Synthesis of 1,2-Oxazine bearing Isoxazole from Cyclization of Dilithiated 1-(3-Arylisoxazol-5-yl) Acetyl ketoxime with Epibromohydrin

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***Abstract*—A series of 1,2-oxazine bearing isoxazole has been synthesized from cyclization of dilithiated 1-(3-arylisoxazol-5-yl) ethanone oxime with epibromohydrin. All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and elemental analyses. Acetyl isoxazoles were used as synthon.**

***Index Terms*—1,2-Oxazine, Acetyl Isoxazole, Epibromohydrin.**

I. INTRODUCTION

Heterocyclic compounds hold a special place in organic chemistry. Their role as lead candidates in drug design cannot be overstated and the appearance of heterocyclic motifs in natural products is astronomically frequent. Amongst five membered heterocycles, isoxazole represent a class of compounds of great importance in biological chemistry. For instance, isoxazole possess broad spectrum of biological activities like[1] anti-tuberculosis, antifungal, anticancer, antiviral, insecticidal, antibiotic activities and precursors for different natural products. Isoxazoline also serves as important building blocks for the synthesis of bioactive molecules.[2] In fact, Valdecoxib, an isoxazole derivative is now widely used in the market as anti-inflammatory drug.[3] 1,2-Oxazines, pyridazine are of pharmacological relevance and represent useful synthetic building blocks. They have been used in the synthesis of an antihypertensive agent,[6] vasodilators,[7] glycosidase inhibitors[8] etc.

Although various heterocycle have been synthesized, our attention was directed to the work of padmavathi[4] *et al* who synthesized isoxazoline bearing Bis(heterocycle) by the reaction of bischalcones and bis sulfones as dipolarophiles with nitrile oxides as 1,3-dipole. 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.[5]

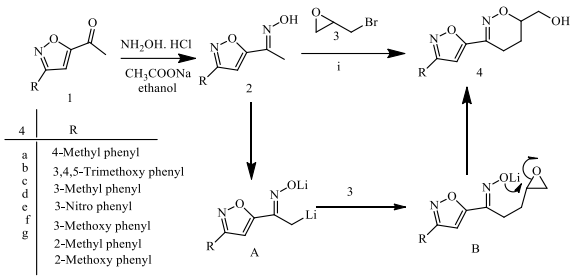
Many syntheses of 1,2-oxazines rely on hetero-Diels–Alder reactions of alkenes with ene–nitroso compounds, derived from α-haloximes[9] or on hetero-Diels–Alder reactions of dienes with nitroso compounds.[8,10] Recently Rai[11] *et al* reported the generation of α-nitrosoolefin and α-azoalkenes from ketoximes and ketone hydrazones followed by hetero Deils-Alder reactions to obtain oxazine and pyrazine derivatives respectively. Other methods rely on cyclizations of alkenyl-substituted oximes in the presence of NBS,[12] diphenyldiselenide,[13] or acid[14] or by photochemical activation.[15] In addition, 1,2-oxazines have been prepared by base-mediated cyclizations of γ-chloroximes[16] and γ-sulfonyloximes.[17] Other syntheses rely on the Lewis-acid catalyzed reaction of allenoximes,[18] acid-catalyzed cyclization of cyclopropyloximes[19] or cyclization of c-nitroketones.[20] Recently, Dang[21] et al efficiently synthesized 1,2-oxazine and pyridazine derivatives from one pot cyclization of dilithiated ketoximes and ketone hydrazones with epibromohydrin.

Herein, we wish to report the synthesis of 5,6-dihydro-6-substituted-3-(3-arylisoxazol-5-yl)-4H-1,2-oxazine by cyclization of isoxazole substituted-dilithiated oximes with epibromohydrin. The present communication deals with the reaction of the dianion of 1-(3-arylisoxazol-5-yl) acetyl ketooxime generated by n-butyllithium, with epibromohydrin afforded the hitherto unknown Bis(heterocycle) bearing both isoxazole and 1,2-oxazine unit.

II. RESULTS AND DISCUSSION

a) Synthesis of 5,6-dihydro-6-hydroxymethyl-3-(3-arylisoxazol-5-yl)-4*H*-1,2-oxazine:

The starting material **1** and its oxime **2** were prepared according to the literature procedure.[22a-b] The reaction of the dianion of 1-(3-arylisoxazol-5-yl) acetyl oxime (**2a**), generated by *n*-butyllithium, with epibromohydrin (**3**) afforded the 1,2-oxazine **4a** (Scheme 1). The formation of **4a** can be explained by SN^2 reaction of the carbon atom of the dianion with the CBr functionality of **3** and subsequent cyclization via the oxygen atom or, alternatively, by attack of the dianion onto the sterically less hindered carbon atom of the epoxide and subsequent cyclization. The reaction proceeded with very good regioselectivity, due to the higher nucleophilicity of the carbanion compared to the alkoxide.



Scheme 1: (i) (1) n-BuLi, 45 min, -78 °C, THF (2) 15 min, 20 °C, (3) 2, -78 f +20 °C, 16 h,

^{1}H NMR, ^{13}C NMR, IR and elemental analyses confirmed the structures of the oxazine derivatives. ^{1}HNMR indicates the presence of single isomer in all the cases. All the ^{1}H NMR of the cycloadducts **4a-g** showed signals due to H-4 as multiplet in the region **(**eg. **4a)** δ 1.80-2.00 ppm, the H-5 protons appeared as multiplet in the region 2.47-2.68 ppm and H-6 proton resonates at 3.48-3.86ppm as multiplet along with the CH_2-OH. ^{13}C NMR spectra of all the oxazines gave consistent signals for the newly formed ring carbons. For instance, C_4, C_5 carbon of oxazine moiety resonates as expected at δ 21.6, 225 ppm respectively, while C_6 carbon resonates at 81.5 ppm. The formation of product was further supported by IR spectroscopy and correct elemental analyses.

III. EXPERIMENTAL

Melting points were determined on Thomas Hoover melting point apparatus and were uncorrected. ^{1}H 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 chromatography was carried out with BDH silica gel G on glass slides. Synthesis of (5,6-dihydro-3-(4-methyl-3-p-tolyl isoxazol-5-yl)-4*H*-1,2-oxazin-6-yl) methanol [4a]: *Typical procedure:* To a solution of 1-(3-arylisoxazol-5-yl) ethanone oxime **2a** (0.5 g, 2.17 mmol, THF 25 mL), n-butyllithium (2.0 mL, 5.0 mmol) was added at -78 °C. The reaction mixture was stirred for 45 min. at -78 °C, another 15 min at room temperature. Subsequently, epibromohydrin (0.2 mL, 2.43 mmol) was added at -78 °C. Again kept at room temperature for 16 h, a saturated aqueous solution of NH_4Cl (15 mL) was added. The organic and the aqueous layers were separated, and the latter was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent of the filtrate was removed in vacuum. The residue was purified by chromatography (chloroform-acetone, 7:3). **4a** was isolated as a pale yellow solid (0.25 g, 40%). mp 138-140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84-2.03 (m, 2H, CH_2), 2.14 (br, 1H, OH), 2.35 (s, 6H, $2CH_3$), 2.50-2.71 (m, 2H, CH_2), 3.45-3.84 (m, 3H, CH_2, CH), 7.13-7.37 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3 (CH_3), 21.4 (CH_2), 22.2 (CH_2), 23.5 (CH_3), 67.8 (CH_2), 81.8 (CH), 100.7 (C), 127.6 (2CH), 129.8 (2CH), 130.1 (C), 138.5 (C), 157.5 (C), 158.9 (C), 164.7 (C). IR (KBr pellets cm^{-1}) ν 3378, 2931, 1678, 1654, 1634, 1626, 1410, 1366, 1218, 1210. Anal. Calcd.for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78; Found: C, 67.08, H, 6.65, N, 9.96 %.

(5,6-dihydro-3-(3-(3,4,5-trimethoxyphenyl)-4-methyl isoxazol-5-yl)-4*H*-1,2-oxazin-6-yl)methanol [4b]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82-2.02 (m, 2H, CH_2), 2.12 (br, 1H, OH), 2.33 (CH_3), 2.48-2.70 (m, 2H, CH_2), 3.44-3.81 (m, 3H, CH_2, CH), 3.83-3.97 (m, 9H, OCH_3), 6.68 (s, 2H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1 (CH_3), 21.1 (CH_2), 22.3 (CH_2), 56.4 ($3OCH_3$) 67.1 (CH_2), 81.5 (CH), 100.6 (C), 104.7 (2CH), 127.5 (C), 139.3 (C), 151.4 (2C), 157.3

(C), 158.6 (C), 164.3 (C). IR (KBr pellets cm^{-1}) ν 3377, 2931, 1663, 1641, 1623, 1618, 1411, 1362, 1216, 1201. Anal. Calcd.for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73; Found: C, 59.63, H, 6.17, N, 7.69%. 44%. mp 149-151 °C.

(5,6-dihydro-3-(4-methyl-3-m-tolylisoxazol-5-yl)-4*H*-1,2-oxazin-6-yl) methanol [4c]: ^1H NMR (300 MHz, $CDCl_3$): δ 1.86-2.08 (m, 2H, CH_2), 2.13 (br, 1H, OH), 2.38 (s, 6H, $3CH_3$), 2.52-2.75 (m, 2H, CH_2), 3.47-3.86 (m, 3H, CH_2, CH), 7.03-7.29 (m, 4H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1 (CH_3), 21.2 (CH_2), 22.3 (CH_2), 24.8 (CH_3), 67.3 (CH_2), 81.8 (CH), 100.8 (C), 124.6 (CH), 129.1 (CH), 129.3 (CH), 130.5 (CH), 133.7 (C), 138.7 (C), 157.6 (C), 159.5 (C), 164.8 (C). IR (KBr pellets cm^{-1}) ν 3367, 2924, 1668, 1644, 1623, 1619, 1411, 1359, 1215, 1211. Anal. Calcd.for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78; Found: C, 67.18, H, 6.30, N, 9.83. Yeild 40 %. Thick oil.

(5,6-dihydro-3-(4-methyl-3-(3-nitrophenyl)isoxazol-5-yl)-4*H*-1,2-oxazin-6-yl)methanol [4d]: ^1H NMR (300 MHz, $CDCl_3$): δ 1.79-2.08 (m, 2H, CH_2), 2.14 (br, 1H, OH), 2.36 (s, 3H, CH_3), 2.57-2.78 (m, 2H, CH_2), 3.45-3.84 (m, 3H, CH_2, CH), 7.62-8.46 (m, 4H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3 (CH_3), 21.2 (CH_2), 22.3 (CH_2), 67.3 (CH_2), 81.8 (CH), 100.8 (C), 121.6 (CH), 122.1 (CH), 130.3 (CH), 133.5 (CH), 134.3 (C), 148.7 (C), 157.6 (C), 159.5 (C), 164.8 (C). IR (KBr pellets cm^{-1}) ν 3353, 2922, 1665, 1619, 1615, 1606, 1414, 1365, 1213, 1205. Anal. Calcd.for $C_{15}H_{15}N_3O_5$: C, 56.78; H, 4.76; N, 13.24; Found: C, 56.88, H, 4.67, N, 13.83 %. Yield 38 %. mp 150-152 °C.

(5,6-dihydro-3-(3-(3-methoxyphenyl)-4-methylisoxazol-5-yl)-4*H*-1,2-oxazin-6-yl)methanol [4e]: ^1H NMR (300 MHz, $CDCl_3$): δ 1.83-2.01 (m, 2H, CH_2), 2.10 (br, 1H, OH), 2.33 (s, 3H, CH_3), 2.48-2.73 (m, 2H, CH_2), 3.35-3.78 (m, 3H, CH, CH_2), 3.75 (s, 3H, OCH_3), 6.76-7.23 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2 (CH_3), 21.3 (CH_2), 22.4 (CH_2), 55.9 (OCH_3), 66.8 (CH_2), 81.7 (CH), 100.7 (C), 111.9 (CH), 114.7 (CH), 119.9 (CH), 130.6 (CH), 134.6 (C), 157.8 (C), 159.2 (C), 161.6 (C), 164.8 (C). IR (KBr pellets cm^{-1}) ν 3343, 2912, 1661, 1621, 1617, 1608, 1412, 1365, 1211, 1201. Anal. Calcd.for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27; Found: C, 63.51, H, 6.10, N, 9.26. Yield 42%. Thick oil.

(5,6-dihydro-3-(4-methyl-3-o-tolylisoxazol-5-yl)-4*H*-1,2-oxazin-6-yl) methanol [4f]: ^1H NMR (300 MHz, $CDCl_3$): δ 1.89-2.06 (m, 2H, CH_2), 2.12 (br, 1H, OH), 2.35 (s, 6H, $2CH_3$), 2.52-2.76 (m, 2H, CH_2), 3.44-3.87 (m, 3H, CH_2, CH), 7.11-7.37 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1 (CH_3), 20.1 (CH_3), 21.3 (CH_2), 22.4 (CH_2), 66.9 (CH_2), 81.2 (CH), 100.6 (C), 126.6 (CH), 127.6 (CH), 128.9 (CH), 129.8 (CH), 130.0 (C), 137.2 (C), 157.6 (C), 159.2 (C), 164.7 (C). IR (KBr pellets cm^{-1}) ν 3330, 2912, 1660, 1621, 1613, 1608, 1411, 1361, 1211, 1202. Anal. Calcd.for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78; Found: C, 67.08, H, 6.45, N, 9.75. Yeild 38 %. mp 134-136 °C

(5,6-dihydro-3-(3-(4-methoxyphenyl)-4-methylisoxaz ol-5-yl)-4*H*-1,2-oxazin-6-yl)methanol **[4g]:** ^1H NMR (300 MHz, $CDCl_3$): δ 1.83-2.01 (m, 2H, CH_2), 2.10 (br, 1H, OH), 2.33 (s, 3H, CH_3), 2.48-2.73 (m, 2H, CH_2), 3.40-3.81 (m, 3H, CH_2, CH), 3.79 (s, 3H, OCH_3), 6.91-7.37 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0 (CH_3), 21.2 (CH_2), 22.1 (CH_2), 55.8 (OCH_3), 66.6 (CH_2), 81.2 (CH), 100.4 (C), 114.9 (2CH), 125.6 (C), 128.6 (2CH), 157.4 (C), 159.0 (C), 160.6 (C), 164.7 (C IR (KBr pellets cm^{-1}) ν 3341, 2922, 1662, 1629, 1618, 1618, 1417, 1366, 1221, 1210. Anal. Calcd.for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27; Found: C, 63.58, H, 6.05, N, 9.22. Yield 36 %.Thick oil.

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