Original Article

Synthesis of new 4-substituted amino pyrido [2,3-d] pyrimidine derivatives under solvent- free conditions

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Abstract

Many classes of chemotherapeutic agents containing pyrimidine derivatives are in clinical use such as antioxidants, antitumour, antimicrobials, antipyretic, antifungal, antibacterial, antihistamines, antihypersentensive. Several fused heterocyclic substituted pyrimidine have also been reported to possess a wide biological activities. A new and efficient synthesis of 4 substituted aminopyrido [2, 3-d] pyrimidine derivatives from 2- Aminopyridine via formamidine formation by nucleophilic addition with primary amines under solvent - free condition is described in present paper.

Keywords: Pyrido [2, 3-d] pyrimidine, 2-Aminopyridine, formamidine, solvent- free condition.

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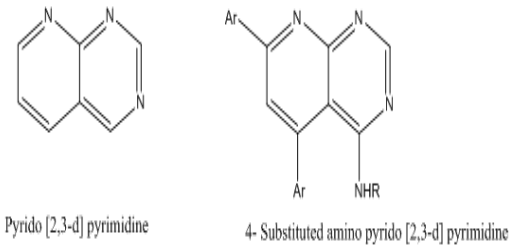
INTRODUCTION

Pyrido [2, 3-d] pyridine ring structure is one of the most interesting heterocyclic in drug design and its derivatives have various potential pharmacological activities various biological activities exhibited by pyrido [2, 3-d] pyrimidine are antitumor[1-3], antimicrobial[4-5] antipyretic[6], antifungal[7], antibacterial[8-10], antihistaminic[11] and antihypersentensive[12-13]. The pyridopyrimidine are an important class of annulated uracils with biological significance because of their connection with the purine, pyridine system[14]. Some pyrido[2,3-d]pyrimidine [fig A] were considered as inhibitors of dihydroflote[15] or tyrosine kinase[16]. The synthesis of the pyrimidine ring required strict reaction condition, time consuming reaction and have low percent yield of produce[17-19]. Our ongoing development of efficient for the preparation of heterocyclic derivatives which are biologically active with versatitily of organic synthon[20-22]. A New and efficient synthesis of 4- substituted aminopyrido [2, 3-d] pyrimidine derivaties from 2-aminopyridines via formamidine formation by using primary amines under nucleophilic addition under solvent free conditions.



Pyrido [2,3-d] pyrimidine — 4- Substituted amino pyrido [2,3-d] pyrimidine

Figure 1: Structure of pyrimidines

MATERIALS AND METHODS

All chemical were purchased from merck, SD-fine, qualigens and sigma-Aldrich. Solvent and Reagents were used without further purification, unless otherwise specified melting points were determined in an open capillary tube and are uncorrected. The TLC were visualized in an Iodine chamber.

Experimental /Methodology

Procedure for the synthesis of arylethylidenemalononitrile [2a-c]

A mixture of aromatic aldehyde [1a-c] (10 mmol) with malononitrile (10 mmol) taken in water was stirred at room temperature for 20-35 min. The white solid obtained which washed by using diethyl ether (50 ml) and recrystallized from absolute ethanol to give product 2a-c.

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compound 2a 2-(4- Chlorobenzylidene) malonoitrile obtained according to the procedure using 1, using 1a (10 mmol ; 1.40 gm) and malonoitrile (10 mmol, 0.66 gm) as a white solid (1.80 gm, 96%) melting point is 163^0C. ^{1}H NMR ($CDCl_3$) ∂_{ppm} : 7.43 (2H, d, J_{H-H}= 8.4, H_{arom}); 7.69 (2H, d, J_{H-H} = 8.4 H_{arom}), 7.83 (1H, s, C= C- H), ^{13}C NMR ($CDCl_3$) ∂_{ppm} : 158.23 (C=C); 141.33 (C_{arom}); 133.82 (C_{arom}); 130.13(2 x C_{arom}); 129.37 (2 x C_{arom}); 113.45 (CN); 112.30 (CN); 83.45 (C=C); IR (neat/ cm^{-1}): 2226; 1585.

ii) General Procedure for the synthesis of 2-aminopyridine [4a-d]:-

A mixture of arylethylidenemalononitriles 2a-c (10 mmol), substituted acetophenones 3a-d(10mmol), and ammonium acetate(10mmol) was heated at 100^0 C for 4 hrs, then cool and poured into ice water 25ml to formed solid ppt and recrystallized from absolute ethanol to give the product 4a-d as white solid compound.

Amino-4-(4-chlorophenyl)-6 (phenylnicotinonitrile) [4b].

This compound was prepared by the reaction of 2-(4-chlorobenzylidene) malononitrile (10 mmol; 1.88 gm), Acetophenone (10 mmol, 1.20 gm) and ammonium acetate (10 mmol; 0.77 gm) or ammonium carbonate (10 mmol; 0.96 gm) following the above general procedure 2. It was obtained white solid having yield (2.84 gm, 93%), melting point 222^0C. ^{1}H NMR ($CDCl_3$) ∂_{ppm} : 8.14 (2H, d, J= 8.4 H_z, H_{arom}); 7.70 (2H, d, J = 8.4 H_{arom}), 7.48-7.50 (3H, m, H_{arom}); 7.23 (1H, s, H_{pyri}); 7.04 (2H, d, J= 8.4 H_{arom}); 6.99 (2H, s, NH_2); C^{13} NMR ($CDCl_3$) ∂_{ppm} : 164.3 (C-NH_2); 158.9 (C=C-ph); 156.8 (C=C-CN); 134.9-128.41 (6xC_{arom}); 128.3-124.55 (6xC_{arom}); 116.3 (CN); 111.8 (C=C-ph); 85.5 (C=C-CN); IR (neat/ cm^{-1}):3462; 2215; 1583; 1559.

General Procedure for the synthesis of N, N- dimethyl-N' (pyridin-2-yl) formamides [5a-d]:-

A mixture of 4a-d (10 mmol) and of N, N- dimethyl formamide dimethyle acetal (10 mmol) was heated at 100^0 C for 3 hrs, then cooling the solid product formed filtered of and washed with absolute ethanol to give the product [5a-d] as white solid compound.

N'- (4- (4- Chlorophenyl)-3 cyano-6 phenylpyridin-2-yl)- N, N- dimethyl -1-formamide

This compound was prepared by the reaction of 2-amino-4- (4- Chlorophenyl)-6- (phenylnicotinonitrile) (10 mmol; 3.35 gm) N, N-dimethyl formamide dimethyl acetal (10 mmol; 1.19 gm) following the above general procedure 3. It was obtained white solid having yield (3.28 gm, 91%), melting point 214^0C. ^{1}H NMR ($CDCl_3$) ∂_{ppm} : 8.62 (2H, s, H_{imine}); 7.85 (2H, d, J = 8.0 H_z, H_{arom}), 7.40 (2H, d, J= 8.0 H_z, H_{arom}); 7.40 (2H, d, J= 8.0 H_z, H_{arom}); 7.25- 7.38 (5H, m, H_{arom}); 7.24 (1H, s, H_{pyri}); 3.02 (3H, s, NCH_3); 2.99 (3H, s, NCH_3); ^{13}C NMR ($CDCl_3$) ∂_{ppm} : 164.3 (C-NΞC); 158.52 (C=C-ph); 156.27 (C-NΞC); 154.15 (C=C-CN); 138.41-129.79 (5xC_{arom}); 129.09-127.36 (5xC_{arom}); 116.62 (CN); 133.92 (C=C-ph); 89.29 (C=C-CN);41.06 (NCH_3); 35.08 (NCH_3); IR (neat/ cm^{-1}):3439; 2214; 1620; 1488.

iv) General Procedure for the synthesis of 4-Substituted Amino pyrido[2, 3-d] Pyrimidine (6-9)

A mixture of 5a-d (10 mmol) and primary amine (10 mmol) was heated at 100^0 C for 4 hrs, then after completion of the reaction the residue was purified by using column chromatography over silica gel using a mixture of n-hexane- ethylacetae (5:5) as the eluent to give product 6-9.

(4- chlorophenyl) –N- cyclohexyl -7- phenylpyrido [2,3-d] pyrimidin-4-amine

This compound prepared by the reaction of (E)- N'- (4-(4- Chlorophenyl)-3 cyano-6 phenylpyridin-2-yl)- N, N-dimethyl -1-formamide (10 mmol ; 3.78 gm) and cyclohexylamine (10 mmol; 0.99 gm) following the above general procedure 4. The product formed was white solid having yield (2.72 gm, 66%), melting point 191^0C. ^{1}H NMR ($CDCl_3$) ∂_{ppm} : 8.11 (1H, s, $H_{pyrimidine}$); 7.78 (2H, m, H_{arom}), 7.35 (2H, d, J_{H-H}= 8.0 H_z, H_{arom}); 7.28- 730 (5H, m, H_{arom}); 7.05 (1H, s, H_{pyri}); 5.19 (1H, s, large NHH); 1.59 -1.62 (2H, m, -NH CH_2 CH_2 CH_2 CH_2 CH_2 CH_2-); 1.232 -1.44 (4H, m, -NH CH_2 CH_2 CH_2 CH_2 CH_2 CH_2-); 1.09 -1.28 (6H, m, -NH CH_2 CH_2 CH_2 CH_2 CH_2 CH_2-); ^{13}C NMR ($CDCl_3$) ∂_{ppm} : 160.24 (C-N=C); 160.06 (N=C-NH); 153.83 (C-NΞC); 137.76 (C=C-ph); 136.13-116.93 (15xC_{arom}); 110.9 (C=C-ph); 50.89 (CHNH-); 31.03 (CH_2); 30.95(CH_2); IR (neat/ cm^{-1}):3496; 2215; 1620; 1495.

RESULTS AND DISCUSSION

Synthesis of this pyrido [2,3-d]pyrimidine derivatives 6-9 is a multistep one (Scheme 1). The first step was based on the formation of 3-cyano-2-aminopyridine 4a-d then, the second step involved the use of formamidines 5a-d as key intermediates. Finally, pyrido [2,3-d] pyrimidine derivatives 6-9 are easily prepared by a cyclization reaction between compounds 5a-d and various primary amines as nucleophilic agents under solvent-free conditions.

Preparation of 3-cyano-2-aminopyridines 4a-d

Continuation of these researches for the synthesis of 2-aminopyridines and aiming to explor the portential of organic synthesis under solvent-free conditions[22-23]. We have developed here an efficient method for the synthesis of 2-amino-3-cyanopyridines 4a-d from arylethylidenemalononitrilles 2a-c (Scheme A).

Scheme A: Synthesis of 2-amino-3-cyanopyridines 4a-d

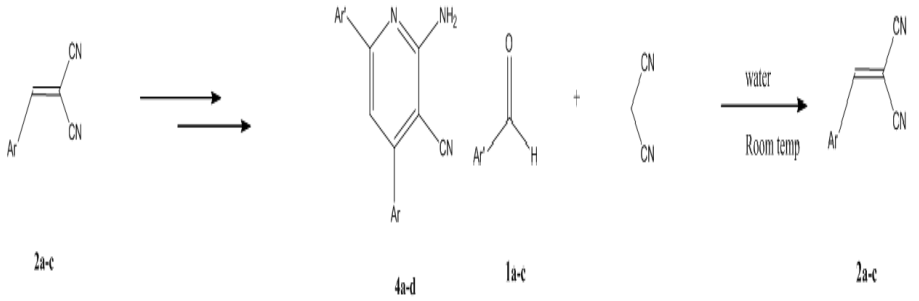


Table 1: Synthesis of Arylethylidenemalononitriles 2a-c

Sr. No.	Ar	Product	Yield (%)
1	Ph	2a	85
2	4-ClC_6H_4	2b	96
3	4-BrC_6H_4	2c	90

Synthesis of arylethylidenemalononitrilles

The reagent Arylethylidenemalononitriles are largely used as key product in organic syntheses, medicine, biology, and agriculture[24-25] Athough arylethylidene-malononitriles have been extensively utilized as starting materials for the synthesis of a variety of polyfunctional heterocyclic compounds[26]. The arylethylidenemalononitriles **2a-c** were prepared by the knoevengel condensation of substituted aromatic aldehydes **1a-c** with malononitrile in water at room temperature, they were obtained in good yields 85-96% (Table 1).

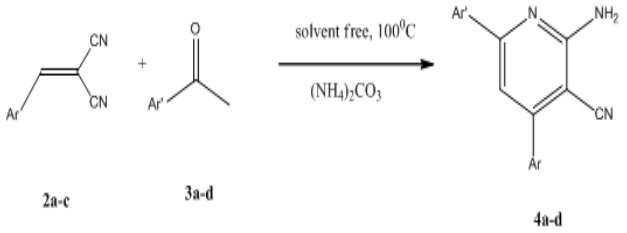


Table 2: Synthesis of 3-cyano-2 aminopyridines 4a-f

Sr. No	Ar	Ar	Product	Yield (%)
1	Ph	Ph	4a	84
2	4-ClC_6H_4	Ph	4b	88
3	4-ClC_6H_4	3-$MeOC_6H_4$	4c	91
4	4-BrC_6H_4	2-$MeOC_6H_4$	4d	88

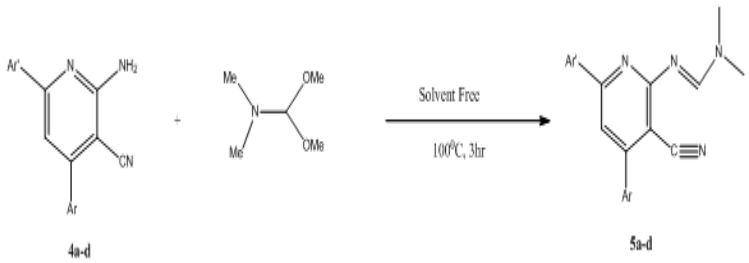


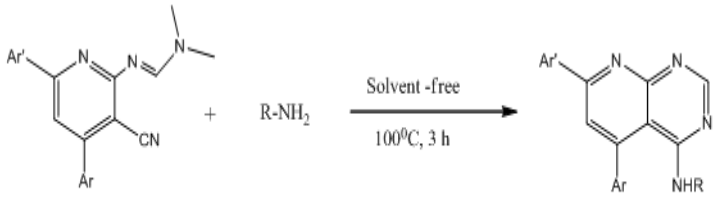
Table 3: Synthesis of N, N- dimethyl- N'- (pyridin-2-yl) formamides 5a-d

Sr. No	Ar	Ar	Product	Yield (%)
1	Ph	Ph	5a	88
2	4-ClC_6H_4	Ph	5b	91
3	4-ClC_6H_4	3-$MeOC_6H_4$	5c	92
4	4-BrC_6H_4	2-$MeOC_6H_4$	5d	90

Cyclization into 2-aminopyridine structures

3-cyno-2-aminopyridines 4a-d were easily obtained, in cascade reaction from arylethylidenemalononitriles 2a-c

and substituted acetophenone 3a-d. The reaction was carried out also under solvent free condition in the presence of ammonium acetate or ammonium carbonate to give yield 80-93% as shown in table 2. Formamidine are very important intermediate for the synthesis of nitrogen heterocycles[28]. According to previous work in the chemistry of enaminonitrile[27] we synthesized N, N, dimethyl-N'-(pyridine-2-yl) formamides 5a-f under solvent free conditions which are prepared by the reaction of 2-aminopyridine 4a-d derivatives with equmolar amount of dimethtylacetal dimethyl-formamide. The mixtyre was heated upto 3 hrs under solvent free condition to formed N, N-dimethyl-N'-(pyridine-2-yl) formamides 5a-d to give excellent yield 88-92%as per table 3.



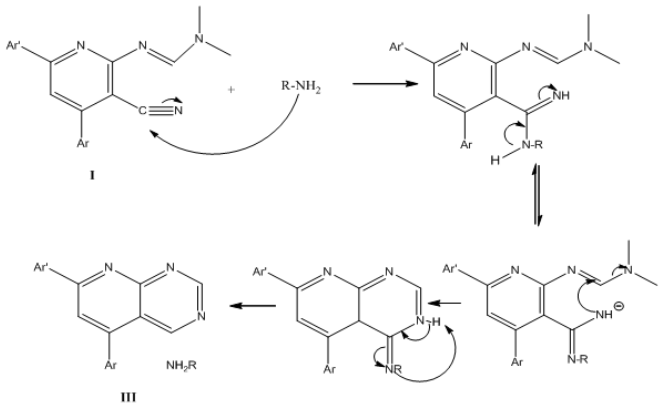
5a-d 6a-9b

Table 4: Synthesis of Pyrido[2,3-d]pyridine derivatives 6a-9b

Sr. No.	Formamidine	R	Product	Yield (%)
1	5a	Bn	6a	75
2	5a	Bu	6b	71
3	5a	Pr	6c	60
4	5a	Cy	6d	62
5	5b	Bn	7a	78
6	5b	Bu	7b	74
7	5b	Pr	7c	62
8	5b	Cy	7d	66
9	5c	Bn	8a	77
10	5c	Bu	8b	70
11	5c	Pr	8c	61
12	5c	Cy	8d	70
13	5a	Bn	9a	72
14	5a	Bu	9b	68

Synthesis of pyrido[2, 3-d] Pyrimidine derivatives (6-9)

In order to to study the reactivity of N, N-dimethyl-N' (pyridine-2-yl) formamides 5a-d which contains a cyno group in ortho positions, we have added various primary amines (benzylamine, butylamine, propylamine, cyclohexylamine) under solvent free conditions (Table 4). An equimolar mixture of precursors 5a-d and different primary amines were heated during 3 hours to obtain compound 6-9 having good yield s 60-78% which is described in Table 4 For the formation of 4-substituted aminopyrido [2,3-d] pyrimidine 6-9 having proposed mechanism described as following way.



First intermediate II was obtained by the reaction between primary amines and cyano groups in ortho position of N, N-dimethyl-N' (pyridine-2-yl) formamidesI. Then an intramolecular cyclization between the imine anion and the double bond of the formamidine was realized and finally the 4- substituded aminopyrido [2,3-d] pyrimidine III were formed by an aromatization step under solvent free conditions.

CONCLUSION

We have synthesized a new 4- substituded aminopyrido [2,3-d] pyrimidine derivatives from primary amine via

formamidine under solvent free condition with high yield which have biological and pharmaceutical importance also make this procedure a useful addition to modern synthetic methods.

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