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# Synthesis and Biological Activity of Some 3, 5-Diarylisoxazoline Derivatives: Reaction of Substituted Chalcones with Hydroxylamine Hydrochloride

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**Abstract:** A series of 3-aryl-5-styrylisoxazoline/ 3,5-diarylisoxazoline derivatives were synthesized by the reaction of appropriately substituted chalcones and hydroxylamine hydrochloride in presence of alkali in ethanol. The synthesized heterocycles have been characterized on the basis of their chemical properties and spectroscopic data. These compounds were tested for biological activity against a variety of test organisms.

**Keywords:** Chalcones, Hydroxylamine hydrochloride, 3,5-Diarylisoxazoline, 3-Aryl-5-styrylisoxazoline.

## Introduction

Among five membered heterocycles**,** isoxazoline represents a class of compounds of great importance in biological chemistry. For instance, isoxazoline posses biological activities[1-8] like insecticidal, antibacterial, antibiotic, antitumour, antifungal, antituberculosis, anti inflammatory and analgesic. Isoxazoline also serves as anti-influenza virus activity[9], inhibition of human leukocyte elastase and cathepsin G[10]. In fact, valdecoxib an isoxazoline derivative is now widely used in the market as anti-inflammatory drug[11]. Benzfuran isoxazolines serves as protein tyrosine phosphatase 1B inhibitors[12].

Some fluorinated methyliminobenzoxazolines and their derivatives have been patented as plant protecting acaricides, fungicides and insecticides[13]. Keeping in view the biological and medicinal importance of chalcones and isoxazolines, we have synthesized some isoxazolines starting from substituted 1,5-diaryl-2,4-pentadiene-1-one and hydroxylamine hydrochloride.

## Experimental

### *General procedures*

Melting points were determined by the open tube capillary method and are uncorrected. The purity of the compounds was controlled by thin layer chromatography (TLC). IR spectra were recorded as KBr pellets on Perkin-Elmer spectrum RX1 spectrophotometer. Carbon, hydrogen and nitrogen were estimated by Thermo Finnigan FLASH EA 1112 elemental analyzer. Mass spectra were measured on JEOL SX 102/DA-6000 mass spectrometer**.** 3,5-Diarylisoxazoline derivatives were prepared according to the reported methods.

### *Synthesis of 1,5-diaryl-2,4-pentadiene-1-one* **(1)**

To a mixture of acetophenone (8.12 mL) and cinnamaldehyde (8.8 mL) in ethanol (110 mL) a solution of NaOH (10 g in 20 mL of water) was added. The reaction mixture was stirred for 4 h and then kept over night at room temperature. After cooling in ice, the reaction mixture was acidified with aqueous HCl (10%). The resulting precipitate was washed with distilled water and dried. The resulting crude was crystallized from ethanol to obtained yellow crystalline product.

### *Synthesis of 3-aryl-5-styrylisoxazoline* **(1a)**

To a mixture of 1,5-diaryl-2,4-pentadiene-1-one (1 g) and hydroxylamine hydrochloride (0.5 g in 5 mL water) in ethanol (25 mL) a solution of sodium hydroxide (1.1 g in 10 mL water) was added. The reaction mixture was refluxed for 4 h. It was allowed to cool at room temperature and then kept overnight in the freezer. A white crystalline solid separated. It was filtered, washed with distilled water and dried. The product was crystallized from ethanol to afford white crystals.

### *Synthesis of 1-(4'-chlorophenyl)-5-phenyl-2,4-pentadiene-1-one* **(2)**

To a mixture of *p*-chloroacetophenone (9.03 mL) and cinnamaldehyde (8.82 mL) in ethanol (110 mL) a solution of NaOH (10 g in 20 mL water) was added. The reaction mixture was stirred for 4 h. It was then kept overnight at room temperature. After cooling in ice, the reaction mixture was acidified with aqueous HCl (10%). The resulting yellow solid was filtered, washed well with distilled water and dried. The product on crystallization from ethanol afforded yellow needles.

### *Synthesis of 3-(4'-chlorophenyl)-5-styrylisoxazoline* **(2a)**

To a mixture of 1-(4**'**-chlorophenyl)-5-phenyl-2,4-pentadiene-1-one (1 g) and hydroxylamine hydrochloride (0.5 g in 5 mL water ) in ethanol (25 mL) a solution of sodium hydroxide (1.1 g in 10 mL water) was added. The reaction mixture was refluxed for 4 h. It was allowed to cool to room temperature and then kept overnight in freezer. A white crystalline solid separated. It was filtered, washed with distilled water and dried. The product was crystallized from ethanol to afford white crystal.

### *Synthesis of 1-(4'-methylphenyl)-5-phenyl-2,4-pentadiene-1-one* **(3)**

To a mixture of *p*-methylacetophenone (9.31 mL) and cinnamaldehyde (8.82 mL) in ethanol (110 mL) a solution of NaOH (10 g in 20 mL water) was added. The reaction mixture was stirred for 4 h. It was then kept overnight at room temperature. After cooling in ice, the reaction mixture was acidified with aqueous HCl (10%). The resulting yellow solid was filtered, washed well with distilled water and dried. The product on crystallization from ethanol afforded yellow needles.

*Synthesis of 3-(4'-methylphenyl)-5-styrylisoxazoline* **(3a)**

To a mixture of 1-(4'-methylphenyl)-5-phenyl-2,4-pentadiene-1-one (1 g) and hydroxylamine hydrochloride (0.5 g in 5 mL water ) in ethanol (25 mL) a solution of sodium hydroxide (1.1 g in 10 mL water) was added. The reaction mixture was refluxed for 4 h. It was allowed to cool to room temperature and then kept overnight in freezer. A white crystalline solid separated. It was filtered, washed with distilled water and dried. The product was crystallized from ethanol to afford white crystal.

*Synthesis of 3-(4'-methoxyphenyl)-5-phenyl-2,4-pentadiene-1-one* **(4)**

To a mixture of *p*-methylacetophenone (10.55 mL) and cinnamaldehyde (8.8 mL) in ethanol (110 mL) a solution of NaOH (10 g in 20 mL water) was added. The reaction mixture was stirred for 4 h. It was then kept overnight at room temperature. After cooling in ice, the reaction mixture was acidified with aqueous HCl (10%). The resulting yellow solid was filtered, washed well with distilled water and dried. The product on crystallization from ethanol afforded yellow needles.

*Synthesis of 3-(4'-methoxyphenyl)-5-styrylisoxazoline* **(4a)**

To a mixture of 1-(4'-methoxyphenyl)-5-phenyl-2,4-pentadiene-1-one (1g) and hydroxylamine hydrochloride (0.5 g in 5 mL water) in ethanol (25 mL) a solution of sodium hydroxide (1.1 g in 10 mL water) was added. The reaction mixture was refluxed for 4 h. It was allowed to cool to room temperature and then kept overnight in freeze. A white crystalline solid separated. It was filtered, washed with distilled water and dried. The product was crystallized from ethanol to afford white crystal.

*Synthesis of 3-phenyl-5-(2-hydroxyphenyl) isoxazoline* **(5)**

To a mixture of 2-hydroxychalcone (2 g) and hydroxylamine hydrochloride (1 g in 10 mL water) in ethanol (110 mL) a solution of NaOH (10 g in 20 mL of water) was added in ethanol (50 mL) .The reaction mixture was refluxed for 4 h and then kept over night at room temperature. After cooling in ice, the reaction mixture was acidified with aqueous HCl (10%). The resulting precipitate was washed with distilled water and dried. The resulting crude was crystallized from ethanol to obtained white crystalline product.

*Synthesis of 3-(4'-methylphenyl)-5-(2-hydroxyphenyl) isoxazoline* **(6)**

To a mixture of 2-hydroxy-4'-methoxychalcone (2 g) and hydroxylamine hydrochloride (1 g in 10 mL water) in ethanol (110 mL) a solution of NaOH (10 g in 20 mL of water) in ethanol (50 mL) was added.The reaction mixture was refluxed for 4 h and then kept over night at room temperature. After cooling in ice, the reaction mixture was acidified with aqueous HCl (10%). The resulting precipitate was washed with distilled water and dried. The resulting crude was crystallized from ethanol to obtained white crystalline product.

*1,5-Diaryl-2,4-pentadiene-1-one* **(1)**

Compound (**1**) was obtained as yellow crystals in 85% yield, m.p. 99-100 °C; IR, $\upsilon_{max}$: 3200, 2920, 1650, 1600, 1590, 1580, 1540, 1350, 1290, 1250, 1200, 1100, 1030, 1000, 820, 760 ,730, 690, 6000 and 480 $cm^{-1}$; MS, m/z: 234, 233, 157, 131, 103, 77. Anal. Calcd. for $C_{17}H_{14}O$: C, 87.17; H, 5.98, Found: C, 87.20; H, 5.88%.

*3-Aryl-5-styrylisoxazoline* **(1a)**

Compound (**1a**) was obtained as white crystals in 80% yield, m.p. 171-172 °C; IR, $\upsilon_{max}$: 3200, 2900, 1610, 1580, 1560,1500, 1440, 1410, 1360, 1260, 1060, 990, 960, 930, 760, 750, 700 and 580 $cm^{-1}$; MS, m/z: 249, 248, 172, 171, 146,103, 77, 69. Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.88; H, 6.02; N, 5.66, Found: C, 81.88; H, 6.02; N, 5.62;%.

*1-(4'-Chlorophenyl)-5-phenyl-2,4-pentadiene-1-one* **(2)**

Compound (**2**) was obtained as yellow crystals in 75% yield, m.p. 139-140 °C; IR, $\upsilon_{max}$: 3010, 2910, 1650,1590, 1580,1570,1450, 1400, 1350, 1290, 1260, 1200, 1150, 1100, 1030, 1015, 990, 820, 730, 690, 670 and 480 $cm^{-1}$; MS, m/z: 268, 267, 232, 190, 178, 166, 152, 112, 76. Anal. Calcd. for $C_{17}H_{13}ClO$: C, 75.58; H, 4.83 Found: C, 76.28; H, 4.29%.

*3-(4'-Chlorophenyl)-5-styrylisoxazoline* **(2a)**

Compound (**2a**) was obtained as white crystals in 78% yield, m.p.173-174 °C; IR, $\upsilon_{max}$:3020, 2930, 1610, 1590, 1550, 1530, 1490,1450, 1420, 1400, 1380, 1350, 1260, 1100, 1010, 980, 910, 860, 840, 820, 750, 690, 550, 530, 500 and 450 $cm^{1}$**;** MS, m/z:286, 285, 250, 209, 183, 173, 148, 114, 79, 78, 71**.** Anal. Calcd. for $C_{17}H_{14}ClNO$: C, 71.32; H, 4.89; N, 4.89. Found: C, 71.36; H, 4.78; N, 4.92%.

*1-(4'-Methylphenyl)-5-phenyl-2,4-pentadiene-1-one* **(3)**

Compound (**3**) was obtained as yellow crystals in 71% yield, m.p. 88-89 °C; IR, $\upsilon_{max}$:3020, 2920, 1650, 1600, 1580, 1560, 1450, 1350, 1290, 1260, 1190, 1160, 1120, 1030, 1020, 1000, 940, 880, 750, 730,, 690 and 600 $cm^{-1}$; MS, m/z: 248, 247, 233, 179, 171, 153, 145, 102, 91, 76. Anal. Calcd. for $C_{18}H_{16}O$: C, 87.09; H, 6.45; N. Found: C, 87.13; H, 6.43%.

*3-(4'-Methylphenyl)-5-styrylisoxazoline* **(3a)**

Compound (**3a**) was obtained as white crystals in 65% yield, m.p. 138-139 °C; IR, $\upsilon_{max}$:3020, 2920, 1610, 1600, 1580, 1560, 1510, 1510, 1490, 1450, 1430, 1390, 1350, 1260, 1190, 180, 980, 950, 910, 830, 810, 750, 700, 620, 550, 530 and 460 $cm^{-1}$; MS, m/z: 261, 260, 246, 184, 169, 158, 143, 92, 89, 74,66. Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.13; H, 6.46; N, 5.32 Found: C, 82.66; H, 5.79; N, 5.36%.

*3-(4'-Methoxyphenyl)-5-phenyl-2, 4-pentadiene-1-one* **(4)**

Compound (**4**) was obtained as yellow crystals in 76% yield, m.p. 83-84 °C; IR, $\upsilon_{max}$:3020, 2940, 1650, 1600, 1590, 1510, 1450, 1420, 1360, 1310, 1290, 1260, 1175, 1120, 1030, 1010, 960, 820, 760, 740, 690, 640, 600 and 510 $cm^{-1}$; MS, m/z: 264, 263, 233, 187, 179, 161, 153, 107, 102,76. Anal. Calcd. for $C_{18}H_{17}O_2$: C, 81.81; H, 6.06; Found: C, 81.83; H, 6.09%.

*3-(4'-Methoxyphenyl)-5-styrylisoxazoline* **(4a)**

Compound (**4a**) was obtained as white crystals in 72% yield, m.p. 109-110 °C; IR, $\upsilon_{max}$:3020, 2930, 1610, 1590, 1560, 1515, 1490, 1450, 1430, 1350, 1260, 1180, 1120, 1040, 1030, 980, 910, 835, 750, 700, 620 and 550 $cm^{-1}$; MS, m/z: 239, 238, 208, 162, 136, 131, 67, 62, 54, 36, 28. Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.42; H, 6.09; N,5.02. Found: 77.88; H, 5.46; N, 5.05%.

*3-Phenyl-5-(2-hydroxyphenyl) isoxazoline* **(5)**

Compound (**5**) was obtained as white crystals in 65% yield, m.p. 149-150 °C; IR $\upsilon_{max}$: 3200 (-OH stretching vibration) 1610, 1590, 1570, 1500, 1460, 1450, 1360, 1290, 1270, 1190, 1170, 1110, 1050, 1000, 960, 935, 875, 840, 765, 750, 690, 610, 530 and 480 $cm^{-1}$; MS, m/z:239, 238, 222, 162, 153, 143, 93, 76, 68. Anal. Calcd. For $C_{15}H_{13}NO_2$: C, 75.31; H, 5.43; N, 5.85. Found: C, 75.29; H, 5.46; N, 5.92%.

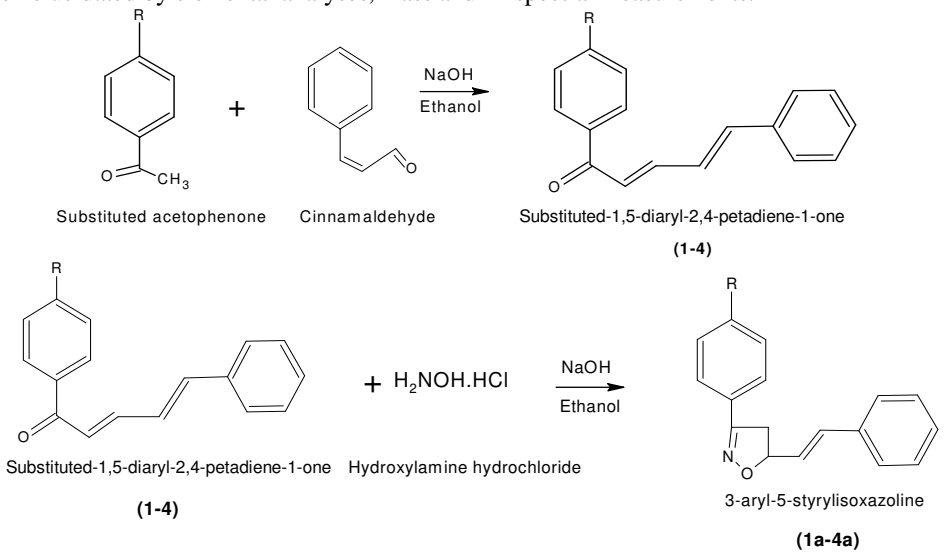
*3-(4'-Methylphenyl)-5-(2-hydroxyphenyl) isoxazoline* **(6)**

Compound (**6**) was obtained as white crystals in 75% yield, m.p. 138-139 °C; IR, $\upsilon_{max}$: 3200 (-OH stretching vibration) 1610, 1590, 1570, 1500, 1460, 1450, 1360, 1290, 1260, 1180, 1155, 1110, 1085, 1050, 980, 960, 935, 920, 875, 840, 765, 750, 690, 610, 530 and 480 $cm^{-1}$;

MS, m/z:253, 252, 238, 236, 161, 159, 144, 90, 75, 67, 58. Anal. Calcd. For $C_{16}H_{15}NO_2$: C, 75.88; H, 5.92; N, 5.53. Found: C, 75.86; H, 5.92; N, 5.55%.

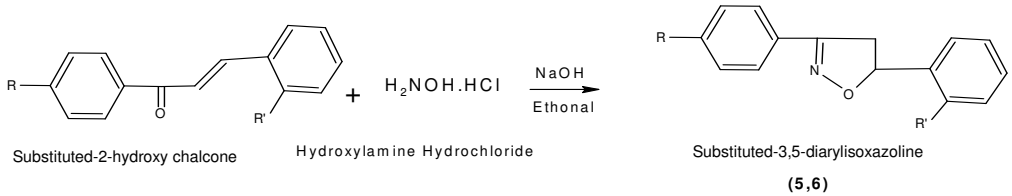
## Results and Discussion

Keeping in view the biological activity and medicinal importance of chalcones and isoxazolines, we synthesized some isoxazolines starting from substituted 1,5-diaryl-2,4-pentadiene-1-ones and hydroxylamine hydrochloride. Substituted 1,5-diaryl-2,4-pentadiene-1-ones **(1-4)** have been prepared by variedly substituted acetophenones and cinnamaldehyde by Claisen-Schmidt condensation. These substituted 1,5-diaryl-2,4-pentadiene-1-ones and substituted 2-hydroxychalcones were refluxed with hydroxylamine hydrochloride in presence of alkali in ethanol for 4 h to afford the corresponding 3-aryl-5-styrylisoxazoline (**1a-4a)** (Scheme 1) and 3,5-diarylisoxazolines **(5,6)**(Scheme 2) respectively. The structures of all new compounds have been elucidated by elemental analyses, mass and IR spectral measurements.




**1,1a**: R=H; **2,2a**: R=Cl; **3,3a**: R=$CH_3$; **4,4a**: R= $OCH_3$

**Scheme 1**. Synthesis of substituted 1,5-diaryl-2,4-pentadiene-1-ones and 3-aryl-5-styrylisoxazoline derivatives.




**5:** R=H; R'=OH, **6:**= R=$CH_3$; R'=OH

**Scheme 2**. Synthesis of substituted-3,5-diarylisoxazoline derivatives

IR spectra of 1,5-diaryl-2,4-pentadiene-1-ones give absorption peak at 1650 $cm^{-1}$ due to C=O group, this lowering in frequency is due to extended conjugation. A group of three bands were found in the region 1600-1500 $cm^{-1}$. This is due to the absorption of aromatic nucleus and olefinic double bond. The IR spectra of isoxazolines show no carbonyl absorption peaks at 1610 $cm^{-1}$ and 1260 $cm^{-1}$ due to C= N and C–O–N stretching frequencies respectively.

## *Biological activity*

The synthesized 3-aryl-5-styrylisoxazoline (**1a-4a)** and 3,5-diarylisoxazolines **(5, 6)** have been subjected to *in vitro* antimicrobial activity against various plant and human pathogenic bacteria and fungi. Antimicrobial activity was carried out against gram positive coccus *Staphylococcus aureus*, *Micrococcus luteus*, gram positive rod *Bacillus megatherium* and gram negative rod *Pseudomonas aeruginosa*, *Proteus vulgaris* and *Klebsiella pneumoniae*. *Candida albicans*, *Saccharomyces cerevisiae* yeast fungus and *Aspergillus niger*, *Penicillium notatum* soil fungi were used for microbial activity. The results are summarized in the Table 1.

**Table 1.** Antimicrobial activity of 3-aryl-5-styrylisoxazoline and 3,5-diarylisoxazoline derivatives.

| Compd. No. | Culture | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | E | F | G | H | I | J |
| **1** | 3 | 6 | | | | | | 4 | | |
| **1a** | 4 | | 5 | | | | | 5 | 2 | 2 |
| **2** | 3 | | | | | | | 4 | | |
| **2a** | 4 | 5 | | | | | | 5 | 2 | |
| **3** | 10 | 5 | 2 | 3 | 2 | | 9 | 7 | 7 | 3 |
| **3a** | 10 | 5 | 3 | 3 | 3 | | | 5 | 8 | 5 |
| **4** | | 5 | | | | | | 4 | | |
| **4a** | | | 2 | | | | | 5 | 2 | |
| **5** | 7 | 5 | 5 | 4 | | 4 | 10 | 3 | 10 | 2 |
| **6** | 6 | 6 | 4 | 5 | | 5 | 8 | 5 | 10 | 3 |

(Diameter of inhibition zone measured in mm, paper disc 5 mm, inhibition zone measured excluding paper disc diameter)

A= *Staphylococcus aureus;* B= *Micrococcus luteus;* C= *Bacillus megatherium;*
D= *Pseudomonas aeruginosa;* E= *Proteus vulgaris;* F= *Klebsiella pneumoniae;*
G= *Aspergillus niger;* H= *Penicillium notatum;* I= *Candida albicans;*
J= *Saccharomyces cerevisiae.*

It can be concluded from the observation that, these substituted 3-aryl-5-styrylisoxazoline (**1a-4a)** and 3,5-diarylisoxazolines **(5, 6)** possess moderate antimicrobial and antifungal activity. The larger inhibition growth was observed when all the compounds were tested against gram positive coccus *Staphylococcus aureus* and soil fungi *Penicillium notatum*. However, moderate inhibition growth was observed when all the compounds were tested with *Micrococcus luteus*, *Candida albicans* and *Saccharomyces cerevisiae*. The compounds were found to be inactive against gram negative bacteria *Pseudomonas aeruginosa*, *Proteus vulgaris* and *Klebsiella pneumoniae.*

In conclusion, we have synthesized a systematically substituted series of new 3-aryl-5-styrylisoxazoline (**1a-4a)** and 3,5-diarylisoxazolines **(5, 6)** derivatives for structure-activity relationship studies. These substituted derivatives are very stable compounds, which renders them beneficial substances for biological or pharmacological trials.

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## References


1. Huisgen R, *Angew Chem Int Ed Engl*., 1963, **2**, 565.
2. Caramella P and Grunanger P, In 1,3-Dipolar Cycloaddition Chemistry, Padwa A, Ed.; Wiley-Interscience, New York, 1984, **1**, 337.
3. Barot V M , *Oriental J Chem*., 2000, **16**, 177.
4. Ankhiwala M D and Hathi M V, *J Indian Chem Soc.*, 1994, **71**, 587.
5. Kedar R M , Vidhale N N and Chincholkar M M , *Oriental J Chem.*, 1996, **12**, 301.
6. Kedar R M, *Oriental J. Chem.*, 1997, **13**, 143.
7. Tangallapally R P, Sun D, Rakesh, Budha N, Lee R E B, Lenaerts A J M, Meibohm B, Lee R E, *Bioorg Med Chem Lett*., 2007, **17(23**), 6638.
8. Habeeb A G, Praveen Rao P N and Knaus E E**,** *J Med Chem.*, 2001**, 44(18)**, 2921.
9. Hiroyuki K, Hiroshi M, Naohiko H, Akira T, Tamio F and Hirohiko S, *Bioorg Med Chem Lett*., 2001, **11(15)**, 1997.
10. Groutas W C, Chang L S, Epp J B, Venkataraman R, Brubaker M J, Stanga M A, Kim Eun-Hong and Keller C E, *Bioorg Med Chem Lett*., 1992, **2**, 1571.
11. Dannahardt G, Kiefer W, Kramer G, Maehrlein S, Nowe U and Fiebich B. *Eur J Med Chem*., 2000, **35**, 499.
12. Ahmad G, Mishra P K, Gupta P, Yadav P P, Tiwari P, Tamrakar A K, Srivastava A K and Maurya R, *Bioorg Med Chem Lett*., 2006, **16(8)**, 2139.
13. Buethner G, Klonke E, Frohberger E P and Hammann I, *Ger Patent*, 221832g, 1973, *Chem. Abstr.,*1974, **86**, 14912.