil from chalcone **1e** and oxime **2a**, IR (neat, cm^{-1}): 3209, 3045, 2977, 1669, 1621, 1231, 1196: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 3.66 (d, 8 Hz 1H, C_4), 3.94 (s, 3H, OCH_3), 5.42 (d, 8 Hz, 1H, C_5), 6.88–8.03 (m, 14H, ArH), 9.00 (s, 1H, NH), ^{13}C–NMR (100 MHz, $CDCl_3$, rt): 45.12, 55.85, 85.7, 108.22, 114.45, 121.40 125.40, 128.04, 129.20, 129.51, 130.14, 132.24, 145.62, 150.87, 154.80, 157.20, 198.90. Anal. Calcd. for $C_{23}H_{19}NO_3$: C 77.29, H 5.36, N 3.92 , found C 77.40, H 5.16, N 3.90. LC-MS m/z: 358.14 $(M + 1)^+$.

2.4n *Isoxazoline **3eb***: Obtained as yellow oil from chalcone **1e** and oxime **2b**, IR (neat, cm^{-1}): 3186, 3052, 2981, 1680, 1623, 1231, 1196: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 3.53 (d, 8.4 Hz, 1H, C_4), 3.86 (s, 6H, OCH_3), 5.30 (d, 8.4 Hz, 1H, C_5), 6.80–8.07 (m, 13H, ArH), 9.10 (br, 1H, NH). ^{13}C–NMR (100 MHz, $CDCl_3$, rt): 43.92, 57.15, 81.76, 104.01, 114.67, 121.87, 125.09, 128.01, 128.37, 128.82, 130.72, 131.21, 135.11, 152.91, 155.03, 161.62, 162.91, 163.14, 198.04. Calcd. for $C_{24}H_{21}NO_4$: C74.40, H 5.46, N 3.62, found C 74.11, H 5.59, N 3.32. LC-MS m/z: 388.15 $(M + 1)^+$.

2.4o *Isoxazoline **3ec***: Obtained as brown oil from chalcone **1e** and oxime **2c**, IR (neat, cm^{-1}): 3213, 3066, 2974, 1681, 1611, 1228, 1184: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 3.55 (d, 8 Hz, 1H, C_4), 3.89–3.97 (2s, 9H, OCH_3), 5.55 (d, 8 Hz, 1H, C_5), 6.81–8.02 (m, 12H, ArH), 9.00 (s, 1H, NH).^{13}C–NMR (100 MHz, $CDCl_3$, rt): 46.49, 57.20, 87.13, 106.72, 113.55, 121.78, 125.61, 127.77, 128.23, 131.64, 134.52, 138.10, 148.13, 150.30, 155.28, 159.90, 160.76, 198.42. Anal. Calcd. for $C_{25}H_{23}NO_5$: C 71.93, H 5.55, N 3.36, found C 71.80, H 5.82, N 3.12. LC-MS m/z: 418.16 $(M + 1)^+$.

2.4p *Isoxazoline **3fa***: Obtained as brown oil from chalcone **1f** and oxime **2a**, IR (neat, cm^{-1}): 3194, 3057, 2982, 1673, 1625, 1288: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 2.97 (s, 6H, $N(CH_3)_2$), 3.43 (d, 8.2 Hz, 1H, C_4), 5.50 (d, 8.2 Hz, 1H, C_5), 7.27–8.24 (m, 14H, ArH), 10.03 (s, 1H, NH). ^{13}C–NMR (100 MHz, $CDCl_3$, rt): 41.16, 46.10, 83.55, 109.78, 114.51, 124.50, 127.71, 128.43, 128.64, 128.92, 130.11, 132.45, 133.63, 138.52, 149.32, 153.13, 158.50, 196.20. Anal. Calcd. for $C_{24}H_{22}N_2O_2$: C 77.81, H 5.99, N 7.56, found C 77.71, H 6.04, N 7.41. LC-MS m/z: 371.20 $(M + 1)^+$.

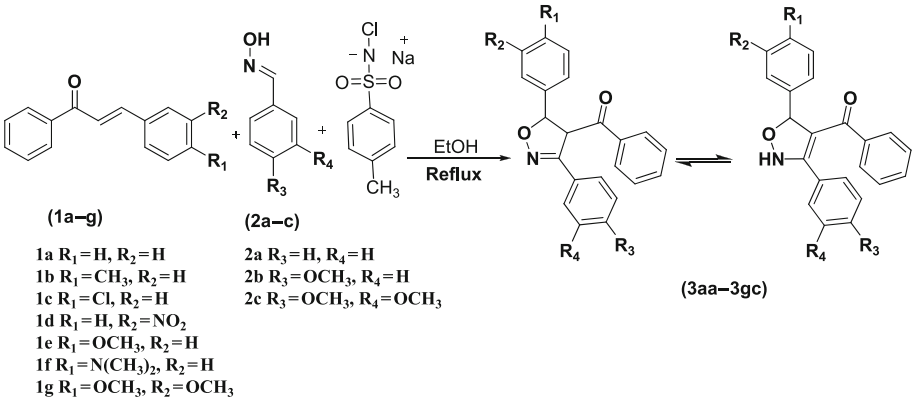
2.4q *Isoxazoline **3fb***: Obtained as yellow oil from chalcone **1f** and oxime **2b**, IR (neat, cm^{-1}): 3112, 3042, 2989, 1690, 1623, 1238, 1184: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 2.77 (s, 6H, $N(CH_3)_2$), 3.30 (d, 8 Hz, 1H, C_4), 3.79 (s, 3H, OCH_3), 5.63 (d, 8 Hz, 1H, C_5), 6.81–8.08 (m, 13H, ArH), 9.13 (br, 1H, NH). ^{13}C–NMR (100 MHz, $CDCl_3$, rt): 40.51, 45.83, 58.41, 85.13, 110.52, 115.12, 121.30, 127.71, 127.93, 128.21, 130.12, 132.21, 132.97, 138.43, 142.45, 154.73, 157.83, 164.11, 199.57. Anal. Calcd. for $C_{25}H_{24}N_2O_3$: C 74.98, H 6.04, N 7.00, found C 74.73, H 5.97, N 7.09. LC-MS m/z: 401.18 $(M + 1)^+$.

2.4r *Isoxazoline **3fc***: Obtained as yellow oil from chalcone **1f** and oxime **2c**, IR (neat, cm^{-1}): 3200, 3062, 2970, 1688, 1619, 1239, 1183: ^{1}H–NMR (400 MHz, $CDCl_3$), rt): δ 2.82 (s, 6H, $N(CH_3)_2$), 3.32 (d, 8.4 Hz, 1H, C_4), 3.85 (s, 6H, OCH_3), 5.43 (d, 8.4 Hz, 1H, C_5), 6.68–8.01 (m, 12H, ArH), 9.74 (s, 1H, NH). ^{13}C–NMR (100 MHz, $CDCl_3$, rt): 42.17, 45.61, 55.23, 86.64, 108.90, 112.20, 115.33, 125.84, 127.73, 128.36, 128.93, 130.44, 131.60, 138.13, 145.50, 148.87, 150.51, 154.73, 157.35, 194.78. Anal. Calcd. for $C_{26}H_{26}N_2O_4$: C 72.54, H 6.09, N 6.51, found C 72.44, H 6.15, N 6.44. LC-MS m/z: 431.19 $(M + 1)^+$.

2.4s *Isoxazoline **3ga***: Obtained as brown oil from chalcone **1g** and oxime **2a**, IR (neat, cm^{-1}): 3158, 3091, 2982, 1681, 1619, 1221, 1189: ^{1}H–NMR (400 MHz, $CDCl_3$, rt): δ 3.46 (d, 8.4 Hz, 1H, C_4), 3.87 (s, 6H, OCH_3), 5.50 (d, 8.4 Hz, 1H, C_5), 6.86–8.20 (m, 13H, ArH), 10.00 (s, 1H, NH),^{13}C–NMR (100 MHz, $CDCl_3$, rt): 45.70, 58.17, 85.48, 109.20, 114.20, 121.25, 128.74, 130.73, 132.19, 132.62, 133.07, 136.53, 144.97, 146.82, 152.80, 156.60, 199.06. Anal. Calcd. for $C_{24}H_{21}NO_4$: C 74.40, H 5.46, N 3.62, found : C 74.31, H 5.77, N 3.44. LC-MS m/z: 388.15 $(M + 1)^+$.

2.4t *Isoxazoline **3gb***: Obtained as yellow oil from chalcone **1g** and oxime **2b**, IR (neat, cm^{-1}): ^{1}H–NMR (400 MHz, $CDCl_3$): δ 3.42 (d, 8.4 Hz, 1H, C_4), 3.79 (s, 9H, OCH_3), 5.25 (d, 8.4 Hz, 1H, C_5), 6.88–8.02 (m, 12H, ArH), 9.12 (br, 1H, NH).^{13}C–NMR (100 Hz, $CDCl_3$, rt): 45.20, 58.90, 84.90, 108.10, 109.5, 112.60, 127.85, 128.00, 128.10, 129.16, 135.35, 136.52, 139.64, 152.30, 156.20, 159.8, 199.30. Anal. Calcd. for $C_{25}H_{23}NO_5$: C 71.93, H 5.55, N 3.36, found C 71.80, H 5.60, N 3.19. LC–MS m/z: 418.16 $(M + 1)^+$.

2.4u *Isoxazoline **3gc***: Obtained as yellow oil from chalcone **1g** and oxime **2c**, IR (neat, cm^{-1}): 3210, 3061, 2974, 1680, 1611, 1235, 1197: ^{1}H–NMR (400 MHz, $CDCl_3$): δ 3.28 (d, 8 Hz, 1H, C_4), 3.79 (s, 12H, OCH_3), 5.65 (d, 8 Hz, 1H, C_5), 6.88–8.02 (m, 11H, ArH), 9.02 (br, 1H, NH). ^{13}C–NMR (100 Hz, $CDCl_3$, rt): 45.06, 58.28, 84.95, 109.11, 115.78, 116.75, 125.61, 127.85, 128.77, 131.85, 133.49, 138.10, 141.16, 146.35, 147.52, 148.64, 152.40, 155.20, 199.21. Anal. Calcd. for $C_{26}H_{25}NO_6$: C 69.79, H 5.63, N 3.13, found C 69.70, H 5.90, N 3.10. LC-MS m/z: 448.17 $(M + 1)^+$.



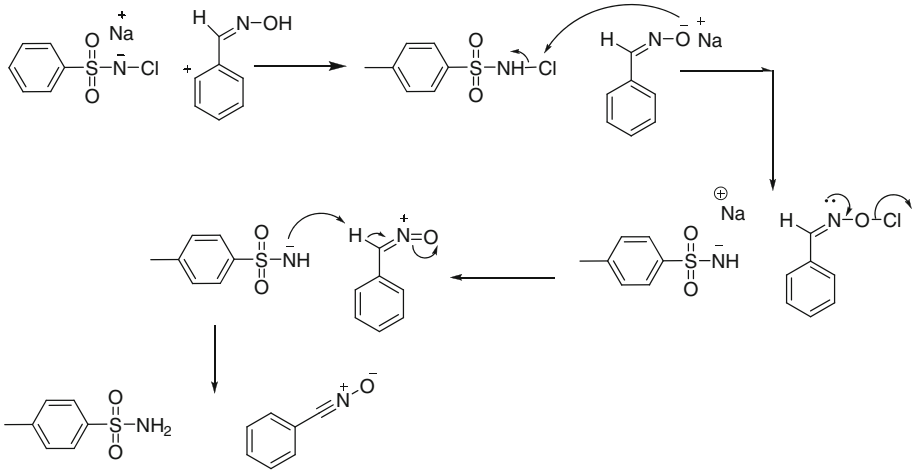
Scheme 1. General scheme for the synthesis of the 3,4,5-trisubstituted-dihydroisoxazoline derivatives.

3. Results and discussion

The reaction sequences for the synthesis of isoxazolines are shown in scheme 1. The desired chalcones (**1a–g**) were prepared in high yield by reacting the corresponding aromatic aldehydes compounds with acetophenone in the present of base.[21] On the other hand the desired aldoximes (**2a–c**) were prepared by reacting the corresponding aromatic aldehyde with hydroxylamine hydrochloride in the presence of sodium acetate.[22] The reaction of the chalcones (**1a–g**) with aldoximes (**2a–c**) in refluxing ethanol gave the respective isoxazolines (**3aa–gc**) 85–90% yields as shown in table 1.

On the basis of ^{1}H–NMR and ^{13}C–NMR spectra ($CDCl_3$, DMSO–d_6) the structures isolated products **3aa–gc** were assigned, therefore the probable mechanism for the formation of the products involves the oxidative dehydrogenation of aromatic aldoximes by chloramine–T affored nitrile oxides which were intercepted *in situ* by chalcones in refluxing ethanol to give the products **3aa–gc**. The products **3aa–gc** have been isolated as apparently pure, but on basis of their spectral ^{1}H–NMR and ^{13}C–NMR ($CDCl_3$) analyses, it is indicated there are two components exist as equilibrium of two tautomeric forms. This is because their ^{1}H–NMR spectra revealed, in each case, two characteristic doublet signals near δ 3.32–3.74 ppm and δ 5.14–5.85 ppm which assignable to the proton of C_4 and C_5 groups in isoxazoline, respectively.

The ^{13}C–NMR spectra at these products also in accordance with proposed structures, for example the ^{13}C–NMR spectra of these compounds revealed the signals at δ 104.01–110.30 ppm, δ 81–88.72 ppm and δ 152.10–155.28 ppm assignable to the C_4,C_5 and −C=N group of isoxazoline ring, respectively. Therefore, the ^{1}H–NMR and ^{13}C–NMR spectra of the products **3aa–gc** revealed that the products most probably exist as an equilibrium of two tautomeric form (I, II) as shown in scheme 1. A tentative mechanism for the generation of nitrile oxide has been proposed in scheme 2. However, the integration of the spectra indicated that the ratio of the most tautormeric form is (50%:50%). The characterization of the products **3aa–gc** by IR technique confirmed the proposed structures for example the IR



Scheme 2. Mechanism for the formation of nitrile oxides from aldoximes.

Table 1. The structure of compounds with their yields (**3aa–gc**).

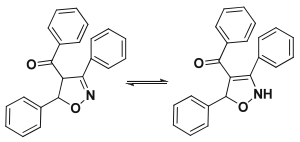
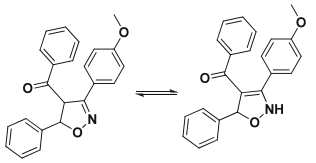
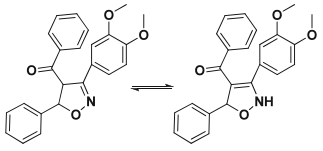
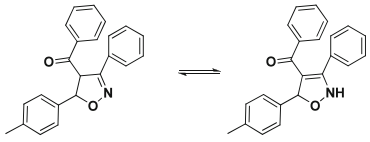
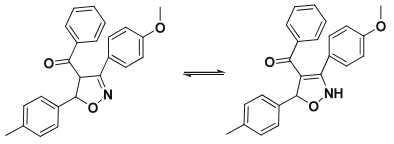
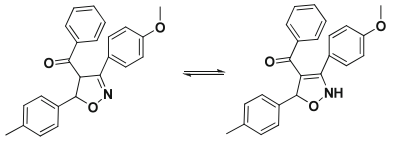
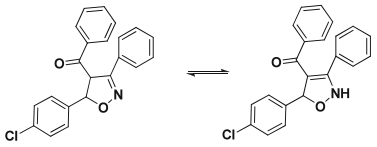
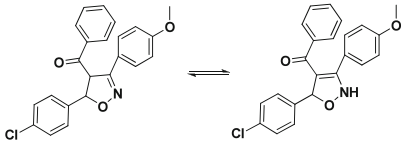
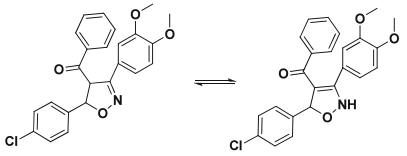
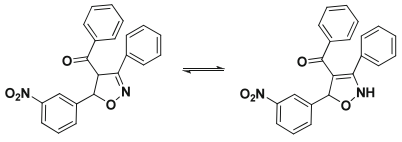
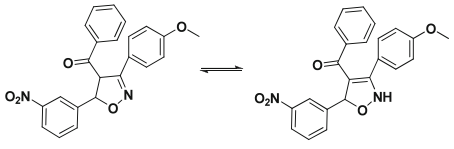
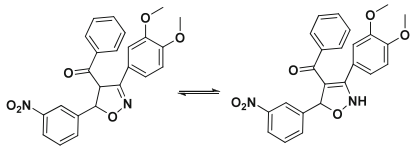
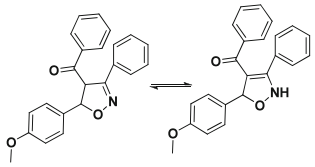
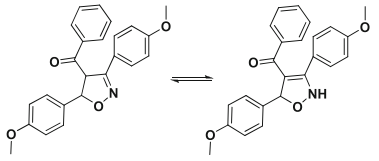
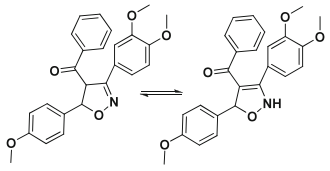
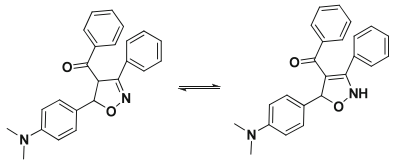
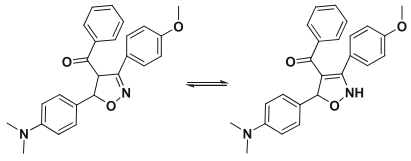
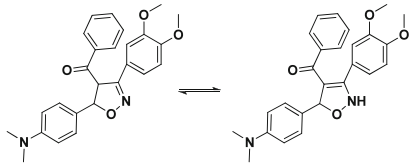
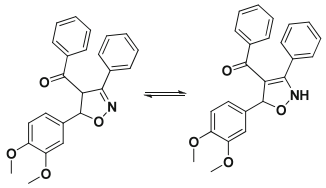
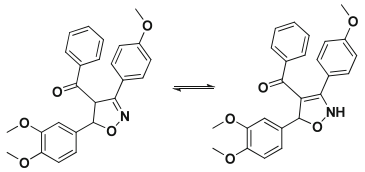
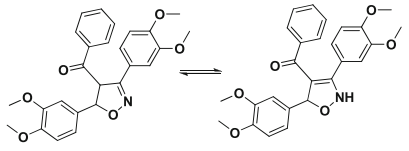
Compound	Compounds	Yield (%)
3aa		82.8
3ab		81.4
3ac		82.0
3ba		82.3
3bb		81.0
3bc		80.0
3ca		83.3
3cb		82.0
3cc		80.9
3da		86.4
3db		80.0

Table 1. *(continued).*

Compound	Compounds	Yield (%)
3dc		83.7
3ea		84.2
3eb		88.0
3ec		81.7
3fa		86.9
3fb		80.4
3fc		84.1
3ga		82.9
3gb		81.7
3gc		89.6

spectra of these compounds revealed new absorption peak at 3112–3218 cm^{-1}, 1660–1694 cm^{-1}, 1609–1628 and 1221–1288 cm^{-1} due to −NH, C=O, C=N and C–O–N stretching frequencies, respectively. Also the IR spectra of these products revealed the aromatic C=C and other substituent absorption at the expected regions.

4. Conclusion

In summary we have synthesized novel isoxazoline derivatives. The successful synthesis of new isoxazoline compounds follows a mild, efficient route with a good yield. It is known that nitrile oxides generated *in situ* react with alkenes and alkynes to give isoxazolines and isoxazoles, respectively. In this research work we synthesized novel isoxazolines by reacting aromatic aldoximes with chalcones (α, β-unsaturated carbonyl compounds). in the presence of chloramine–T which we wish to manipulate further.

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