January 2008 *Volume 4 Issue 1*

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 4(1), 2008 [44-47]

Synthesis of diethyl-1,4-dihydro-2,6-dimethyl-4-[(5chloro) pyrazole)]-3, 5-pyredinedicarboxylates: as calcium antagonist

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Received: 22nd May, 2007 ; Accepted: 27th May, 2007

ABSTRACT

By the reaction of **(2a-f)** with ethylacetoacetate and ammonia (or amines) in presence of alcohol resulted in new 1,4-dihydropyridine derivatives **(3a-f)** having a 5-chloropyrazole ring at 4-position of 1,4-dihydropyridine ring. These molecules may represent novel analogous of calcium chennel blocking agent.

KEYWORDS

Dihydropyridines;
Pyrazole;
Calcium antagonists;
Hantzsch synthesis.

INTRODUCTION

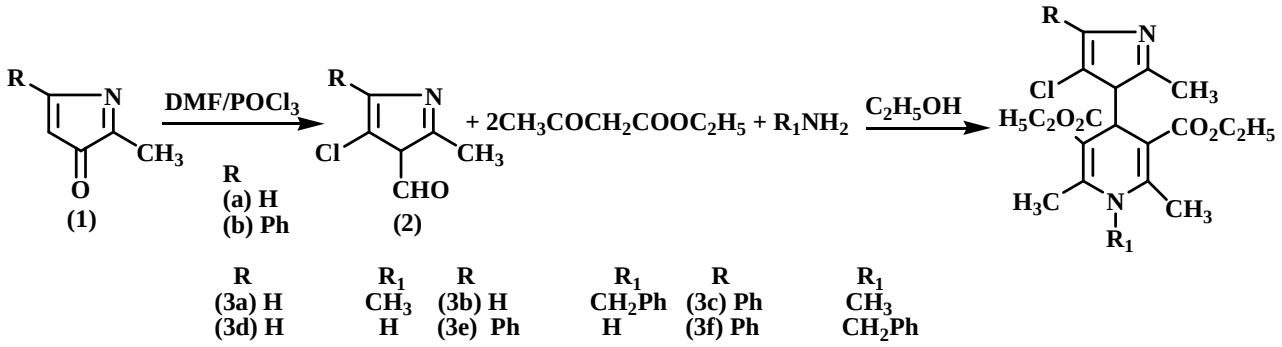
The present work is the extension of our earlier work in which we introduce 6-cholorothiouracil at 4-position of 1,4-dihydropyridine ring[1]. The presence of 1,4-dihydropyridine ring in naturally occurring compounds and coenzumes such as NADH & NADPH made these compounds an interesting area of research[2,3].

Structure activity relationships determined the effect of substitution on the 1,4-dihydropyridine ring. Although even the simple 2,6-dimethyl-3,5-dicarbalkoxy-1,4-dihydropyridines have some hypotensive activity in the anesthetized animals, good activity is generally observed with those compounds having cyclic substituent at the 4-position. It is well known that 4-aryl 1,4-dihydropyridines form an important class of calcium antagonists[4-11]. For instance, nifedipine[12] is used clinically against angina pectoris and hypertension.

In this present work we combined 1,4-dihydropy ridine ring with 5-chloropyrazole unit. It is well known that 5-chloropyrazole derivatives are used as materials for drugs and agrochemicals. Thus incorporation of 5-chloropyrazole at 4-position of 1,4-dihydropyridine may improve the bioactivity of such systems. We are now reporting the synthesis of new 1,4-dihydropyridine derivatives having a 5-chloropyraole unit at 4-position of 1,4-dihydropyridine ring by employing the Hantzsch synthesis[13]. Hence aldehydes **(2a-f)** were reacted with ethylacetoacetate and appropriate amines (such as ammonia, methylamine and benzyl amine) to get corresponding dihydropyridines (SCHEME). The aldehydes **(2a-f)** used in this reaction were prepared by the Vilsmeier-Haack reaction[14] of the corresponding pyrazolones **(1a-f)** respectively with phosphorous oxy chloride in dimethylformamide.

EXPERIMENTAL

All reported ^{1}HNMR spectra were recorded with Bucker(300MHz) spectrometer. Chemical shifts are reported as δ values relative to TMS peak defined at δ=0.00. Mass spectra were recorded on Geol GC-MS spectrometer by using electron ionization (EI) at



SCHEME 1

70ev and only major peaks are quoted. C H and N were analyzed on Perkin Elmer 240 analyzer. Analytical TLC was carried out on commercially prepared plates coated with 0.25mm of Merck Silica gel $60F_{254}$. Solvents were dried and distilled prior the use under an inert atmosphere. Unless otherwise specified all starting materials were purchased from commercial suppliers and were used without further purification. Melting points are incorrect

Preparation of 3-methyl-1H-2-pyrazolin-5-one[15] (1a)

A mixture of ethylacetoacetate(2.0ml, 0.026mol) and phenyl hydrazine (1.5ml, 0.026mol) was heated in an oil bath at 110-120^{0}C for 4hrs. The reaction mixture was cooled and diethyl ether (50ml) was added to it. After shaking, the solid obtained was filtered, washed with diethyl ether dried and recrystallized from ethanol to give white crystaline compound 3-Methyl-1H-2-pyrazolin-5-one **(1a)**.

Preparation of 5-chloro-3-methyl-1H-2-pyrazole-4-carboxaldehyde[16] (2a)

3-Methyl-1H-2-pyrazolin-5-one(1a, 2.0g, 0.01 mol) in dimethylformamide (2.7ml, 0.034mol) was cooled to 0^{0}C in an ice bath. Phosphorous oxychloride (3.2ml, 0.034mol) was then added to it drop wise maintaining the temperature between 10-12^{0}C. The reaction mixture was refluxed for one and half hr. After that reaction mixture was cooled, poured in crushed ice with constant stirring and left for 1hr at room temperature. The solid thus separated was filtered, dried and crystallized from ethanol as pale yellow flakes of 5-Chloro-3-methyl-1H-2-pyrazole-4-carboxaldehyde **(2a)**.

General method for the preparation of 1, 4-dihydro pyridines

One mol of an aldehyde and two mol of ethyl acetoacetate were dissolved in an equal volume of ethyl alcohol. Two moles of concentrated aqueous ammonia were added and the mixture was refluxed for 3hrs on a steam bath. The product obtained was extracted with dichloromethane and the crude product obtained was purified by column chromatography.

Thus the compound **(2a)** (0.4025g, 1mmol) was refluxed with R-NH_2 (R=H, 0.017g, 1mmol) and ethyl acetoacetate (0.16g, 2mmol) in equal volume of ethyl alcohol for 3hrs. Water was added in the reaction mixture and the product was extracted with dichloro methane. The organic layer was washed with brine solution, dried and concentrated at reduced pressure to give yellow solid compound. The crude product obtained was purified by column chromatography (hexane-chloroform, 1:9) and the structure, 4-[5-chloro-3-methyl-1H-pyrazole]-1,2,6-trimethyl-3,5-dicarbethoxy -1,4-dihydropyridine 3a was assigned on the basis of its spectral data (NMR,IR, and Mass) and CHN analysis. Its ^{1}H NMR (δ, $CDCl_3$, 300MHz) showed a singlet at 1.91 for six protons of CH_3, a triplet at 1.27 indicating the presence of $–CO_2CH_2CH_3$ protons, a quartet 4.09 indicating the presence of $-CO_2CH_2CH_3$ protons, a singlet at 2.91 indicating the presence of $–NCH_3$ protons and a singlet at 4.57 indicating the presence of proton at 4-position. Its mass spectrum gives M^+ at 382 (M^+), M. P. 135-137^{0}C.

Aldehydes **(2b)** was also reacted with ethylaceto acetate and ammonia (or amines) in ethanol to get corresponding 1,4-dihydropyridines (analytical data for all included in the TABLES 1 and 2).

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Pharmacology

All the compounds prepared were tested for negative inotropic and chronotropic effects on the frog heart as per the method mentioned by Hedge and Rao[17].

The test compounds of varying concentration 10^{-11}M to 10^{-8}M for compounds**(3a-f)** were made by dissolving with **(1-3)** drops of alcohol and diluted with water. The resulting solution was then injected into the lower portion of canula so that the entire drug goes into the heart with ringer solution.

The kymograph were recorded with the speed of 2.5mm/sec. for test compounds and was compared with the standard calcium channel blocker i.e. nifedipine of different concentration and number of heartbeats were counted for each test compound in duplicate (The details are given in TABLE 3).

TABLE 1

S.no.	R	R_1	Mol. formula	Yield*(%)	M.P.(^{0}C)
3a	H	CH_3	$C_{18}H_{24}N_3O_4Cl$	78.23	135-137
3b	H	CH_2Ph	$C_{24}H_{28}N_3O_4Cl$	76.00	171-173
3c	Ph	CH_3	$C_{24}H_{28}N_3O_4Cl$	78.73	156-158
3d	H	H	$C_{17}H_{22}N_3O_4Cl$	74.19	131-133
3e	Ph	H	$C_{23}H_{26}N_3O_4Cl$	78.41	139-141
3f	Ph	CH_2Ph	$C_{30}H_{32}N_3O_4Cl$	79.00	173-175

***yield of isolated and purified compounds**

RESULTS AND DISCUSSION

The tested compounds slow down the heart rate and so they show negative chronotropic and inotropic effect on isolated frog heart. It was concluded from the results that the compounds having substituion at nitrogen of 1,4-dihydropyridine ring show poor calcium antagonist activity however the presence of 5-chloropyrazole at position-4 of 1,4-dihydropyridine ring enhances the activity.

ACKNOWLEDGMENT

The authors are highly thankful to the Director of

TABLE 3: Effect of nifedipine and compounds (3a-f) at various molar concentration on heart rate in isolated heart of frog

Comp. no.	Control	10^{-11}M	10^{-10}M	10^{-9}M	10^{-8}M
Nifedipine heart rate (beats/min) (mean ±s.d.)	53±4.2	53±4.1	53±4.3	53±4.3	53±4.3
3a	52±4.0	52±4.0	51±4.2	46±3.9	40±4.2
3b	50±3.2	49±4.2	47±3.6	46±4.0	39±4.5
3c	53±4.5	52±4.3	50±4.0	44±4.2	39±4.3
3d	51±3.7	50±43.6	50±4.0	45±4.2	36±3.9
3e	52±4.3	52±3.9	50±4.2	44±3.7	36±3.7
3f	51±4.1	51±4.0	49±3.9	47±3.7	40±4.2

TABLE 2

Sr. no.	CHN found (Calculated)	IR(KBr)cm^{-1}	^{1}HNMR (300MHz, $CDCl_3$, δppm)	Mass(EI) m/z
3a	56.62 (56.69), 6.25 (6.29), 11.10 (11.0)	2927.46,1 606.54, 1384.48, 1273.70, 1176.70	1.27(t, 6H, $CO_2CH_2C\underline{H}_3$), 4.09(q, 4H, $CO_2C\underline{H}_2CH_3$), 2.91(s, 3H, NCH_3), 2.17(s, 3H, CH_3), 1.91(s, 6H, 2,6-CH_3), 4.57(s, 1H, H-4), 4.21(brs, 1H, NH).	382(M^+), 293, 181, 136, 112, 45
3b	62.90 (62.95), 6.09 (6.12), 9.12 (9.18)	2927.66, 1607.3, 1454.5,1235.47, 1171.38, 1116.3.	1.25(t, 6H, $CO_2CH_2C\underline{H}_3$), 4.10 (q, 4H, $CO_2C\underline{H}_2CH_3$), 4.52 (s, 2H, $C\underline{H}_2C_6H_5$), 2.33(s, 3H, CH_3), 1.90(s, 6H, 2,6-CH_3), 4.84(s, 1H, H-4), 4.32(brs, 1H, NH).7.27-7.34(m, 5H, C_6H_5).	458(M^+), 369, 257,166,136, 112, 91.
3c	62.90 (62.95), 6.08 (6.12),9.20 (9.18)	2927.00, 1606.40, 1501.12,1171.63, 1210.13, 1171.63.	1.10(t, 6H, $CO_2CH_2C\underline{H}_3$), 3.95(q, 4H, $CO_2C\underline{H}_2CH_3$), 2.75(s, 3H, NCH_3),2.11 (m, 9H, 3xCH_3), 1.90(s, 6H, 2,6-CH_3), 4.47(s, 1H, H-4), 7.26(m, 5H, C_6H_5)	458(M^+), 266, 154,109, 112, 45.
3d	55.54 (55.51), 6.01 (5.99), 11.39 (11.43)	2927.24, 1726.17, 1445.78, 1260.72, 1097.31, 1075.54.	1.18(t, 6H, $CO_2CH_2C\underline{H}_3$), 4.02(q, 4H, $CO_2C\underline{H}_2CH_3$),2.23 (m, 9H, 3xCH_3), 4.71(s, 1H, H-4), 6.01(brs, 1H, NH).	368(M^+), 279, 167,137, 112, 30.
3e	62.19 (62.23), 5.83 (5.86), 9.43 (9.47)	2927.09, 1693.17, 1501.35, 1366.70, 1306.24, 1211.56.	1.23(t, 6H, $CO_2CH_2C\underline{H}_3$), 4.01(q, 4H, $CO_2C\underline{H}_2CH_3$),1.95(s, 3H, CH_3), 2.20(s, 6H, 2,6-CH_3), 5.01(s, 1H, H-4), 6.04(brs, 1H, NH),7.26(m, 5H, C_6H_5).	444(M^+), 252, 140,112, 110,31.
3f	67.45 (67.48), 6.04 (6.0), 7.83 (7.87)	2928.26, 1606.61, 1454.02,1235.61, 1171.89, 1116.58	1.17(t, 6H, $CO_2CH_2C\underline{H}_3$), 4.00(q, 4H, $CO_2C\underline{H}_2CH_3$), 4.49(s, 2H, $\underline{H}_2C_6H_5$),2.23 (s, 3H, CH_3), 1.81 (s, 6H, 2,6-CH_3), 4.93 (s, 1H, H-4),7.16-7.26(m, 10H, C_6H_5).	534(M^+), 342, 230,192, 139, 91, 30

Dr. B.R.Ambedkar Center for Bio-medical Research, University of Delhi, Delhi (India) for providing necessary facilities.

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