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SYNTHESIS AND CHARACTERIZATION OF SOME NEW 4-SUBSTITUTED-6-(*p*-AMINOPHENYL)-2-AMINOPYRIDINE-3-CARBONITRILE DERIVATIVES

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ABSTRACT

4-Substituted-6-(*p*-aminophenyl)-2-aminopyridine-3-carbonitrile derivatives were prepared by using 4-amino acetophenone as starting material, which is treated with malononitrile, ammonium acetate and various types of benzaldehyde consists of electron releasing and electron withdrawing groups on it *via* one-pot reaction by using benzene as solvent. This method provides an envirofriendly, easy workup and gives compounds in high yield. The synthesized 4-substituted-6-(*p*-aminophenyl)-2-aminopyridine-3-carbonitrile derivatives were characterized by physical properties and spectral studies (IR, ^{1}H NMR & Mass).

Keywords: Carbonitrile; Acetophenone; Aminopyridine; Synthesis.

INTRODUCTION

Pyridine is a 6 member unsaturated heteroaromatic ring system contain nitrogen as heteroatom with the formula C_5H_5N. Pyridine is one of the most popular N-heteroaromatics incorporated into the structure of many pharmaceuticals. Pyridine functionalities have been widely used but still generate much interest due to their wide range of application in medicinal chemistry. The naturally occurring B_6-vitamins pyridoxine, pyrodoxal, pyridoxamine and codecarbaxylase contain a pyridine nucleus [1].

Among them, 2-amino-3-carbonitrile pyridines with different alkyl and aryl groups were found to have various biological activities such as anti-microbial [2], anti-fungal [3], anti-hypertensive [4], anti-inflammatory, analgesic [5-6], anti-pyretic, adenosine receptor antagonists [7], cardiotonic [8], anti-tumor [9], as well as IKK-β inhibitor properties [10], potent inhibitor of HIV-1 integrase [11]. Besides this, they are important and useful intermediates in preparing variety of heterocyclic compounds [12-15]. Therefore, the synthesis of 4-substituted-6-(*p*-aminophenyl)-2-aminopyridine-3-carbonitriles attract much interest in heterocyclic chemistry.

EXPERIMENTAL

Materials and Instruments: Melting points were determined by using electrical melting point apparatus and are uncorrected. Materials and reagents were obtained from commercial suppliers (Merck grade) and were used without further purification. IR spectra were recorded in KBr discs on a Bruker analyzer. ^{1}H NMR spectra were recorded on a Bruker (400 MHz) spectrometer (chemical shifts in □ , ppm) in DMSO using TMS as internal standard. Mass spectra were recorded on a Thermo analyzer. The progress of the reaction was monitored by TLC using Silica Gel G (Merck).

Typical procedure for the synthesis of 4-Substituted-6-(p-aminophenyl)-2-aminopyridine-3-carbonitrile derivatives (**4a-i**): The condensation of various aromatic aldehydes (0.001 mol) and 4-aminoacetophenone (0.001 mol) with malononitrile (0.001 mol), anhydrous ammonium acetate (0.008 mol) were dissolved in 35 ml of benzene and heated to reflux for 6 hours. Completion of the reaction was monitored by TLC using Silica Gel G. After completion of the reaction, it was allowed to cool. The solvent was removed under reduced pressure and absolute ethanol was added to the residue. The

obtained precipitate was collected by filtration and purified by recrystallization by using ethanol gives the desired product.

Spectroscopic Data

4-(2'-methoxyphenyl)-6-(p-aminophenyl)-2-aminopyridine-3-carbonitrile (4a): yellow powder; yield 72.3%; mp 212°C; IR [cm^{-1}, KBr]: 3353, 3242 (NH_2), 2213 (C≡N), 1519 (C=N), 1171 (C-O-C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.412 (2H, s, NH_2), 3.801 (3H, s, C-2'-OCH_3), 6.757 (2H, s, NH_2), 6.839-6.860 (2H, d, *J*=8.4 Hz, C-3"&5"-H), 7.051 (1H, s, C-5-H), 7.062-7.100 (1H, t, C-4'-H), 7.163-7.193 (1H, d, *J*=10.2 Hz, C-3'-H), 7.307-7.329 (1H, d, *J*=8.8 Hz, C-6'-H), 7.452-7.496 (1H, t, C-5'-H), 7.946-7.968 (2H, d, *J*=8.8 Hz, C-2"&6"-H); MS (m/z ratio) 316.2.

4-(3',4'-dimethoxyphenyl)-6-(p-aminophenyl)-2-aminopyridine-3-carbonitrile (4b): yellow powder; yield 75.8%; mp 258°C; IR [cm^{-1}, KBr]: 3297, 3167 (NH_2), 2222 (C≡N), 1575 (C=N), 1142 (C-O-C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.310 (2H, s, NH_2), 3.804 (3H, s, C-4'-OCH_3), 3.896 (3H, s, C-3'-OCH_3), 6.793 (2H, s, NH_2), 6.849-6.870 (2H, d, *J*=8.4 Hz, C-3"&5"-H), 7.177 (1H, s, C-5-H), 7.598-7.624 (1H, d, *J*=6.0 Hz, C-5'-H), 7.642-7.647 (1H, d, *J*=5.4 Hz, C-6'-H), 7.994-8.015 (2H, d, *J*=8.4 Hz, C-2"&6"-H), 8.352 (1H, s, C-2'-H); MS (m/z ratio) 347.3 (MH^+).

4-(3',4',5'-trimethoxyphenyl)-6-(p-aminophenyl)-2-aminopyridine-3-carbonitrile (4c): brown powder; yield 78.6%; mp 255°C; IR [cm^{-1}, KBr]: 3201, 3169 (NH_2), 2219 (C≡N), 1550 (C=N), 1257 (C-O-C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.308 (2H, s, NH_2), 3.745 (3H, s, C-4'-OCH_3), 7.219 (1H, s, C-5-H), 3.868 (6H, s, C-3'&5'-OCH_3), 6.852-6.874 (2H, d, *J*=8.8 Hz, C-3"&5"-H), 6.969 (2H, s, NH_2), 8.006-8.028 (2H, d, *J*=8.8 Hz, C-2"&6"-H), 8.390 (2H, s, C-2'&6'-H); MS (m/z ratio) 376.1.

4-(4'-hydroxyphenyl)-6-(p-aminophenyl)-2-aminopyridine-3-carbonitrile (4d): light yellow powder; yield 78.3%; mp 235°C; IR [cm^{-1}, KBr]: 3450 (OH), 3233, 3113(NH_2), 2217(C≡N), 1589(C=N); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.462 (2H, s, NH_2), 6.625-6.645 (2H, d, *J*=8.0 Hz, C-3"&5"-H), 6.928(2H, s, NH_2), 7.209 (1H, s, C-5-H), 7.511-7.531 (2H, d, *J*=8.0 Hz, C- 3'&5'-H), 7.803-7.825 (2H, d, *J*=8.8 Hz, C- 2'&6'-H), 7.905-7.925 (2H, d, *J*=8.0 Hz, C-2"&6"-H), 9.878 (1H, s, OH); MS (m/z ratio) 302.3.

4-(4'-chlorophenyl)-6-(p-aminophenyl)-2-aminopyridine-3-carbonitrile (4e): yellow powder; yield 76.8%; mp 258°C; IR [cm^{-1}, KBr]: 3253, 3128(NH_2), 2207(C≡N), 1599(C=N), 772(C-Cl); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.286 (2H, s, NH_2), 6.844-6.866 (2H, d, *J*=8.8 Hz, C-3"&5"-H), 6.911(2H, s, NH_2), 7.170 (1H, s, C-5-H), 7.608-7.629 (2H, d, *J*=8.4 Hz, C- 3'&5'-H), 7.679-7.700 (2H, d, *J*=8.4 Hz, C- 2'&6'-H), 7.993-8.014 (2H, d, *J*=8.4 Hz, C-2"&6"-H); MS (m/z ratio) 320.7.

4-(2',4'-dichlorophenyl)-6-(p-aminophenyl)-2-aminopyridine-3-carbonitrile (4f): brown powder; yield 68.9%; mp 250°C; IR [cm^{-1}, KBr]: 3303, 3227 (NH_2), 2217 (C≡N), 1591 (C=N), 778 (C-Cl); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.338 (2H, s, NH_2), 6.871-6.893 (2H, d, *J*=8.8 Hz, C-3"&5"-H), 6.929 (2H, s, NH_2), 7.106 (1H, s,C-5-H), 7.194-7.214 (1H, d, *J*=8.0 Hz,C-6'-H), 7.344-7.364 (1H, d, *J*=8.0 Hz, C-5'- H), 7.483(1H, s, C-3'-H), 7.970-7.997 (2H, d, *J*=10.8 Hz, C-2"&6"-H); MS (m/z ratio) 356.3 (MH^+).

4-(4'-fluorophenyl)-6-(p-aminophenyl)-2-aminopyridine-3-carbonitrile (4g): yellow powder; yield 71.5%; mp 268°C; IR [cm^{-1}, KBr]: 3233, 3122(NH_2), 2217(C≡N), 1592(C=N), 1049(C-F); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.274 (2H, s, NH_2), 6.824-6.845 (2H, d, *J*=8.4 Hz, C-3"&5"-H), 6.909(2H, s, NH_2), 7.186 (1H, s, C-5-H), 7.625-7.649 (2H, d, *J*=9.6 Hz, C- 3'&5'-H), 7.711-7.734 (2H, d, *J*=9.2 Hz, C- 2'&6'-H), 7.892-7.913 (2H, d, *J*=8.4 Hz, C-2"&6"-H); MS (m/z ratio) 304.3.

4-(4'-bromophenyl)-6-(p-aminophenyl)-2-aminopyridine-3-carbonitrile (4h): light yellow powder; yield 63.5%; mp 248°C; IR [cm^{-1}, KBr]: 3265, 3137(NH_2), 2220(C≡N),1596(C=N), 578(C-Br); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.321 (2H, s, NH_2), 6.723-6.744 (2H, d, *J*=8.4 Hz, C-3"&5"-H), 6.962(2H, s, NH_2), 7.218 (1H, s, C-5-H), 7.613-7.633 (2H, d, *J*=8.0 Hz, C- 3'&5'-H), 7.812-7.833 (2H, d, *J*=8.4 Hz, C- 2'&6'-H), 7.913-7.935 (2H, d, *J*=8.8 Hz, C-2"&6"-H); MS (m/z ratio) 365.2.

4-(2'-chlorophenyl)-6-(p-aminophenyl)-2-aminopyridine-3-carbonitrile (4i): yellow powder; yield 85.5%; mp 243°C; IR [cm^{-1}, KBr]: 3261, 3153 (NH_2), 2212(C≡N), 1594 (C=N), 755 (C-Cl); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.119 (2H, s, NH_2), 6.727-6.749(2H, d, *J*=8.8 Hz, C-3"&5"-H), 6.950(1H, s, NH_2),7.001-7.023(1H, d, *J*=8.8 Hz, C-3'-H), 7.058 (1H,s,C-5-H), 7.079-7.102(1H, t, C-4'-H), 7.206-7.227 (1H, d, *J*=8.4 Hz, C-6'-H), 7.401-7.445 (1H, t, C-5'-H), 7.942-7.964(2H, d, *J*=8.8 Hz, C-2"&6"-H); MS (m/z ratio) 320.7.

RESULTS & DISCUSSION

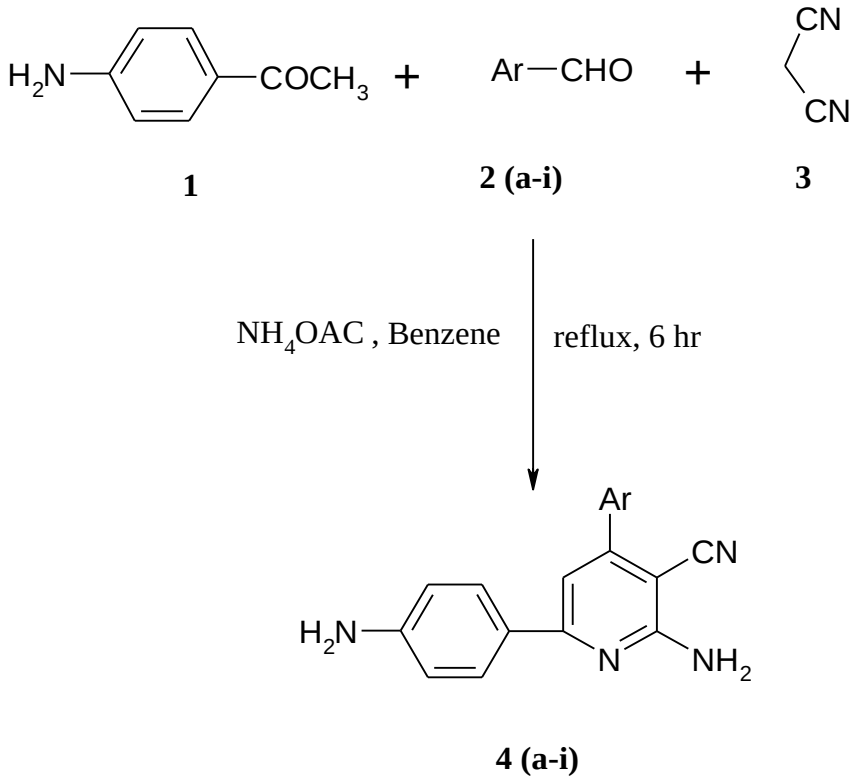
The synthesis of 4-Substituted-6-(*p*-aminophenyl)-2-aminopyridine-3-carbonitrile derivatives has been accomplished *via* one-pot reaction, involving condensation of 4-amino acetophenone, malononitrile, ammonium acetate, different benzaldehydes and benzene as solvent. In the past, many solvents have been utilized to improve the

reaction conditions and yields of the products such as ethanol, toluene, etc.

In the present investigation, the reaction mixture consists of 4-amino acetophenone, malononitrile, ammonium acetate, substituted benzaldehyde and benzene refluxed for nearly 6 hr (Scheme 1). The homogeneous mixture turns to precipitate by the addition of ethanol and led to the isolation of pure products in good yields. Under similar conditions, aromatic aldehydes bearing electron withdrawing & electron donating groups afford the corresponding 4-Substituted-6-(*p*-aminophenyl)-2-aminopyridine-3-carbonitrile derivatives in high yields and purity. During the work-up of the reaction mixture, first it was cooled, and then adds ethanol to get precipitate. Filter it, dry and then recrystallize it with ethanol. Reaction time, % yield and melting points were depicted in the Table 1**.** All the products were characterized by IR, ^{1}H NMR & Mass spectral data.

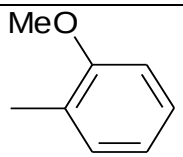
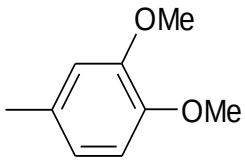
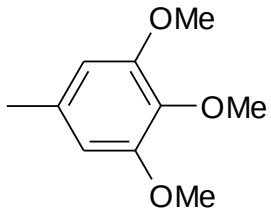
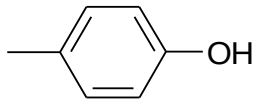
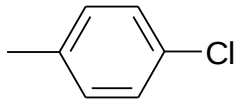
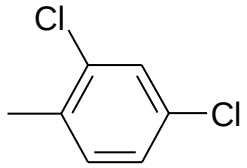
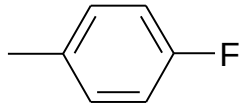
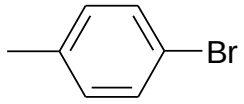
CONCLUSION

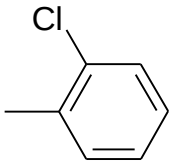
In conclusion, we have developed an efficient method for the direct preparation of 4-Substituted-6-(*p*-aminophenyl)-2-aminopyridine-3-carbonitrile derivatives using benzene as solvent in good yields & purity from the readily available starting materials.



Scheme 1: Synthesis of 4-substituted-6-(*p*-aminophenyl)-2-aminopyridine-3-carbonitriles using benzene as solvent

Table 1: Synthesis of 4-substituted-6-(*p*-aminophenyl)-2-aminopyridine-3-carbonitriles (4a-i)

Compound	Ar	Time (hr)	Yield (%)	Melting point (°C)
4a		6	72.3	212
4b		5.5	75.8	258
4c		6	78.6	255
4d		6	78.3	235
4e		5	76.8	258
4f		6	68.9	250
4g		6	71.5	268
4h		5.5	63.5	248

4i		5	85.5	243

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