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Synthesis of new series Tetrahydro-6-(3-arylisoxazol-5-yl)-2-phenylpyridazines using 1-(3-arylisoxazol-5-yl)ethanone

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Abstract: *Bis(*heterocycle*)* bearing isoxazole in combination of phenyl pyridazine has been synthesized via cyclization of 1-(3-arylisoxazol-5-yl)ethano-phenylhydrazone with allyl alcohol assisted by the chloramine-T and triethyl amine. Obtained Tetrahydro-6-(3-arylisoxazol-5-yl)-2-phenylpyridazines were well characterized by the NMR, IR and elemental analysis.

IndexTerms - 1-(3-Arylisoxazol-5-yl)ethanone, α-azoalkenes, Allyl alcohol and Chloramine T.

I. INTRODUCTION

Heterocyclic compounds footing a special habitation in organic chemistry. Their role as lead candidates in drug design cannot be overstated and the appearance of heterocyclic ideas in natural products is astronomically frequent. For instance, phenyl pyridazine is of pharmacological relevance and represent useful synthetic building blocks. They have been used in the synthesis of an antihypertensive agent,[1] vasodilators,[2] glycosidase inhibitors[3] etc. Amongst five membered heterocycles**,** isoxazole represent a class of compounds of great importance in biological chemistry. Isoxazole possess broad spectrum of biological activities like[4] 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.[5] In fact, Valdecoxib, an isoxazole derivative is now widely used in the market as anti-inflammatory drug.[6]

Although various *Bis*(heterocycle) have been synthesized, our attention was directed to the work of padmavathi[7] *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. In this area of research, 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.[8]

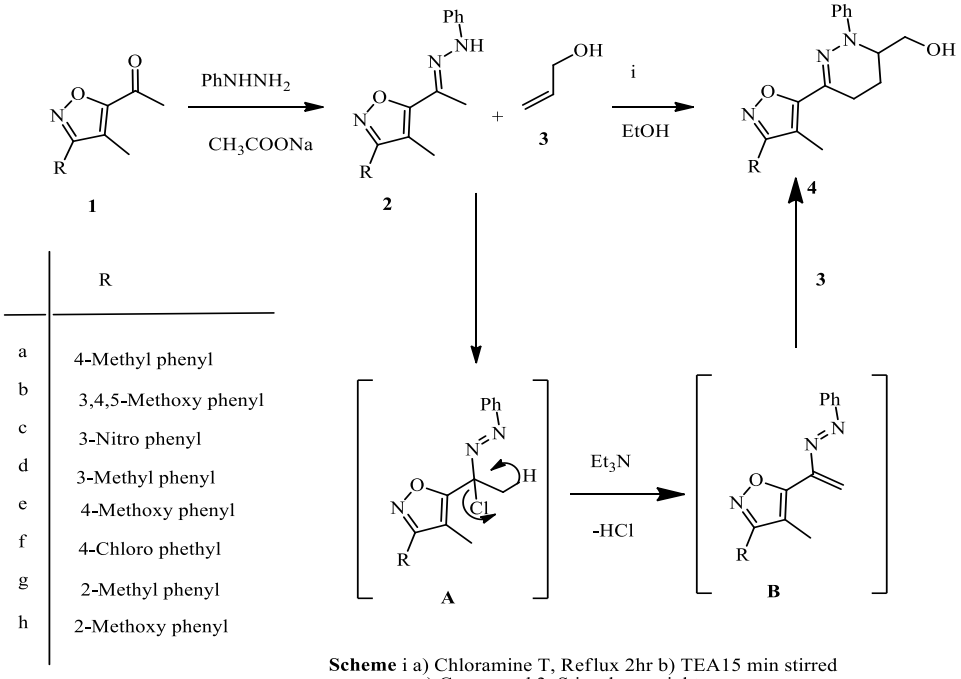
Many syntheses of pyridazines rely on hetero-Diels–Alder reactions of azo alkenes with olefin compound. [9,10] Rai[11] *et al* reported the generation of α-nitrosoolefin and α-azoalkenes from ketoximes and ketone hydrazones followed by hetero Deils-Alder reactions to obtain oxazine and pyrazine derivatives respectively. Recently, Dang[12] *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 tetrahydro-6-(3-arylisoxazol-5-yl)-2-phenylpyridazines by cyclization of hydrazones with allylalcohol. The present communication deals with the reaction of the dianion of 1-(3-arylisoxazol-5-yl)azoalkene (generated by chloramine T and Triethylamine) with dienophiles afforded the hitherto unknown *Bis*(heterocycle) bearing both isoxazole and pyridazine unit.

2. Results and Discussion:

Synthesis of (2,3,4,5-tetrahydro-2-phenyl-6-(3-arylisoxazol-5-yl)pyridazin-3-yl)methanol:

The 1-(3-arylisoxazol-5-yl)ethanone phenyl hydrazones (2**a-h**) were prepared from the corresponding 1-(3-arylisoxazol-5-yl)ethanone (**1a-h**) according to a literature procedure[13c] (Scheme 1). The reaction of allylalcohol (**3**) with the α-azoalkenes **2b** from 1-(3-arylisoxazol-5-yl)ethanone phenyl hydrazones (2**a-h**) followed by hetero Deils-Alder reactions to obtain tetrahydro-6-(3-arylisoxazol-5-yl)-2-phenylpyridazines derivatives **4a-h** at elevated temperature. α-Azoalkenes **2b** were generated by the action of chloramine-T and triethylamine on 1-(3-arylisoxazol-5-yl)ethanone phenyl hydrazones via the formation of α-haloazoalkenes **2a**. Later reaction of α-azoalkenes **2b** with allylalcohol **3** afforded the tetrahydro-6-(3-arylisoxazol-5-yl)-2-phenylpyridazines **4a**.



	R
a	4-Methyl phenyl
b	3,4,5-Methoxy phenyl
c	3-Nitro phenyl
d	3-Methyl phenyl
e	4-Methoxy phenyl
f	4-Chloro phethyl
g	2-Methyl phenyl
h	2-Methoxy phenyl

Scheme i a) Chloramine T, Reflux 2hr b) TEA15 min stirred c) Compound 3, Stirred overnight

All the ^{1}H NMR of the cycloadducts **4a-h** showed signals due to H-4 as multiplet in the region **(**eg. **4a)** δ 1.76-1.89 ppm, the H-5 protons appeared as multiplet in the region 2.43-2.58 ppm and H-6 proton resonates at 2.79-2.96 ppm as multiplet. ^{13}C NMR spectra of all the pyridazines gave consistent signals for the newly formed ring carbons. For instance, C_4, C_5 carbon of pyridazine moiety resonates as expected at δ 17.7, 19.1 ppm respectively, while C_6 carbon resonates at 63.9 ppm. The formation of product was further supported by IR spectroscopy and correct elemental analyses.

3. Experimental section:

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 chromatographic studies were carried out with BDH silica gel G on glass slides.

Synthesis of (2,3,4,5-tetrahydro-6-(4-methyl-3-p-tolylisoxazol-5-yl)-2-phenyl pyridazin-3-yl)methanol [4a]: ***Typical procedure*****:** To a solution of 1-(3-arylisoxazol-5-yl) ethanone hydrazone **2b** (0.5 g, 1.64 mmol, Ethanol 25 mL), chloramine T (0.5 g, 1.77 mmol) was added at room temperature. The reaction

mixture was stirred for 2 hr at room temperature. Subsequently, triethylamine (0.17 mL, 1.6 mmol) was added. Stirring continued with the addition of allyl alcohol (0.10 mL, 1.69 mmol) at refluxing temperature for 10 h. After completion of the reaction, alcohol was removed; 5% aqueous solution of NaOH (15 mL) and ethyl acetate (15 mL) were added. The organic and the aqueous layers were separated, and the latter was extracted with ethyl acetate (2 × 15 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 (Ethylacetate/*n*-hexane, 6.0:4.0). **4a** was isolated as a yellow solid (0.270 g, 44 %). mp 185-187 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71–1.87 (m, 2H, CH_2), 2.13 (br, 1H, OH), 2.36 (s, 6H, CH_3), 2.42–2.57 (m, 2H, CH_2), 2.79-2.96 (m, 1H, CH), 3.69–3.92 (m, 2H, CH_2), 6.55–7.07 (m, 5H, H_{Ar}), 7.14-7.38 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2.2 (CH_2), 18.9 (CH_2), 19.2 (CH_3), 24.6 (CH_3), 53.3 (CH_2), 63.8 (CH), 101.8 (C), 113.8 (2CH), 117.6 (CH), 127.6 (2CH), 129.8 (4CH), 130.3 (C), 138.6 (C), 143.9 (C), 155.7 (C), 157.7 (C), 159.2 (C). IR (KBr pellets cm^{-1}) ν 3393, 2922, 1685, 1639, 1625, 1606, 1419, 1365, 1216, 1961. Anal. Calcd.for$C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63; Found: C, 73.18, H, 6.67, N, 11.80 %.

(2,3,4,5-tetrahydro-6-(3-(3,4,5-trimethoxyphenyl)-4-methylisoxazol-5-yl)-2-phenylpyridazin-3-yl)methanol [4b]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70–1.84 (m, 2H, CH_2), 2.14 (br, 1H, OH), 2.38 (s, 3H, CH_3), 2.40–2.56 (m, 2H, CH_2), 2.73-2.84 (m, 1H, CH), 3.66–3.93 (m, 11H, OCH_3, OCH_2), 6.48–7.08 (m, 7H, H_{Ar}). ^{13}C NMR (100 MHz, CDCl3): δ 16.9 (CH_2), 18.6 (CH_2), 20.0 (CH_3), 53.6 (CH), 56.3 (2 OCH_3), 56.7 (OCH_3), 61.9 (CH_2), 100.9 (C), 104.9 (2CH), 113.7 (2CH), 117.5 (CH), 127.7 (C), 129.7 (2CH), 139.5 (C), 144.1 (C), 151.5 (2C), 155.8 (C), 157.6 (C), 159.0 (C). IR (KBr pellets cm^{-1}) ν 3385, 2910, 1684, 1634, 1615, 1610, 1413, 1365, 1211, 1956. Anal. Calcd.for $C_{24}H_{27}N_3O_5$: C, 65.89; H, 6.22; N, 9.60; Found: C, 65.78, H, 6.27, N, 9.70. Yield 44%. mp 198-200 ℃.

(2,3,4,5-tetrahydro-6-(4-methyl-3-(3-nitrophenyl)isoxazol-5-yl)-2-phenylpyridazin-3-yl)methanol [4c]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76–1.83 (m, 2H, CH_2), 2.17 (br, 1H, OH), 2.36 (s, 3H, CH_3), 2.43–2.58 (m, 2H, CH_2), 2.75-2.88 (m, 1H, CH), 3.63–3.90 (m, 2H, OCH_2), 6.48–7.05 (m, 7H, H_{Ar}), 7.56-8.38 (m, 2H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6 (CH_2), 18.4 (CH_2), 20.0 (CH_3), 53.2 (CH), 61.5 (CH_2), 100.5 (C), 113.6 (2CH), 117.3 (CH), 121.3 (CH), 122.4 (CH), 129.7 (2CH), 130.7 (CH), 133.7 (CH), 134.2 (C), 143.9 (C), 148.8 (C), 155.8 (C), 157.5 (C), 159.0 (C). IR (KBr pellets cm^{-1}) ν 3398, 2922, 1686, 1644, 1622, 1610, 1415, 1367, 1216, 1966. Anal. Calcd.for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.14; N, 14.28; Found: C, 64.45, H, 5.15, N, 14.19%. Yield 48 %. mp 201-203 ℃.

(2,3,4,5-tetrahydro-6-(4-methyl-3-m-tolylisoxazol-5-yl)-2-phenylpyridazin-3-yl)methanol [4d]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72–1.76 (m, 2H, CH_2), 2.18 (br, 1H, OH), 2.33 (s, 6H, CH_3), 2.38–2.52 (m, 2H, CH_2), 2.69-2.80 (m, 1H, CH), 3.66–3.90 (m, 2H, CH_2), 6.50–7.04 (m, 6H, H_{Ar}), 7.21-7.29 (m, 3H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9 (CH_2), 18.6 (CH_2), 19.9 (CH_3), 24.8 (CH_3), 53.6 (CH), 63.9 (CH_2), 101.8 (C), 113.9 (2CH), 117.6 (CH), 124.6 (CH), 129.3 (CH), 129.4 (CH), 129.8 (2CH), 130.3 (C), 133.6 (CH), 138.9 (C), 144.3 (C), 155.9 (C), 157.7 (C), 159.2 (C). IR (KBr pellets cm^{-1}) ν 3398, 2922, 1687, 1639, 1627, 1606, 1419, 1365, 1215, 1953. Anal. Calcd.for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63%. Found: C, 72.96, H, 6.67, N, 12.68. Yield 34%. Thick oil.

(2,3,4,5-tetrahydro-6-(3-(4-methoxyphenyl)-4-methylisoxazol-5-yl)-2-phenylpyridazin-3-yl)methanol [4e]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.77–1.83 (m, 2H, CH_2), 2.15 (br, 1H, OH), 2.38 (s, 3H, CH_3), 2.43–2.58 (m, 2H, CH_2), 2.76-2.89 (m, 1H, CH), 3.66–3.90 (m, 5H, OCH_3, OCH_2), 6.48–7.36 (m, 9H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8 (CH_2), 18.5 (CH_2), 20.1 (CH_3), 53.3 (CH), 56.2 (OCH_3), 61.4 (CH_2), 100.6 (C), 113.7 (2CH), 114.9 (2CH), 117.3 (CH), 125.8 (C), 128.7 (2CH), 129.7 (2CH), 144.0 (C), 155.8 (C), 157.6 (C), 159.1 (C), 160.8 (C). IR (KBr pellets cm^{-1}) ν 3389, 2916, 1686, 1639, 1616, 1610, 1413, 1367, 1214, 1959. Anal. Calcd.for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13; Found: C, 71.1, H, 6.27, N, 10.9%. Yield 34 %. Thick oil.

(6-(3-(4-chlorophenyl)-4-methylisoxazol-5-yl)-2,3,4,5-tetrahydro-2-phenylpyridazin-3-yl)methanol [4f]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.75–1.81 (m, 2H, CH_2), 2.11 (br, 1H, OH), 2.35 (s, 3H, CH_3), 2.39–2.52 (m, 2H, CH_2), 2.73-2.85 (m, 1H, CH), 3.62–3.88 (m, 2H, OCH_2), 6.48–7.05 (m, 7H, H_{Ar}), 7.32-7.43 (m, 4H, H_{Ar}).. ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7 (CH_2), 18.5 (CH_2), 20.2 (CH_3), 53.2 (CH), 61.6 (CH_2), 100.7 (C), 113.6 (2CH), 117.3 (CH), 128.9 (2CH), 129.5 (2CH), 129.8 (2CH), 131.3 (C), 134.7 (C), 143.9 (C), 148.8 (C), 155.8 (C), 157.5 (C), 159.0 (C). IR (KBr pellets cm^{-1}) ν 3392, 2920, 1681, 1641 1622, 1610, 1412, 1363 1216, 1963. Anal. Calcd. for $C_{21}H_{20}ClN_3O_2$, C, 66.05; H, 5.28; N, 11.00; Found: C, 66.45, H, 5.15, N, 11.19 %. Yield 44%. mp 179-181 °C.

(2,3,4,5-tetrahydro-6-(4-methyl-3-o-tolylisoxazol-5-yl)-2-phenylpyridazin-3-yl)methanol [4g]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.74–1.79 (m, 2H, CH_2), 2.12 (br, 1H, OH), 2.35 (s, 6H, CH_3), 2.42–2.57 (m, 2H, CH_2), 2.72-2.85 (m, 1H, CH), 3.63–3.89 (m, 2H, CH_2), 6.51–7.07 (m, 5H, H_{Ar}), 7.11-7.38 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8 (CH_2), 17.9 (CH_3), 18.6 (CH_2), 19.4 (CH_3), 53.3 (CH), 62.8 (CH_2), 100.8 (C), 113.8 (2CH), 117.4 (CH), 126.5 (CH), 127.6 (CH), 128.8 (CH), 129.5 (CH), 129.8 (3CH), 136.8 (C), 143.7 (C), 155.7 (C), 157.7 (C), 159.0 (C). IR (KBr pellets cm^{-1}) ν 3391, 2913, 1688, 1634, 1617, 1611, 1415, 1365, 1215, 1960. Anal. Calcd. for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63; Found: C, 73.18, H, 6.67, N, 11.80 %. Yield 40 %. Thick oil.

(2,3,4,5-tetrahydro-6-(3-(2-methoxyphenyl)-4-methylisoxazol-5-yl)-2-phenylpyridazin-3-yl)methanol [4h]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.74–1.80 (m, 2H, CH_2), 2.11 (br, 1H, OH), 2.33 (s, 3H, CH_3), 2.40–2.56 (m, 2H, CH_2), 2.73-2.87 (m, 1H, CH), 3.62–3.89 (m, 5H, OCH_3, OCH_2), 6.48–6.90 (m, 5H, H_{Ar}), 7.05-7.38 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8 (CH_2), 18.6 (CH_2), 20.1 (CH_3), 53.2 (CH), 56.4 (OCH_3), 61.6 (CH_2), 100.7 (C), 113.7 (2CH), 114.9 (CH), 117.4 (CH), 119.1 (C), 121.7 (CH), 128.7 (CH), 129.7 (2CH), 130.2 (CH), 144.0 (C), 155.8 (C), 157.6 (2C), 159.1 (C). IR (KBr pellets cm^{-1}) ν 3381, 2911, 1678, 1634, 1612, 1610, 1410, 1367, 1214, 1962. Anal. Calcd.for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13; Found: C, 70.00, H, 6.26, N, 11.19%. Yield 41 %. Thick oil.\

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