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# SYNTHESIS OF DIETHYL-1, 4-DIHYDRO-2, 6-DIMETHYL-4-[(5-CHLORO) PYRAZOLE)]-3, 5-PYRIDINEDICARBOXYLATES AS CALCIUM ANTAGONIST

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## 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.

**Key words:** Dihydropyridines, Pyrazole, Calcium antagonists, Hantzsh 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 coenzymes such as NADH and 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-dihydropyridine 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-dihydropyridine 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-dihydropyridine ring with 5-chloropyrazole unit. It is well known that 5-chloropyrazole at 4-position of 1, 4-dihydropyridine may

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improve the bioactivity of such systems. We are now reporting the synthesis of new 1, 4-dihydropyridine derivatives having a 5-chloropyrazole 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 oxychloride in dimethylformamide.

## EXPERIMENTAL

All reported $^1$H NMR spectra were recorded with Bucker (300 MHz) 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 70 eV 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 0.25 mm of Merck Silia gel 60$F_{254}$. Solvents were dried and distilled prior to 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-1 H-2-pyrazolin-5-one[15] (1a)

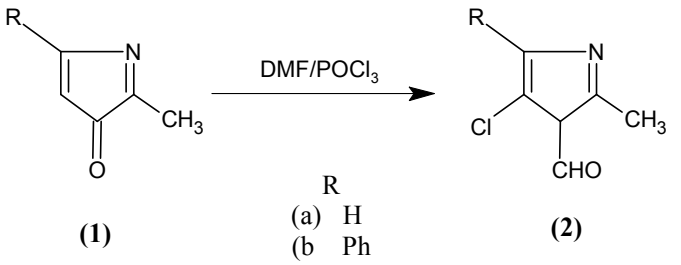
A mixture of ethylacetoacetate (2.0 mL, 0.026 mol) and phenyl hydrazine (1.5 mL, 0.026 mol) was heated in an oil bath at 110-120ºC for 4 hrs. The reaction mixture was cooled and diethyl ether (50 mL) was added to it. After shaking, the sold obtained was filtered, washed with diethyl ether dried and recrystallized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

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

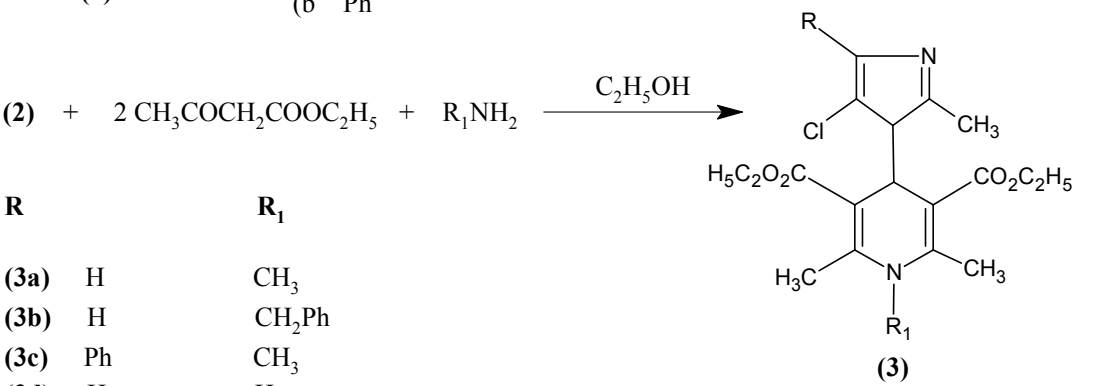
3-Methyl-1H-2-pyrazolin-one (**1a**, 2.0 g, 0.01 mol) in dimethylformamide (2.7 mL, 0.034 mol) was cooled to 0ºC in an ice bath. Phosphorous oxychloride (3.2 mL, 0.034 mol) was then added to it dropwise maintaining the temperature between 10-12ºC. The reaction mixture was refluxed for one and half hr. After that reaction mixture was cooled, poured in crushed ice with constant stirring and left for 1 hr 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-dihydropyridines

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 3 hrs. on a steam bath. The product obtained was extracted with dichloromethane and the crude product obtained was purified by column chromatography.




**(1)** R: (a) H, (b) Ph **(2)**




**(3)**

| R | | $R_1$ |
|---|---|---|
| **(3a)** | H | $CH_3$ |
| **(3b)** | H | $CH_2Ph$ |
| **(3c)** | Ph | $CH_3$ |
| **(3d)** | H | H |
| **(3e)** | Ph | H |
| **(3f)** | Ph | $CH_2Ph$ |

**Scheme**

Thus the compound **(2a)** (0.4025 g, 1 mmol) was refluxed with R-$NH_2$ (R=H, 0.017 g, 1mmol) and ethyl acetoacetate (0.16 g, 2 mmol) in equal volume of ethyl alcohol for 3 hrs. Water was added in the reaction mixture and the product was extracted with dichloromethane. 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 $^1H$ NMR (δ, $CDCl_3$, 300 $MH_z$) 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.

Aldehyde **(2b)** was also reacted with ethylacetoacetate and ammonia (or amines) in ethanol to get corresponding 1, 4-dihydropyridine (analytical data for all included in the Tables 1 and 2).

**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.

## 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.

**Table 2.**

| S.No. | CHN Found (Calculated) | IR (KBr) $cm^{-1}$ | $^1H$ NMR (300MHz, $CDCl_3$, d,ppm) | 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, 1176.60 | 1.27 (t, 6H, $CO_2CH_2CH_3$), 4.09 (q, 4H, $CO_2CH_2CH_3$), 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, $CO_2CH_2CH_3$), 4.10 (q, 4H, $CO_2CH_2CH_3$), 4.52 (s, 2H, $CH_2C_6H_5$), 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, $5H_4$, $C_6H_5$) | 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, $CO_2CH_2CH_3$), 3.95 (q, 4H, $CO_2CH_2CH_3$), 2.57 (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, $CO_2CH_2CH_3$), 4.02 (q, 4H, $CO_2CH_2CH_3$), 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, $CO_2CH_2CH_3$), 4.01 (q, 4H, $CO_2CH_2CH_3$), 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, $CO_2CH_2CH_3$), 4.00 (q, 4H, $CO_2CH_2CH_3$), 4.49 (s, 2H, $CH_2C_6H_5$), 2.33 (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. |

**Table 3. Effect of Nifedipine and compounds 3a-f at various molar concentration on heart rate in isolated heart of frog-**

| Compound no. | (Mean ± S. D.) | | | | |
|---|---|---|---|---|---|
| | **Control** | **$10^{-11}$M** | **$10^{-10}$M** | **$10^{-9}$M** | **$10^{-8}$M** |
| **Nifedipine heart rate (beats/min)** | 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 |

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

## 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 substitution at nitrogen of 1, 4-dihydropyridine ring show poor calcium antagonist activity however the presence of 5-chloropyrazole at position – 4-position of 1, 4-dihydropyridine ring enhances the activity.

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