A Solvent-Free Protocol for One Pot Conversion of Baylis Hillman Acetates to Pyridopyrimidinones

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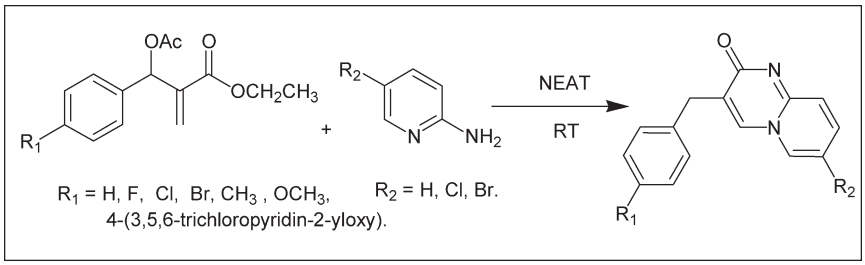

A facile one pot transformation of Baylis Hillman acetates to pyrido[1,2-a]pyrimidin-2-ones by reaction with 2-amino pyridine in a total solvent-free protocol is illustrated. The 3-substituted-2H-pyrido[1,2-a]pyrimidin-2-ones are obtained in pure form without involving any purification technique or solvent.

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INTRODUCTION

Pyrimidines are integral constituents of cellular molecular framework like DNA, RNA [1], etc. Heterofused pyrimidines have been found to exhibit antiviral [2], antibacterial [3], anti-AIDS [4], antiplatelet [5], antithrombotic[6], antinociceptive [7] activities, etc. Their applications were especially attractive due to their inhibition of multidrug resistance [8]. Among the fused pyrimidines, pyrido[1,2-a]pyrimidinone motif is an essential part of marketed pharmaceuticals like the antiasthamatic pemirolast (A) [9], an antiulcerative drug (B) [10], the tranquillizer pirenperone (C) [11], and the antiallergic barmastine (D) [12] (Figure 1). The diverse biological activities exhibited by these structural moieties justify our interest in further exploration of the pyrido[1,2-a]pyrimidin-2-ones for potential applications in agrochemical and pharmaceutical area.

Pyrido[1,2-a]pyrimidines have been synthesized by different methods depending on the side chains/ring substitutions required. Condensation of 2-aminopyridine with alkyl acrylates [13], methyl propiolate [14], dimethyl allene-1,3-dicarboxylate [15], diethyl *N*,*N*-dimethylaminomethylene malonate [16], α-acetyl-γ-butyrolactone [17], etc., have been attempted. Transformation of Baylis Hillman acetates by condensation with 2-aminopyridine to 3-substituted-2H-pyrido[1,2-a]pyrimidin-2-ones has also been reported [18]. Versatility of this reaction found to be more suitable for generating diversely substituted 2H-pyrido[1,2-a]pyrimidin-2-ones library of compounds for exploring their biological potential.

RESULTS AND DISCUSSION

At the outset, we attempted the one pot reaction of methyl 2-(acetoxy(phenyl)methyl)acrylate (**1a**) with 2-aminopyridine (**2**) under the conditions described by Basavaiah and Satyanarayana [18]. The reaction proceeds in (1:1) MeOH, H_2O solvent mixture to produce 3-benzyl-2H-pyrido [1,2-a]pyrimidin-2-one (**3a**) in 6 h and 75% yield. As we planned to prepare a library of compounds in an efficient and quick manner for an ongoing project work, we have relooked at this well-known reaction, seeking improvisation. Initially, a solvent-free condensation has been attempted (Scheme 1). To our surprise, the reaction proceeded within minutes, and solid product was precipitated out. Mere filtration of the reaction mixture by trituration with water gave product **3a** (entry 1, Table 1) pure enough for all purposes including high-resolution mass spectrometry. The spectral data and melting points of **3a** were comparable with those of reported in literature [18] further proving that no purification of the product was essential.

Inspired by this result, we then went on to test the scope of this total solvent-free conversion by varying both the Baylis Hillman acetates and substitutions on 2-aminopyridine. The representative set of acetates and 5-substituted-2-aminopyridines exploited are listed in Table 1. All transformations were facile and occurred at room temperature in good yields. In all cases, the pure products were obtained by simple filtration. The transformations with simple 2-aminopyridine were rapid and occurred within few minutes. Reaction with

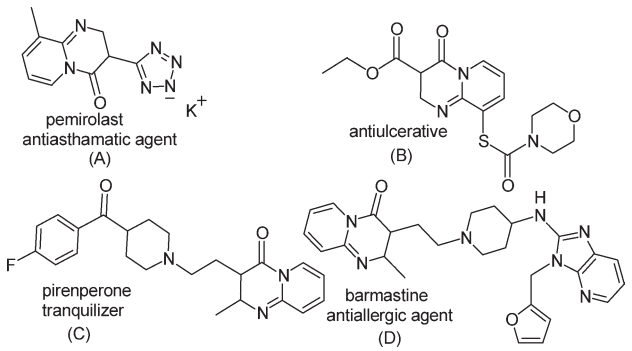


Figure 1. Marketed pharmaceuticals with pyrido[1,2-a]pyrimidinone motif.

5-substituted-2-aminopyridines on the other hand was little slow, taking few hours to complete. The yield was better with halo substitutions on the 2-aminopyridine ring compared with nitro substitution, with which the reaction did not take place at all. This is most probably because of strong electron withdrawing effect of nitro substitution compared with halo substitutions or no substitution on 2-aminopyridine ring. The substitutions on Baylis Hillman acetates were also influencing the reaction yields with methoxy substitution or the phenoxy substitution (entries 16 and 19, Table 1) resulting in the products in 89% and 97% yield, respectively.

Condensation of Baylis Hillman acetate with 2-amino pyridine may result in two different pyridopyrimidinone structural frameworks, structure (A) or structure (B) (Figure 2). Based on NMR studies, Basavaiah and Satyanarayana assigned the condensation product as structure A. To establish the structure unequivocally, we have collected the X-ray diffraction data of single crystal for **3l** (entry 12) (Figure 3). The diffraction pattern confirmed that the pyrido[1,2-a] pyrimidin-2-ones formed by the condensation possess structure A, as shown by earlier study.

A comparative study of both solvent-free and under solvent reaction conditions [18] has been attempted to demonstrate the superiority of the solvent-free protocol, and the results are tabulated in Table 2. All reactions occurred at room temperature. We found a definite advantage of the solvent-free protocol especially in terms of reaction time and yields.

CONCLUSION

To conclude, we have succeeded in simplifying the important organic transformation of synthesis of substituted 2H-pyrido[1,2-a]pyrimidin-2-ones by avoiding solvent usage in any stage of the protocol, thus making this facile approach more versatile and green. Further, the reaction occurs at room temperature without any lengthy workup or purification techniques, thus enhancing its synthetic utility. The biological profile of the synthesized substituted 2H-pyrido[1,2-a]pyrimidin-2-ones is being investigated and will be published elsewhere.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. NMR spectra were obtained on JCAMP DX-50 instrument (300 MHz for ^{1}H and 75 MHz for ^{13}C), and $CDCl_3$ and DMSO-d_6 used as solvents; J values are in Hz. Chemical shifts are reported in δ (ppm) down field from internal standared TMS. Electronic ionization MS spectra were recorded on thermofunigan ESI ion trap mass spectrometer. HRMS data were recorded on QSTAR XL Hybrid MS/MS system under ESI condition. IR spectra were recorded on a Thermo Nicolet NEXUS 670 spectrometer in KBr with absorption in cm^{-1}.

General procedure for synthesis of 3a–3s. A mixture of Baylis Hillman acetate (2 mmol) and 2-aminopyridine (2 mmol) stirred at room temperature. The progress of the reaction is monitored by TLC. After the completion of the reaction, the solid product obtained was filtered off by triturating with water. The white solid products collected were pure enough for all practical purposes. Occasionally, some products especially, substituted amino pyridines were washed with an additional amount of water.

Spectral data of compounds 3.

3-Benzyl-2H-pyrido[1,2-a]pyrimidin-2-one (3a). White solid, yield: 84%; m.p. 219–222°C (decom.) [18]; IR (KBr): (ν_{max}, cm^{-1}): 1650, 1602 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.84 (2H, s, CH_2), 6.74–6.78 (1H, t, Ar-H, J = 6.6 Hz), 7.21–7.30 (5H, m, Ar-H), 7.48–7.53 (1H, t, Ar-H, J = 7.3 Hz), 7.58 (1H, s, Ar-H), 7.70 (1H, s, Ar-H), 7.87–7.90 (1H, d, Ar-H, J = 6.9 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 53.2, 129.6, 132.2, 142.1, 145.8, 147.1, 147.9 (2C), 148.4 (2C), 153.6, 155.9, 156.0, 158.3, 170.3; ESI Mass (m/z) 237 (M + H$^+$); HRMS (EI): m/z Calculated value = 237.1027, Observed value = 237.1039.

3-Benzyl-7-chloro-2H-pyrido[I,2-a]pyrimidin-2-one (3b). White solid, yield: 71%; m.p. 236–239°C (decom.); IR (KBr): (ν_{max}, cm^{-1}): 1655, 1616 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.82 (2H, s, CH_2) 7.18–7.21 (1H, d, Ar-H, J = 9.6 Hz), 7.28–7.29 (3H, m, Ar-H), 7.46–7.49 (1H, d, Ar-H, J = 9.6 Hz), 7.69 (2H, s, Ar-H), 7.85 (1H, s, Ar-H), 8.30 (1H, s, Ar-H); ESI Mass (m/z) 271 (M$^+$); HRMS (EI): m/z Calculated value = 271.0638, Observed value = 271.0633.

3-Benzyl-7-bromo-2H-pyrido[I,2-a]pyrimidin-2-one (3c). White solid, yield: 68%; m.p. 237–240°C (decom.); IR (KBr): (ν_{max}, cm^{-1}): 1653, 1616 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.79 (2H, s, CH_2), 7.10–7.13 (1H, d, Ar-

Scheme 1

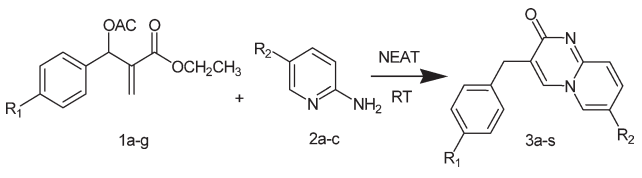
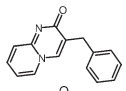
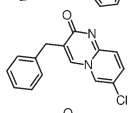
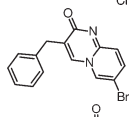
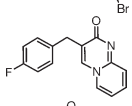
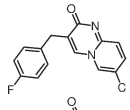
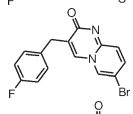
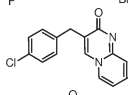
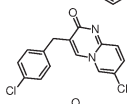
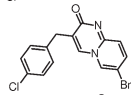
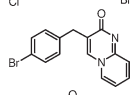
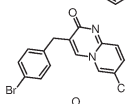
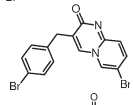
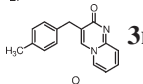
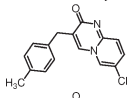
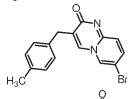
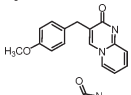
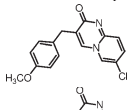
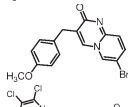
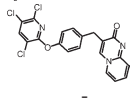


Table 1

Synthesis of substituted 2*H*-pyrido[1,2-a]pyrimidin-2-one.

Entry	R_1	R_2	Product	Time	Yield* (%)
1	H	H	 **3a**	5 min	84
2	H	Cl	 **3b**	4 h	71
3	H	Br	 **3c**	5 h	68
4	F	H	 **3d**	15 min	74
5	F	Cl	 **3e**	12 h	59
6	F	Br	 **3f**	16 h	58
7	Cl	H	 **3g**	10 min	81
8	Cl	Cl	 **3h**	6 h	64
9	Cl	Br	 **3i**	6 h	63
10	Br	H	 **3j**	10 min	86
11	Br	Cl	 **3k**	3 h	70
12	Br	Br	 **3l**	4 h	65
13	CH_3	H	 **3m**	10 min	82
14	CH_3	Cl	 **3n**	14 h	59
15	CH_3	Br	 **3o**	10 h	57
16	OCH_3	H	 **3p**	8 min	89
17	OCH_3	Cl	 **3q**	6 h	60
18	OCH_3	Br	 **3r**	15 h	59
19	3,5,6-trichloropyridin-2-yloxy	H	 **3s**	15 min	97
20	H	NO_2	-	72 h	-

* Yields refer to isolated and pure compounds. All compounds gave spectral data consistent with their structures.

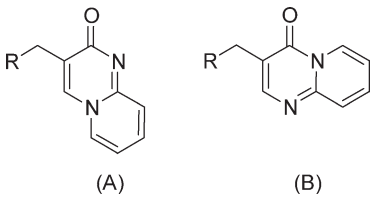


Figure 2. Possible structure of pyridopyrimidinones formed.

H, J = 9.4 Hz), 7.27–7.29 (3H, m, Ar-H), 7.56–7.60 (1H, d, Ar-H, J = 9.4 Hz), 7.87 (2H, s, Ar-H), 7.96 (1H, s, Ar-H), 8.47 (1H, s, Ar-H); ESI Mass (*m/z*) 315 (M^+); HRMS (EI): *m/z* Calculated value = 315.0132, Observed value = 315.0123.

3-(4-Fluorobenzyl)-2H-pyrido[1,2-a]pyrimidin-2-one (3d). White solid, yield: 74%; m.p. 220–224°C (decom.); IR (KBr): ($\nu_{max,}$ cm^{-1}): 1654, 1585 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.82 (2H, s, CH_2), 6.73–6.78 (1H, t, Ar-H), J = 6.9 Hz), 6.96–7.01 (2H, t, Ar-H, J = 8.6 Hz), 7.21–7.24 (1H, d, Ar-H, J = 8.8 Hz), 7.27–7.32 (2H, dd, Ar-H, J = 5.6 and 8.4 Hz), 7.47–7.53 (1H, t, Ar-H, J = 8.1 Hz), 7.74 (1H, s, Ar-H), 7.90–7.92 (1H, d, Ar-H, J = 6.7 Hz); ^{13}C-NMR (75 MHz, DMSO- d_6) δ: 52.2, 99.5, 132.3, 134.4, 134.7, 142.1, 147.0, 150.3, 150.4, 153.6, 154.3, 155.9, 156.1, 178.9, 182.1; ESI Mass (*m/z*) 255 (M + H^+); HRMS (EI): Calculated value = 255.0933, Observed value = 255.0945.

3-(4-Fluorobenzyl)-7-chloro-2H-pyrido[1,2-a]pyrimidin-2-one (3e). White solid, yield: 59%; m.p. 240–243°C (decom.); IR (KBr): ($\nu_{max,}$ cm^{-1}): 1656, 1598 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.82 (2H, s, CH_2), 6.73–6.78 (1H, t, Ar-H, J = 7.1 Hz), 6.96–7.01 (2H, t, Ar-H, J = 8.6 Hz), 7.21–7.24 (1H, d, Ar-H, J = 8.8 Hz), 7.27–7.32 (1H, dd, Ar-H, J = 5.6 and 8.4 Hz), 7.47–7.53 (1H, t, Ar-H, J = 8.8 Hz), 7.74 (1H, s, Ar-H), 7.90–7.92 (1H, d, Ar-H, J = 6.7 Hz); ESI Mass (*m/z*) 289 (M^+); HRMS (EI): *m/z* Calculated value = 289.0543, Observed value = 289.0554.

3-(4-Fluorobenzyl)-7-bromo-2H-pyrido[1,2-a]pyrimidin-2-one (3f). White solid, yield: 58%; m.p. 235–239°C (decom.); IR (KBr): ($\nu_{max,}$ cm^{-1}): 1654, 1597 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.79 (2H, s, CH_2), 6.96–7.01 (2H, t, Ar-H, J = 8.6 Hz), 7.13–7.16 (1H, d, Ar-H, J = 9.6 Hz), 7.27–7.31 (2H, dd, Ar-H, J = 5.4 and 9.8 Hz), 7.53–7.56 (1H, dd, Ar-H, J = 2.2 and 9.8 Hz), 7.88 (1H, s, Ar-H), 8.39 (1H, s, Ar-H); ^{13}C-NMR (75 MHz, $CDCl_3$-DMSO-d_6) δ: 33.3, 105.6, 115.3, 115.6, 119.1, 124.4, 128.1, 131.2, 131.3, 134.2, 134.8, 136.4, 139.3, 140.4, 143.3; ESI Mass (*m/z*) 333 (M^+); HRMS (EI): Calculated value = 333.0038, Observed value = 333.0026.

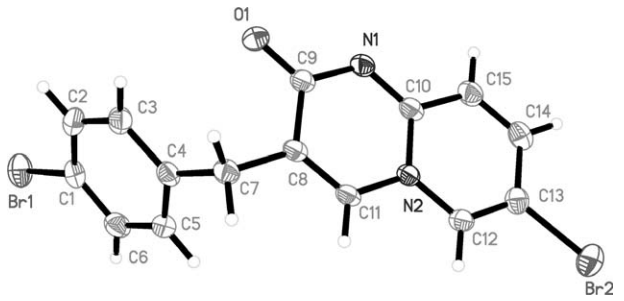


Figure 3. The molecular structure of **3l**, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius.

3-(4-Chlorobenzyl)-2H-pyrido[1,2-a]pyrimidin-2-one (3g). White solid, yield: 78%; m.p. 234–238°C (decom.) [18]; IR (KBr): ($\nu_{max,}$ cm^{-1}): 1652, 1588 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.73 (2H, s, CH_2), 6.76–6.79 (1H, t, Ar-H, J = 6.8 Hz), 7.11–7.13 (1H, d, Ar-H, J = 8.7 Hz), 7.20–7.27 (3H, m, Ar-H), 7.50–7.53 (1H, t, Ar-H, J = 7.8), 7.88 (1H, s, Ar-H), 8.03 (1H, s, Ar-H), 8.04–8.06 (1H, d, Ar-H, J = 6.8 Hz); ESI Mass (*m/z*) 271 (M^+); HRMS (EI): *m/z* Calculated value = 271.0638, Observed value = 271.0640.

3-(4-Chlorobenzyl)-7-chloro-2H-pyrido[1,2-a]pyrimidin-2-one (3h). White solid, yield: 64%; m.p. 239–242°C (decom.); IR (KBr): ($\nu_{max,}$ cm^{-1}): 1655, 1617 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.77 (2H, s, CH_2), 7.16–7.19 (1H, d, Ar-H, J = 9.6 Hz), 7.24–7.30 (4H, m, Ar-H), 7.50–7.53 (1H, d, Ar-H, J = 9.6 Hz), 7.84 (1H, s, Ar-H), 8.01 (1H, s, Ar-H); ESI Mass (*m/z*) 305 (M^+); HRMS (EI): *m/z* Calculated value = 305.0248, Observed value = 305.0253.

Table 2

Comparative study of solvent and solvent-free conditions for synthesis of substituted 2*H*-pyrido[1,2-a]pyrimidin-2-one.

			MeOH:H_2O (1:1)		Solvent Free Conditions[c]	
Product	R_1	R_2	Time (h)	Yield (%)	Time	Yield (%)
3a	H	H	6[a]	77	5 min	84
3g	Cl	H	6[a]	74	10 min	81
3m	CH_3	H	6[a]	74	10 min	82
3p	OCH_3	H	6[a]	56	8 min	89
3b	H	Cl	24[b]	55	4 h	71
3c	H	Br	24[b]	51	5 h	68
3h	Cl	Cl	24[b]	47	6 h	64
3i	Cl	Br	24[b]	45	6 h	63

[a] Reported by Basavaiah.
[b] Experiments carried in solvent system (MeOH:H_2O) in our lab for comparision.
[c] Reactions done at our lab.

3-(4-Chlorobenzyl)-7-bromo-2H-pyrido[1,2-a]pyrimidin-2-one (3i). White solid, yield: 63%; m.p. 236–240°C (decom.); IR (KBr): ($\nu_{max,}$ cm^{-1}): 1653, 1614 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.75 (2H, s, CH_2), 7.08–7.10 (1H, d, Ar-H, J = 9.7 Hz), 7.23 (4H, s, Ar-H), 7.51–7.53 (1H, d, Ar-H, J = 11.7 Hz), 7.89 (1H, s, Ar-H), 8.41 (1H, s, Ar-H); ^{13}C -NMR (75 MHz, $CDCl_3$-DMSO-d_6) δ: 33.7, 100.2, 112.6, 125.5, 127.9, 129.1 (2C), 130.9 (2C), 131.6, 134.2, 136.3, 138.6, 164.9, 171.3; ESI Mass (*m/z*) 349 (M^+); HRMS (EI): Calculated value = 348.9743, Observed value = 348.9731.

3-(4-Bromobenzyl)-2H-pyrido[1,2-a]pyrimidin-2-one (3j). White solid, yield: 86%; m.p. 238–241°C (decom.); IR (KBr): ($\nu_{max,}$ cm^{-1}): 1652, 1586 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.79 (2H, s, CH_2), 6.75–6.80 (1H, t, Ar-H, J = 6.7 Hz), 7.04–7.07 (1H, d, Ar-H, J = 8.3 Hz), 7.22–7.28 (3H, t, Ar-H, J = 8.3 Hz), 7.40–7.43 (2H, d, Ar-H, J = 8.3 Hz), 7.89 (1H, s, Ar-H), 8.00–8.02 (1H, d, Ar-H, J = 6.0 Hz); ESI Mass (*m/z*) 315 (M^+); HRMS (EI): *m/z* Calculated value = 315.0132, Observed value = 315.0143.

3-(4-Bromobenzyl)-7-chloro-2H-pyrido[1,2-a]pyrimidin-2-one (3k). White solid, yield: 70%; m.p. 240–242°C (decom.); IR (KBr): ($\nu_{max,}$ cm^{-1}): 1655, 1615 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.78 (2H, s, CH_2), 7.18–7.22 (3H, m, Ar-H), 7.40–7.43 (2H, d, Ar-H, J = 8.9 Hz), 7.46–7.49 (1H, d, Ar-H, J = 9.8 Hz), 7.90 (1H, s, Ar-H), 8.35 (1H, s, Ar-H); ESI Mass (*m/z*) 349 (M^+); HRMS (EI): *m/z* Calculated value = 348.9743, Observed value = 348.9757.

3-(4-Bromobenzyl)-7-bromo-2H-pyrido[1,2-a]pyrimidin-2-one (3l). White solid, yield: 65%; m.p. 239–240°C (decom.); IR (KBr): ($\nu_{max,}$ cm^{-1}): 1652, 1615 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.78 (2H, s, CH_2), 7.12–7.15 (1H, d, Ar-H, J = 9.8 Hz), 7.20–7.22 (2H, d, Ar-H, J = 8.0 Hz), 7.41–7.43 (2H, d, Ar-H, J = 8.0 Hz), 7.54–7.57 (1H, d, Ar-H, J = 8.9 Hz), 7.67 (1H, s, Ar-H), 7.89 (1H, s, Ar-H);ESI Mass (*m/z*) 394 (M^+); HRMS (EI): *m/z* Calculated value = 394.9206, Observed value = 394.9216.

3-(4-Methylbenzyl)-2H-pyrido[1,2-a]pyrimidin-2-one (3m). White solid, yield: 82%; m.p. 232–234°C (decom.) [18]; IR (KBr): ($\nu_{max,}$ cm^{-1}): 1649, 1600 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 2.32 (3H, s, CH_3), 3.77 (2H, s, CH_2), 6.75–6.77 (1H, t, Ar-H, J = 6.3 Hz), 7.07–7.20 (5H, m, Ar-H), 7.49–7.52 (1H, t, Ar-H, J = 8.1 Hz), 7.77 (1H, s, Ar-H), 7.94–7.96 (1H, d, Ar-H, J = 7.2 Hz); ESI Mass (*m/z*) 251 (M + H^+); HRMS (EI): *m/z* Calculated value = 251.1184, Observed value = 251.1195.

3-(4-Methylbenzyl)-7-chloro-2H-pyrido[1,2-a]pyrimidin-2-one (3n). White solid, yield: 59%; m.p. 233–236°C (decom.); IR (KBr): ($\nu_{max,}$ cm^{-1}): 1655, 1616 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 2.31 (3H, s, CH_2), 3.73 (2H, s, CH_2), 7.06–7.18 (5H, m, Ar-H), 7.52–7.55 (1H, dd, Ar-H, J = 2.2 and 9.6 Hz), 7.96 (1H, s, Ar-H), 8.42–8.43 (1H, d, Ar-H, J = 1.8 Hz); ESI Mass (*m/z*) 285 (M^+); HRMS (EI): *m/z* Calculated value = 285.08 14, Observed value = 285.0822.

3-(4-Methylbenzyl)-7-bromo-2H-pyrido[1,2-a]pyrimidin-2-one (3o). White solid, yield: 57%; m.p. 234–238°C (decom.); IR (KBr): ($\nu_{max,}$ cm^{-1}): 1652, 1609 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 2.32 (3H, s, CH_3), 3.74 (2H, s, CH_2), 7.07–7.09 (2H, d, Ar-H, J = 8.3 Hz), 7.13–7.16 (2H, d, Ar-H, J = 8.1 Hz), 7.56–7.59 (1H, d, Ar-H, J = 9.6 Hz), 7.86–7.89 (2H, d, Ar-H, J = 10.3 Hz), 8.45 (1H, brs, Ar-H); ^{13}C -NMR (75 MHz, DMSO-d_6) δ: 20.6, 32.2, 112.1, 115.1, 117.1, 123.8, 127.9, 128.8 (2C), 128.9 (2C), 133.7, 135.7, 138.8, 168.7; ESI Mass (*m/z*) 329 (M^+); HRMS (EI): Calculated value = 329.0289, Observed value = 329.0276.

3-(4-Methoxybenzyl)-2H-pyrido[1,2-a]pyrimidin-2-one (3p). White solid, yield: 89%; m.p. 220–224°C (decom.) [18]; IR (KBr): ($\nu_{max,}$ cm^{-1}): 1651, 1605 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.76 (2H, s, CH_2), 3.77 (3H, s, CH_3), 6.74–6.83 (3H, m, Ar-H), 7.18–7.22 (3H, m, Ar-H), 7.48–7.54 (1H, t, Ar-H, J = 6.9 Hz), 7.71 (1H, s, Ar-H), 7.93–7.95 (1H, d, Ar-H, J = 6.6 Hz); ESI Mass (*m/z*) 267 (M + H^+); HRMS (EI): *m/z* Calculated value = 267.1133, Observed value = 267.1132.

3-(4-Methoxybenzyl)-7-chloro-2H-pyrido[1,2-a]pyrimidin-2-one (3q). White solid, yield: 60%; m.p. 2220–225°C (decom.); IR (KBr): ($\nu_{max,}$ cm^{-1}): 1654, 1600 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.72 (2H, s, CH_2), 3.77 (3H, s, CH_3), 6.80–6.83 (2H, d, Ar-H, J = 8.1 Hz), 7. 17–7.19 (2H, d, Ar-H, J = 7.3 Hz), 7.48–7.52 (1H, d, Ar-H, J = 11.3 Hz), 7.83–7.86 (2H, d, Ar-H, J = 9.2 Hz), 8.38 (1H, s, Ar-H); ^{13}C -NMR (75 MHz, DMSO-d_6) δ: 32.8, 54.9, 101.2, 107.6, 113.2, 113.7 (2C), 123.8 (2C), 128.2, 130.0, 131.7, 135.7, 136.7, 149.2, 164.5; ESI Mass (*m/z*) 301 (M^+); HRMS (EI): Calculated value = 301.0743, Observed value = 301.0731.

3-(4-Methoxybenzyl)-7-bromo-2H-pyrido[1,2-a]pyrimidin-2-one (3r). White solid, yield: 59%; m.p. 222–226°C (decom.); IR (KBr): ($\nu_{max,}$ cm^{-1}): 1651, 1600 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.69 (2H, s, CH_2), 3.75 (3H, s, CH_3), 6.80 (2H, s, Ar-H), 7.10 (1H, s, Ar-H), 7.18 (1H, s, Ar-H), 7.63 (1H, s, Ar-H), 7.96 (1H, s, Ar-H), 8.02 (1H, s, Ar-H), 8.53 (1H, s, Ar-H); ESI Mass (*m/z*) 345 (M^+); HRMS (EI): *m/z* Calculated value = 345.0238, Observed value = 345.0244.

3-(4-(3,5,6-trichloropyridin-2-yloxy)benzyl)-2H-pyrido[1,2-a]pyrimidin-2-one (3s). White solid, yield: 97%; m.p. 232–236°C (decom.); IR (KBr): ($\nu_{max,}$ cm^{-1}): 1651, 1604 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ (ppm): 3.77 (2H, s, CH_2), 6.93–6.97 (1H, t, Ar-H, J = 7.1 Hz), 7.13–7.17 (3H, t, Ar-H, J = 5.0 Hz), 7.37–7.40 (2H, d, Ar-H, J = 8.3 Hz), 7.64–7.69 (1H, t, Ar-H, J = 7.5 Hz), 8.15–8.18 (1H, d, Ar-H, J = 7.3 Hz), 8.30 (1H, s, Ar-H), 8.53 (1H, s, Ar-H); ESI Mass (*m/z*) 432 (M^+); HRMS (EI): *m/z* Calculated value = 432.1023, Observed value = 432.1024.

Structural data of 3l. X-ray data for the compound **3l** were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ= 0.71073 Å) with ω-scan method. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined from the setting angles of 6092 reflections for (**3l**).

Integration and scaling of intensity data were accomplished using SAINT program. The structures were solved by Direct Methods using SHELXS97 and refinement was carried out by full-matrix least-squares technique using SHELXL97. Anisotropic displacement parameters were included for all non-hydrogen atoms. All the H atoms were positioned geometrically and treated as riding on their parent C atoms, with C—H distances of 0.93–0.97 Å, and with $U_{iso}(H) = 1.2U_{eq}(C)$ for other H atoms. CCDC-760517 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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