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Synthesis Of Novel Series of 1,2-Oxazine Bearing *Bis*(Heterocycle) Via [4+2] Cycloaddition Reaction of Isoxazole Substituted α-Nitrosoolefin

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ABSTRACT

Bis (heterocycle) bearing isoxazole in combination of 1,2-oxazine has been synthesized via 1,3-dipolar cycloaddition reaction of nitrile oxide with acetyl acetone followed by the [4 + 2] cycloaddition of α-nitrosoolefin with different dienophiles. The α-nitrosoolefin obtained from the isoxazole-substituted ketoxime by the action of chloramine-T.

Keywords: *Bis*(heterocycle), α-nitrosoolefin, chloramine-T.

INTRODUCTION

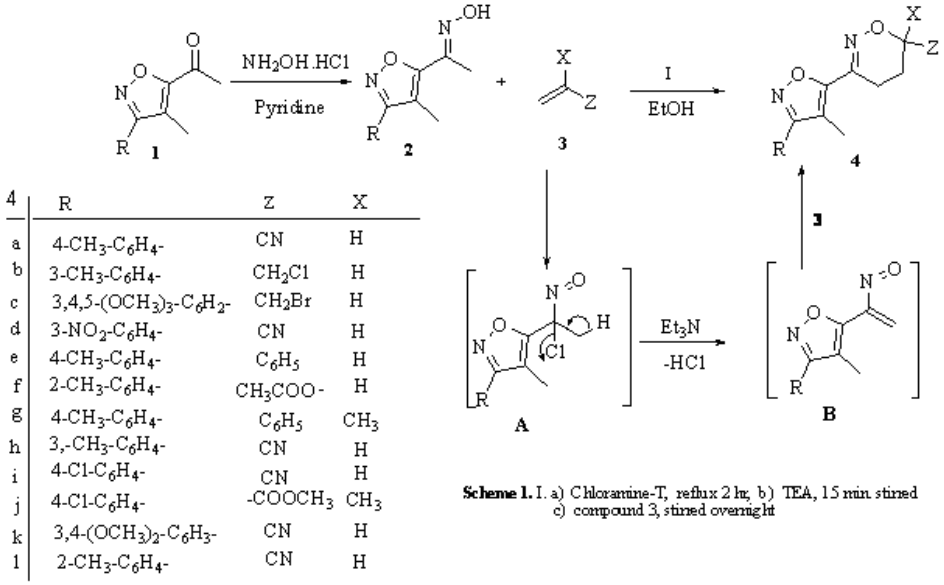
The development of simple synthetic routes to widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis [1]. α-Nitrosoolefin is normally prepared *in situ* by 1,4-elimination from α-monohaloketoximes [2] or isolated occasionally as relatively stable compound [3], which has attracted much attention owing to its usefulness as diene for a [4 + 2] cycloaddition reaction. The [4 + 2] cycloaddition reactions of α-nitrosoolefin with olefinic compounds are of synthetic interest since 5,6-dihydro-4*H*-1,2-oxazine derivatives formed are important in the synthesis of an antihypertensive agent [4] vasodilators [5], glycosidase inhibitors [6] etc. Many syntheses of 1,2-oxazines rely on hetero Diels–Alder reactions of alkenes with ene-nitroso compounds derived from α-haloximes [7] or on hetero-Diels–Alder reactions of dienes with nitroso compounds [8] Other methods rely on cyclization of alkenyl-substituted oximes in the presence of NBS [9], diphenyldiselenide [10], an acid [11] or by photochemical activation [12]. Recently Rai *et al* [13] reported the generation of α-nitrosoolefin and α-azoalkenes from ketoximes and ketone hydrazones followed by hetero Diels-Alder reactions to obtain 1,2-oxazine and 1,2-pyrazine derivatives respectively.

The [3 + 2] cycloaddition reaction of nitrile oxides and olefins to give isoxazole has long been valued as an important transformation for chemical synthesis. These heterocyclic products are not only themselves of interest but are also valuable because they may be readily elaborated to a variety of highly functionalized compounds [14]. In fact, Valdecoxib [15] isoxazoline derivative is now widely used in the market as anti-inflammatory drugs. Although various *Bis*(heterocycle) have been synthesized, the present attention was

directed to the work of Padmavathi *et al*,[16], who synthesized isoxazoline bearing *Bis*(heterocycle) by the reaction of bis chalcones and bis sulfones as dipolarophiles with nitrile oxides as 1,3-dipole.

In our laboratory, Rai *et al*, [17] extensively used chloramine-T for the generation of nitrile oxide and nitrile imines from aldoxime and aldehyde hydrazone respectively. Nitrile oxides have been excellent 1,3-dipole for the [3 + 2] cycloaddition reaction with different olefins [18] (acetyl acetone, acrylonitrile, vinyl acetate etc). Recently, we have reported the synthesis of ether-linked *Bis* (isoxazoline) via 1,3-dipolar cycloaddition reactions of nitrile oxides with allyl alcohol and allyl ethers [19].

As a part of the current studies on the development of new heterocycles, it is considered worthwhile to prepare *Bis* (heterocycle) bearing both isoxazole and 1,2-oxazine moieties starting from simple aromatic aldoxime and acetyl acetone. The present communication deals with the synthesis of hitherto unknown *Bis* (heterocycle) bearing isoxazole in combination of 1,2-oxazine unit.



4	R	Z	X
a	4-CH_3-C_6H_4-	CN	H
b	3-CH_3-C_6H_4-	CH_2Cl	H
c	3,4,5-$(OCH_3)_3$-C_6H_2-	CH_2Br	H
d	3-NO_2-C_6H_4-	CN	H
e	4-CH_3-C_6H_4-	C_6H_5	H
f	2-CH_3-C_6H_4-	CH_3COO-	H
g	4-CH_3-C_6H_4-	C_6H_5	CH_3
h	3,-CH_3-C_6H_4-	CN	H
i	4-Cl-C_6H_4-	CN	H
j	4-Cl-C_6H_4-	-$COOCH_3$	CH_3
k	3,4-$(OCH_3)_2$-C_6H_3-	CN	H
l	2-CH_3-C_6H_4-	CN	H

Scheme 1. I. a) Chloramine-T, reflux 2 hr, b) TEA, 15 min. stirred c) compound 3, stirred overnight

MATERIALS AND METHODS

Melting points were determined on Thomas Hoover melting point apparatus and were uncorrected. ^1H NMR spectra were recorded on a Bruker AM 300 MHz spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were measured on Jeol 400 (100 MHz) instrument. The chemical shifts are expressed in δ and following abbreviations were used. s=singlet, d=doublet, t=triplet and m=multiplet. Infrared (IR) spectra were recorded on Shimadzu 8300 IR spectrometer. Elemental analyses were obtained on a Vario-EL instrument. Thin layer chromatographic studies were carried out with BDH silica gel G on glass slides.

General procedure for the synthesis of 1,2-oxazine bearing Bis(heterocycle):

5,6-Dihydro-3-(4-methyl-3-*p*-tolylisoxazol-5-yl)-4*H*-1,2-oxazine-6-carbonitrile[4a]Typical procedure: A mixture of **2a** (0.5 g, 2.17 mmol) and chloramine-T trihydrate (0.63 g, 2.18 mmol) in ethanol was refluxed for 2 h. The mixture was cooled to room temperature followed by the addition of triethylamine (1 mL) and stirring at room temperature for 15 min. To this, a solution of acrylonitrile (0.12 g, 2.18 mmol) in ethanol (5 mL) was added and stirred overnight. It was then concentrated under reduced pressure and the residue was extracted with ethylacetate (2 x 25 mL). The extract was then washed with water (15 mL), 1*N* aq. NaOH and then with water. The product was dried over anhydrous Na_2SO_4. The residue was purified

by chromatography (chloroform-acetone, 8:2). **4a** was isolated as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85-2.12 (m, 2H, CH_2), 2.34 (s, 6H, $2CH_3$), 2.45-2.61 (m, 2H, CH_2), 4.25 (dd, *J* = 6.2 Hz, 2.0 Hz, 1H, CH), 7.14–7.38 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.8 (CH_3), 15.9 (CH_2), 21.2 (CH_2), 24.4 (CH_3), 70.5 (CH), 100.7 (C), 118.7 (C), 127.7 (2CH), 129.7 (2CH), 130.4 (C), 138.7 (C), 157.7 (C), 158.9 (C), 164.8 (C). IR (KBr pellets) ν is 3028, 2931, 2262, 1678, 1654, 1634, 1626, 1410, 1366, 1218, 1210 cm^{-1}. Anal.Calc. for $C_{16}H_{15}N_3O_2$: C 68.31, H 5.37 and N 14.94. Found: C 68.33, H 5.35 and N 14.97. Yield 67 % and m.p. 133-135 °C.

Spectral data of the compounds

6-(Chloromethyl)-5,6-dihydro-3-(4-methyl-3-*m*-tolylisoxazol-5-yl)-4*H*-1,2-oxazine [4b]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82-2.01 (m, 2H, CH_2), 2.35 (s, 6H, $2CH_3$), 2.42-2.59 (m, 2H, CH_2), 3.48 (dd, *J* = 5.8, 2.0 Hz, 2H, CH_2Cl), 3.69 (m, 1H, CH), 7.13–7.37 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1 (CH_3), 16.9 (CH_2), 21.4 (CH_2), 24.5 (CH_3), 46.8 (CH_2), 81.6 (CH), 100.5 (C), 127.4 (2CH), 129.7 (2CH), 130.1 (C), 138.5 (C), 157.5 (C), 158.9 (C), 164.7 (C). IR (KBr pellets) ν is 3017, 2924, 1668, 1644, 1623, 1619, 1411, 1359, 1215, 1211, 863 cm^{-1}. Anal. Calc. for $C_{16}H_{17}ClN_2O_2$: C 63.05, H 5.62, and N 9.19. Found: C 63.08, H 5.65 and N 8.16. Yield 58 % and m.p. 128-130 °C.

6-(Bromomethyl)-5,6-dihydro-3-(3-(3,4,5-trimethoxyphenyl)-4-methylisoxazol-5-yl)-4*H*-1,2-oxazine [4c]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76-1.99 (m, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.39-2.56 (m, 2H, CH_2), 3.38-3.62 (m, 3H, CH, CH_2Br), 3.83 (s, 6H, OCH3), 3.87 (s, 3H, OCH3), 6.57 (s, 2H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2 (CH_3), 17.9 (CH_2), 20.1 (CH_3), 19.9 (CH_2), 21.4 (CH_2), 35.9 (CH_2), 82.6 (CH), 100.7 (C), 104.9 (2CH), 127.5 (C), 139.7 (2CH), 151.5 (2C), 157.9 (C), 159.1 (C), 164.9 (C). IR (KBr pellets) ν is 3027, 2931, 1663, 1641, 1623, 1618, 1411, 1362, 1216, 1201, 852 cm^{-1}. Anal. Calc. for $C_{18}H_{21}BrN_2O_5$: C 50.84, H 4.98 and N 6.59. Found: C 50.91, H 4.87 and N 6.66. Yield 55 %, m.p. 140-142 °C.

5,6-Dihydro-3-(4-methyl-3-(3-nitrophenyl)isoxazol-5-yl)-4*H*-1,2-oxazine-6-carbonitrile [4d]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85-2.11 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.50-2.67 (m, 2H, CH_2), 4.26 (dd, *J* = 6.2 Hz, 2.0 Hz, 1H, CH), 7.56-8.44 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.0 (CH_3), 15.9 (CH_2), 21.5 (CH_2), 70.5 (CH), 100.7 (C), 118.7 (C), 121.7 (CH), 122.7 (CH), 130.3 (CH), 133.7 (CH), 134.7 (CH), 148.8 (C), 157.7 (C), 158.9 (C), 164.7 (C). IR (KBr pellets) ν is 3053, 2922, 2267, 1665, 1619, 1615, 1606, 1414, 1365, 1213, 1205 cm^{-1}. Anal. Calc. for $C_{15}H_{12}N_4O_4$: C 57.69, H 3.87 and N 17.94. Found: C 68.33, H 5.35 and N 14.9.Yield 60 %. m.p. 161-163 °C

5,6-Dihydro-3-(4-methyl-3-*p*-tolylisoxazol-5-yl)-6-phenyl-4*H*-1,2-oxazine [4e]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83-2.05 (m, 2H, CH_2), 2.35 (s, 6H, $2CH_3$), 2.47-2.66 (m, 2H, CH_2), 4.43 (dd, *J* = 6.0, 2.0 Hz, 1H, CH), 7.14–7.38 (m, 9H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6 (CH_3), 21.9 (CH_2), 22.4 (CH_2), 24.4 (CH_3), 81.5 (CH), 100.6 (C), 126.3 (CH), 127.6 (2CH), 128.4 (2CH), 128.9 (2CH), 129.7 (2CH), 130.3 (C), 138.6 (C), 138.7 (C), 157.5 (C), 158.8 (C), 164.7 (C). IR (KBr pellets) ν is 3038, 2930, 1675, 1654, 1634, 1624, 1410, 1366, 1218, 1210 cm^{-1}. Anal. Calc. for $C_{21}H_{20}N_2O_2$: C 75.88, H 6.06 and N 8.43. Found: C 75.83, H 6.07 and N 8.47, yield 52 %, thick oil.

5,6-Dihydro-3-(4-methyl-3-*o*-tolylisoxazol-5-yl)-4*H*-1,2-oxazin-6-yl acetate [4f]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80-2.06 (m, 2H, CH_2), 2.08 (s, 3H, CH_3), 2.33 (s, 6H, $2CH_3$), 2.53-2.70 (m, 2H, CH_2), 5.67 (dd, *J* = 5.6, 2.0 Hz, 1H, CH), 7.11–7.34 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.8 (CH_3), 18.3 (CH_2), 19.4 (CH_2), 21.2 (CH_3), 24.4 (CH_3), 100.6 (C), 104.8 (CH), 127.5 (2CH), 129.7 (2CH), 130.3 (C), 138.5 (C), 157.6 (C), 158.6 (C), 164.7 (C), 170.5 (C). IR (KBr pellets) ν is 3030, 2912, 1742, 1660, 1621, 1613, 1608, 1411, 1361, 1211, 1202 cm^{-1}. Anal. Calc. for $C_{17}H_{18}N_2O_4$: C 64.96, H 5.77and N 8.91. Found: C 64.93, H 5.75 and N 8.95; yield 62 %, m.p. 160-162 °C.

5,6-Dihydro-6-methyl-3-(4-methyl-3-*p*-tolylisoxazol-5-yl)-6-phenyl-4*H*-1,2-oxazine [4g]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (s, 3H, CH_3), 1.83-2.07 (m, 2H, CH_2), 2.36 (s, 6H, $2CH_3$), 2.46-2.60 (m, 2H, CH_2), 7.13–7.37 (m, 9H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (CH_3), 19.5 (CH_2), 24.4 (CH_3), 24.7

(CH_3), 29.5 (CH_2), 79.5 (CH), 100.7 (C), 126.3 (CH), 127.7 (2CH), 128.4 (2CH), 129.1 (2CH), 129.8 (2CH), 130.3 (C), 138.7 (C), 140.2 (C), 157.5 (C), 158.9 (C), 164.7 (C). IR (KBr pellets) ν is 3032, 2931, 1678, 1654, 1634, 1626, 1410, 1366, 1218, 1210 cm^{-1}. Anal. Calc. for $C_{22}H_{22}N_2O_2$: C 76.28, H 6.40 and N 8.09. Found: C 76.24, H 6.43 and N 8.11; yield 52 %,thick oil.

5,6-Dihydro-3-(4-methyl-3-*m*-tolylisoxazol-5-yl)-4*H*-1,2-oxazine-6-carbonitrile [4h]: ^{1}H NMR (300 MHz, CDCl3): δ 1.87-2.03 (m, 2H, CH_2), 2.34 (s, 6H, $2CH_3$), 2.53-2.67 (m, 2H, CH_2), 4.27 (dd, *J* = 6.2, 2.2 Hz, 1H, CH), 7.14–7.38 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7 (CH_3), 18.9 (CH_2), 21.2 (CH_2), 24.4 (CH_3), 70.5 (CH), 100.7 (C), 118.7 (C), 127.7 (2CH), 129.7 (2CH), 130.4 (C), 138.7 (C), 157.7 (C), 158.9 (C), 164.8 (C). IR (KBr pellets) ν is 3027, 2924, 2282, 1668, 1644, 1623, 1619, 1411, 1359, 1215, 1211 cm^{-1}. Anal. Calc. for $C_{16}H_{15}N_3O_2$: C 68.31, H 5.37 and N 14.94. Found: C 68.33, H 5.35 and N 14.97; yield 58 %, thick oil.

3-(3-(4-Chlorophenyl)-4-methylisoxazol-5-yl)-5,6-dihydro-4*H*-1,2-oxazine-6-carbonitrile [4i]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82-2.01 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.47-2.60 (m, 2H, CH_2), 4.22 (dd, *J* = 6.0, 2.2 Hz, 1H, CH), 7.34-7.48 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6 (CH_3), 15.7 (CH_2), 21.2 (CH_2), 70.5 (CH), 100.7 (C), 118.7 (C), 128.7 (2CH), 129.7 (2CH), 131.4 (C), 134.7 (C), 157.7 (C), 158.9 (C), 164.7 (C). IR (KBr pellets) ν is 3043, 2912, 2291, 1661, 1621, 1617, 1608, 1412, 1365, 1211, 1201 cm^{-1}. Anal. Calc.for $C_{15}H_{12}ClN_3O_2$; C 59.71, H 4.01 and N 13.93. Found: C 68.33, H 5.35 and N 14.97; yield 49 %, m.p. 137-139 °C.

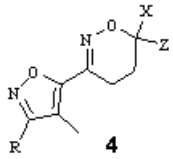
Methyl3-(3-(4-chlorophenyl)-4-methylisoxazol-5-yl)-5,6-dihydro-6-methyl-4*H*-1,2-oxazine-6-carboxy late [4j]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 3H, CH_3), 1.80-2.06 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.53-2.67 (m, 2H, CH_2), 3.86 (s, 3H, OCH_3), 5.11 (dd, *J* = 6.0, 2.0 Hz, 1H, CH), 7.11–7.34 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2 (CH_3), 18.3 (CH_2), 19.4 (CH_2), 21.2 (CH_3), 24.4 (CH_3), 100.6 (C), 104.8 (CH), 127.5 (2CH), 129.7 (2CH), 130.3 (C), 138.5 (C), 157.6 (C), 158.6 (C), 164.7 (C), 170.5 (C). IR (KBr pellets) ν is 3038, 2912, 1664, 1624, 1617, 1608, 1412, 1368, 1215, 1206 cm^{-1}. Anal. Calc. for $C_{17}H_{18}N_2O_4$: C 64.96, H 5.77 and N 8.91. Found: C 64.93, H 5.75 and N 8.95; yield 59 %, m.p. 146-148 °C.

5,6-Dihydro-3-(3-(3,4-dimethoxyphenyl)-4-methylisoxazol-5-yl)-4*H*-1,2-oxazine-6-arbonitrile [4k]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85-2.03 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.44-2.60 (m, 2H, CH_2), 3.77 (s, 6H, 2-OCH_3), 4.20 (dd, *J* = 6.8, 2.4 Hz, 1H, CH), 6.77-6.95 (m, 3H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.5 (CH_3), 19.2 (CH_2), 21.5 (CH_2), 56.5 (2-OCH_3), 70.5 (CH), 100.7 (C), 112.5 (CH), 115.9 (CH), 118.7 (C), 120.7 (CH), 126.7 (CH), 149.8 (C), 150.7 (C), 157.7 (C), 158.9 (C), 164.7 (C). IR (KBr pellets) ν is 3027, 2934, 2276, 1665, 1640, 1628, 1618, 1411, 1360, 1216, 1210 cm^{-1}. Anal. Calc.for $C_{17}H_{17}N_3O_4$; C 62.38, H 5.23 and N 12.84. Found: C 68.33, H 5.35 and N 14.9l; yield 63 %, m.p. 166-168 °C.

5,6-Dihydro-3-(4-methyl-3-*o*-tolylisoxazol-5-yl)-4*H*-1,2-oxazine-6-carbonitrile [4l]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.81-1.99 (m, 2H, CH_2), 2.34 (s, 6H, $2CH_3$), 2.49-2.66 (m, 2H, CH_2), 4.25 (dd, *J* = 6.4, 2.0 Hz, 1H, CH), 7.14–7.38 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.3 (CH_3), 18.9 (CH_2), 21.2 (CH_2), 24.4 (CH_3), 70.5 (CH), 100.7 (C), 118.7 (C), 127.7 (2CH), 129.7 (2CH), 130.4 (C), 138.7 (C), 157.7 (C), 158.9 (C), 164.8 (C). IR (KBr pellets) ν is 3030, 2916, 2280, 1660, 1621, 1613, 1608, 1411, 1361, 1211, 1202 cm^{-1}. Anal. Calc. for $C_{16}H_{15}N_3O_2$: C 68.31, H 5.37 and N 14.94. Found: C 68.33, H 5.35 and N 14.97; yield 58 %, thick oil.

RESULTS AND DISCUSSION

Synthetic route discussed hereafter is depicted in the **scheme 1.** The starting material **1** and its oxime **2** were prepared according to the literature procedure [18a-b] The reaction between ketoxime of 1-(3-arylisoxazol-5-yl) ethanone **1** and chloramine-T trihydrate resulted in the formation of 5-(1-chloro-1-



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nitrosoethyl)-3-arylisoxazole (α-monohaloketoximes) **A**. This was stirred for 15 min with triethylamine gave 5-(1-Nitrosovinyl)-3-arylisoxazole (α-nitrosoolefin) **B** and *in situ* stirred overnight with different dienophiles **3** resulted the formation of *Bis*(heterocycle) derivatives **4(a-l)** with good yield and purity.

^{1}H NMR, ^{13}C NMR, IR and elemental analyses were used to confirm the structures of the *Bis* (heterocycle) derivatives. As expected, the cycloaddition is regioselective. ^{1}H NMR of the newly synthesized compounds **4(a-l)** (when X = H), showed signals due to CH-6 as doublet of doublet in the region δ 3.48-5.67 ppm, while in cycloadduct **4** (X=CH_3) there was no signal in the said region and CH-5 protons appeared as multiplet at δ 1.76-2.11 ppm and CH-4 protons appeared as multiplet at δ 2.39-2.70 ppm. ^{13}C NMR spectra of all the 1,2-oxazines gave consistent signals for the newly formed ring carbons. For instance, in **4a** C_4 and C_5 carbon of oxazine moiety showed signals at δ 21.2 and 15.9 respectively, while C_6 carbon resonates at δ 70.5 ppm. Formation of the products was further supported by IR spectroscopy and elemental analyses.

CONCLUSIONS

In summary, we have synthesized new series of *Bis*(heterocycle) bearing isoxazole in combination of 1,2-oxazine via 1,3-dipolar cycloaddition reaction of nitrile oxide with acetyl acetone followed by the (4 + 2) cycloaddition of α-nitrosoolefin with different dienophiles. The products were obtained with good yield and very high purity.

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