Synthesis of 4-[2-(methyl-2-pyridin-2yl-amino)-ethoxy] – benzaldehyde derivatives

***L.K.Ravindranath[1], Rangaraju.K[2], K.Srikanth[3] and S.Radhakrishana[4]**

[1]Department of Chemistry S.K. University Anantapur, Andrapradesh, India
[2]Department of Chemistry S.K. University Anantapur, Andrapradesh, India
[3]Department of Chemistry S.K. University Anantapur, Andrapradesh, India
[4]Department of Chemistry S.K. University Anantapur, Andrapradesh, India

ABSTRACT:

Several 2,4-thiazolidindiones were prepared from corresponding aryl aldehydes by Knovengel condensation between Aldehydes and 2,4-thiazolidindione which shows anti-hyperglycemic potency such as Pioglitazone and Rosiglitazone. In our attempt we have prepared 4-[2-(methyl-2-pyridin-2yl-amino)-ethoxy]–benzaldehyde derivatives. Condensation of aryl Aldehydes with aryl ketones by Aldol condensation and the derivatives may have comparable biological importance.

Key words: 2, 4-thiazolidindiones, pioglitazone, Rosiglitazone, Aldol condensation.

INTRODUCTION

4-[2-(methyl-2-pyridin-2yl-amino)-ethoxy]–benzaldehyde is intermediate to synthesis of Rosiglitazone. Rosiglitazone malate is oral antidiadetic agent which acts primarily by increasing insulin sensitivity.

Rosiglitazone malate is used in the management of type 2 diabetes mellitus also known as non-insulin-dependent diabetes mellitus (NIDDM). Rosiglitazone maleate improves glycemic control while reducing circulating insulin levels. Pharmacological studies in animal models indicate that rosiglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors.

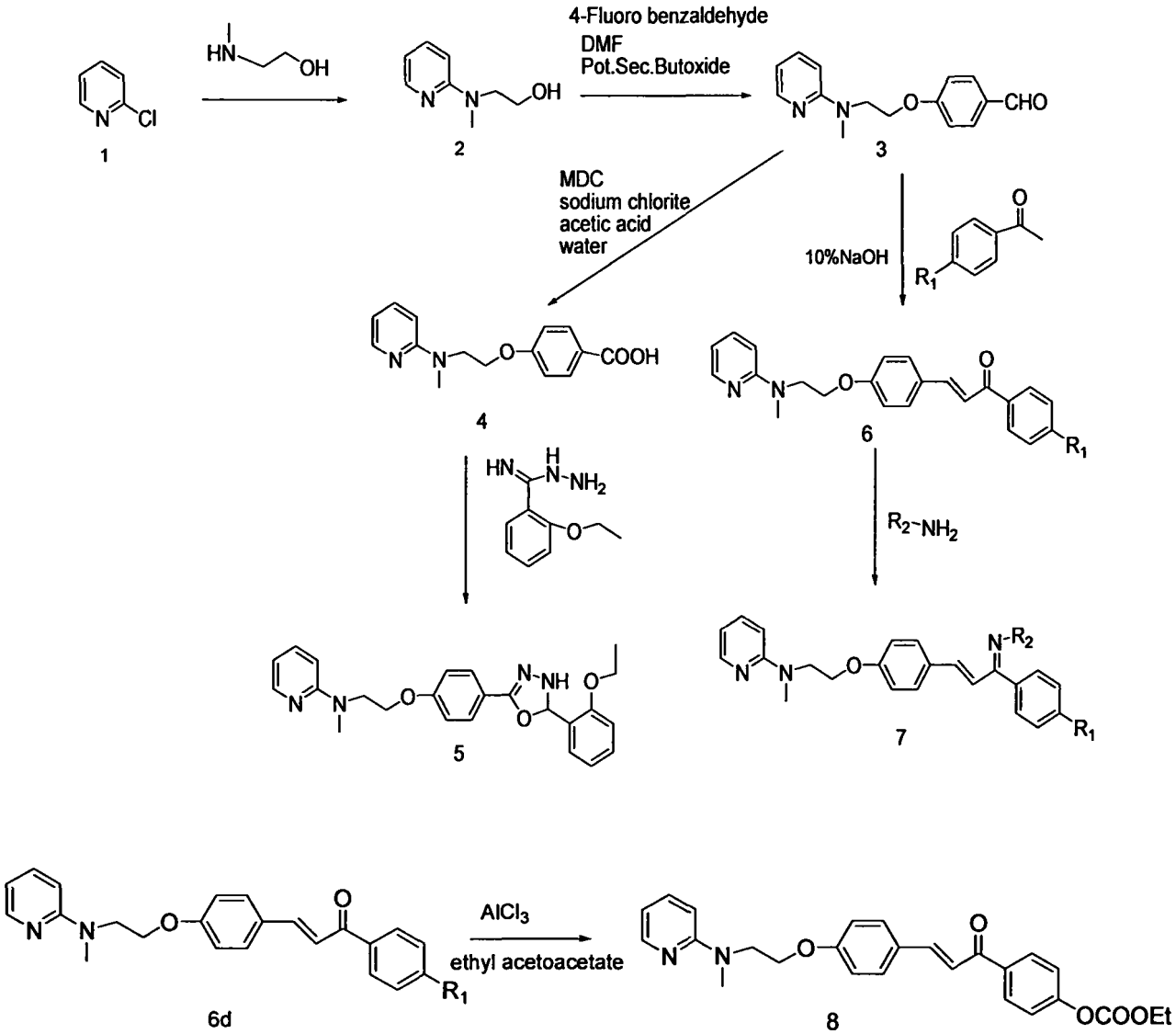
Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical and material interest, which is documented by a steadily increasing number of publications and patents. For instance, 2-amino-1,3,4-oxadiazoles act as muscle relaxants [1] and show antimitotic activity [2] Analgesic, anti-inflammatory, anticonvulsive, diuretic and antiemetic properties are exhibited by 5-aryl-2-hydroxymethyl-1,3,4-oxadiazole derivatives,[3] and 2-hydroxyphenyl-1,3,4-oxadiazole acts as a hypnotic and as a sedative [4] Some material applications of 1,3,4-oxadiazole derivatives lie in the fields of photo sensitizers [5] and liquid crystals.[6]

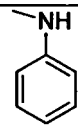
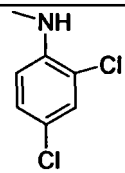
RESULTS AND DISCUSSION

The Aldehydes **3** were prepared using reaction of a 2-halogeno pyridine with 2-amino ethanol gave hetero cyclic amino alcohols in good yields. Reaction of the anion of the amino alcohol with 4-fiuoro benzaldehyde in DMF was employed then gave 4-[2-(methyl-2-pyridin-2yl-amino)-ethoxy] –benzaldehyde **3** in excellent yields.

Condensation of aryl Aldehydes **3** with substituted aryl Ketones by Aldol condensation gives the condensed product **6** which was subjected with number of hydrazine derivatives the compounds **(7a-7d)** was obtained with good yield and purity.

Scheme-I


4-Fluoro benzaldehyde
DMF
Pot.Sec.Butoxide
MDC
sodium chlorite
acetic acid
water
10%NaOH
1
2
3
4
5
6
7
6d
8
AlCl3
ethyl acetoacetate
OCOOEt

Compound	R_1	R_2
6a	F	---
6b	Cl	---
6c	I	---
6d	OH	---
7a	F	-NH2OH
7b	F	-NH2-NH2
7c	F	
7d	F	

EXPERMENTAL

Melting points were determined on a Thomas-Hoover capillary. IR spectra were recorded on a Nicolet 550 series II Maguna FT-IR spectrometer .^{1}H NMR spectra were measured on Varian Gemini 200 MHz spectrometer in DMSO-d_6 with TMS as the internal standard. Mass spectra were recorded on Shimadzu LCMS-QP8000, LC-MS and AB-4000 Q-trap LC-MS/MS. Silica gel column chromatography using Merck silica gel 60ASTM(70-230) mesh.

Synthesis of 2-(N-methyl-N-(Pyridin-2-yl) amino) ethanol (2)

To a mixture of 2-chloropyridine, (40.0 g, 0.352 mol) and 2-aminoethanol (48.2 g, 0.790 mol) heated to 145-155^{0}C and maintained for 10-12 h, the reaction was monitored by TLC, after completion of the reaction, cool to 25-35^{0}C , added saturated sodium chloride solution (~ 98 mL), and extracted with toluene (4 x 50 mL), the combined organic layer was distilled, yielded 14 g. ^{1}H-NMR ($CDCl_3$, δppm): 3.10(s, 3H ,N-CH_3),3.6-3.85(m, 4H, $(CH_2)_2$) 5.25(s, 1H, exchanges with D_2O) 6.6(m , 2H,Ar-H), 7.40(t, 1H,Ar-H), 8.10(d, 1H,Ar-H),4.78(s, 1H,OH). ^{13}C-NMR ($CDCl_3$, δppm) 34.7, 58.6, 61.4, 106.2, 117.9, 138.3, 148.1, 154.1 EI ms: m/z: 152.09; Anal.Calcd.for $C_8H_{12}N_2O$ (152.09) C: 63.13; H: 7.95; N: 18.41; Found C: 63.21; H: 7.99; N: 18.52.

Synthesis of 4-[2-(methyl-2-pyridin-2yl-amino)-ethoxy] –benzaldehyde (3)

The crude compound (10 g), KOH (2.62g), and DMF (30 mL) were stirred for 10 h under nitrogen at 25-35^{0}C temperature, after completion of the reaction (monitored by TLC) water (500 mL) was added and stirred for 2-4 h, the obtained solid was filtered and washed with water suck dry for 1-1.5 h, to gave 4-[2-(methyl-2-pyridin-2yl-amino)-ethoxy] –benzaldehyde. ^{1}H-NMR ($CDCl_3$, δppm): 3.21 (s, 3H,N-CH_3) 3.73 (m,2H,N-CH_2) 3.98(m, 2H,O-CH_2) 6.43-8.02 (m, 8H, Ar -H); 9.92 (s,1H,CHO). ^{13}C-NMR ($CDCl_3$, δppm) 34.7, 58.8, 66.1, 106.2, 114.9, 117.9, 128, 131.9, 138.3, 148.1, 154, 165.2,191. EI ms: m/z: 256.12; Anal.Calcd.for $C_{15}H_{16}N_2O_2$ (256.3) C: 70.29; H: 6.29; N: 10.93; Found C: 70.40; H: 6.39; N: 11.10.

Procedure for the preparation of 4-[2-(methyl-pyridene-2-yl-amino)-ethoxy]-benzoic acid (4)

4-[2-(methyl-2-pyridin-2yl-amino)-ethoxy]–benzaldehyde 1.0g (0.00039 mol) and dicholoro methane into the RB flask cooled to 0.5^{0}C added solution of sodium chlorite 1.08 g (0.0117 mol) and acetic acid 2.5 mL at 0-5^{0}C. Stirred the reaction mass for 30 min. TLC checked for starting material completion. After completion of starting material added 5 mL water and extract with dichloro methane 10 mL, organic layer separated distilled out completely and scratched the solid material.^{1}H-NMR ($CDCl_3$, δppm): 3.21 (s, 3H,N-CH_3) 4.14-4.24 (m,4H,(CH2)2), 6.63-8.16 (m, 8H, Ar -H); 12,74 (s,COOH) ^{13}C-NMR ($CDCl_3$, δppm) 34.7, 58.8, 66.1, 106.2, 114.3, 117.9, 121.8, 130.9, 138.3, 148.1, 154.1, 164.6, 169.3. EI ms: m/z: 272.12; Anal.Calcd.for $C_{15}H_{16}N_2O_3$ (272.3) C: 66.16; H: 5.92; N: 10.29; Found C: 68.23; H: 6.11; N: 10.31.

Procedure for the preparation of (2-{4-[5-[(2-ethoxy phenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenoxy)ethyl)-N-methyl pyriden-2-amine (5)

The mixture of 25 mL methanol, and2-ethoxybenzimidohydrazide (4.9 g 0.0275 mol) and compound 4 (5.0 g 0.0183 mol) was heated to 60-65^0 C and maintained checked TLC , starting material absent, distilled methanol completely, cooled the residue to 25^{0}C and added toluene 25 mL followed by the addition of phosphorous oxy chloride 2.5 mL (0.0275 mol) heated to 80^{0}C with stirring for 3 h. Evaporated to dryness under reduced pressure. Added water and adjusted P_H 8-5 with caustic lye charged dichloromethane and stirred for 10 min, layer separated and isolated in acetonitrite. ^{1}H-NMR (DMSO-d_6, δppm): 6.61-8.01 (m, 8H, Ar -H) 3.21 (s, 3H, N-CH_3) 4.09-4.24 (m,6H,$(CH_2)_3$) 1.32 (s,3H,CH_3) ^{13}C-NMR ($CDCl_3$, δppm) 14.8, 34.7, 58.8, 66.1,73.1, 106.2, , 112.2, 114.5, 117.9, 120.1, 126.7, 128.1, 138.3, 148.1, 153.3, 154 . EI ms: m/z: 418.2; Anal.Calcd.for $C_{29}H_{25}N_4O_3$ (418.49) C: 68.88; H: 6.26; N: 13.39; Found C: 68.97; H: 6.31; N: 13.41.

Synthesis of 1-(4-fluoro-phenyl)-3-{4-[2-(methyl-pyriden-2-yl-amino)-ethoxy]-phenyl}-propenone (6)

4-[2-(methyl-2-pyridin-2yl-amino)-ethoxy]–benzaldehyde 2.0 g (0.0079 mol) , 4-fluro benzaldehyde (0.0102 mol) , 10% sodium hydroxide 3.5 mL, followed by the addition of ethanol 20 mL were stirred for 2-3 h, at 25-35^{0}C . TLC observed absence of starting material. After completion of starting material charged 20 mL water and stirred reaction mass for 45 min and filter the solid and washed with water and the compound, dried in oven under vacuum for 4 h at 35^{0}C. ^{1}H-NMR ($CDCl_3$, δppm): 3.1 (s, 3H, N-CH_3) 4.24 (m,2H, O-CH_2) 4.14 (m, 2H, N-CH_2), 6.63-8.16 (m, 12H, Ar -H); 8.06 (d,1H,Ar-CH),7.59 (d,1H,CO-CH). ^{13}C-NMR ($CDCl_3$, δppm) 34.7, 58.8, 66.1, 106.2, 116.0, 117.9, 121.3, 131.5, 138.3, 148.1, 154.1, 158.6, 168.7. EI ms: m/z: 376.16; Anal.Calcd.for $C_{23}H_{21}FN_2O_2$ (376.42) C: 73.39; H: 5.62; N: 7.44; Found C: 73.51; H: 5.74; N: 7.61.

In similar way we have prepared derivatives having R_1 as chloride, iodide and hydroxyl groups

Procedure for the preparation of 1-(4-fluoro-phenyl)-3-{4-[2-(methyl-pyriden-2-yl-amino)-ethoxy]-phenyl}-propenone oxime (7a)

To solution of 6a 1.0 g (0.0027 mol) in 5.0 mL of isopropyl alcohol charged K_2CO_3 0.5 g (0.0035 mol) and hydroxyl amine hydrochloride (0.0044 mol) heated to reflux. TLC checked after 2 h, no starting material observed, distilled solvent completely under vacuum and charged dichloro methane 20 mL to reaction mass and washed reaction mass with water (2X 15 mL) concentrated organic layer under vacuum and solid material scratched. ^{1}H-NMR (DMSO-d_6, δppm): 1.14 (s, 3H, CH_3) 2.39 (s,3H,Ar-CH_3) 7.4 (s, 1H, Ar - NH) 10.2 (s, 1H, CONH) 3.92 (s, 2H, N-CH_2- CO) 10.47

(s, 1H, Indole NH) 6.43-7.62 (m, 8H, Ar -H); ^{13}C-NMR ($CDCl_3$, δppm) 34.7, 58.8, 66.1, 106.2, 114.3, 115.6, 117.9, 120.6, 126.8, 128.7, 130.8, 138.3, 142.4, 148.1, 154.1, 158.6, 164.6, 165.2. EI ms: m/z: 391.17; Anal.Calcd.for $C_{23}H_{22}FN_3O_2$ (391.44) C: 70.57; H: 5.66; N: 10.73; Found C: 70.59; H: 5.71; N: 10.80.

Procedure for the preparation of (2-{4-[3-(4-fluoro-phenyl)-3-hydrazono-propenyl]-phenoxy}-ethyl)-methyl-pyriden-2-yl-amine (7b)

To solution of 6a 0.5 g (0.00132 mol) in 2.5 mL of isopropyl alcohol charged hydrazine Di hydrochloride 0.2 g (0.00199 mol) and cooled the reaction mass to 0 -5^{0}C followed by the addition of 2 g K_2CO_3 and stirred for 30 min and checked TLC observed starting material absent, filter the solid and washed with ethanol. ^{1}H-NMR (DMSO-d_6, δppm): 1.14 (s, 3H, CH_3) 2.39(s,3H,Ar-CH_3) 7.4(s, 1H, Ar - NH) 10.2 (s, 1H, CONH) 3.92 (s, 2H, N-CH_2- CO) 10.47 (s, 1H, Indole NH) 6.43-7.62 (m, 8H, Ar -H); ^{13}C-NMR ($CDCl_3$, δppm) 34.7, 58.8, 66.1, 106.2, 114.3, 115.6, 118.7, 126.8, 129.8, 138.3, 148.1, 154.1, 158.6, 165.2. EI ms: m/z: 390.19; Anal.Calcd.for $C_{23}H_{23}FN_4O$ (390.45) C: 70.75; H: 5.94; N: 14.35; Found C: 70.81; H: 5.99; N: 14.41.

Procedure for the preparation of (2-{4-[3-(4-fluoro-phenyl)-3-(phenyl-hydrazono)-propenyl]-phenoxy}-ethyl)-methyl-pyriden-2-yl-amine (7c)

To solution of 6a 4.0 g (0.005319 mol) in 5.0 mL of ethanol charged hydrazine hydro chloride 3.0 g (0.010638 mol) and cooled the reaction mass to 0-5^{0}C then adjusted P^H to 1.0 with methanolic HCl, stirred for 30 min checked TLC observed starting materials absent, filter the solid and washed with isopropyl alcohol.^{1}H-NMR (DMSO-d_6, δppm): 1.14 (s, 3H, CH_3) 2.39(s,3H,Ar-CH_3) 7.4(s, 1H, Ar - NH) 10.2 (s, 1H, CONH) 3.92 (s, 2H, N-CH_2- CO) 10.47 (s, 1H, Indole NH) 6.43-7.62 (m, 8H, Ar -H); ^{13}C-NMR ($CDCl_3$, δppm) 34.7, 58.8, 66.1, 106.2, 113.3, 117.9, 122.4, 126.8, 129.8, 130.8, 138.9, 143, 148.1, 154.1, 158.6, 165.2 . EI ms: m/z: 466.22; Anal.Calcd.for $C_{29}H_{27}FN_4O$ (466.55) C: 74.66; H: 5.83 N: 12.01; Found C: 74.71 H: 5.89 N: 12.13.

Procedure for the preparation of (2-{4-[3-(2,4-dichloro-phenyl)-hydrazono]-3-3-(4-fluoro-phenyl)-propenyl]-phenoxy}-ethyl)-methyl-pyridin-2-yl-amine (7d)

To solution of 6a 0.5 g (0.0013 mol) in 5.0 mL of ethanol charged 2, 4 dicholoro phenyl hydrazine 0.5 g (0.0026 mol) and cooled the reaction mass to 0 -5^{0}C then adjusted P^H with 1.0 mL methanolic HCl stirred reaction mass for 30 min checked TLC shows absence of starting material, filter the solid and washed with isopropyl alcohol.^{1}H-NMR (DMSO-d_6, δppm): 1.14 (s, 3H, CH_3) 2.39(s,3H,Ar-CH_3) 7.4(s, 1H, Ar - NH) 10.2 (s, 1H, CONH) 3.92 (s, 2H, N-CH_2- CO) 10.47 (s, 1H, Indole NH) 6.43-7.62 (m, 8H, Ar -H); ^{13}C-NMR ($CDCl_3$, δppm) 34.7, 58.8, 66.1, 106.2, 114.3, 117.9, 124.6, 125.7, 127.7, 130.8, 138.3, 145.2, 148.1, 154.1, 158.6, 165.2. EI ms: m/z: 534.14; Anal.Calcd.for $C_{29}H_{25}N_4OCl_2F$ (535.44) C: 65.05; H: 4.71; N: 10.46; Found C: 65.15; H: 4.79; N:10.56.

Procedure for the preparation of {4-(3-{4-[2-(methyl-pyriden-2-yl-amino)-ethoxy]-phenyl}-acryloyl)-phenyl-acetic acid ethyl ester (8)

To solution of 6d 0.5 g in 5.0 mL of dichloromethane charged ethylacetoacetate 0.5 g and aluminium chloride 0.5 g at 0 -5^{0}C, stirred reaction mass for 1h. Checked TLC observed starting materials absent, filter the undissolved solid and washed with DCM 1.0 mL, and organic layer washed with water and distilled organic layer completely under vacuum. ^{1}H-NMR ($CDCl_3$, δppm): 2.47 (s, 3H,N-CH_3) 3.48-4.21 (m,6H,$(CH2)_3$), 6.60-8.11 (m, 12H, Ar -H); 7.50-7.90 (d,Ar-CH) ^{13}C-NMR ($CDCl_3$, δppm) 13.8, 34.7, 58.8, 66.1, 106.2, 114.3, 117.9, 122.1, 126.8, 129.8, 130.3, 134.7, 138.3,

145.1, 153.1, 157.1, 189.7. EI ms: m/z: 446.18; Anal.Calcd.for $C_{26}H_{26}N_2O_5$ (446.5) C: 69.94; H: 5.87; N: 6.27; Found C: 66.99; H: 5.92; N: 6.35.

REFERENCES

1. Yale, H. L.; Losee, K. *J. Med. Chem.* 1966, *9*, 478.
2. Ghiran, D.; Schwartz, I.; Simiti, I. *Farmacia* 1974, *22*,141.
3. Thomas, J. *Ger. Offen.* 2403357 (1974); *Chem. Abstr.*1974, *81*, 136153.
4. Adelstein, G. W.; Yen, C. H.; Dajani, E. Z.; Bianchi, R. G.*J. Med. Chem.*1976,*19*,1221.
5. Schinzel, E.; Martini, T.; Spatzeier, W; Probst, H. *DE. P.*3126464 (1983/1981), Hoechst AG; *Chem. Abst.* 1983, *98*, 199850.
6. Chudgar, N. K.; Shah, S. N.; Vora, R. A. *Mol. Cryst. Liq.Cryst.* 1989, *172*, 51

Received on November 7, 2009.