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# Synthesis of Novel Hantzsch Dihydropyridine Derivatives

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A one-pot synthesis of novel Hantzsch dihydropyridine derivatives *via* a three-component cyclocondensation reaction of *p*-nitro acetoacetanilide, aromatic aldehyde and aqueous ammonia solution is presented. The protocol avoids the use of expensive catalyst, toxic solvent and chromatographic separation.

**Key Words: Hantzsch reaction, Three component, Dihydropyridine derivatives.**

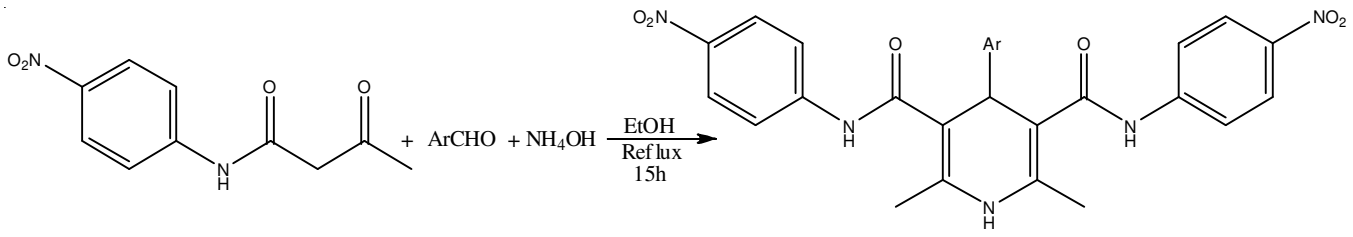
## INTRODUCTION

The design and development of multi component reactions for the generation of heterocycles receive growing interest[1-5]. Multi component reactions contribute to the requirments of an environmentally friendly process by reducting the number of synthetic steps, energy consumption and wast production. One such reaction is the synthesis of 1,4-dihydropyridine derivatives. 1,4-Dihyrdopyridine derivatives are valuable compounds and useful in synthetic, therapeutic and bioorganic chemistry[6-9]. 1,4-Dihydropyridines are an important class of heterocycles with a wide range of biological and pharmacological activities such as antithrombotic[10,11], analgesic activity[12], antianginal[13-15], antitumor[16], antiinflammatory activity[17,18], antitubercular activity[19] and anticonvulsant[20]. The 4-substituted hantzsch dihydropyridines, analogues of NADH coenzymes, are important classes of drugs[21]. Amlodipine besylate, nifedipine and related dihydropyridines are $Ca^{2+}$ channel blockers that are the most important classes of drugs for the treatment of cardiovascular diseases, including hypertension. 1, 4-Dihydropyridines are generally synthesized by classical Hantzsch reaction, which involves the condensation of an aldehyde, β-ketoester and ammonia or ammonium acetate in refluxing ethanol or acetic acid for a longer time[22]. There are several efficient methods developed for the synthesis of 1, 4-dihydropyridines which comprise the use of metal triflates[23], TMSCL-NaI[24], ionic liquid[25,26], high temperature in refluxing solvents[27] and silica sulfuric acid[28]. However, many of these methods have some drawbeaks such as use of expensive catalyst, low yields of the products, tedious procedure, harsh reaction conditions and difficult work-up. Because of the importance of dihydropyridine derivatives in organic synthesis, the development of a convenient, efficient and practically useful process for synthesis 1,4-dihydropyridine derivatives is in demand. Prompted by these findings and due to our interest in the synthesis of heterocyclic compounds[29] and in continuation of our previous works on the applications of reusable catalyst in organic reactions[30-34], herein we wish to report an efficient synthesis of 2,6-dimethyl -*N,N-bis*-(4-nitrophenyl)-4-aryl-1,4-dihydropyridine-3,5-dicarboxamide derivatives (**4a-e**) *via* a three-component cyclocondensation reaction of *p*-nitro acetoacetanilide (**1**), aromatic aldehyde (**2a-e**) and aqueous ammonia solution (**3**) in ambient catalyst (**Scheme-I**).

## EXPERIMENTAL

All chemicals were available commercially and used without additional purification. In all cases the products were identified by their spectroscopic properties. *p*-Nitro acetoacetanilide (1) were prepared according to a reported method for *p*-chloro acetoacetanilide[35]. Melting points were recorded on an electrothermal type 9100 melting points apparatus. The IR spectra were obtained using a shimadzu IR-470 spectrophotometer as KBr disks. $^1$H NMR and $^{13}$C NMR spectra were recorded with a DRX-500 Avance Bruker spectrophotometer.

**Synthesis of 2,6-dimethyl-*N,N-bis*-(4-nitrophenyl)-4-aryl-1, 4-dihydropyridine-3,5-dicarboxamide derivatives 4a-e:** A mixture of *p*-nitro acetoacetanilide (10 mmol), aromatic aldehyde (5 mmol) and 25 % aqueous ammonia solution (3 mL) in refluxing ethanol (15 mL) was stirred for 15 h. One milliliter of 25 % aqueous ammonia solution was added for every 3 h during the reflux. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature. The Precipitate was filtered and washed with cold methanol to afford the pure product **4a-e.**




(1) 2a-e (3) 4a-e

**Scheme-I:** Synthesis of 2,6- dimethyl-*N,N-bis*-(4-nitropenyl)-4-aryl-1,4-dihydropyridine-3,5-dicarboxamide derivatives

**2,6-Dimethyl-*N,N-bis*-(4-nitrophenyl)-4-phenyl-1,4-dihydropyridine-3, 5-dicarboxamide (4a):** Yellow solid, m.p. 268-272 ºC, yield 73 % IR (KBr, $\nu_{max}$, $cm^{-1}$): 3371 (N-H), 3260 (N-H), 1705 (C=O, amide), 1600 (C=C, Ar), 1545 (N=O), 1339 (N=O). $^1$H NMR (DMSO-$d_6$) δ: 2.14 [s, 6H, $(CH_3)_2$], 5.17 (s, 1H, CH), 7.09-7.12 (m, 1H, Ar-H), 7.22 (m, 2H, Ar-H), 7.23 (d, 2H, Ar-H, *J* = 9.2 Hz), 7.85 (d, 4H, Ar-H, *J* = 8.8 Hz), 8.18 (d, 4H, Ar-H, *J* = 8.8Hz), 8.43 (s, 1H, NH), 10.01 [s, 2H, $(NH)_2$]. $^{13}$C NMR (DMSO-$d_6$) δ : 18.0 $(CH_3)_2$, 41.9 (CH), 106.1 (C), 119.3 $(CH)_4$, 125.2 $(CH)_4$, 126.6 $(C_2)$, 127.5 $(C_2)$, 128.7 $(C_2)$, 139.9 (CH), 142.1 $(CH_2)$, 146.4 $(CH_2)$, 147.1 (C-$NO_2)_2$, 168.4 (C=O)$_2$.

**4-(2,4-Dichlorophenyl)-2,6-dimethyl-*N,N-bis*-(4-nitrophenyl)-1,4-dihydropyridine -3,5-dicarboxamide (4b):** Yellow solid, m.p. 163-167 ºC, yield 78 % IR (KBr, $\nu_{max}$, $cm^{-1}$): 3423 (N-H), 3307 (N-H), 1689 (C=O, amide), 1598 (C=C, Ar), 1535 (N=O), 1333 (N=O). $^1$H NMR (DMSO-$d_6$) δ : 2.12 [s, 6H, $(CH_3)_2$], 5.46 (s, 1H, CH), 7.35 (s, 1H, Ar-H), 7.40-7.41 (m, 2H, Ar-H), 7.82 (d, 4H, Ar-H, *J* = 9.2 Hz), 8.19 (d, 4H, Ar-H, *J* = 9.2 Hz), 8.56 (s, 1H, NH), 10.15 (s, 2H, $(NH)_2$. $^{13}$C NMR (DMSO-$d_6$) δ: 17.7 $(CH_3)_2$, 40.6 (CH), 105.8 (C), 119.1 $(CH)_4$, 125.3 $(CH)_4$, 128.4 (C), 128.5 (C), 131.3 $(C_2)$, 131.8 $(C_2)$, 132.5 $(C_2)$, 140.0 (CH), 142.2 (CH), 144.4 (C-$NO_2)_2$, 146.3 (CH), 167.9 (C=O)$_2$.

**2,6-Dimethyl-4-(4-hydroxyphenyl)-*N,N-bis*-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxamide (4c):** Yellow solid, m.p. 240-245 ºC, yield 75 % IR (KBr, $\nu_{max}$, $cm^{-1}$): 3397 (N-H), 3378 (N-H), 1673 (C=O, amide), 1593 (C=C, Ar), 1535 (N=O), 1327 (N=O). $^1$H NMR (DMSO-$d_6$) δ: 2.12 (s, 6H, $(CH_3)_2$, 5.06 (s, 1H, CH), 6.59 (d, 2H, Ar-H, *J* = 8.8 Hz), 7.02 (d, 2H, Ar-H, *J* = 8.8 Hz), 7.84 (d, 4H, Ar-H, *J* = 9.2 Hz), 8.18 (d, 4H, Ar-H, *J* = 9.2 Hz), 8.43 (s, 1H, NH), 9.13 (s, 1H, OH), 9.91 (s, 2H, $(NH)_2$. $^{13}$C NMR (DMSO-$d_6$) δ : 18.0 $(CH_3)_2$, 41.1 (CH), 106.5 (C), 115.4 $(C_2)$, 119.2 $(CH)_4$, 125.3 $(CH)_4$, 128.6 $(C_2)$, 137.7 $(C_2)$, 139.4 (C), 142.1 $(CH)_2$, 146.4 $(CH)_2$, 156.1 (C-$NO_2)_2$, 168.5 (C=O)$_2$.

**2,6-Dimethyl-*N,N-bis*-(4-nitrophenyl)-4-(*p*-tolyl)-1,4-dihydropyridine-3,5-dicarboxamide (4d):** Yellow solid, m.p. 259-263 ºC, yield 81 % IR (KBr, $\nu_{max}$, $cm^{-1}$): 3423 (N-H), 3378 (N-H), 1667 (C=O, amide), 1596 (C=C, Ar), 1538 (N=O), 1330 (N=O). $^1$H NMR (DMSO-$d_6$) δ : 2.13 [s, 6H, $(CH_3)_2$], 2.19 (s, 3H, $CH_3$), 5.14 (s, 1H, CH), 7.02 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.11 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.85 (d, 4H, Ar-H, *J* = 9.2 Hz), 8.18 (d, 4H, Ar-H, *J* = 9.2 Hz), 8.39 (s, 1H, NH), 9.97 [s, 2H, $(NH)_2$]. $^{13}$C NMR (DMSO-$d_6$) δ : 18.0 $(CH_3)_2$, 21.0 $(CH_3)$, 41.6 (CH), 106.3 (C), 119.2 $(CH)_4$, 125.3 $(CH)_4$, 127.5 $(C_2)$, 129.3 $(C_2)$, 135.6 $(C_2)$, 139.7 (C), 142.1 $(CH)_2$, 144.2 (C-$NO_2)_2$, 146.4 $(CH)_2$, 168.4 (C=O)$_2$.

**4-(4-Chlorophenyl)-2,6-dimethyl-*N,N*-bis-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxamide (4e):** Yellow solid, m.p. 270-274 ºC, yield 76 % IR (KBr, $\nu_{max}$, $cm^{-1}$): 3442 (N-H), 3371 (N-H), 1673 (C=O, amide), 1592 (C=C, Ar), 1535 (N=O), 1333 (N=O). $^1$H NMR (DMSO-$d_6$) δ : 2.14 [s, 6H, $(CH_3)_2$], 5.17 (s, 1H, CH), 7.23 (d, 2H, Ar-H, *J* = 8.4 Hz), 7.29 (d, 2H, Ar-H, *J* = 8.4 Hz), 7.84 (d, 4H, Ar-H, *J* = 9.2 Hz), 8.18 (d, 4H, Ar-H, *J* = 9.2 Hz), 8.49 (s, 1H, NH), 10.04 [s, 2H, $(NH)_2$]. $^{13}$C NMR (DMSO-$d_6$) δ: 18.0 $(CH_3)_2$, 41.4 (CH), 105.8 (C), 119.3 $(CH)_4$, 125.2 $(CH)_4$, 128.6 $(C_2)$, 129.4 $(C_2)$, 131.1 $(C_2)$, 140.1 (C), 142.2 $(CH)_2$, 146.1 (C-$NO_2)_2$, 146.3 $(CH)_2$, 168.2 (C=O)$_2$.

## RESULTS AND DISCUSSION

In view of different biological and chemical applications of 1,4-dihydropyridine derivatives, the development of suitable synthetic approach for their generation has been a topic of great interest in recent times. Although many publications have already reported the synthesis of 1,4-dihydropyridine derivatives[22-28], very little has been covered regarding the 2,6-dimethyl-*N,N-bis*-(4-aryl)-4-aryl-1,4-dihydropyridine-3,5-dicarboxamide derivatives[35]. Kumar *et al.*[35] were the first who described the method of employing the reaction of *p*-chloro acetoacetanilide, aromatic aldehyde and excess of aqueous ammonia solution using ethanol as a solvent under reflux condition. In this communication, we report a facile and efficient synthesis of 2,6-dimethyl-*N,N- bis*-(4-nitrophenyl)-4-aryl-1,4-dihydro-pyridine-3,5-dicarboxamide derivatives, starting from *p*-nitro acetoacetanilide (**1**), aromatic aldehyde (**2**) and aqueous ammonia solution (**3**). The reaction between *p*-nitro acetoacetanilide and aromatic aldehyde in the presence of $NH_3$ at ambient catalyst in ethanol led to the corresponding 2,6-dimethyl -*N,N-bis*-(4-nitrophenyl)-4-aryl-1,4-dihydropyridine-3,5-dicarboxamide derivatives in good yield (Table-1). Table-1 contains the results of study. The structures of compounds **4a-e** were deduced from their IR, $^1$H NMR and $^{13}$C NMR spectral data.

### Conclusion

In summary, we have described an efficient and simple method for the preparation of 2,6-dimethyl-*N,N-bis*-(4-nitrophenyl)-4-aryl-1, 4-dihydropyridine-3, 5-dicarboxamide derivatives *via* a cyclocondensation reaction of *p*-nitro acetoacetanilide, aromatic aldehyde and aqueous ammonia solution in refluxing ethanol.

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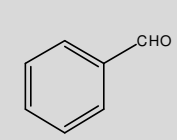
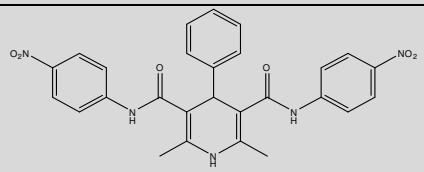
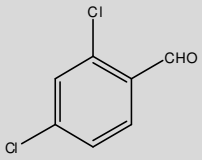
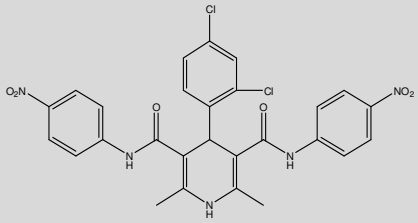
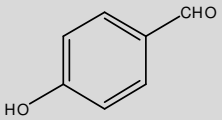
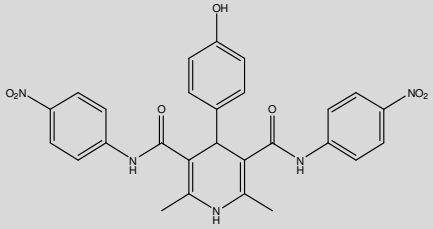
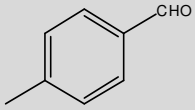
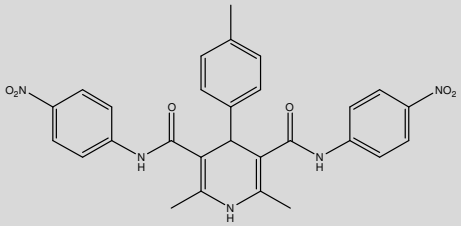
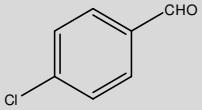
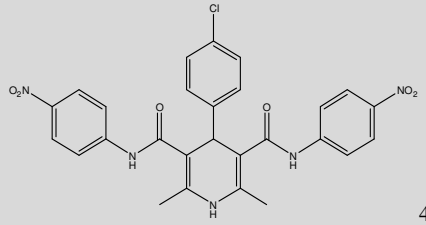
TABLE-1
SYNTHESIS OF 2,6-DIMETHYL-*N*,*N*-*BIS*-(4-NITROPHENYL)-4-ARYL-1,4-DIHYDROPYRIDINE-3,5-DICARBOXAMIDE DERIVATIVES[a]

| Entry | Aromatic aldehyde | Product[b] | Yield (%)[c] | m.p. (ºC) |
|---|---|---|---|---|
| 1 |  |  4a | 73 | 268-272 |
| 2 |  |  4b | 78 | 163-167 |
| 3 |  |  4c | 75 | 240-245 |
| 4 |  |  4d | 81 | 259-263 |
| 5 |  |  4e | 76 | 270-274 |

[a](10 mmol) *p*-nitro acetoacetanilide, (5 mmol) aromatic aldehyde and (3 mL) 25 % aqueous ammonia solution in ethanol. [b]All the products were characterized by IR, $^1$H NMR and $^{13}$C NMR spectral data. [c]Isolated yields

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