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Synthesis and characterization of 8-(N-substituted phenyl)-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]-pyridines

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ABSTRACT

A series of new 8-(N-substituted phenyl)-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]-pyridines ***6a-d*** *were prepared by condensation of aq. HCl with hydrazinodioxolane derivatives* ***5a-d*** *which were prepared by the action of hydrazine hydrate on chlorodioxolane derivatives* ***4a-d*** *which in turns have been prepared by the action of ethylene glycol on target compounds* ***3a-d****. The structures of the newly synthesized compounds have been confirmed on the basis of elemental analysis and spectral studies.*

Keywords: Dihdropyridines, Vilsmeier-Haack reaction, pyrazolodihydropyridines.

INTRODUCTION

1,4-dihydropyridines and their derivatives are an important class of bioactive molecules in the pharmaceutical field[1]. The dihydropyridine heterocyclic ring is a common feature of a variety of bioactive compounds including anticonvulsant, antidiabetic, antianxiety, antidepressive, antitumor, analgesic, sedative, vasodilator, bronchodilator, hypnotic and anti-inflammatory agents[2].

Diydropyridines are reported as calcium channel blockers[3] and are clinically useful agents for the treatment of cardiovascular diseases such as anginapectoris[4] and hypertension[5].These are also used as antioxidants and are important for developing drugs. However, these are relatively difficult to synthesize.

Many derivatives of 1,4-dihydropyridines with more valuable pharmacological properties[6-8], which make further searches in the 1,4-dihydropyridine series extremely urgent.

Pyrazolopyridines and its hydroderivatives are very interesting pyrazole derivatives with wide-ranging biological activities[9]. A number of pyrazolopyridines exhibit a wide range of biological activities, including interesting anxiolytic activity (e.g. tracazolate), dopamine D3 receptor antagonist, antiherpetic and antiallergic properties[10]. In view of these findings, in continuation of our work and interest in V-H reaction[11-17], it was contemplated to synthesize some new pyrazolo derivatives **6a-d** (**Scheme-II**).

MATERIALS AND METHODS

All melting points were determined in open capillary and are uncorrected. The IR spectra were recorded on FT-IR spectrophotometer. ^{1}HNMR spectra were recorded on varian USA Mercury plus 300 MHz NMR spectrometer with $CDCl_3$ as a solvent using TMS as internal reference (chemical shift in δ ppm). The starting compounds were synthesized according to **scheme-I.** Glutaric acid **1** was converted into *N*-substituted phenyl glutarimides **2a-d** which were then diformylated using Vilsmeier-Haack reaction to form **3a-d.**

General procedure for the synthesis of 2,6-dichloro-3,5-bis-[1,3]dioxolan-2-yl-1-(*N*-substituted-phenyl)-1,4-dihydropyridines 4a-d.

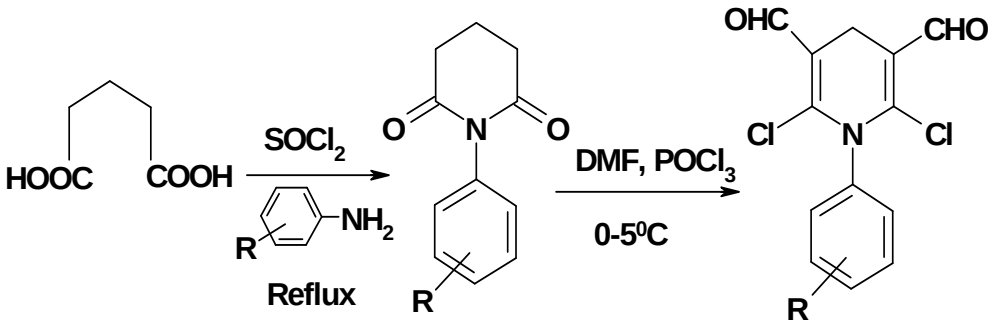
The corresponding 2,6-dichloro-1-(*N*-substituted phenyl)-1,4-dihydropyridine-3,5-dicarbaldehyde **3a-d** (1mmole) was suspended in toluene (20 ml), and ethylene glycol (0.37 gm, 6 mmole) and few crystals of P-toluene sulphonic acid were added. The reaction mixture was refluxed for 4 hrs. with the continuous removal of the formed water by the aid of Dean-Stark trap. After completion of reaction, saturated aq. sodium carbonate (20 ml) was added. The organic layer was separated, washed with water, dried and evaporated under vaccume which gave pale yellow solid. It was recrystalised from ethanol to afford a pure 2,6-dichloro-3,5-bis-[1,3]dioxolan-2-yl-1-(*N*-substituted-phenyl)-1,4-dihydropyridines **4a-d (Scheme-II).**

General procedure for the synthesis of 2,6-dihydrazino-3,5-bis-[1,3]dioxolan-2-yl-1-(*N*-substituted-phenyl)-1,4-dihydropyridines 5a-d.

A solution of 2,6-dichloro-3,5-bis-[1,3]dioxolan-2-yl-1-(*N*-substituted-phenyl)-1,4-dihydropyridines **4a-d** (1 mmole) in ethanol and hydrazine hydrate (20 mmol) was heated under reflux for 3-4 hrs. Then cooled solution was evaporated and residue recrystalized from ethanol to give a pure 2,6-dihydrazino-3,5-bis-[1,3]dioxolan-2-yl-1-(*N*-substituted-phenyl)-1,4-dihydropyridine **5a-d (Scheme-II).**

General procedure for the synthesis of 8-(N-substituted phenyl)-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]-pyridines 6a-d:

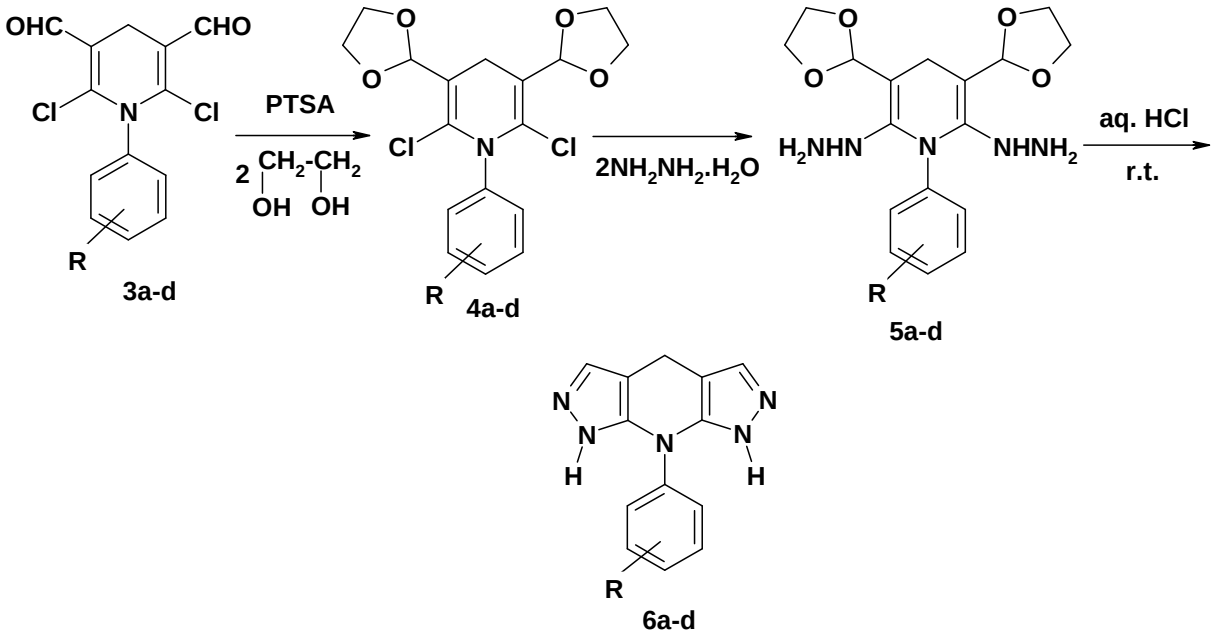
A solution of **5a-d** (1 mmol) in aqueous 2*M* HCl (20 mL) was stirred at r.t. for 40 minutes. During this time a yellow to orange precipitate of hydrochloride salt of **6a-d** was formed which was dissolved in water (20 mL). The acidic solution was neutralized with 2*M* NaOH and the resulting precipitate was filtered off and washed with water then recrystallized from ethanol to give pure **6a-d (Scheme-II).**



1 **2a-d** **3a-d**

R, a = -H, b = -4CH$_3$, c = -2Cl, d = -4Cl

(Scheme-I)



R, a = -H, b = -4CH_3, c = -2Cl, d = -4Cl
(Scheme-II)

2,6-Dichloro-3,5-bis-[1,3]dioxolan-2-yl-1-phenyl-1,4-dihydropyridine 4a:
Pale yellow solid, 72% yield, m.p. 57-59^{0}C, 2964 (-CH str), 1450 (ArC=C), 1248 (C-N), 1050 (C-O), 755 (C-Cl).

2,6-Dichloro-3,5-bis-[1,3]dioxolan-2-yl-1-(4-methyl-phenyl)-1,4-dihydropyridine 4b:
Light yellow solid, 82% yield, m. p.66-68^{0}C, IR (KBr): 2988 (CH_3), 2950 (CHstr.), 1460 (ArC=C),1250 (C-N), 1040 (C-O), 754 (C-Cl) cm^{-1}.

2,6-Dichloro-3,5-bis-[1,3]dioxolan-2-yl-1-(2-chloro-phenyl)-1,4-dihydropyridine 4c:
Pale yellow solid**,** 68% yield, m. p.49-51^{0}C, IR (KBr): 2930 (CH str.), 1475 (ArC=C), 1240 (C-N), 1035 (C-O), 780 (C-Cl) cm^{-1}.

2,6-Dichloro-3,5-bis-[1,3]dioxolan-2-yl-1-(4-chloro-phenyl)-1,4-dihydropyridine 4d:
Faint yellow solid**,** 78%yield, m. p.101-103^{0}C, IR (KBr): 2935 (CH str.), 1448 (ArC=C), 1247 (C-N), 1050 (C-O), 760 (C-Cl) cm^{-1}.

2,6-Dihydrazino-3,5-bis-[1,3]dioxolan-2-yl-1-phenyl-1,4-dihydropyridine 5a:
Deep yellow solid, 78% yield, m.p. 69-71^{0}C; IR (KBr): 3305(–NHstr.), 2923(-CHstr.), 1447(-ArC=C), 1242(-C-N), 1055 (-C-O) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 2.0 (s, 6H, 2NHNH_2), 3.15 (s, 2H, CH_2), 3.90-4.00 (m, 8H, 2OCH_2CH_2O), 5.58 (s, 2H, 2CH), 7.01-6.46 (m, 4H, ArH); Anal.Calcd. for $C_{17}H_{23}O_4N_5$:C, 56.49; H, 6.41; N, 19.37. Found: C, 56.30; H, 6.21; N, 19.22.

2,6-Dihydrazino-3,5-bis-[1,3]dioxolan-2-yl-1-(4-methyl-phenyl)-1,4-dihydro-pyridine 5b:
Yellow solid, 80%yield, m. p.81-83^{0}C; IR (KBr): 3250 (NH str.),2950(CH_3), 2922 (CH str.),1480 (ArC=C),1260 (C-N), 1062 (C-O) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 2.0 (s, 6H, 2NHNH_2), 3.15 (s, 2H, CH_2), 3.90-4.00 (m, 8H, 2OCH_2CH_2O), 5.58 (s, 2H, 2CH), 7.01-6.46 (m, 4H, ArH); Anal.Calcd. for $C_{18}H_{25}O_4N_5$: C, 57.58; H, 6.71; N, 18.65, Found : C, 57.48; H, 6.50; N, 18.51.

2,6-Dihydrazino-3,5-bis-[1,3]dioxolan-2-yl-1-(2-chloro-phenyl)-1,4-dihydro- pyridine 5c:
Yellow solid, 75% yield, m. p. 62-64^{0}C; IR (KBr): 3306 (NH str.), 2930 (CH str.), 1475 (ArC=C),1255 (C-N), 1060 (C-O) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 2.2 (s, 6H, 2NHNH_2), 3.00 (s, 2H, CH_2), 4.05- 4.16 (m, 8H, 2-OCH_2CH_2O-), 5.85 (s, 2H, 2CH), 7.20-6.50 (m, 4H, ArH); Anal.Calcd. for $C_{17}H_{22}O_4N_5Cl$: C, 51.57; H, 5.60; N, 17.69 , Found : C, 51.40; H, 5.49; N, 17.38.

2,6-Dihydrazino-3,5-bis-[1,3]dioxolan-2-yl-1-(4-chloro-phenyl)-1,4-dihydropyridine5d:
Deep yellow solid**,** 82% yield, m. p. 85-87^{0}C; IR (KBr): 3326 (NH str.), 2923 (CH str.), 1481 (ArC=C),1260 (C-N), 1076 (C-O) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 2.4 (s, 6H, 2NHNH_2), 2.88 (s, 2H, CH_2),4.08-4.14 (m, 8H, 2-OCH_2CH_2O-), 5.65 (s, 2H, 2CH), 7.40-6.70 (m, 4H, ArH); Anal.Calcd. for $C_{17}H_{22}O_4N_5Cl$: C, 51.57; H, 5.60; N, 17.69, Found: C, 51.38; H, 5.52; N, 17.35., LC-MS [ESI] m/z (%)**:** 394 (100), 372 (18), 242 (10).

8-(phenyl)-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]-pyridine 6a:
Faint yellow solid, 64% yield, m.p. 182-184^{0}C IR (KBr): 3198(NH),1598(C=N),1442(ArC=C), 1247(C-N) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 3.81(s, 2H, CH_2), 6.81-6.34(m, 5H, ArH), 7.4(s, 2H, 2HC=N), 13.7(s, 2H, 2NH).

8-(4-methyl-phenyl)-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]-pyridine 6b:
Creamy solid, 71% yield, m.p. 198-200^{0}C, IR (KBr): 3200(NH), 2921 (CH_3), 1602(C=N), 1405(ArC=C), 1248(C-N) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ2.35(s, 3H, CH_3), 3.15(s, 2H, CH_2), 6.90-6.50(m, 4H, ArH), 7.9(s, 2H, 2HC=N), 13.2(s, 2H, 2NH).

8-(2-chloro-phenyl)-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]-pyridine 6c:
Yellow solid, 70% yield, m.p. 224-226^{0}C IR (KBr): 3178(NH),1598(C=N),1480(ArC=C), 1240(C-N) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 3.52(s, 2H, CH_2), 6.87-6.40(m, 4H, ArH), 7.6(s, 2H, 2HC=N), 13.5(s, 2H, 2NH).

8-(4-chloro-phenyl)-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]-pyridine 6d:
Dark yellow solid, 65% yield, m.p. 214-216^{0}C IR (KBr): 3202(NH),1604(C=N),1447(ArC=C), 1254(C-N) cm^{-1}; ^{1}HNMR ($CDCl_3$): δ3.15(s, 2H, CH_2), 6.87-6.34(m, 4H, ArH), 7.4(s, 2H, 2HC=N), 13.7(s, 2H, 2NH).

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