# The Reaction of 2-Aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes And Hydroxylamine Hydrochloride: Facile Synthesis of Differently Substituted Isoxazoles



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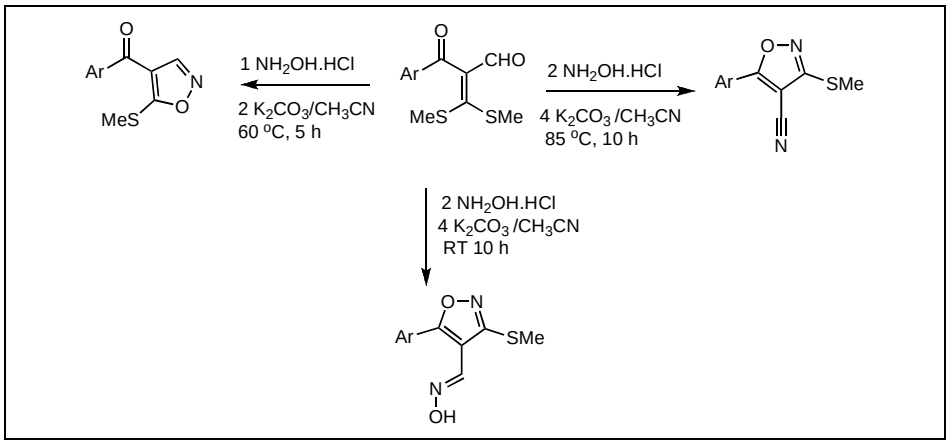


2-Aroyl-3,3-bis(alkylsulfanyl)acrylaldehyde was utilized for the synthesis of three different isoxazoles by reacting with hydroxylaminehydrochloride. We synthesized differently substituted isoxazoles like (aryl)[5-(methylsulfanyl)-4-isoxazolyl]methanones, 3-(methylsulfanyl)-5-phenyl-4-isoxazolecarbonitriles and 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oximes in good yields by varying the substrate-reagent stoichiometry and temperature of the reaction medium.

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## INTRODUCTION

Isoxazoles are a class of heterocyclic compounds having a remarkable number of applications and have been demonstrated to be very versatile building blocks in organic synthesis [1]. The biological activities of substituted isoxazoles have made them a focus of medicinal chemistry over the years. They are used as potent drugs in a number of medicinal fields [2]. Some isoxazole derivatives display agrochemical properties, namely herbicidal and soil fungicidal activity and have applications as pesticides and insecticides [3]. Isoxazoles have also been used as dyes, electric insulating oils, high temperature lubricants *etc*., while polyisoxazoles have applications as semicondutors [4].

The construction of the isoxazole ring can be achieved by either 1,3-dipolar cycloaddition of alkenes and alkynes with nitrile oxide or by the reaction of hydroxylamine with a three-carbon atom component [5]. Junjappa *et al* have investigated in detail the reaction of hydroxylamine with α-oxoketene dithioacetals using different reaction conditions to afford alkylthio isoxazoles in high yields [6].

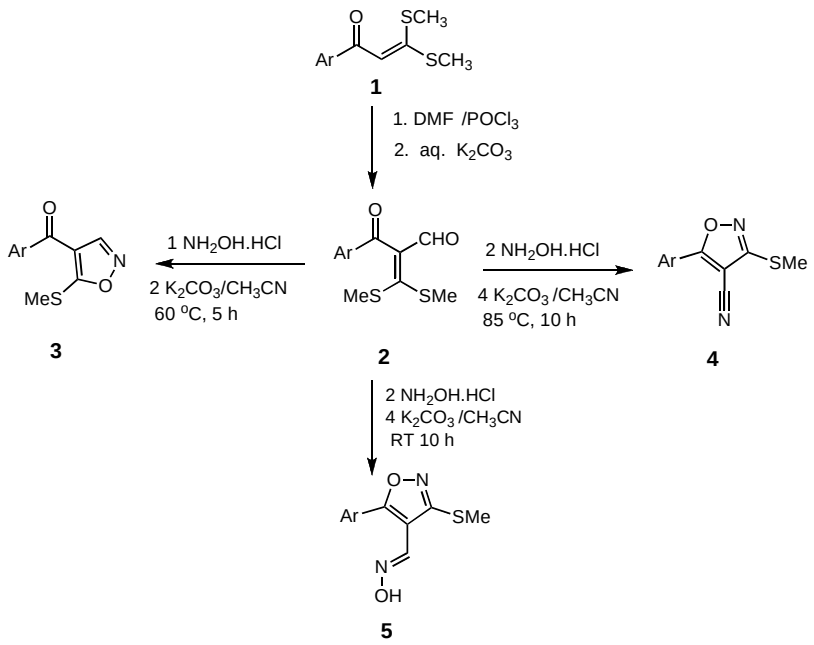
Earlier we had reported the synthesis of 2-aroyl-3,3-bis(alkylsulfanyl) acrylaldehydes from α-oxoketene dithioacetals [7]. During the course of our studies directed towards exploring the synthetic potential of 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes [8], we set out to study the reaction of asymmetric bifunctional heteronucleophiles like hydroxylamine with 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes in order to synthesize isoxazoles.

## RESULTS AND DISCUSSION

Recently isoxazoles are used for chemical attachment on semiconductor surfaces, which exhibit promising applications in a wide spectrum of technological areas [9]. Moreover it was proved that 5-alkylthioisoxazoles have anthelmintic activity [10]. Therefore synthesis of isoxazoles with potential functional groups, which can act as intermediates for further transformations or can attach to semiconductors, will be of prime importance. We expected that 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes **2**, with different functional groups could afford a variety of isoxazoles which could have promising applications. Thus varying the substrate-reagent stoichiometry and

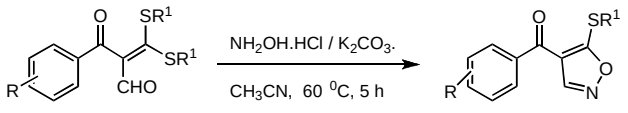
temperature of the reaction medium we synthesized three different isoxazoles, (aryl)[5-(methylsulfanyl)-4-isoxazolyl]methanones (**3**), 3-(methyl sulfanyl)-5-phenyl-4-isoxazolecarbonitriles (**4**) and 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oximes (**5**) in good yields by the reaction of 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes **2** and hydroxylamine (Scheme 1).

**Scheme 1**




**Synthesis of (aryl)[5-(methylsulfanyl)-4-isoxazolyl]-methanones (3).** For the synthesis of (aryl)[5-(methylsulfanyl)-4-isoxazolyl]methanones **3**, we treated 2-benzoyl-3,3-bis(alkylsulfanyl)acrylaldehyde **2** with one equivalent of hydroxylamine hydrochloride in the presence of 2 equivalents of $K_2CO_3$ in acetonitrile . The reaction mixture was heated at 60 ℃ for 5 h. The reaction was extended to other substituted acrylaldehydes to get the corresponding isoxazoles in 60 - 90% yields (Scheme 2). The structure of the reaction products **3a-f** were established and confirmed by their elemental analyses and spectral data (MS, IR, $^1$H NMR, $^{13}$C NMR).

**Scheme 2**



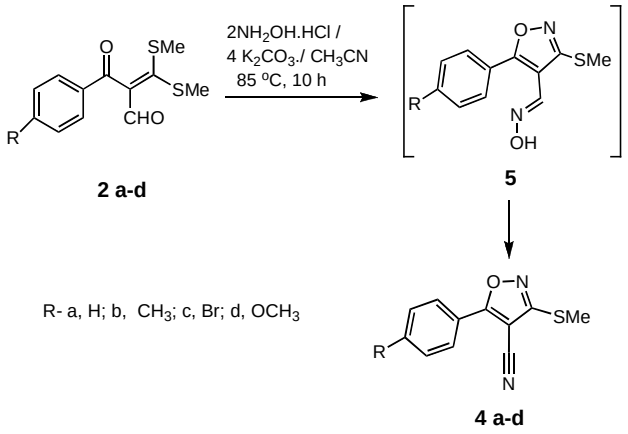

R - a, 4-Cl; b, 4-$OCH_3$; c, 3-$OCH_3$; d, 3, 4-$(OCH_3)_2$; e, 4-H; f , 4-H.
$R^1$- (a-e) , Me and f , $PhCH_2$

The above reaction could be explained as follows. When 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes **2** were treated with one equivalent of hydroxylamine hydrochloride at 60 ℃, the amino group on the hydroxylamine reacted with the more reactive aldehyde group to form the corresponding aldoxime intermediate. An intramolecular conjugate addition reaction of the hydroxyl group on the aldoxime to the ketene dithioacetal moiety, followed by the elimination of an alkylsulfanyl group resulted in the formation of the expected (aryl)[5-(methyl/arylsulfanyl)-4-isoxazolyl]methanones **3** [11].

**Synthesis of 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbonitriles (4).** The reaction of 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes **2** with 2 equivalents of hydroxylamine hydrochloride in acetonitrile at 85 ℃ for 10 h afforded 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbonitriles. We were curious to know whether both the carbonyl groups would be involve in the reaction leading to the formation of isoxazoloisoxazoles. Although both the carbonyl groups in the acrylaldehydes were reactive towards hydroxylamine the product formed suggested that the after the aldoxime formation, N,S-acetal intermediate was formed by a second molecule of hydroxylamine. This intermediate underwent cyclisation reaction with the second carbonyl group producing an isoxazolealdoxime **5**. This isoxazolealdoxime eliminated a water molecule at 85 ℃ to afford 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbonitriles **4** in 30 - 56% yields (Scheme 3). The structure of the reaction products **4b-d** were established and confirmed by their elemental analyses and spectral data

(MS, IR, $^1$H NMR, $^{13}$C NMR). Compound **4a** was reported by Rudorf *et al* and its melting point was compared with the reported value [11d].

**Scheme 3**




**Synthesis of 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oximes (5).** In order to get the expected isoxazoloisoxazoles in the above reaction we have to prevent the dehydration reaction of the intermediate oxime **5**. So the 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes **2** were treated with **2** equivalents of hydroxylamine hydrochloride in the presence of potassium carbonate in acetonitrile at room temperature for 10 h. The reaction afforded only 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbaldehydeoximes **5** in 40 - 54% yields and still no isoxaloisoxazoles were obtained (Scheme 4). Mechanism proposed in the synthesis of isoxazolecarbonitrile **4** was further proved by the isolation of 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbaldehydeoximes **5** in this reaction which was carried out at room temperature. The structure of the reaction products **5a-d** were established and confirmed by their elemental analyses and spectral data (MS, IR, $^1$H NMR, $^{13}$C NMR). Thermal cyclisation might enhance the conversion of **5** to isoxazoloisoxazole by the alkanethiol elimination and number of new heterocycles had been reported starting from oximes [12]. Therefore compound **5** could be a starting material for number of new compounds.

To summarize, we have accomplished the synthesis of three different isoxazoles starting from a single compound by varying the substrate-reagent stoichiometry and temperature of the reaction medium. Due to the potential functional groups present in the new isoxazoles, they could have been precursors for a variety of annulated heterocycles having promising applications especially as agrochemicals or as industrially useful compounds.

## EXPERIMENTAL

**General.** Melting points were determined on Buchi 530 melting point apparatus and were uncorrected. The IR spectra were recorded on KBr pellets using a Schimadzu IR-470 spectrometer and the frequencies are reported in cm$^{-1}$. The $^1$H NMR and $^{13}$C NMR spectra were recorded on (300 MHz and 75 MHz spectrometer) using TMS as internal standard and $CDCl_3$ or acetone-$d_6$ as solvents. The CHN analyses were done on an Elementar Vario EL III Serial Number 11042022 instrument. The FAB mass spectra were recorded on a JOEL SX 102/DA-6000 Mass Spectrometer/Data System using Argon as the FAB gas. The EIMS spectra were recorded on a MICROMASS QUATTRO 11 triple quadrupole mass spectrometer.

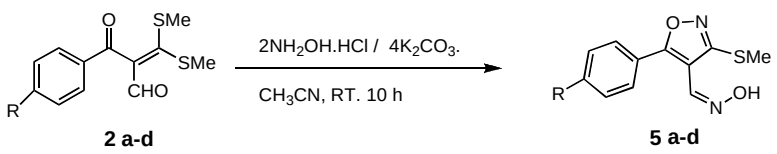
All commercially available reagents were purified before use. The aroylketene dithioacetals and α-formylketene dithioacetals were prepared by known procedure [1,13]. Anhydrous sodium sulfate was used as drying agent. All purified compounds gave a single spot upon TLC analyses on silica gel 7GF using an ethyl acetate/hexane mixture as eluent. Iodine vapors or $KMnO_4$ solution in water was used as developing agent for TLC.

### Synthesis of (Aryl)[5-(methylsulfanyl)-4-isoxazolyl]methanones from 2-aroyl-3,3-bis(alkylsulfanyl) acrylaldehydes (3).

**General Procedure.** 2-Aroyl-3,3-bis(alkylsulfanyl)acrylaldehyde **2** (0.5 g, 2 mmol) was dissolved in acetonitrile (20 mL) at room temperature. To the above solution hydroxylamine hydrochloride (0.14 g, 2 mmol) followed by $K_2CO_3$ (0.55 g, 4 mmol) were added and the reaction mixture was heated to 60 ºC for 5 h. It was cooled and poured into ice-cold water. The semisolid obtained was extracted using ethyl acetate (3 X 25 mL), dried with anhydrous sodium sulfate and purified using column chromatography on silica gel with hexane as the eluent. Recrystallised from hexane/ethyl acetate (4:1) solution.

**(4-Chlorophenyl)[5-methylsulfanyl)-4-isoxazolyl]methanone 3a.** Yield 70% (0.35 g); White solid; mp 98 ºC; IR (KBr $\nu_{max}$) 1674, 1550, 1362 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ = 2.47 (s, 3H, $SCH_3$), 7.45 - 7.5 (m, 2H, ArH), 8.02 - 8.06 (m, 2H, ArH), 8.69 (s, 1H, 3CH isoxazole); $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 11.9 ($SCH_3$), 115.7 (4C isoxazole), 124.4 (4C ArH), 129.3 (3, 3'C ArH), 130.2 (2, 2' C ArH), 138.0 (1C ArH), 150.6 (3C isoxazole), 168.0 (5C isoxazole), 184.1 (=CO); FABMS: m/z (%) 254 (100), 206 (65), 165 (5), 107 (5); *Anal:* $C_{11}H_8ClNO_2S$

**Scheme 4**




R- a, H; b, Br; c, 4-$OCH_3$; d, $CH_3$

(253.71) Calcd: C, 52.08; H, 3.18; N, 5.52; S, 12.61; Found: C, 52.3; H, 3.12; N, 5.58, S; 12.69.

**(4-Methoxyphenyl)[5-methylsulfanyl)-4-isoxazolyl]-methanone 3b.** Yield 70% (0.35 g); white solid; mp 100 °C; IR (KBr $\nu_{max}$) 1658, 1608, 1515, 1263 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ = 2.41 (s, 3H, $SCH_3$), 3.78 (s, 3H, OMe), 6.93 (d, J = 9 Hz, 2H, ArH), 8.02 (d, J = 9Hz, 2H, ArH), 8.58 (s, 1H, 3CH isoxazole proton); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 11.7 ($SCH_3$), 55.3 (OMe), 114.4 (3, 3'C ArH), 114.5 (4C isoxazole), 118.4 (1C ArH), 126.7 ( 2, 2'C ArH), 150.4 ( 3C isoxazole), 163.4 (4C ArH), 169.1 (5C isoxazole), 184.0 (=CO); FABMS: m/z (%) 250 (100), 202 (95), 155( 50), 120(45), 107 (50), 89 (45). 250 (2), 202 (40), 135 (100), 107 (45), 102 (54); *Anal:* $C_{12}H_{11}NO_3$ (249.59); Calcd: C, 57.82; H, 4.45; N, 5.62; S, 12.86. Found: C, 57.84; H, 4.65; N, 5.52; S, 12.75.

**(3-Methoxyphenyl)[5-methylsulfanyl)-4-isoxazolyl]methanone 3c.** Yield-65% (0.32 g); white solid; mp 80 °C; IR (KBr $\nu_{max}$): 2930, 1658, 1566, 1473, 1296 $cm^{-1.}$ $^1H$ NMR (300 MHz, $CDCl_3$) δ = 2.47 (s, 3H, $SCH_3$), 3.88 (s, 3H, OMe)., 7.07 (s, 1H, ArH), 7.38 (s, 1H, ArH), 7.64 - 7.67 (m, 2H, ArH), 8.69 (s, 1H,3CH isoxazole); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 11.9 ($SCH_3$), 55.4 (OMe), 113.7 (4C isoxazole), 115.7 (2C ArH), 118.2 (4C ArH), 121.2 (6C ArH), 127.0 (5C ArH), 129.9 (1C, ArH ), 150.4 (3C isoxazole), 159.5 (3C ArH), 169.0 (5C isoxazole), 184.0 ( =CO); EIMS m/z (%) 250 (2), 202 (40),135 (100), 107 (45), 102(54); *Anal:* $C_{12}H_{11}NO_3S$ (249.59); *Anal:* $C_{12}H_{11}NO_3S$ (249.59); Calcd: C, 57.82; H, 4.45; N, 5.62; S, 12.86. Found: C, 57.87; H, 4.48; N, 5.61; S, 12.36.

**(3,4-Dimethoxyphenyl)[5-methylsulfanyl)-4-isoxazolyl]-methanone 3d.** Yield 90% (0.5 g); white solid; mp 80 °C. IR (KBr $\nu_{max}$) 2935, 1662, 1604, 573, 1485, 1276 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 2.48 (s, 3H, SMe), 3.96 (s, 3H, OMe), 3.98 (s, 3H, OMe), 6.99 (d, J = 9 Hz, 1H, ArH), 7.77 (s, 1H, ArH ), 7.85 - 7.81(m, 1H, ArH), 8.69 (s,1H, isoxazole); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 11.9 ($SCH_3$), 56.0 (OMe), 56.1 (OMe), 110.7 (4C isoxazole), 111.5 (2C ArH), 114.6 (5C ArH ), 118.6 (6C ArH), 122.7 (1C ArH), 148.7 (3C isoxazole), 150.6 (3C ArH), 152.1 (4C ArH), 168.9 (5C isoxazole), 184.1 ( =CO); EIMS m/z (%) 280 (15), 232 (50), 204 (20), 177(50) 165(80).; *Anal:* $C_{13}H_{13}NO_4S$ (279.31): Calcd: C, 55.90; H, 4.69; N, 5.01; S, 11.48. Found: C, 55.67; H, 4.63; N, 5.13; S, 11.44.

**[5-(Methylsulfanyl)-4-isoxazolyl](phenyl)methanone 3e.** Yield 65% (0.28 g); white solid;. mp 68 °C; IR (KBr $\nu_{max}$): 1662, 1596, 1577 $cm^{-1}$ ; $^1H$ NMR (300 MHz, $CDCl_3$ ): δ = 2.68 (s, $SCH_3$), 7.23 (s, 1H ArH), 7.51 (d, J = 8.49 Hz, 2H, ArH), 8.07 (d, J = 9 Hz, 2H, ArH), 8.70 (s, 3CH isoxazole proton), ); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 11.7 ($SCH_3$), 114.4 (3, 3'C ArH), 114.5 (4C isoxazole), 118.4 (1C ArH), 126.70 ( 2, 2'C ArH), 150.4 (3C isoxazole), 163.4 (4C ArH), 169.1 (5C isoxazole), 184.0 (=CO); EIMS m/z (%): 220 (5), 172 (3), 167 (40), 150 (10), 105 (100); *Anal:* $C_{11}H_9NO_2S$ (219.26): Calcd: C, 60.26; H, 4.14; N, 6.39; S, 14.62. Found: C, 59.97; H, 4.18; N, 6.34; S, 14.73.

**[5-(Benzylsulfanyl)-4-isoxazolyl](phenyl)methanone 3f.** Yield 60 % (0.35 g); white solid; mp 110 °C; IR (KBr $\nu_{max}$) 1643, 1596, 1562 $cm^{-1}$; 1H NMR (300 MHz, $CDCl_3$): δ = 4.41 (s, 2H, $SCH_2Ph$), 7.44 - 7.52 (m, 6H, ArH), 7.56 - 7.76 (m, 2H, ArH ), 7.76 - 7.79 (m, 2H, ArH ), 8.74 (s, 1H, 3 CH isoxazole); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 35.5 ($\underline{S}CH_2Ph$), 108.2 (4C isoxazole), 119.3, 127.5, 128.4, 128.83, 129.2, 133.1, 136.2, 140.6 (ArH), 160.7 (3C isoxazole), 162.5 (5C isoxazole), 186.7 (CO); FABMS: m/z (%): 296(85); *Anal:* $C_{17}H_{13}NO_2S$ (295.36): Calcd: C, 69.13; H, 4.44; N, 4.74; S, Found: C, 69.47; H, 4.47; N, 4.69.

**Synthesis of 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbonitriles from 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehydes (4).**

**General procedure.** 2-Aroyl-3,3-bis(alkylsulfanyl)acrylaldehyde **2** (0.5 g, 2 mmol) was dissolved in acetonitrile (20 mL) at room temperature. To this solution hydroxylamine hydrochloride (0.28 g, 4 mmol) followed by and $K_2CO_3$ (1.1 g, 8 mmol) were added and the reaction mixture was refluxed at 85 °C for 10 h. It was cooled and poured into ice-cold water. The semisolid obtained was extracted with ethyl acetate (3 X 25 mL), dried with anhydrous sodium sulfate and purified by column chromatography on silica gel using hexane as the eluent. Recrystallised from hexane/ethyl acetate (4:1) solution.

**3-(Methylsulfanyl)-5-phenyl-4-isoxazolecarbonitrile 4a.** Yield 30% (0.12 g); white solid; mp 108-110 °C ( Reported value-106-108 °C) [11d]; IR (KBr $\nu_{max}$) 2229, 1604, 1568, 1496 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ = 2.68 (s, 3H, $SCH_3$), 7.72 - 7.62 (m, 3H, ArH ), 8.01 - 8.05 (m, 2H, ArH ); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 13.6 ($SCH_3$), 111.2 (-CN), 124.7 (4C isoxazole), 126.8 (3,3'C ArH), 129.4 (2,2'C ArH), 132.8 (4C ArH), 162.3 (3C isoxazole), 174.4 (5C isoxazole); FABMS (m/z, %): 217 (100); *Anal:* $C_{11}H_8N_2OS$ (216.26) Calcd: C, 61.09, H, 3.73, N, 12.95, S, 14.83. Found: C, 61.28; H, 3.68; N, 13.08; S, 14.70

**5-(4-Methylphenyl-3-(methylsulfanyl)-4-isoxazolecarbonitrile 4b.** Yield; 43% (0.19 g); white solid; mp 96 °C;. IR (KBr $\nu_{max}$) 2993, 2223, 1604, 1562, 1427 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 2.44 (s, 3H, Me), 2.67 (s, 3H, $SCH_3$), 7.36 (d, J = 8.9 Hz, 2H, ArH ), 7.94 (d, J = 9 Hz, 2H, ArH ); $^{13}C$ NMR (75.47 MHz, $CDCl_3$): δ = 12.0 (SMe), 21.5 ($CH_3$), 116.5 (CN), 126.8 (4C isoxazole), 127.6, 128.4 and 129.8, 144.7 (ArH), 162.2 (3C, isoxazole), 174.6 (5C isoxaxole); EIMS: m/z (%) 231 (20), 216 (5), 208 (25), 202 (30), 149 (23), 119 (100), 102 (50); Anal.: $C_{12}H_{10}N_2OS$ (230.29); Calcd.: C, 62.59; H, 4.38; N, 12.16; S, 13.92. Found: C, 62.38; H 4.33; N, 12.08; S, 14.06.

**5-(4-Bromophenyl-3-(methylsulfanyl)-4-isoxazolecarbonitrile 4c.** Yield: 56% (0.33 g); white solid; mp 148 °C; IR (KBr $\nu_{max}$) 2927, 2233, 1600,1558, 1488 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ = 2.69 (s, 3H, $SCH_3$), 7.72 (d, J = 9Hz, 2H, ArH ), 7.92 (d, J = 9Hz, 2H, ArH); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 11.9 (SMe), 116.6 (CN). 127.8 (4C isoxazole), 128.7, 129.5 and 129.8, 145.7 (ArH), 163.5 (3C, isoxazole), 176.6 (5C isoxaxole); FABMS (m/z, %): 297 (100), 295 (98), 226 (2), 185 (40), 183 (40), 120 (5), 107 (8); *Anal:* $C_{11}H_7BrN_2OS$ (295.16); Calcd.: C, 44.76; H, 2.39; N, 9.49. Found: C, 44.81; H, 2.34; N, 9.57

**5-(4-Methoxyphenyl-3-(methylsulfanyl)-4-isoxazolecarbonitrile 4d.** Yield; 41% (0.2 g); white solid; mp 142 °C; IR (KBr $\nu_{max}$) 2923, 2229, 1610,1585,1508 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ = 2.67 (s, 3H, SMe), 3.90 (s, 3H, $OCH_3$), 7.05 (d, J= 9 Hz, 2H, ArH ), 8.01 (d, J = 9 Hz, 2H, ArH ); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 12.02 (SMe), 54.9 ($OCH_3$), d 114.5 (CN). 126.8 (4C isoxazole), 127.9, 128.8 and 129.8, 146.7 (ArH carbons), 162.2 (3C, isoxazole), 176.6 (5C isoxaxole); FABMS (m/z, %): 247 (100), *Anal:* $C_{12}H_{10}N_2O_2S$ (246.29): Calcd.: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.82; H, 4.13; N, 11.43.

**Synthesis of 5-aryl-3-(methylsulfanyl)-4-isoxazolecarbaldehydeoximes from 2-aroyl-3,3-bis(alkylsulfanyl) acrylaldehydes**

**General procedure.** 2-Aroyl-3,3-bis(alkylsulfanyl)acrylaldehyde (0.5 g, 2 mmol) was dissolved in acetonitrile (20 mL) at room temperature. To the above solution hydroxylamine hydrochloride (0.28 g, 4 mmol) followed by $K_2CO_3$ (1.1 g, 8 mmol) were added and the reaction mixture was stirred for 10 h.

It was poured into ice cold water and the semisolid obtained was extracted with ethyl acetate (3 X 25 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated off. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (8:2) as the eluent. The solid was recrystallised from hexane/ethyl acetate (4:1) solution.

**3-(Methylsulfanyl)-5-phenyl-4-isoxazolecarbaldehyde oxime 5a**. Yield 42% (0.19 g); white solid; mp 182 ℃; IR (KBr $\nu_{max}$) 3331, 1639, 1566, 1450 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ = 2.68 (s, 3H, $SCH_3$), 7.51 - 7.55 (m, 3H, ArH), 7.60 - 7.69 (m, 3H, two ArH and one aldoxime proton), 8.23 (s, 1H, OH proton); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 13.8 ($SCH_3$), 108.6 (4C isoxazole), 126.8 (4C ArH), 127.5 (2, 2'C ArH), 128.9 (3, 3'C ArH), 130.6 (1C ArH), 139.6(3C isoxazole), 159.8 (aldoxime), 167.6 (5C isoxazole); FABMS: m/z (%): 235(100); *Anal:* $C_{11}H_{10}N_2O_2S$ (234.38): Calcd: C, 56.39; H, 4.30; N, 11.96. Found: C, 56.02; H 4.24; N, 11.79.

**5-(4-Bromophenyl)-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oxime 5b.** Yield; 43% (0.26 g); white solid; mp 186 ℃; IR (KBr $\nu_{max}$): 3336, 1643, 1596, 1488 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ + DMSO, 1:1) $\delta$ = 2.58 (s, 3H, $SCH_3$), 7.58 - 7.61 (m, 2H, ArH), 7.67 - 7.70 (m, 2H, ArH), 8.13 (s, 1 H, aldoxime), 11.43 (s, 1H, OH proton); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 13.80 ($SCH_3$), 107.7 (4C isoxazole), 125.6 (4C ArH), 127.5 (2, 2'C ArH), 128.9 (3, 3'C ArH), 130.7 (1C ArH), 140.6 (3C isoxazole), 160.8 (aldoxime), 166.8 (5C isoxazole); FABMS: m/z (%): 315 (50), 313 (50), 279 (20), 259 (20), 219 (60), 149 (80), 123 (40), 107 (60); *Anal:* $C_{11}H_9BrN_2O_2S$ (313.17): Calcd: C, 42.19; H 2.90; N, 8.95. Found: C, 42.45; H, 3.01; N, 8.98.

**5-(4-Methoxyphenyl)-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oxime 5c.** Yield; 40% (0.21 g); white solid; mp 180 ℃; IR (KBr $\nu_{max}$) 3321, 1643, 1608, 1512 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.63 (s, 3H, $SCH_3$), 3.88 (s, $OCH_3$), 7.04 - 7.01 (m, 2H, ArH), 7.63 - 7.60 (m, 2H, ArH), 7.79 (s, 1H aldoxime), 8.21 (s,1H, OH ); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ = 13.5 ($SCH_3$), 55.7 ($OCH_3$) 110.6 (4C isoxazole), 125.8 (4C ArH), 127.8 (2, 2'C ArH), 128.7 (3, 3'C ArH), 130.6 (1C ArH), 139.4 (3C isoxazole), 158.4 (aldoxime), 166.7 (5C isoxazole); FABMS: (m/z, %): 265 (98), 242 (5), 180 (5), 121 (80, 107 (40), 88 (20); *Anal:* $C_{12}H_{12}N_2O_3S$ (264.30): Calcd: C, 54.53; H, 4.58; N, 10.60. Found: C, 54.23; H, 4.56; N, 10.66.

**5-(4-Methylphenyl)-3-(methylsulfanyl)-4-isoxazolecarbaldehyde oxime 5d.** Yield; 54% (0.26g); white solid; mp 174 ℃; IR (KBr $\nu_{max}$) 3331, 1656, 1608, 1512 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 2.43 (s, 3H, $CH_3$), 2.63 (s, 3H, $SCH_3$), 7.31 - 7.33 (m, 2H, ArH), 7.54 - 7.76 (m, 2H, ArH), 7.65 (s, 1H aldoxime), 8.23 (s, 1H, OH proton.), $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 13.8 ($SCH_3$), 21.4 ($CH_3$) 108.5 (4C isoxazole), 126.3 (4C ArH), 127.9 (2, 2'C ArH), 128.9 (3, 3'C ArH), 131.6 (1C ArH), 138.7 (3C isoxazole), 160.8 (aldoxime), 167.2 (5C isoxazole); FABMS: (m/z, %): 249(100), 188(1), 167(2), 119(48), 107(5), 89(.5); *Anal:* $C_{12}H_{12}N_2O_2S$ (248.30): Calcd: C, 58.05; H, 4.87; N, 11.28. Found: C, 57.97; H, 4.82; N, 11.34.

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