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Simple route for the synthesis of pyrido [1, 2-*a*] pyrimidine derivatives

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ABSTRACT

*Facile synthesis of p-substituted benzoyl-3-(2-amino-N-hetero-2-alkenenitrile **4** was obtained by one pot three component reaction of aroylacetonitrile **1,** 2-amino-N-hetero compound **2** and orthoestes **3,** at 80°C with 65-70% yield. The alkylnitrile 4 was cyclized to pyrido[1,2-a] pyrimidine derivatives 5 in presence of Conc. hydrochloric acid with 60 -89% yields.*

Keywords: Aroylacetonitrile, alkenenitrile, period [1, 2-a] pyrimidine, One pot three component reaction

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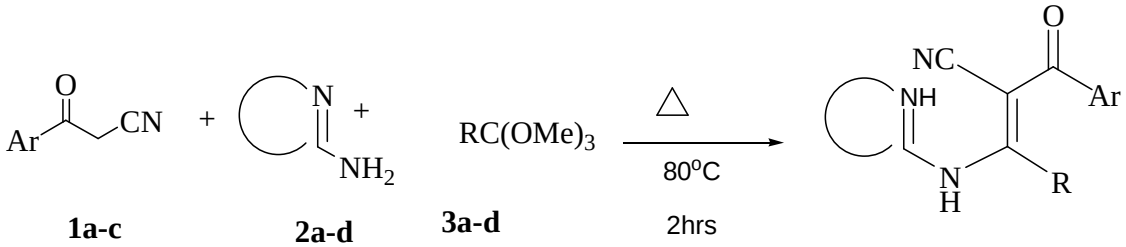
INTRODUCTION

Pyrido[1,2-a]pyrimidine derivatives are useful antihypertensive and and tranquilliseres [1]. These compounds were also used as bronchodilators [2], and antiallergic agents [3]. Korte et al. have reported the synthesis of pyrido [1, 2-a] pyrimidine derivativatives by condensation of 2-aminoheterocyclic compounds with α-acetyl γ- butyrolactone [4]. H. Junek and his co-workers has communicated the synthesis of pyrido[1,2-a]pyrimidine derivatives by starting with 2-aminopyridines, trimethylorthoesters and benzoylacetonitrile [5]. We have also synthesized pyrido[1,2-a]pyrimidines by condensation of 2-amino heterocyclic compounds with α-acetyl γ- butyrolactone and α-formyl γ-valyrolactone [6]. In our previous communications, we have reported the synthesis of pyrano fused heterocyclic compounds [7], and facile synthesis of cytosine derivatives [8]. Now we wish to report synthesis of pyrido[1,2-a]pyrimidine derivatives in this communication.

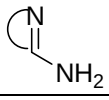
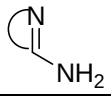
MATERIALS AND METHODS

Melting points were determined on a Gallenkamp melting point apparatus. The ^{1}H (300 MHz) and ^{13}C (75MHz) NMR spectra were recorded on a Varian XL-300 Spectrometer. Chemical shifts were reported in ppm relative to tetramethylsilane (TMS), and multiplicities are given as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Infrared spectra were recorded as KBr pellets on a Shimadzu FTIR-408 spectrophotometer. Mass spectra were recorded on a Shimadzu LC-MS:EI QP 2010A mass spectrometer with an ionization potential of 70eV. Elemental analyses were performed on Quest flash 1112 Series EA Analyzer. Reactions were monitored by thin layer chromatography (TLC), carried out on 0.2 mm silica gel 60 F_{254} Merck plates using UV light (254 and 366 nm) for detection and for column chromatography 5-20µm (Merck, 60-120 mesh) silica gel is used. Column dimension is 39× 2 cm and elution volume is 200-400 mL. Common reagent-grade chemicals are either commercially available and were used without further purification or were prepared by standard literature procedures.



1a-c **2a-d** **3a-d** **4a-u**

3	a	b	c	d
R	H	CH_3	C_2H_5	C_4H_9

1,4	Ar		R	1,4	Ar		R
a	*p*-Cl-C_6H_4		H	**l**	*p*-Br-C_6H_4		C_4H_9
b	*p*-Me-C_6H_4		H	**m**	*p*-Cl-C_6H_4		H
c	*p*-Br-C_6H_4		H	**n**	*p*-Me-C_6H_4		H
d	*p*-Cl-C_6H_4		CH_3	**o**	*p*-Br-C_6H_4		H
e	*p*-Me-C_6H_4		CH_3	**p**	*p*-Cl-C_6H_4		CH_3
f	*p*-Br-C_6H_4		CH_3	**q**	*p*-Me-C_6H_4		CH_3
g	*p*-Cl-C_6H_4		C_2H_5	**r**	*p*-Br-C_6H_4		CH_3
h	*p*-Me-C_6H_4		C_2H_5	**s**	*p*-Cl-C_6H_4		C_2H_5
i	*p*-Br-C_6H_4		C_2H_5	**t**	*p*-Me-C_6H_4		C_2H_5
j	*p*-Cl-C_6H_4		C_4H_9	**u**	*p*-Br-C_6H_4		C_2H_5
k	*p*-Me-C_6H_4		C_4H_9				

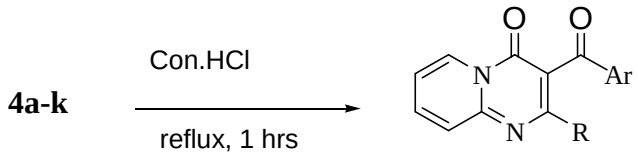
Scheme 1 Synthesis of 2-p-substituted benzoyl-3-(2-pyridylamino/2-pyrimidylamino)-2-alkenenitriles (4a-u)

General procedure for synthesis of (4a-u):

The mixture of p-substituted benzoylacetonitrile **1** (0.01mol), 2-aminopyridine/ 2-aminopyrimidine (**2a-d)** (0.01mol) and trimethylorthoesters (**3a-d)** (0.012mol) was heated at 80°C in oil bath for 2hrs. (TLC check). The solid separated was stirred in petroleum ether (30 mL) and filtered. It was dried and crystallized from ethanol.

Alternate procedure:

The solution of parasubstitutedbenzoylacetonitrile **1** (0.01mol), 2-aminopyridine/ 2-aminopyrimidine (**2a-d)** (0.01mol) and trimethylorthoesters (**3a-d)** (0.01mol) in toluene (30mL) was refluxed for 5-6 hrs. (TLC check). The solid separated on cooling was filtered, dried and crystallized from ethanol.



5a-k

4,5	Ar	R	4,5	Ar	R
a	*p*-Cl-C_6H_4	H	**g**	*p*-Cl-C_6H_4	C_2H_5
b	*p*-Me-C_6H_4	H	**h**	*p*-Me-C_6H_4	C_2H_5
c	*p*-Br-C_6H_4	H	**i**	*p*-Br-C_6H_4	C_2H_5
d	*p*-Cl-C_6H_4	CH_3	**j**	*p*-Cl-C_6H_4	C_4H_9
e	*p*-Me-C_6H_4	CH_3	**k**	*p*-Me-C_6H_4	C_4H_9
f	*p*-Br-C_6H_4	CH_3			

Scheme 2 Synthesis of 2-alkyl-3-p-substituted benzoyl-4-oxo-4H-pyrido[1,2-a]pyrimidines (5a-k)

2-p-chlorobenzoyl-3-(2-pyridylamino)-2-propenenitrile **(4a)**
Yield (2.19g, 77%), m.p.:161°C; IR: cm^{-1}=3450, 2245, 1630, 1540, 1450.; ^{1}HNMR: δ=7.00-8.80(m; 8H, Ar-H), 8.21(d; 1H, J=12Hz, =CH), 12.47(d; 1H, J=12Hz, NH) ppm; *Anal. Calcd. for* $C_{15}H_{10}N_3OCl$ (283.71);calcd.:C63.50, H 3.55; found C 63.30, H 3.32.

2-p-methoxybenzoyl-3-(2-pyridylamino)-2-propenenitrile **(4b)**
Yield (2.52g, 95%), m.p.:170°C; IR: cm^{-1}=3448, 2247, 1645, 1620, 11580, 1530.; ^{1}HNMR: δ=2.4(s; 3H, P-Me), 7.20-9.10(m; 8H, Ar-H), 8.32(d; 1H, J=12Hz, =CH), 121.18(d; 1H, J=12Hz, NH) ppm; *Anal. Calcd. for* $C_{16}H_{13}N_3O$ (263.29);calcd.:C72.98, H 4.93; found C 72.75, H5.02.

2-p-bromobenzoyl-2-pyridylamino)-2-propenenitrile **(4c)**
Yield (2.39g, 71%), m.p.:176°C; IR: cm^{-1}=3452, 2250, 1640, 1585, 1500, 1440.; ^{1}HNMR: δ=6.96-9.19(m; 8H, Ar-H), 8.20(d; 1H, J=12Hz, =CH), 10.93(d; 1H, J=12Hz, NH) ppm; *Anal. Calcd. for* $C_{15}H_{10}N_3OBr$ (328.16);calcd.:C 54.90, H 3.07; found C 54.67, H 2.90.

2-p-chlorobenzoyl-3-methyl-3-(2-pyridylamino)-2-propenenitrile **(4d)**
Yield (2.44g, 86%), m.p.:134°C; IR: cm^{-1}=3450, 2200, 1630, 1600, 1570, 1440; ^{1}HNMR: δ=2.86(s; 3H, P-Me), 7.11-8.48(m; 8H, Ar-H) ppm; *Anal. Calcd. for* $C_{16}H_{12}N_3OCl$ (283.71);calcd.:C 64.54, H 4.06; found C 64.44, H 4.16.

2-Paramethylbenzoyl-3-methyl-3-(2-pyridylamino)-2-propenenitrile **(4e)**
Yield (2.05g, 74%), m.p.:135°C; IR: cm^{-1}=3450, 2245, 1670, 1600, 1570; ^{1}HNMR: δ=2.41(s; 3H, P-Me), 2.85(s; 3H, =C-CH_3), 7.11-8.44(m; 8H, Ar-H), ppm; *Anal. Calcd. for* $C_{17}H_{15}N_3O$ (277.32); calcd.: C 73.62, H 5.45; found C 73.62, H 5.35.

2-Parabromobenzoyl-3-methyl-3-(2-pyridylamino)-2-propenenitrile **(4f)**
Yield (2.98g, 87%), m.p.:152°C; IR: cm^{-1}=3448, 2200, 1620, 1600, 1570; ^{1}HNMR: δ=2.85(s; 3H, =C-CH_3), 7.11-8.47(m; 8H, Ar-H), ppm; *Anal. Calcd. for* $C_{16}H_{12}N_3OBr$ (342.19); calcd.:C 56.15, H 3.53; found C 56.21, H 3.23.

2-Parachlorobenzoyl-3-ethyl-3-(2-pyridylamino)-2-propenenitrile **(4g)**
Yield (2.32g, 75%), m.p.:110°C; IR: cm^{-1}=3450, 2200, 1630, 1590, 1550; ^{1}HNMR: δ=1.42(t, 3H, J=7Hz, -CH_3), 3.32(q, 2H, J=7Hz, =C-CH_2), 7.11-8.47(m; 8H, Ar-H), ppm; *Anal. Calcd. for* $C_{17}H_{14}N_3OCl$ (311.77); calcd.:C 65.49, H 4.52; found C 65.35, H 4.60.

2-Paramethylbenzoyl-3-ethyl-3-(2-pyridylamino)-2-propenenitrile **(4h)**
Yield (2.03g, 70%), m.p.:98°C; IR: cm^{-1}=3450, 2245, 1640, 1600, 1560; ^{1}HNMR: δ=1.42(t, 3H, J=7Hz, -CH_3), 2.41(s, 3H, P-Me), 3.33(q, J=7Hz, =C-CH_2), 7.10-8.48(m; 8H, Ar-H), ppm; *Anal. Calcd. for* $C_{18}H_{17}N_3O$ (291.35); calcd.:C 74.20, H 5.88; found C 74.40, H 5.75.

2-Parabromobenzoyl-3-ethyl-3-(2-pyridylamino)-2-propenenitrile **(4i)**
Yield (2.42g, 69%), m.p.116°C; IR: cm^{-1}=3452, 2200, 1630, 1600, 1560, 1430; ^{1}HNMR: δ=1.42(t, 3H, J=7Hz, -CH_3), 3.33(q, 2H, J=7Hz, =C-CH_2), 7.09-8.47(m; 8H, Ar-H), ppm; *Anal. Calcd. for* $C_{17}H_{14}N_3OBr$ (356.22); calcd.:C 57.12, H 3.96; found C 57.22, H 3.85.

2-Parachlorobenzoyl-3-butyl-3-(2-pyridylamino)-2-propenenitrile **(4j)**
Yield (2.36g, 69%), m.p.:88°C; IR: cm^{-1}=3448, 2200, 1620, 1600, 1555; ^{1}HNMR: δ=0.94(t, 3H, J=7Hz, -CH_3), 1.50(q, 2H, J=7Hz, -CH_2), 1.80(q, 2H, J=7Hz, -CH_2), 3.28(q, 2H, J=7Hz, =C-CH_2), 7.10-8.45(m; 8H, Ar-H), ppm; *Anal. Calcd. for* $C_{19}H_{18}N_3OCl$ (339.82); calcd.:C 67.15, H 5.33; found C 67.05, H 5.43.

2-Paramethylbenzoyl-3-butyl-3-(2-pyridylamino)-2-propenenitrile **(4k)**
Yield (2.76g, 72%), m.p.:81°C; IR: cm^{-1}=3450, 2200, 1640, 1620, 1550, 1440; ^{1}HNMR: δ=0.95(t, 3H, J=7Hz, -CH_3), 1.48(q, 2H, J=7Hz, -CH_2), 1.78(q, 2H, J=7Hz, -CH_2), 2.41(s, 3H, P-Me), 3.33(q, 2H, J=7Hz, =C-CH_2), 7.07-8.44(m; 8H, Ar-H), ppm;

Anal. Calcd. for $C_{20}H_{21}N_3O$ (339.82); calcd.:C 75.20, H 6.62; found C 75.17, H 6.60.
2-Parabromobenzoyl-3-butyl-3-(2-pyridylamino)-2-propenenitrile **(4l)**
Yield (2.76g, 72%), m.p.:74°C; IR: cm^{-1}=3452, 2245, 1640, 1620, 1540, 1440; ^{1}HNMR: δ=0.94(t, 3H, J=7Hz, -CH_3), 1.48(q, 2H, J=7Hz, -CH_2), 1.78(q, 2H, J=7Hz, -CH_2), 3.28(q, 2H, J=7Hz, =C-CH_2), 7.09-8.47(m; 8H, Ar-H), ppm; $C_{19}H_{18}N_3OBr$ (384027); *Anal. Calcd. for* C 59.18, H 4.72; found C 59.40, H 4.60.

General procedure synthesis of pyrido [1, 2-a]pyrimidine derivatives (5a-k).
The clear solution of **4** (0.001 mol) in conc. hydrochloric acid (5 mL) was refluxed for 1 hr. (TLC check), then the reaction mixture was poured in ice cold water (30mL). The solution was neutralized and the solid separated was filtered, dried and crystallized from methanol.

3-Parachlorobenzoyl-4-oxo-4H-pyrido [1, 2-a]pyrimidine **(5a)**
Yield (0.255g, 89%), m.p.:199°C; IR: cm^{-1}=1700, 1650, 1600, 1580, 1530; ^{1}H NMR: δ=7.24-9.20(m, 8H, Ar-H), 8.77(s, 1H, =CH) ppm, *Anal. Calcd. for* $C_{15}H_9N_2O_2Cl$ (284.70); calcd.: C 63.28, H 3.18; found: C 63.10, H 3.21.

3-Paramethylbenzoyl-4-oxo-4H-pyrido [1,2-a]pyrimidine **(5b)**
Yield (0.219g, 83%), m.p.:160°C; IR: cm^{-1}=1710, 1640, 1610, 1570, 1500; ^{1}H NMR: δ=2.43(s, 3H, p-Me), 7.24-9.22(m, 8H, Ar-H), 8.74(s, 1H, =CH) ppm, *Anal. Calcd. for* $C_{16}H_{12}N_2O_2$ (264.28); calcd.: C 72.71, H 4.57; found: C 72.55, H 4.59.

3-Parabromobenzoyl-4-oxo-4H-pyrido [1,2-a]pyrimidine **(5c)**
Yield (0.213g, 65%), m.p.:200°C; IR: cm^{-1}=1710, 1650, 1600, 1580, 1510; ^{1}H NMR: δ=7.34-9.20(m, 8H, Ar-H), 8.77(s, 1H, =CH) ppm, *Anal. Calcd. for* $C_{15}H_9N_2O_2Br$ (329.15); calcd.: C 54.73, H 2.75; found: C 54.60, H 2.89.

2-Methyl-3-parachlorobenzoyl-4-oxo-4H-pyrido [1,2-a]pyrimidine **(5d)**
Yield (0.207g, 69%), m.p.:213°C; IR: cm^{-1}=1662, 1629, 1579, 1521, 1461; ^{1}H NMR: δ=2.35(s, 3H, =C-CH_3), 7.39-8.96 (m, 8H, Ar-H); *Anal. Calcd. for* $C_{16}H_{11}N_2O_2Cl$ (298.72); calcd.: C 64.33, H 3.71; found: C 64.22, H 3.60.

2-Methyl-3-paramethylbenzoyl-4-oxo-4H-pyrido [1,2-a]pyrimidine **(5e)**
Yield (0.190g, 66%), m.p.:191°C; IR: cm^{-1}=1690, 1650, 1610, 1530, 1460; ^{1}H NMR: δ=2.41(s, 3H, p-Me), 2.44(s, 3H, =C-CH_3), 7.16-9.03 (m, 8H, Ar-H) ppm, *Anal. Calcd. for* $C_{17}H_{14}N_2O_2$ (278.30); calcd.: C 73.36, H 5.07; found: C 73.48, H 4.98.

2-Methyl-3-paramethylbenzoyl-4-oxo-4H-pyrido [1,2-a]pyrimidine **(5e)**
Yield (0.190g, 66%), m.p.:191°C; IR: cm^{-1}=1690, 1650, 1610, 1530, 1460; ^{1}H NMR: δ=2.41(s, 3H, p-Me), 2.44(s, 3H, =C-CH_3), 7.16-9.03 (m, 8H, Ar-H) ppm; *Anal. Calcd. for* $C_{17}H_{14}N_2O_2$ (278.30); calcd.: C 73.36, H 5.07; found: C 73.48, H 4.98.

2-Methyl-3-parabromobenzoyl-4-oxo-4H-pyrido [1,2-a]pyrimidine **(5f)**
Yield (0.237g, 80%), m.p.:225°C; IR: cm^{-1}=1680, 1650, 1620, 1590, 1560; ^{1}H NMR: δ=2.44(s, 3H, =C-CH_3), 7.19-9.02 (m, 8H, Ar-H) ppm; *Anal. Calcd. for* $C_{16}H_{11}N_2O_2Br$ (343.17); calcd.: C 55.99, H 3.23; found: C 56.11, H 3.15.

2-Ethyl-3-parabromobenzoyl-4-oxo-4H-pyrido [1,2-a]pyrimidine **(5g)**
Yield (0.203g, 65%), m.p.:146°C; IR: cm^{-1}=1680, 1620, 1600, 1560, 1500; ^{1}H NMR: δ=1.15(t, 3H, J=7Hz, -CH_3), 3.45(q, 2H, J=7Hz, =C-CH_2), 7.38-8.89 (m, 8H, Ar-H) ppm; *Anal. Calcd. for* $C_{17}H_{13}N_2O_2Cl$ (312.75); calcd.: C 65.28, H 4.18; found: C 65.18, H 4.10.

2-Ethyl-3-paramethylbenzoyl-4-oxo-4H-pyrido[1,2-a]pyrimidine **(5h*)***
Yield (0.175g, 60%), m.p.:142°C; IR: cm^{-1}=1680, 1660, 1610, 1560, 1520, 1500; ^{1}H NMR: δ=1.27(t, 3H, J=7Hz, -CH_3), 2.41(s, 3H, p-Me), 2.72(q, 2H, J=7Hz, =C-CH_2), 7.14-9.02 (m, 8H, Ar-H) ppm; *Anal. Calcd. for* $C_{18}H_{16}N_2O_2$ (292.33); calcd.: C 73.95, H 5.51; found: C 73.90, H 5.31.

2-Ethyl-3-parabromobenzoyl-4-oxo-4H-pyrido[1,2-a]pyrimidine **(5i*)***
Yield (0.253g, 71%), m.p.:171°C; IR: cm^{-1}=1670, 1630, 1600, 1570, 1500; ^{1}H NMR: δ=1.28(t, 3H, J=7Hz, -CH_3), 2.71(q, 2H, J=7Hz, =C-CH_2), 7.22-9.02 (m, 8H, Ar-H) ppm; *Anal. Calcd. for* $C_{17}H_{13}N_2O_2Br$ (357.20); calcd.: C 57.16, H 3.66; found: C 57.22, H 3.50.

2-Butyl-3-parachlorobenzoyl-4-oxo-4H-pyrido[1,2-a]pyrimidine **(5j*)***
Yield (0.290g, 85%), m.p.:112°C; IR: cm^{-1}=1700, 1670, 1600, 1570, 1530; ^{1}H NMR: δ=0.77(t, 3H, J=7Hz, -CH_3), 1.22(q, 2H, J=7Hz, -CH_2), 1.59(q, 2H, J=7Hz, -CH_2), 3.44(q, 2H, J=7Hz, =C-CH_2), 7.35-8.89(m, 8H, Ar-H) ppm; *Anal. Calcd. for* $C_{19}H_{17}N_2O_2$ (340.80); calcd.: C 66.96, H 5.02; found: C 67.01, H 5.09.

2-Butyl-3-paramethylbenzoyl-4-oxo-4H-pyrido[1,2-a]pyrimidine **(5k*)***
Yield (0.262g, 82%), m.p.:96°C; IR: cm^{-1}=1680, 1610, 1570, 1550, 1500; ^{1}H NMR: δ=0.85(t, 3H, J=7Hz, -CH_3), 1.34(q, 2H, J=7Hz, -CH_2), 1.70(q, 2H, J=7Hz, -CH_2), 2.41(s, 3H, p-Me), 2.68(q, 2H, J=7Hz, =C-CH_2), 7.35-8.89(m, 8H, Ar-H) ppm; *Anal. Calcd. for* $C_{20}H_{20}N_2O_2$ (320.39); calcd.: C 74.97, H 6.29; found: C 74.78, H 6.34.

RESULTS AND DISCUSSION

P-substituted benzoyl-3-(2-pyridylamino / 2-pyrimidylamino)-2-alkenenitriles **4** were obtained by condensation of *p*-substituted benzoylacetonitrile **(1a-c)** with 2-aminopyridine **(2a)** or 2-aminopyrimidine **(2b)** and trimethylorthoesters **3,** at 80°C, in 70% yield. Compound **4** could be synthesized in 60% yield by refluxing three fold mixtures of compounds **1, 2** and **3** in toluene. Cyclization of compounds (**4a-k)** with hydrochloric acid gave 3-*p*-substituted benzoyl-4-oxo-4H-pyrido [1, 2-a]pyrimidine derivatives **(5a-k)** in good yields. All the new compounds were well characterized by IR, NMR and elemental analysis given in experimental section.

CONCLUSION

We have explored a facile and efficient protocol for the synthesis of 3-*p*-substituted benzoyl-4-oxo-4H-pyrido [1, 2-a]pyrimidine derivatives with 60-89% yields. Particularly valuable features of present method include broad substrate scope, short reaction time, straight forward procedure and easy aqueous work up that facilitated 80-85% recovery of pure product and use of inexpensive chemicals and reagents.

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