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Substituted Pyridopyrimidinones, 1: Convenient PTC Alkylation and Halogenation of 2-Hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one

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ABSTRACT: *Alkylation of 2-hydroxy-4H-pyrido[1,2-a]-pyrimidin-4-one (**1**) was investigated under solid–liquid phase transfer catalysis conditions (PTC), using tetrabutylammonium bromide and potassium carbonate. The reaction with alkyl halides led to the formation of various 2-alkoxy products, in fair yields. Reaction of compound **1** with epichlorohydrin and chloroacetonitrile, under the same PTC conditions, afforded novel O1,O3-disubstituted glycerol and oxazolopyridopyrimidone betaine derivatives, respectively. Some 3-halo-, 3,3-dihalo, and/or 2,3-dihalopyrido[1,2-a]pyrimidines were also prepared using different halogenating agents at different reaction conditions.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:19–27, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20245

INTRODUCTION

Over the last 80 years and from the time when Tschitschibabin prepared 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and characterized it as pyrido-[1,2-*a*]-pyrimidine-2,4-dione, under the name of malonyl-α-aminopyridine [1], many synthetic and reaction studies had been carried out to deal with its derivatives. The distinguished and unique chemical properties [2–5] and biological applications of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives [6–10] evoked an interest for the continuation of the synthetic and chemical researches in this field. Herein, we will obtain new derivatives of pyrido[1,2-*a*]pyrimidin-4-one via convenient alkylation under phase transfer catalysis conditions (PTC). The phase transfer catalysis technique is of increasing importance in organic reactions, in particular alkylation processes [11,12]. We have modified the classic alkylation by application of the PTC technique, which is expected to be more suitable for these alkylation reactions. Also halogenation reactions of the titled compound were carried out in order to obtain new optionally functionalized pyrido[1,2-*a*]pyrimidin-4-ones of synthetic importance.

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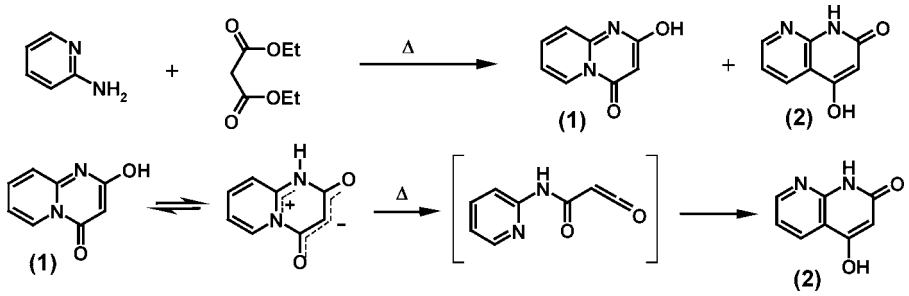
RESULTS AND DISCUSSION

It is reported that 2-hydroxy-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one (**1**) is smoothly prepared via thermal condensation of 2-aminopyridine with diethyl malonate [1,2,13,14]. According to this method, we separated two different malonyl heterocycles via differential crystallization. The major product was characterized as the pyridopyrimidinone **1** and the minor product as 4-hydroxy-1,8-naphthyridin-2(1*H*)-one (**2**) [15]. While carrying out the reaction by gently heating at 100–110°C for ca. 6 h reduced the amount of naphthyridinone by product, while at elevated temperatures (ca. 180–200°C) the amount of naphthyridinone **2** increased, reaching up to 40% of the converted 2-aminopyridine. The formation of naphthyridinone **2** can be attributed to the reported thermal rearrangement of the



SCHEME 1

pyridopyrimidin-4-ones via carbonyl ketene intermediate [16] (Scheme 1).

Etherification is one of the most common PTC reactions and is applicable to a wide variety of alcohols and phenols. The advantage of PTC is due to its effectiveness, easiness, higher yield, shorter time, inexpensive inorganic base, and environment friendly green methodology [13,17]. Reaction of compound **1** with alkyl halides, namely methyl iodide, ethyl iodide, propyl bromide, and allyl bromide, was carried out under the PTC conditions using K_2CO_3, tetrabutylammonium bromide (TBAB), in acetone. Figure 1 shows a mechanistic pathway for the alkylation of compound **1**, which may proceed via an S_N2-mechanism.

The corresponding 2-alkoxy-4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones **3a–d** were obtained in 58–86%. However, using traditional heating method without addition of TBAB, the phase transfer catalyst, the yields did not exceed 42% in the best cases (see Table 1). ^{1}H NMR of the product **3d** revealed the specific set of signals due to the allyloxy grouping as doublet at δ 4.87 due to ($OCH_2CH{=}CH_2$), and the signal of proton at position-3 appeared very near at δ 4.94, as a singlet. This confirmed that O-alkylation took place and the formation of either 3-alkylated derivative **4** or N-alkylated derivative **5** should be excluded under the present conditions (Scheme 2).

Similarly, alkyl haloacetates, viz. methyl chloroacetate and ethyl bromoacetate, when reacted with compound **1** the corresponding alkyl [(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]acetates (**3e,f**) were obtained. The chemical shifts, at δ 5.02 ppm

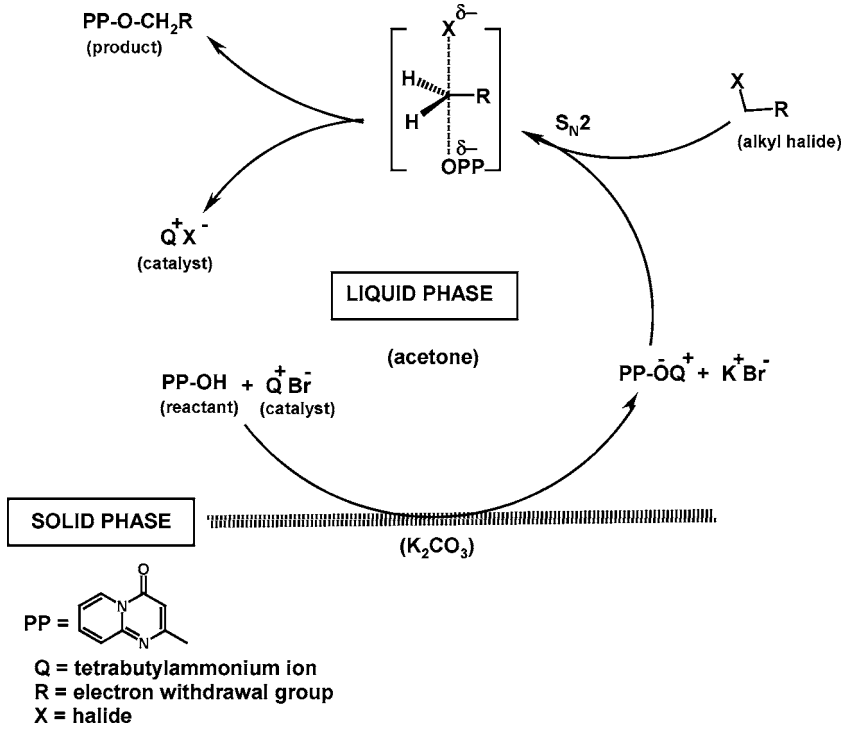


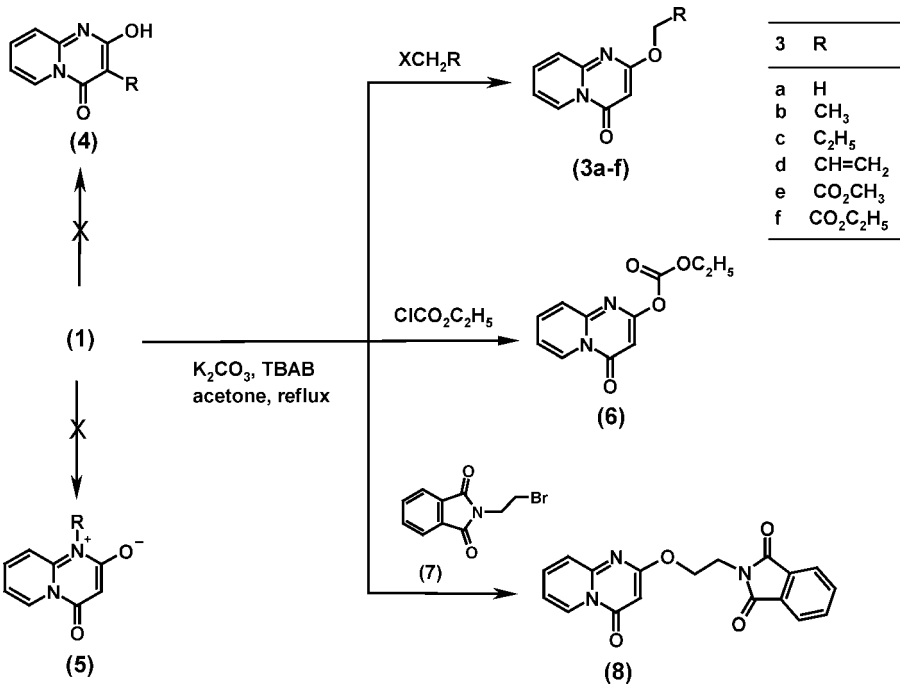
FIGURE 1 PTC alkylation of 2-hydroxypyrido[1,2-*a*]pyrimidin-4(*H*)-one.

TABLE 1 Reaction Time and Yields of Alkylation of Compound **1**

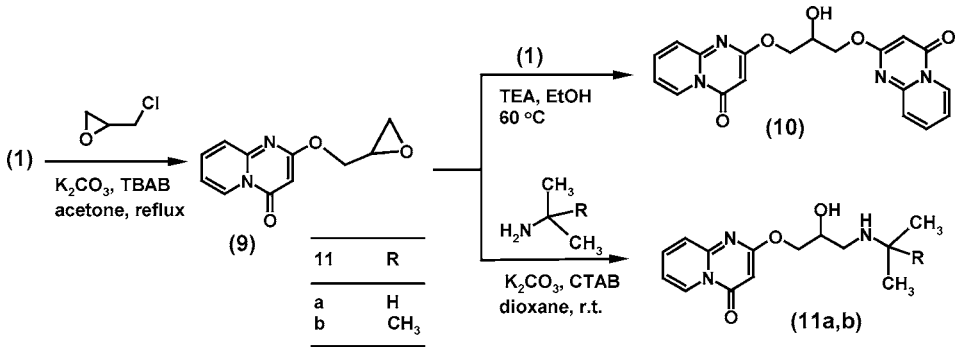
		Classic Method (without TBAB)		*Phase Transfer Catalysis Method (Using TBAB)*	
Product	*Reagent*	*Time (h)*	*Yield (%)*	*Time (h)*	*Yield (%)*
3a	CH_3I	16	41 [20]	4	86
3b	CH_3CH_2I	12	38	4	79
3c	$CH_3CH_2CH_2Br$	8	9.5 [3]	4	73
3d	$CH_2{=}CHCH_2Br$	12	14	6	58
3e	$ClCH_2CO_2CH_3$	24	20	8	63
3f	$ClCH_2CO_2C_2H_5$	24	22	8	88
6	$ClCO_2C_2H_5$	24	26	4	71
8	Compound **7**	12	42	4	68
9	Epichlorohydrin	16	18	8	62

for **3e** ($R = CO_2CH_3$), and at δ 4.99 ppm for **3f** ($R = CO_2C_2H_5$), indicated that O-alkylation selectivity took place. Ethyl(4-oxo-4*H*-pyrido[1,2-*a*]-pyrimidin-2-yl)carbonate (**6**) was obtained, in 71% yield, when compound **1** was allowed to react with ethyl chloroformate under the same PTC conditions. Treatment of the compound **1** with *N*-(2-bromoethyl)phthalimide (**7**) using the PTC conditions furnished 2-{2-[(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]ethyl}-isoindole-1,3-(2*H*)-dione (**8**) (Scheme 2). IR spectrum of compound **8** revealed additional (C=O) stretching vibrations at ν 1713 and 1692 cm^{-1} characteristic for phthalimide moiety [18], while ^1H NMR spectrum showed two triplet sets of signals at δ 3.73 and 4.01 specific for (NCH_2-CH_2O).

2-[(Oxiran-2-yl)methoxy]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**9**) was obtained via treatment of compound **1** with epichlorohydrin under the PTC conditions [19]. Triethylamine-catalyzed addition of compound **1** to the oxiran **9** afforded 2-{2-hydroxy-3-[(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]propoxy}-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**10**). Due to the reported potential antihypertensive activity of naphthyridinone oxime ethers obtained by addition of alkyl amines to its oxiranylmethyl precursors [20], the compound **9** was subjected to



SCHEME 2



SCHEME 3

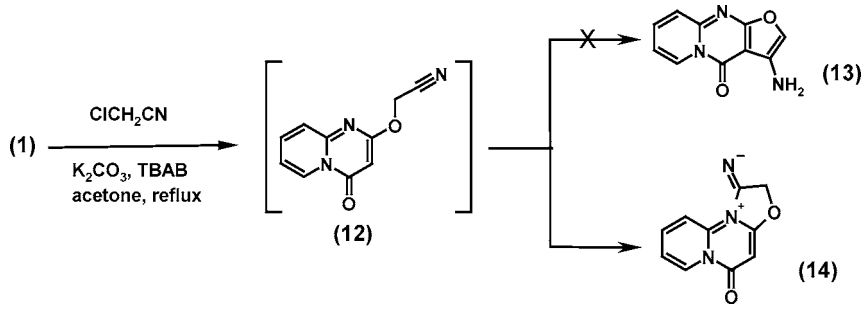
react with *iso*-propylamine and *tert*-butylamine. The addition took place in good yields in the presence of potassium carbonate and cetyltrimethylammonium bromide (CTAB), affording the corresponding 2-(3-alkylamino-2-hydroxypropoxy) pyridopyrimidinones **11a,b** (R = H, R = CH_3) (Scheme 3).

Under the same PTC conditions, chloroacetonitrile was reacted with compound **1** in order to give[(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]acetonitrile (**12**). Unexpectedly, IR spectrum did not show the absorption band characteristic for C≡N. ^{1}H NMR showed that pyrimidinone β-proton is more downfield shifted (δ 5.83) than its ordinary position ($\delta \approx 5.0$). In addition, the deuterium nonexchangeable two protons, which appeared as a singlet peak at δ 4.81, interpreted as methylenic protons excluding the formation of aminofuropyridopyrimidinone **13**. Anyhow, these results can be explained if we assumed that the product exhibited the stable mesoionic form (5-oxo-5*H*-oxazolo-[3, 2-*c*]pyrido[1,2-*a*]pyrimidin-11-ium-1(2*H*)-ylidene)azanide (**14**) (Scheme 4).

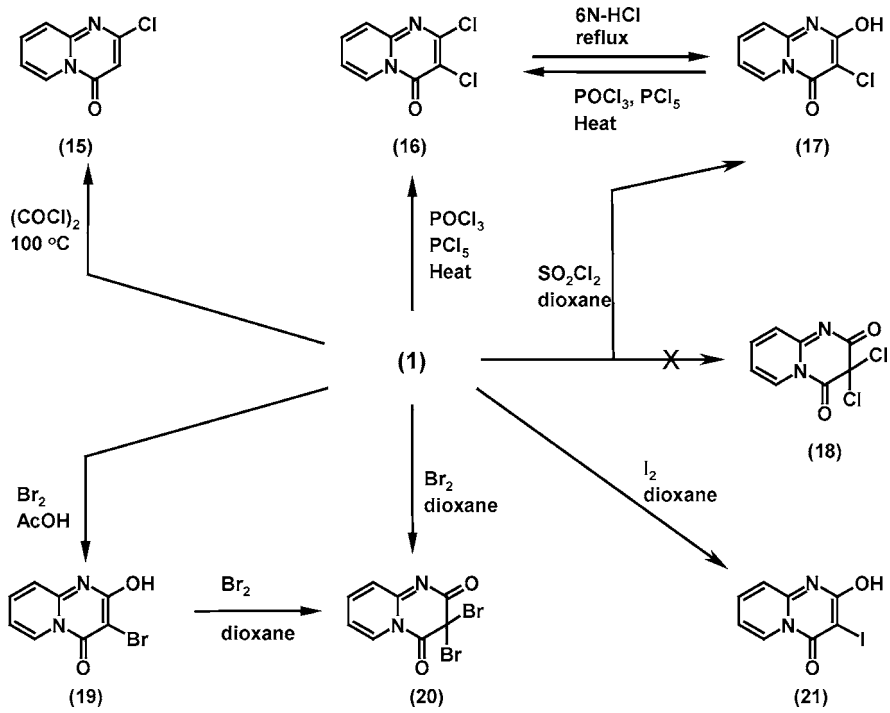
Chlorination of pyridopyrimidinone **1** with phosphoryl chloride was found to be temperature dependent. Thus, heating of the compound **1** with phosphoryl chloride, at 100–105°C, furnished only 2-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**15**) [2,21]. Interestingly, the same compound was obtained in higher yield (88%) on using oxalyl chloride instead of phosphoryl chloride [22]. Under drastic thermal conditions (200–220°C), a mixture of phosphoryl chloride and phosphorus pentachloride led to the formation of 2,3-dichloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**16**) (Scheme 5).

It is well known that sulfuryl chloride is a suitable reagent for C-chlorination of fused γ-hydroxy-α-pyridone derivatives [5,15,23]. Thus, the reaction of compound **1** with sulfuryl chloride led to only 3-chloro-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**17**), in 67% yield. Analytical and spectral data showed no evidence for the formation of the expected product 3,3-dichloro-2*H*-pyrido[1,2-*a*]pyrimidine-2,4(3*H*)-dione (**18**). Nevertheless, the compound **17** was obtained earlier, as a byproduct during chlorination of compound **1** [2]. Conversion of compound **17** into the 2,3-dichloro derivative **16** was affected by the action of phosphorus oxychloride. Conversely, acid hydrolysis of compound **16** led to the 3-chloro-2-hydroxy derivative **17** (Scheme 5).

3-Bromo-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**19**) was prepared by reaction of compound **1** with bromine in acetic acid at room temperature [24]. Treating compound **1** with excess bromine in dioxane led to the formation of



SCHEME 4



SCHEME 5

3,3-dibromo-2*H*-pyrido[1,2-*a*]pyrimidin-2,4(3*H*)-one (**20**). IR spectrum represented two characteristic absorption vibrations at ν 1720 and 1690 cm^{-1} corresponding to 2,4-dioxo groups. ^1H NMR spectrum showed four sets of peaks at δ 7.49, 7.75, 8.08, and 9.03 due to 1,2-disubstituted pyridine protons. Moreover, the mono-bromo derivative **19** was smoothly converted into the dibromo derivative **20** on treating with excess bromine in dioxane. Finally, the compound **1** was selectively iodinated using iodine in dioxane to give 2-hydroxy-3-iodo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**21**) in 77% yield (Scheme 5).

CONCLUSION

In general, it is remarked that alkylation under the PTC conditions neither C3- nor N1-alkylation took place, while the reaction selectivity took place at the hydroxy group leading to O-alkylation derivatives. Halogenation with replacement of one or two protons at position 3 of 2-hydroxy-4*H*-pyrido[1,2-*a*] pyrimidin-4-one was observed on treating with sulfuryl chloride, bromine, and iodine in the proper solvents. Chlorination with phosphoryl chloride and/or phosphorus pentachloride led to the formation of the 2-chloro and 2,3-dichloro derivatives. Oxalyl chloride is suitable for replacement of hydroxyl group at position 2 affording only the 2-chloro derivative.

EXPERIMENTAL SECTION

Melting points are uncorrected and were determined in open capillary tubes on a digital Gallen-Kamp MFB-595. IR spectra were taken on a Perkin–Elmer FT-IR 1650, using samples in KBr disks. ^1H NMR spectra were recorded on Varian Gemini-200 spectrometer (200 MHz), using DMSO-d_6 or C*D*Cl_3 as solvents and TMS as internal reference. Mass spectra were determined on a Shimadzu GC-MS-QP 1000 EX instrument or HP-MS 5988 mass spectrometer by direct inlet, operating at 70 eV. Elemental microanalyses were performed on a Perkin–Elmer CHN-2400 analyzer.

*2-Hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (**1**) and 4-Hydroxy-1,8-naphthydrin-2(1H)-one (**2**)*

A mixture of 2-aminopyridine (0.1 mol) and freshly distilled dry diethyl malonate (0.12 mol) was heated at 100–110°C until complete precipitation for about 6 h. The mixture was then cooled, triturated with diethyl ether (100 mL), washed several times with diethyl ether to remove unreacted materials, and crystallized from water to give the compound **1**, mp 296–298°C, (lit. mp 295–298°C [13]; 305–308°C [14]). This first crop was crystallized from DMF without significant change in the melting points (297–299°C). The mother-liquor of water crystallization was concentrated to one third of its initial volume and left

to stand at room temperature overnight to give compound **2**. Then the obtained sandy crystalline material was collected by filtration, mp 292–294°C (lit. mp 292–294°C [15]).

PTC-Alkylation of Compound **1***: Preparation of Ethers* **3a–f, 6, 8, 9***, and Compound* **14**

General Method. To a mixture of the compound **1** (1.62 g, 10 mmol), potassium carbonate (2.79 g, 20 mmol) and TBAB (0.3 g), in dry acetone (50 mL), the proper alkylating agent (11 mmol), namely methyl iodide (0.7 mL), ethyl iodide (0.9 mL), propyl bromide (1 mL), allyl bromide (1 mL), methyl chloroacetate (1 mL), ethyl bromoacetate (1.3 mL), ethyl chloroformate (1.1 mL), 2-(2-bromoethyl)isoindole-1,3(2*H*)-dione (**7**) (2.97 g), epichlorohydrin (0.9 mL), and chloroacetonitrile (0.7 mL), was added. Then the mixture was heated under reflux on a water bath for 4–8 h (Table 1) and filtered off while hot. The solvent was evaporated in vacuum, and the solid residue was crystallized from the proper solvent to give the title compounds. The filtration solid residue was dissolved in cold water (25 mL) and extracted with chloroform (3 × 25 mL). The combined extracts were dried over anhydrous sodium sulfate (10 g), filtered off and evaporated to recover unreacted material **1**.

Classic Method. The method described by Katritzky and Waring [3] using the proper alkyl halide and potassium or sodium methoxide was conducted as traditional alkylation method for compound **1** (see Table 1).

*2-Methoxy-4H-pyrido[1,2-a]pyrimidin-4-one (***3a***).* mp 145–147°C (methanol); yield 1.52 g (86%), lit. [21] mp 146–148°C (41%).

*2-Ethoxy-4H-pyrido[1,2-a]pyrimidin-4-one (***3b***).* mp 114–116°C (ethanol); yield 1.51 g (79%). IR (KBr), ν_{max}(cm^{-1}) 1711 (C=O), 1634 (C=N), 1575, 1536; ^{1}H NMR (C*D*Cl$_3$), δ 1.26 (t, $J = 7$ Hz, 3H, OCH$_2$C*H*$_3$), 4.04 (q, $J = 7$ Hz, 2H, OC*H*$_2$CH$_3$), 5.58 (s, 1H, 3-H), 7.32 (t, 1H, 7-H), 7.52 (d, 1H, 9-H), 7.78 (t, 1H, 8-H), 8.99 (d, 1H, 6-H). Anal Calcd for $C_{10}H_{10}N_2O_2$ (190.20): C, 63.15; H, 5.30; N, 14.73. Found: C, 62.90; H, 5.22; N, 14.56%.

*2-Propoxy-4H-pyrido[1,2-a]pyrimidin-4-one (***3c***).* mp 88–90°C (ethanol); yield 1.49 g (73%), lit. [3] mp 87–92°C (9.5%).

*2-Allyloxy-4H-pyrido[1,2-a]pyrimidin-4-one (***3d***).* mp 203–205°C (ethanol); yield 1.17 g (58%). IR (KBr), ν_{max}(cm^{-1}) 1700 (C=O), 1648 (C=N), 1620 (C=C), 1557, 1508; ^{1}H NMR (DMSO-d_6), δ 4.87 (d, $J = 5.6$ Hz, 2H, OC*H*$_2$CH=CH$_2$), 4.94 (s, 1H, 3-H), 5.04–5.19 (two d, $J = 10.5$, 16.8 Hz, 2H, OCH$_2$CH=C*H*$_2$), 5.90 (m, 1H, OCH$_2$C*H*=CH$_2$), 7.44 (t, 1H, 7-H), 7.67 (d, 1H, 9-H), 8.29 (t, 1H, 8-H), 9.17 (d, 1H, 6-H). Anal Calcd for $C_{11}H_{10}N_2O_2$ (202.21): C, 65.34; H, 4.98; N, 13.85. Found: C, 65.25; H, 4.86; N, 13.77%.

*Methyl[(4-Oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]acetate (***3e***).* mp 128–129°C (methanol); yield 1.47 g (63%). IR (KBr), ν_{max}(cm^{-1}) 1765 (C=O), 1693 (C=O), 1634 (C=N), 1573, 1530; ^{1}H NMR (DMSO-d_6), δ 3.70 (s, 3H, OCH$_3$), 5.02 (s, 2H, OCH$_2$CO), 5.77 (s, 1H, 3-H), 7.38 (t, 1H, 7-H), 7.55 (d, 1H, 9-H), 8.03 (t, 1H, 8-H), 8.98 (d, 1H, 6-H). Anal Calcd for $C_{11}H_{10}N_2O_4$ (234.21): C, 56.41; H, 4.30; N, 11.96. Found: C, 56.40; H, 4.52; N, 11.62%.

*Ethyl[(4-Oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]-acetate (***3f***).* mp 106–107°C (acetone); yield 2.18 g (88%). IR (KBr), ν_{max}(cm^{-1}) 1748 (C=O), 1691 (C=O), 1636 (C=N), 1572, 1527; ^{1}H NMR (DMSO-d_6), δ 1.21 (t, $J = 6.8$ Hz, 3H, OCH$_2$C*H*$_3$), 4.17 (q, $J = 6.8$ Hz, 2H, OC*H*$_2$CH$_3$), 4.99 (s, 2H, OCH$_2$CO), 5.77 (s, 1H, 3-H), 7.41 (t, 1H, 7-H), 7.54 (d, 1H, 9-H), 8.01 (t, 1H, 8-H), 8.98 (d, 1H, 6-H); MS, *m/z* (*I*%) 249 (11) [M + 1]$^+$, 248 (80) M$^+$, 220 (21), 203 (19), 175 (54), 148 (16), 145 (40), 134 (34), 118 (29), 79 (13), 78 (100). Anal Calcd for $C_{12}H_{12}N_2O_4$ (248.24): C, 58.06; H, 4.87; N, 11.28. Found: C, 58.08; H, 5.24; N, 11.10%.

*Ethyl(4-Oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)carbonate (***6***).* mp 102–104°C (ethanol); yield 1.66 g (71%). IR (KBr), ν_{max}(cm^{-1}) 1748 (C=O), 1691 (C=O), 1636 (C=N), 1572, 1527; ^{1}H NMR (DMSO-d_6), δ 1.32 (t, $J = 6.6$ Hz, 3H,OCH$_2$C*H*$_3$), 4.31 (q, $J = 6.6$ Hz, 2H, OC*H*$_2$CH$_3$), 6.28 (s, 1H, 3-H), 7.48 (t, 1H, 7-H), 7.72 (d, 1H, 9-H), 8.10 (t, 1H, 8-H), 9.02 (d, 1H, 6-H). Anal Calcd for $C_{11}H_{10}N_2O_4$ (234.21): C, 56.41; H, 4.30; N, 11.96. Found: C, 56.50; H, 4.22; N, 11.75%.

*2-{2-[(4-Oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]-ethyl}isoindole-1,3(2H)-dione (***8***).* mp 183–185°C (acetic acid); yield 2.28 g (68%). IR (KBr), ν_{max}(cm^{-1}) 1713 (C=O), 1690 (C=O), 1620 (C=N), 1600, 1572, 1529; ^{1}H NMR (DMSO-d_6), δ 3.73 (t, $J = 6.2$ Hz, 2H, NC*H*$_2$CH$_2$O), 4.01 (t, $J = 6.2$ Hz, 2H, NCH$_2$C*H*$_2$O), 5.60 (s, 1H, 3-H), 7.35 (t, 1H, 7-H), 7.64 (d, 1H, 9-H), 7.80–7.89 (m, 5H, H$_{arom}$ + 8-H), 8.86 (d, 1H, 6-H). Anal Calcd for $C_{18}H_{13}N_3O_4$ (335.32): C, 64.48; H, 3.91; N, 12.53. Found: C, 64.21; H, 3.74; N, 12.46%.

*2-[(Oxiran-2-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (**9**).* mp 150–152°C (ethanol); yield 1.35 g (62%). IR (KBr), ν_{max}(cm^{-1}) 1700 (C=O), 1633 (C=N), 1600, 1572, 1527; ^{1}H NMR (DMSO-d_6), δ 3.42 (m, 1H, CH_{oxiran}), 3.47 (d, $J = 5.8$ Hz, 2H, $CH_{2oxiran}$), 4.42 (d, $J = 5.4$ Hz, 2H, OCH_2), 5.67 (s, 1H, 3-H), 7.28 (t, 1H, 7-H), 7.51 (d, 1H, 9-H), 7.96 (t, 1H, 8-H), 8.90 (d, 1H, 6-H). Anal Calcd for $C_{11}H_{10}N_2O_3$ (218.21): C, 60.55; H, 4.62; N, 12.84. Found: C, 60.39; H, 4.55; N, 12.82%.

*(5-Oxo-5H-oxazolo[3,2-c]pyrido[1,2-a]pyrimidin-11-ium-1(2H)-ylidene)azanide (**14**).* mp 157–159°C (acetone); yield 1.13 g (56%). IR (KBr), ν_{max}(cm^{-1}) 1707 (C=O), 1640 (C=N), 1578, 1531; ^{1}H NMR (DMSO-d_6), δ 4.81 (s, 2H, 2-CH_2), 5.83 (s, 1H, 4-H), 7.32 (t, 1H, 8-H), 7.82 (d, 1H, 10-H), 7.94 (t, 1H, 9-H), 9.08 (d, 1H, 7-H); MS, *m/z* (*I*%) 202 (12) $[M+1]^+$, 201 (100) M^+, 173 (30), 146 (14), 133 (64), 118 (34), 105 (58), 78 (96), 69 (42). Anal Calcd for $C_{10}H_7N_3O_2$ (201.19): C, 59.70; H, 3.51; N, 20.89. Found: C, 59.60; H, 3.78; N, 20.73%.

*2-{2-Hydroxy-3-[(4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]propoxy}-4H-pyrido[1,2-a]pyrimidin-4-one (**10**)*

Equimolar amounts (5 mmol) of the oxiran derivative **9** (1.09 g) and compound **1** (0.81 g) in absolute ethanol (15 mL) were treated with triethylamine (0.1 mL), and the mixture was gently warmed at 60°C for 2 h. The precipitate that formed was then filtered off and crystallized from ethanol (95%) to give compound **10**, mp 218–220°C; yield 1.01 g (53%). IR (KBr), ν_{max}(cm^{-1}) 1700 (C=O), 1685 (C=O), 1635 (C=N), 1570, 1530, 1459; ^{1}H NMR (DMSO-d_6), δ 3.45 (s, 1H, OH), 4.19 (m, 1H, C*H*OH), 4.35 (d, $J = 5.8$ Hz, 4H, $(OCH_2)_2CHOH$), 5.68 (s, 2H, 3-H), 7.31 (t, 2H, 7-H), 7.53 (d, 2H, 9-H), 7.97 (t, 2H, 8-H), 8.92 (d, 2H, 6-H). Anal Calcd for $C_{19}H_{16}N_4O_5$ (380.36): C, 60.00; H, 4.24; N, 14.73. Found: C, 59.88; H, 4.21; N, 14.56%.

*Addition of Alkyl Amines to Oxirane **9**: Preparation of Propanolamines **11a,b***

General Method. A solution of the suitable alkyl amine (5 mmol), namely *iso*-propylamine (0.5 mL), *tert*-butylamine (0.6 mL) in dioxane (10 mL), was added to a mixture of oxirane **9** (1.09 g, 5 mmol), dry potassium carbonate (1.39 g, 10 mmol), and CTAB (0.5 g) in dioxane (25 mL). Then the mixture was stirred at room temperature for 24 h. The organic solution was evaporated to dryness in vacuum, and the crude residue was treated with water and extracted with chloroform. The combined extracts were dried over anhydrous sodium sulfate, filtered off and the filtrate was evaporated in vacuum. The residue was crystallized from the proper solvent to give the propanolamines **11a,b**.

*2-[2-Hydroxy-3-(isopropylamino)propoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (**11a**).* mp 101–102°C (methanol); yield 1.14 g (82%). IR (KBr), ν_{max}(cm^{-1}) 3426 (N–H), 1690 (C=O), 1624 (C=N), 1587, 1512; ^{1}H NMR (C*D*Cl_3), δ 1.18 (d, 6H, $NCH(CH_3)_2$), 2.61 (m, 1H, $NCH(CH_3)_2$), 2.93 (d, $J = 5.6$ Hz, 2H, NCH_2CHOH), 3.86 (m, 1H, $(CH_2)_2CHOH$), 4.11 (d, $J = 6.2$ Hz, 2H, OCH_2CHOH), 4.48 (d, 1H, OH), 5.88 (s, 1H, 3-H), 7.26 (t, 1H, 7-H), 7.49 (d, 1H, 9-H), 7.71 (t, 1H, 8-H), 9.01 (d, 1H, 6-H). Anal. Calcd for $C_{14}H_{19}N_3O_3$ (277.33): C, 60.63; H, 5.91; N, 15.15. Found: C, 60.45; H, 5.86; N, 14.97%.

*2-[2-Hydroxy-3-(tert-butylamino)propoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (**11b**).* mp 87–89°C (petroleum ether (60–80°C)); yield 1.08 g (74%). IR (KBr), ν_{max}(cm^{-1}) 4422 (N–H), 1689 (C=O), 1618 (C=N), 1578, 1522; ^{1}H NMR (C*D*Cl_3), δ 1.12 (s, 9H, $NC(CH_3)_3$), 2.91 (d, $J = 6.0$ Hz, 2H, NCH_2CHOH), 3.88 (m, 1H, $(CH_2)_2CHOH$), 4.18 (d, $J = 6.2$ Hz, 2H, OCH_2CHOH), 4.45 (d, 1H, OH), 5.83 (s, 1H, 3-H), 7.31 (t, 1H, 7-H), 7.54 (d, 1H, 9-H), 7.76 (t, 1H, 8-H), 8.95 (d, 1H, 6-H). Anal Calcd for $C_{15}H_{21}N_3O_3$ (291.35): C, 61.84; H, 7.27; N, 14.42. Found: C, 61.60; H, 7.26; N, 14.27%.

*2-Chloro-4H-pyrido[1,2-a]pyrimidin-4-one (**15**)*

A mixture of compound **1** (1.62 g, 10 mmol) and oxalyl chloride (2.7 mL, 30 mmol) was heated on boiling water bath under reflux for 1 h. Then the reaction mixture was left to cool and quenched with crushed ice. The precipitate so formed was then filtered off and crystallized from water to give the chloroderivative **15**, mp 156–158°C; yield 1.59 g (88%). An authentic sample was prepared using phosphoryl chloride, mp 156–158°C; yield 0.8 g (44%), according to lit. [2]. IR (KBr), ν_{max}(cm^{-1}) 1709 (C=O), 1638 (C=N), 1568, 1524, 1480, 845, 776; ^{1}H NMR (DMSO-d_6), δ 6.48 (s, 1H, 3-H), 7.49 (t, 1H, 7-H), 7.72 (d, 1H, 9-H), 8.12 (t, 1H, 8-H), 8.98 (d, 1H, 6-H). Anal Calcd for $C_8H_5ClN_2O$ (180.59): C, 53.21; H, 2.79; Cl, 19.63; N, 15.51. Found: C, 53.20; H, 2.66; Cl, 19.50; N, 15.32%.

*2,3-Dichloro-4H-pyrido[1,2-a]pyrimidin-4-one (**16**)*

To a mixture of phosphorus pentachloride (5.3 g, 25 mmol) and phosphoryl chloride (4.7 mL,

50 mmol) was added 10 mmol of either compounds **1** (1.62 g) or **17** (1.96 g) and the mixture was heated on a mantle at 200–220°C for 0.5 h. Then the reaction mixture was left to cool and poured onto crushed ice to give a suspension. Complete precipitation was achieved by treating the aqueous suspension with sodium hydroxide (8%) until neutralization. The precipitate so formed was then filtered off and crystallized from acetone to give the dichloroderivative **16**, mp 222–224°C; yield 1.14 g (53%), lit. [2] mp 225.8–226.5°C. IR (KBr), ν_{max}(cm^{-1}) 1696 (C=O), 1630 (C=N), 1555, 1514, 1465, 823, 777; ^{1}H NMR (DMSO-d_6), δ 7.53 (t, 1H, 7-H), 7.76 (d, 1H, 9-H), 8.22 (t, 1H, 8-H), 9.02 (d, 1H, 6-H). Anal Calcd for $C_8H_4Cl_2N_2O$ (215.04): C, 44.68; H, 1.87; Cl, 32.97; N, 13.03. Found: C, 44.43; H, 1.58; Cl, 32.80; N, 12.82%.

*3-Chloro-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (**17**)*

Method A. To a stirred warm (60°C) suspension of compound **1** (1.62 g, 10 mmol) in dry dioxane (20 mL), sulfuryl chloride (2 mL, 25 mmol) in dry dioxane (10 mL) was added dropwise over a period of 15 min. Then the reaction mixture was heated under reflux for 30 min, left to cool and poured onto crushed ice, and the yellow precipitate so formed was collected at a suction pump and crystallized to give compound **17**, mp 288–290°C; yield 1.32 g (67%), lit. [2] mp 290°C. IR (KBr), ν_{max}(cm^{-1}) 2641 (H-bonded OH), 1700 (C=O), 1625 (C=N), 1584, 1527, 1480; ^{1}H NMR (DMSO-d_6), δ 7.42 (t, 1H, 7-H), 7.47 (d, 1H, 9-H), 8.16 (t, 1H, 8-H), 8.96 (d, 1H, 6-H), 12.59 (b, 1H, OH). Anal Calcd for $C_8H_5ClN_2O_2$ (196.59): C, 48.88; H, 2.56; Cl, 18.03; N, 14.25. Found: C, 48.79; H, 2.54; Cl, 17.90; N, 14.20%.

Method B. The 2,3-dichloro derivative **16** (1.08 g, 5 mmol) was suspended in hydrochloric acid (20 mL, 6 N) and heated under reflux for 2 h. The reaction mixture was then cooled and neutralized with sodium hydroxide. Then this aqueous solution was extracted with chloroform (3 × 20 mL). The combined organic extract was dried over anhydrous sodium sulfate (5 g), filtered off and evaporated to give a solid residue, which was crystallized to furnish the derivative **17**, identified by mp, mixed mp, and spectra.

*3-Bromo-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (**19**).* To a stirred solution of the compound **1** (1.62 g, 10 mmol) in glacial acetic acid (25 mL), a solution of bromine (1.6 g, 10 mmol) in glacial acetic acid (10 mL) was dropwisely added with continuous stirring. The mixture was kept over night in an ice-bath. The crystalline product so formed was collected by filtration and recrystallized from acetic acid to give the monobromo derivative **19**, mp 299–300°C; yield 1.64 g (68%). IR (KBr), ν_{max}(cm^{-1}) 2805–2664 (H-bonded OH), 1696 (C=O), 1636 (C=N), 1557, 1542, 1473; ^{1}H NMR (DMSO-d_6), δ 7.45 (t, 1H, 7-H), 7.78 (d, 1H, 9-H), 8.12 (t, 1H, 8-H), 8.98 (d, 1H, 6-H), 12.05 (b, 1H, OH). Anal Calcd for $C_8H_5BrN_2O_2$ (241.05): C, 39.86; H, 2.09; Br, 33.15; N, 11.62. Found: C, 39.80; H, 2.04; Br, 33.10; N, 11.49%.

*3,3-Dibromopyrido[1,2-a]pyrimidine-2,4(3H)-dione (**20**)*

To a stirred warm (50–60°C) solution of 5 mmol of either the compound **1** (0.81 g) or **19** (1.2 g), in dioxane (25 mL) and water (5 mL), a solution of bromine (2.4 g, 15 mmol) in dioxane (10 mL) was dropped over a period of 20 min. After complete addition, the reaction mixture was heated under reflux for 30 min. The excess solvent was evaporated in vacuum, and the residue was crystallized from benzene to give the dibromo derivative **20**, mp 235–238°C; yield 1.19 g (74%). IR (KBr), ν_{max}(cm^{-1}) 1720 (C=O), 1690 (C=O), 1633 (C=N), 1576, 1544, 1453, 1318, 887, 776; ^{1}H NMR (DMSO-d_6), δ .49 (t, 1H, 7-H), 7.75 (d, 1H, 9-H), 8.08 (t, 1H, 8-H), 9.03 (d, 1H, 6-H). Anal Calcd for $C_8H_4Br_2N_2O_2$ (319.94): C, 30.03; H, 1.26; Br, 49.95; N, 8.76. Found: C, 29.78; H, 1.20; Br, 49.70; N, 8.70%.

*2-Hydroxy-3-iodo-4H-pyrido[1,2-a]pyrimidin-4-one (**21**)*

To a stirred solution of compound **1** (1.62 g, 10 mmol) and iodine (5.07 g, 20 mmol) in dry dioxane (15 mL) was added 4-methylmorpholine (1.33 mL, 12 mmol) at room temperature for 3 h. Afterwards, the solvent was evaporated in vacuum till dryness. The residue was treated with a solution of sodium hydrogen sulfite (20 mL, 1 M), and water (50 mL) was added. The mixture was extracted with chloroform (3 × 50 mL). The organic extract was washed with water, dried over sodium sulfate, and concentrated. The yellow crystals, which so precipitated, was filtered and crystallized from dioxane affording the iodo-derivative **21**, mp 226–228°C; yield 1.64 g (68%). IR (KBr), ν_{max}(cm^{-1}) 2662 (H-bonded OH), 1699 (C=O), 1635 (C=N), 1602, 1571, 1545, 1473, 882, 776; ^{1}H NMR (DMSO-d_6), δg.33 (t, 1H, 7-H), 7.58 (d, 1H, 9-H), 7.79 (t, 1H, 8-H), 8.84 (d, 1H, 6-H), 11.92 (b, 1H, OH). Anal Calcd for $C_8H_5IN_2O_2$ (288.05): C, 33.36; H, 1.75; I, 44.06; N, 9.73. Found: C, 33.21; H, 1.57; I, 43.80; N, 9.69%.

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