Original $S_{RN}1$ Reactions on New Non-Nitrated Heterocyclic System

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Received 2 July 2008

Abstract: A new 3-bromo-2-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was prepared and reacted under experimental conditions of $S_{RN}1$ reactions with different sulfur- and carbon-centered nucleophiles. A $S_{RN}1$ reaction in non-nitrated 4*H*-pyrido[1,2-*a*]pyrimidin-4-one series is described for the first time.

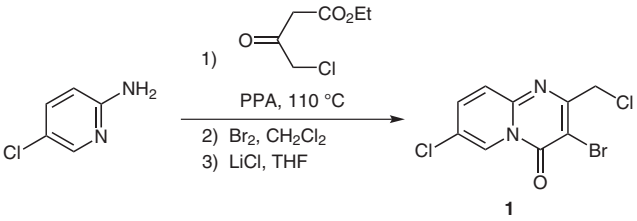
Key words: single-electron transfer, 4*H*-pyrido[1,2-*a*]pyrimidin-4-one, inhibitors, alkylation, spectroscopy

A number of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives displays antioxidant,[1] anticancer,[2] vasodilator,[3] antihypertensive[4] as well as CNS[5–8] activity. Furthermore, some 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones are able to potentiate the antibacterial activity of some fluoroquinolones,[9] and are also selective inhibitors of cell death in mutant hungtingtin-expressing cells.[10]

Unimolecular radical nucleophilic substitution ($S_{RN}1$) has been found to be an excellent synthetic pathway for many types of aromatic, heterocyclic, and aliphatic substrates with suitable leaving groups.[11–13] The $S_{RN}1$ reaction was shown to require substrates substituted with an electron-attracting group at an appropriate position.[14] Indeed, most non-nitrated-substituted nitrobenzyl derivatives undergo S_N2 rather than $S_{RN}1$ reaction.[13,15] As well as non-nitrated heterocycles studied for the moment resulted in O-alkylation reactions, or no reactivity at all was observed with nitronate anions.[16]

In continuation of our study on the reactivity of 2-(chloromethyl)-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one series in electron-transfer reactions,[17–19] and as part of a program directed toward the preparation of more complex structures of pharmacological interest, we prepared 3-bromo-7-chloro-2-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1**) and studied its reactivity with different nucleophiles, under $S_{RN}1$ experimental conditions, in order to determine the reactivity of the non-nitrated heterocycle under these conditions.

The starting material was obtained by condensing 2-amino-5-chloropyridine with 4-chloroacetoacetate in PPA using Ferrarini procedure[20] providing 7-chloro-2-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one which was brominated at 3-position with elemental bromine (1.1 equiv) at room temperature[21,22] followed by a treatment with lithium chloride in THF (Scheme 1).



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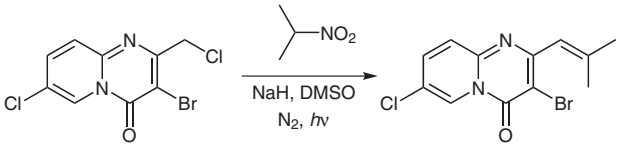
Scheme 1 Preparation of 3-bromo-7-chloro-2-(chloromethyl)pyrido-[1,2-*a*]pyrimidin-4-one

Careful examination, by cyclic voltammetry, of the starting material **1** [Ep_{c1} = –1,45 V vs. SCE, first peak measured in DMF–NBu_4PF_6 (0.1 M)], indicated that this substrate might be a good electron acceptor[23] and this therefore prompted us to use nitronate anion for studying a possible $S_{RN}1$ mechanism.[24] Then, C-alkylation of nitronate anion with this alkylating agent, not substituted with a nitro group, could be expected.

Under $S_{RN}1$ experimental conditions (inert atmosphere, photostimulation), the reaction of 3-bromo-7-chloro-2-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1**) with 2-nitropropane anion gave the ethylenic derivative **2** resulting from the consecutive C-alkylation and nitrous acid elimination (Scheme 2).[25] Sodium hydride (60%) in DMSO was used to form the corresponding carbanion.



1 **2** 49%

Scheme 2 Reaction of **1** with 2-nitropropane anion under $S_{RN}1$ reaction conditions

The X-ray structure analysis of a crystal of **2** confirmed that reactivity with 2-nitropropane anion takes place only at chloromethyl group (Figure 1). No product of an eventual displacement of the bromine atom at 3-position or aromatic substitution at 7-position was isolated.

In order to validate the hypothesis of a single-electron-transfer mechanism, inhibition reactions were performed by adding catalytic amounts (10 mol%) of $CuCl_2$ or TEMPO to the reaction mixture (Table 1), which are clas-

SYNLETT 2008, No. 18, pp 2836–2840
Advanced online publication: 15.10.2008
DOI: 10.1055/s-0028-1083499; Art ID: G21508ST

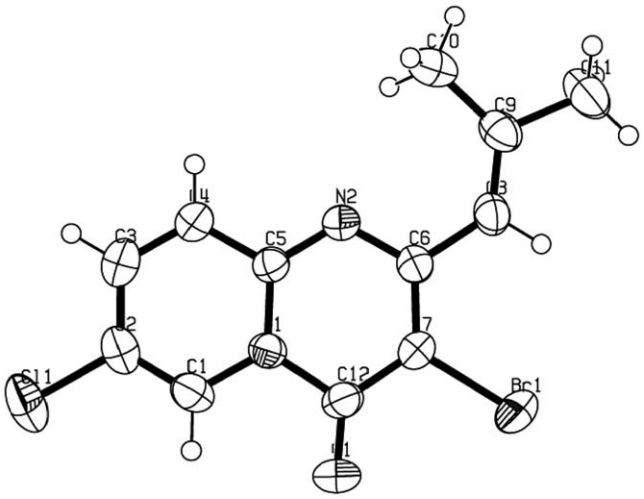


Figure 1 ORTEP plot of 3-bromo-7-chloro-2-(2-methylprop-1-enyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**2**)

Table 1 Inhibition Reactions with 2-Nitropropane Anion[a]

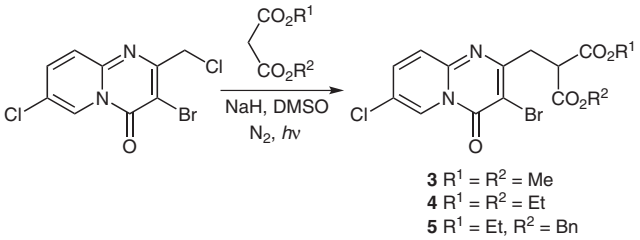
Entry	Inhibitor	Product (%)
1	–	**2** (49)
2	$CuCl_2$	**2** (18)
3	TEMPO	**2** (9)

[a] All the reactions are performed using 1 equiv of **1**, 3 equiv of 2-nitropropane, and 3 equiv of NaH in DMSO at r.t., under inert atmosphere and photostimulation for 45 min.

sical inhibitors used for the mechanistic studies of $S_{RN}1$ reactions.[26] For a coherent comparison, the reaction times were identical for inhibition study and corresponded to the optimized conditions without inhibitor.

This reaction is strongly inhibited by TEMPO, a free radical scavenger.

The nature of the nucleophile is crucial for $S_{RN}1$ reactions and therefore an understanding of the relationship between the nucleophile and the substrate, in single-electron-transfer reactions, is of use.[13] We have thus investigated the reactivity of **1** with other conventional nucleophiles as for example, alkyl malonate anions (Scheme 3, Table 2, entry 1–3).



Scheme 3 Reaction of **1** with alkyl malonate anions under $S_{RN}1$ reaction conditions

Table 2 Reaction of **1** with Alkyl Malonate Anions under $S_{RN}1$ Reaction Conditions[a]

Entry	R^1	R^2	Time (min)	Product (%)
1	Me	Me	50	**3** (69)
2	Et	Et	45	**4** (67)
3	Et	Bn	120	**5** (61)

[a] All the reactions are performed using 1 equiv of **1**, 3 equiv of alkyl malonate, and 3 equiv of NaH in DMSO at r.t., under inert atmosphere and photostimulation until disappearance of the starting material as monitored by TLC.

The reactions of **1** with alkyl malonate anion provide the expected C-alkylated products[27] in moderate to good yields (61–69%, Table 2).

In the aim of verifying the nature of the mechanism, we performed the inhibition reactions using $CuCl_2$ and TEMPO (Table 3). Catalytic amount of TEMPO completely stops the C-alkylation reaction (Table 3, entry 3), and the starting material **1** is the only product collected after the reaction workup. This suggests that the reaction of **1** with diethyl malonate anion follows exclusively a free radical chain mechanism ($S_{RN}1$).

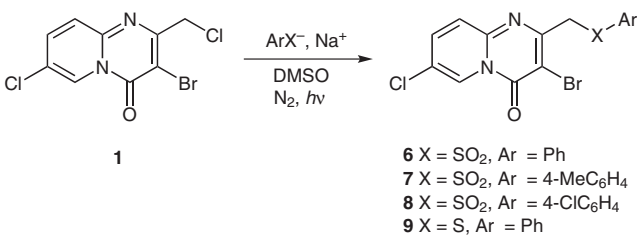
Table 3 Inhibition Reactions with Diethyl Malonate Anion[a]

Entry	Inhibitor	Product (%)
1	–	**4** (67)
2	$CuCl_2$	**4** (28)
3	TEMPO	**4** (0)

[a] All the reactions are performed using 1 equiv of **1**, 3 equiv of diethyl malonate, and 3 equiv of NaH in DMSO at r.t., under inert atmosphere and photostimulation for 45 min.

Furthermore, C-alkylation was confirmed by X-ray structure analysis of a crystal of **4**, showing that, like 2-nitropropane anion, malonate anions also react only with chloromethyl group (Figure 2).

In order to extend the reaction to a wide variety of nucleophiles, we continued the study with S-centered anions (Scheme 4, Table 4).[28] The reaction between the sodium salt of arylsulfinic acids (Table 4, entries 1–3) or thiophenol (Table 4, entry 4) and **1** in DMSO gave the required S-alkylated products[29] in good to excellent yields (78–92%).



Scheme 4 Reaction of **1** with S-centered anions under $S_{RN}1$ reaction conditions

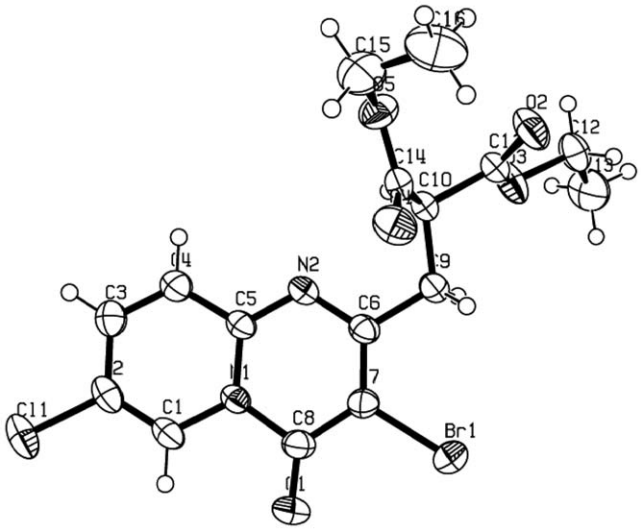


Figure 2 ORTEP plot of diethyl 2-[(3-bromo-7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)methyl]malonate (**4**)

Table 4 Reaction of **1** with Alkyl Malonate Anions under $S_{RN}1$ Reaction Conditions

Entry	Anion	Time (h)	Product (%)
1[a]	$PhSO_2^-$, Na^+	1	**6** (84)
2[a]	4-$MeC_6H_4SO_2^-$, Na^+	1.5	**7** (88)
3[a]	4-$ClC_6H_4SO_2^-$, Na^+	2.5	**8** (78)
4[b]	PhS^-, Na^+	18	**9** (92)

[a] All the reactions are performed using 1 equiv of **1**, 2 equiv of sodium arylsulfinate in DMSO at r.t., under inert atmosphere and photostimulation until disappearance of the starting material as monitored by TLC.
[b] The reaction is performed using 1 equiv of **1**, 2.2 equiv of thiophenol, and 2.2 equiv of NaH in DMSO at r.t., under inert atmosphere and photostimulation until disappearance of the starting material as monitored by TLC.

To identify the main mechanism of the reaction, we studied the reactivity of this last reaction by addition of inhibitor (Table 5, entries 2, 3, 5, and 6).

Reaction-rate decreases are not significant and the reactions thus seem to follow a S_N2 mechanism.

All these results lead to believe that **1** is an appropriate substrate for single-electron-transfer reactions with C-centered nucleophiles. Indeed, some examples from the literature show that the carbonyl group is an electron-transfer inducer in heterocyclic series.[30] Furthermore, in analogy with quinonic derivatives,[31] the system formed by a carbonyl group added to a bromine atom could stabilize the intermediate radical, facilitating the $S_{RN}1$ reaction.

In conclusion, we have shown in this work that the 3-bromo-7-chloro-2-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one reacts with various carbon- and sulfur-centered anions by substitution only at the chloromethyl group. The reaction with C-centered nucleophiles is very probably mediated by $S_{RN}1$ mechanism. These results constitute the first example of $S_{RN}1$ on a non-nitrated heterocyclic substrate. Generalization with other nitronate anions and the pharmacological evaluation of synthesized compounds are under active investigation. Others derivatives with substituent on the 3-position will be synthesized to study the effect on the reduction potential and on the $S_{RN}1$ reactivity.

Table 5 Inhibition Reactions with *p*-Tolylsulfinate and Thiophenol Anions

Entry	Anion	Inhibitor	Product (%)
1[a]	4-$MeC_6H_4SO_2^-$, Na^+	–	**7** (88)
2[a]	4-$MeC_6H_4SO_2^-$, Na^+	$CuCl_2$	**7** (80)
3[a]	4-$MeC_6H_4SO_2^-$, Na^+	TEMPO	**7** (71)
4[b]	PhS^-, Na^+	–	**9** (92)
5[b]	PhS^-, Na^+	$CuCl_2$	**9** (89)
6[b]	PhS^-, Na^+	TEMPO	**9** (88)

[a] All the reactions are performed using 1 equiv of **1**, 2 equiv of sodium arylsulfinate in DMSO at r.t., under inert atmosphere and photostimulation for 90 min.
[b] All the reactions are performed using 1 equiv of **1**, 2.2 equiv of thiophenol, and 2.2 equiv of NaH in DMSO at r.t., under inert atmosphere and photostimulation for 18 h.

Acknowledgment

This work is supported by the CNRS and the Universities of Aix-Marseille. The authors thank M. Médebielle for cyclic voltammetry measurements, V. Remusat for NMR spectra recording, the Spectropole team for various analytical measurements, and M. Giorgi for the X-ray crystal-structure determinations.

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(22) **Analytical Data for 3-Bromo-7-chloro-2-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (1)**
White needles, mp 175 °C (*i*-PrOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.75 (s, 2 H), 7.67 (dd, *J* = 9.4, 0.7 Hz, 1 H), 7.75 (dd, *J* = 9.4, 2.2 Hz, 1 H), 9.06 (dd, *J* = 2.2, 0.7 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 46.0, 103.0, 125.3, 125.5, 127.4, 137.9, 147.7, 154.1, 159.7. Anal. Calcd for $C_9H_5BrCl_2N_2O$: C, 35.10; H, 1.64; N, 9.10. Found: C, 35.11; H, 1.65; N, 8.96.
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(25) **Analytical Data for 3-Bromo-7-chloro-2-(2-methylprop-1-enyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (2)**
Shiny white plates, mp 175 °C (EtOH–Et_2O). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.03 (d, *J* = 1.2 Hz, 3 H), 2.18 (d, *J* = 1.2 Hz, 3 H), 6.58 (sept, *J* = 1.2 Hz, 1 H, CH), 7.55 (dd, *J* = 9.5, 0.8 Hz, 1 H), 7.64 (dd, *J* = 9.5, 2.2 Hz, 1 H), 9.02 (dd, *J* = 2.2, 0.8 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.5, 28.1, 102.4, 122.4, 124.2, 125.2, 127.1, 137.0, 146.5, 149.2, 154.4, 159.7. Anal. Calcd for $C_{12}H_{10}BrClN_2O$: C, 45.96; H, 3.21; N, 8.93. Found: C, 45.74; H, 3.24; N, 8.86.
Crystal Data for Compound 2
$C_{12}H_{10}BrClN_2O$, colorless prism (0.3 × 0.2 × 0.05 mm^3), MW = 313.58, monoclinic, space group $P2_1/c$ (*T* = 293 K), *a* = 7.1901(2) Å, *b* = 15.5874(4) Å, *c* = 11.3226(3) Å, β = 107.471(1)°; *V* = 1210.44(6) Å^3, *Z* = 4, D_{calc} = 1.721 g cm^{-1}, μ = 3.600 mm^{-1}, *F*(000) = 624, index ranges $-9 \le h \le 9$, $0 \le k \le 21$, $0 \le l \le 15$; θ range = 2.29–28.68°, 154 variables and 0 restraints, were refined for 2136 reflections with $I \ge 2\sigma(I)$ to *R1* = 0.0403, *wR*2 = 0.1078, *GooF* = 1.050. CCDC 691139 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/data_request/cif of from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax:+44 (1223)336033; email: deposit@ccdc.cam.ac.uk.
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(27) **General Procedure and Analytical Data for Compounds 3–5**
A solution of 60% NaH (3 equiv) in DMSO under an inert atmosphere was treated with dialkyl malonate (3 equiv) and stirred for 20 min. A solution of **1** (1 equiv) in DMSO was then added and the mixture was irradiated with a 60 W tungsten lamp and stirred until disappearance of the starting material as monitored by TLC. At this time, the mixture was poured into cold H_2O. The aqueous solution was extracted with EtOAc. The organic layers were washed with brine, dried over anhyd Na_2SO_4, and evaporated under reduced pressure. The residue was purified by chromatography column on SiO_2. Wanted products were recrystallized with BuOH or *i*-PrOH.
Dimethyl 2-{(3-Bromo-7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)methyl}malonate (3)
Pale yellow crystals, mp 147 °C (*i*-PrOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.55 (d, *J* = 7.4 Hz, 2 H), 3.77 (s, 6 H), 4.24 (t, *J* = 7.4 Hz, 1 H), 7.55 (d, *J* = 9.4 Hz, 1 H), 7.70 (dd, *J* = 9.4, 2.2 Hz, 1 H), 9.04 (d, *J* = 2.2 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 36.0, 49.3, 61.6, 102.9, 124.9, 125.3, 127.0, 137.4, 146.9, 153.6, 162.2, 168.8. Anal. Calcd for $C_{14}H_{12}BrClN_2O_5$: C, 41.66; H, 3.00; N, 6.94. Found: C, 41.52; H, 2.94; N, 6.94.
Diethyl 2-{(3-Bromo-7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)methyl}malonate (4)
White needles, mp 111 °C (BuOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 6 H), 3.53 (q, *J* = 7.4 Hz, 2 H), 4.22 (m, 5 H), 7.49 (d, *J* = 9.5 Hz, 1 H), 7.68 (dd, *J* = 9.5, 2.3 Hz, 1 H), 9.03 (d, *J* = 2.3 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 36.0, 49.3, 61.6, 102.9, 124.9, 125.3, 127.0, 137.4, 146.9, 153.6, 162.2, 168.8. Anal. Calcd for $C_{16}H_{16}BrClN_2O_5$: C, 44.52; H, 3.74; N, 6.49. Found: C, 44.76; H, 3.76; N, 6.46.
Crystal Data for Compound 4
$C_{16}H_{16}BrClN_2O_5$, colorless prism (0.3 × 0.2 × 0.05 mm^3),

MW = 431.67, triclinic, space group $P\bar{1}$ (*T* = 293 K), *a* = 8.0149(2) Å, *b* = 8.9522(2) Å, *c* = 12.8072(3) Å, α = 81.6805(9)°, β = 76.2696(8)°, γ = 81.9220(9)°; *V* = 877.87(4) Å^3, *Z* = 2, D_{calc} = 1.633 g cm^{-1}, μ = 2.523 mm^{-1}, *F*(000) = 436, index ranges $-10 \le h \le 10$, $-11 \le k \le 11$, $0 \le l \le 17$; θ range = 1.65–28.69°, 228 variables and 0 restraints, were refined for 3563 reflections with $I \ge 2\sigma(I)$ to *R1* = 0.0330, *wR*2 = 0.0889, *GooF* = 1.047. CCDC 691140 contains the supplementary crystallographic data for this paper.

Benzyl Ethyl 2-{(3-Bromo-7-chloro-4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidin-2-yl)methyl}malonate (5)

Yellowish solid, mp 275 °C (BuOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 3 H), 3.54 (dd, *J* = 7.9, 7.0 Hz, 2 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 4.24 (dd, *J* = 7.9, 7.0 Hz, 1 H), 5.18 (s, 2 H), 7.24–7.32 (m, 6 H), 7.64 (dd, *J* = 9.4, 2.3 Hz, 2 H), 8.97 (d, *J* = 2.3 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 36.0, 49.3, 61.7, 67.0, 102.8, 128.8, 125.2, 126.9, 128.2, 128.3, 128.4, 135.4, 137.3, 146.7, 153.4, 161.8, 168.5, 168.6. Anal. Calcd for $C_{21}H_{18}BrClN_2O_5$: C, 51.09; H, 3.67; N, 5.67. Found: C, 51.24; H, 3.76; N, 5.74.

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(29) **Analytical Data for Compounds 6–9**

3-Bromo-7-chloro-2-(phenylsulfonyl-methyl)-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one (6)

Beige needles, mp 234 °C (*i*-PrOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.81 (s, 2 H), 7.48–7.57 (m, 3 H), 7.64–7.74 (m, 2 H), 7.84–7.89 (m, 2 H), 9.01 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 63.9, 105.9, 125.3, 125.6, 127.3, 128.6, 129.2, 134.1, 137.9, 139.4, 147.0, 153.3, 153.9. Anal. Calcd for $C_{15}H_{10}BrClN_2O_3S$: C, 43.55; H, 2.44; N, 6.77; S, 7.75. Found: C, 44.08; H, 2.53; N, 6.72; S, 7.78.

3-Bromo-7-chloro-2-(tosylmethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7)

White needles, mp 225 °C (*i*-PrOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 4.79 (s, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.55 (dd, *J* = 9.5, 0.7 Hz, 1 H), 7.69–7.76 (m, 3 H), 9.01 (dd, *J* = 2.3, 0.7 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7, 64.0, 105.9, 125.2, 125.6, 127.4, 128.6, 129.8, 136.5, 137.9, 145.3, 147.0, 153.5, 153.9. Anal. Calcd for $C_{16}H_{12}BrClN_2O_3S$: C, 44.93; H, 2.83; N, 6.55; S, 7.50. Found: C, 44.93; H, 2.78; N, 6.45; S, 7.23.

3-Bromo-7-chloro-2-[(4-chlorophenyl-sulfonyl)methyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (8)

White needles, mp 263 °C (EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.80 (s, 2 H), 7.49 (dd, *J* = 9.5, 0.7 Hz, 1 H), 7.50 (d, *J* = 8.8 Hz, 2 H), 7.73 (dd, *J* = 9.5, 2.2 Hz, 1 H), 7.80 (d, *J* = 8.8 Hz, 2 H), 9.02 (dd, *J* = 2.2, 0.7 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 63.9, 105.8, 125.3, 125.7, 127.2, 129.5, 130.1, 137.9, 138.1, 141.0, 147.0, 153.1, 153.8. Anal. Calcd for $C_{15}H_9BrCl_2N_2O_3S$: C, 40.20; H, 2.02; N, 6.25; S, 7.16. Found: C, 40.31; H, 2.02; N, 6.30; S, 6.92.

3-Bromo-7-chloro-2-(phenylthiomethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (9)

White plates, mp 156 °C (*i*-PrOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.37 (s, 2 H), 7.19–7.35 (m, 3 H), 7.45–7.48 (m, 2 H), 7.71 (d, *J* = 9.5 Hz, 1 H), 8.06 (dd, *J* = 9.5, 2.3 Hz, 1 H), 8.92 (d, *J* = 2.3 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 40.2, 101.6, 124.3, 125.4, 126.7, 127.3, 129.2, 129.6, 135.5, 138.5, 147.5, 153.6, 161.3. Anal. Calcd for $C_{15}H_{10}BrClN_2OS$: C, 47.20; H, 2.64; N, 7.34; S, 8.40. Found: C, 47.00; H, 2.60; N, 7.46; S, 8.21.

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