Efficient and Original Microwave-Assisted Suzuki–Miyaura Cross-Coupling Reaction in the 4*H*-Pyrido[1,2-*a*]pyrimidin-4-one Series

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Abstract: An efficient synthesis of new series of various 3-aryl, 3-heteroaryl, and 3-styryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones by palladium-catalyzed Suzuki–Miyaura cross-coupling reactions using microwave irradiation is described. The coupling process is tolerant of electron-poor, electron-rich, and bulky boronic acid derivatives, and leads to the desired products in good yields.

Key words: cross-coupling, 4*H*-pyrido[1,2-*a*]pyrimidin-4-one, palladium, Suzuki reaction, arylation

4*H*-Pyrido[1,2-*a*]pyrimidin-4-one derivatives are currently the object of renewed interest in the pharmacological field, and many publications have reported their pharmacological activities in various biological areas.[1–12] In continuation of our studies, and directed by an interest in the use of microwave heating in Suzuki–Miyaura cross-coupling reactions,[13] we prepared the 7-chloro-2-(chloromethyl)-3-iodo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**2**) and studied its reactivity with a range of aryl, heteroaryl, and styrylboronic acids under Suzuki–Miyaura conditions. The Suzuki–Miyaura cross-coupling reaction is known to be an extremely efficient synthetic route for the synthesis of functionalized heterocycles.[14]

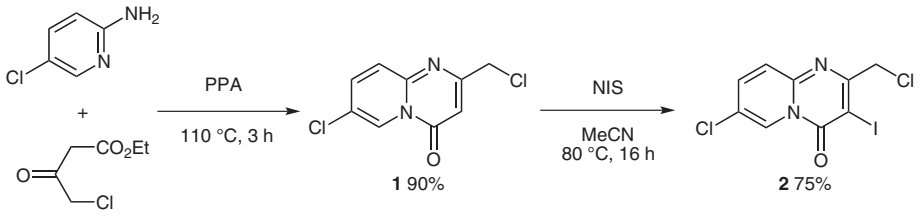
Microwave irradiation has recently become a possible way to improve reaction yields and reduce reaction times[15] compared to conventional heating. It has already been shown that microwave irradiation can significantly promote the Suzuki–Miyaura cross-coupling reaction.[16]

Only a few examples of Suzuki–Miyaura cross-coupling reactions in 4*H*-pyrido[1,2-*a*]pyrimidin-4-one series have been reported,[17] and none of them involve microwave irradiation. Herein, we report an efficient synthesis of new 3-aryl, 3-heteroaryl, and 3-styryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives under microwave irradiation.

The choice of starting material was dictated by the intended use of the derivatives, which required the presence of Csp^2–Cl and Csp^3–Cl moieties. Indeed, in continuation of our study on the reactivity in electron transfer reactions, and as a part of our program directed toward the preparation of more complex structures of pharmacological interest in heterocyclic series,[18] we recently developed a new non-nitrated substrate capable of reacting under $S_{RN}1$ conditions.[18a] The study involved various nucleophiles, and a mechanistic study showed that C-alkylations followed a radical chain mechanism. Furthermore, only the chloromethyl group reacted by substitution. Thus, new substrates bearing various functional groups at the 3-position needed to be accessed in order to investigate the influence of the substituent on electron-transfer reactivity toward different nucleophiles. Finally, in order to increase the selectivity of the cross-coupling reaction between the 3- and 7-positions, we decided to investigate the 7-chloro-3-iodo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivative.

The required starting material for the Suzuki–Miyaura cross-coupling study was obtained by condensing 2-amino-5-chloropyridine with ethyl 4-chloroacetoacetate in polyphosphoric acid (PPA) using the Ferrarini procedure,[19] providing 7-chloro-2-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1**), which reacted with *N*-iodosuccinimide in acetonitrile at reflux to give 7-chloro-2-(chloromethyl)-3-iodo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**2**; Scheme 1).

Initial trials of the Suzuki–Miyaura cross-coupling reaction were tested under similar experimental conditions to those described by Barbeau et al. (Scheme 2).[20] The reaction was carried out by using 4-methoxyphenylboronic acid (1.5 equiv), tetrakis(triphenylphosphine)palladium(0) (0.05 equiv), and potassium carbonate (3 equiv) in



Scheme 1 Preparation of the starting material **2**

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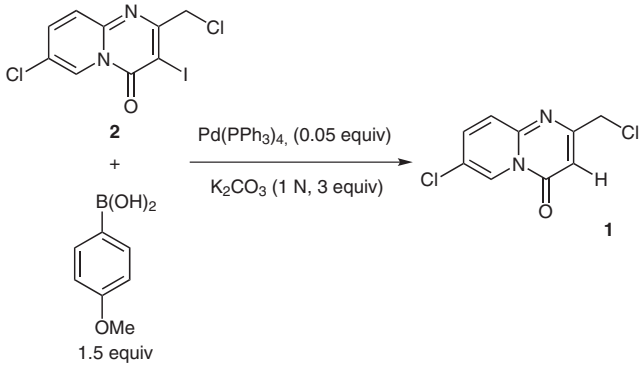
dioxane at 100 °C (Table 1, entry 1). After three hours, only a mixture of the starting material **2** and the reduced compound **1** were obtained (Table 1, entry 1). The formation of compound **1** suggested that a palladium-catalyzed reduction of aromatic halides took place, as previously observed in the literature.[21] The use of microwave irradiation and 1,2-dimethoxyethane–ethanol (9:1) as solvent did not result in any selectivity, and also led to a mixture of **1** and **2** (Table 1, entries 2 and 3).

With the chloromethyl group in the 2-position of compound **2**, the 3-position was apparently too reactive. We therefore investigated the reactivity of the (7-chloro-3-iodo-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)methyl acetate (**3**) after acetylation of the chloromethyl group. The acetylation reaction was carried out in *N*,*N*-dimethylformamide, using potassium acetate at room temperature for 12 hours, which gave **3** in 76% yield (Scheme 3).

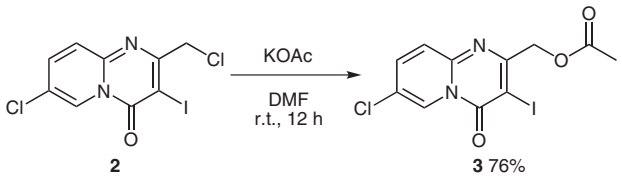


Scheme 2 Suzuki–Miyaura reaction of **2**

Table 1 Suzuki–Miyaura Reaction of **2**[a]

Entry	Solvent	Conditions	Yield **1/2** (%)
1	dioxane	K_2CO_3, 100 °C, 3 h	38:55
2	dioxane	K_2CO_3, MW, 100 °C, 3 h	37:42
3	DME–EtOH	K_2CO_3, MW, 80 °C, 2 h	43:33

[a] Reaction conditions: **2** (1 equiv), 4-methoxyphenyl boronic acid (1.5 equiv), [$Pd(PPh_3)_4$] (0.05 equiv), K_2CO_3 (3 equiv).



Scheme 3 Acetylation of the chloromethyl group of **2**

We then investigated the reactivity of **3** in the Suzuki–Miyaura reaction. The initial conditions used to carry out the cross-coupling reaction involved $Pd(PPh_3)_4$ (5 mol%) as a catalyst, potassium carbonate (3 equiv) as the base, and 4-(methoxyphenyl)boronic acid (1.5 equiv) in dioxane–ethanol (9:1), as shown in Scheme 4. Under these conditions, the reaction led to the formation of the desired product **5** after eight hours, in moderate yield (19%; Table 2, entry 1). In addition to the desired compound, the reduced product **4** was also obtained in 58% yield.

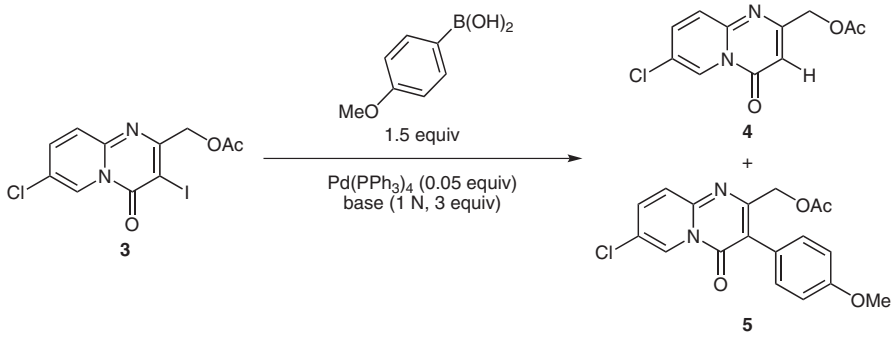
We then decided to evaluate the influence of microwave irradiation on this cross-coupling reaction according to our previous studies. Three reaction parameters were examined: solvent, temperature, and reaction times (Table 2). Indeed, the crucial role played by the solvent in determining the reaction rate of Suzuki–Miyaura reactions is well established.[22]

As a result, optimized microwave-assisted experimental conditions were established that permitted the synthesis of

Table 2 Suzuki–Miyaura Coupling Reaction of **3** with 4-Methoxyphenylboronic Acid[a]

Entry	Solvent (9:1)	Conditions	Yield **4/5** (%)
1	dioxane–EtOH	K_2CO_3, 100 °C, 8 h	58:19
2	dioxane–EtOH	K_2CO_3, MW, 100 °C, 5 h	50:10
3	DMF–EtOH	K_2CO_3, MW, 120 °C, 4 h	18:20
4	DME–EtOH	K_2CO_3, MW, 80 °C, 5 h	0:39
5	DME–EtOH	Na_2CO_3, MW, 80 °C, 3 h	10:28
6	DME–EtOH	K_2CO_3, MW, 100 °C, 2 h	0:79
7	H_2O–EtOH	K_2CO_3, MW, 100 °C, 2 h	0:0[b]
8	DME–EtOH	K_2CO_3, 100 °C, 9 h	0:40

[a] Reaction conditions: 4-methoxyphenylboronic acid (1.5 equiv), [$Pd(PPh_3)_4$] (0.05 equiv), K_2CO_3 (3 equiv), solvent/EtOH (9:1).
[b] The experimental conditions furnished 7-chloro-2-(hydroxymethyl)-3-(4-methoxyphenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**5′**) from the one-pot cross-coupling reaction and hydrolysis of the acetyl group in 33% yield.

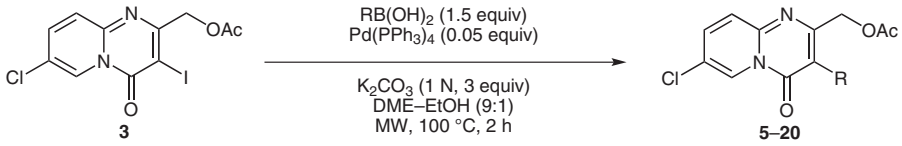


Scheme 4 Suzuki–Miyaura cross-coupling reaction

[7-chloro-3-(4-methoxyphenyl)-4-oxo-4*H*-pyrido[1,2-*a*]-pyrimidin-2-yl] methyl acetate (**5**) in 79% yield in two hours (Table 2, entry 6). Furthermore, no trace of the reduced compound **4** was detected. Using conventional heating, the same reaction took place after nine hours in 40% yield. Thus, the use of microwave irradiation reduces the reaction time up to four-fold and gives higher yields compared to classical heating methodology (Table 2, entries 6 and 8).

To evaluate the scope and the limitations of this procedure, we performed coupling reactions with 16 variously substituted boronic acid derivatives (Scheme 5). The results show, as illustrated in Table 3, that this coupling reaction is applicable to all aryl, heteroaryl, and styryl boronic acid derivatives used in our study.

These experimental conditions allowed compounds **18**–**20** to be synthesized by reaction of **3** with (*E*)-4-(trifluoromethyl)styrylboronic acid, (*E*)-styrylboronic acid, and (*E*)-4-methylstyrylboronic acid in excellent yields (Table 3, entries 14–16), which constitutes an interesting alternative to the Heck reaction. The reaction was 100% stereoselective, and the *E*-configuration of the alkene unit of (*E*)-**18**, (*E*)-**19**, and (*E*)-**20** was clear from their respective ^{1}H NMR spectra (^3J = 16.0 Hz), which confirmed the presence of the *E*-isomer exclusively.



Scheme 5 Suzuki–Miyaura cross-coupling reaction under the optimized conditions

Table 3 Suzuki–Miyaura Coupling Reaction of **3** with Aryl, Heteroaryl, and Styrylboronic Acid Derivatives under the Optimized Conditions[a]

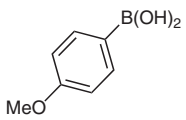
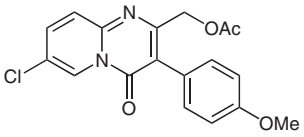
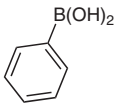
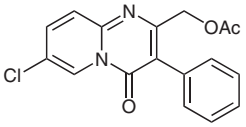
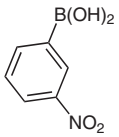
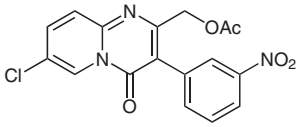
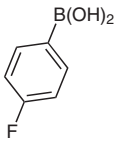
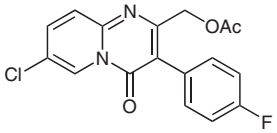
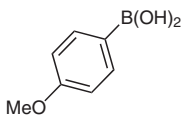
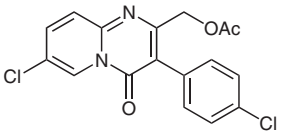
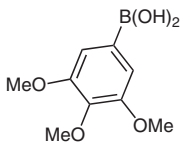
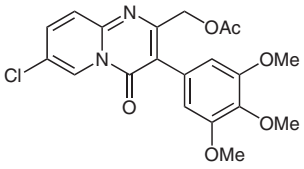
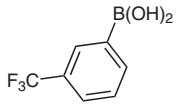
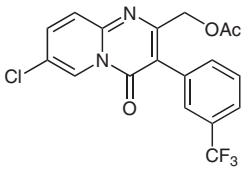
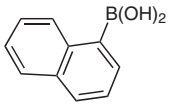
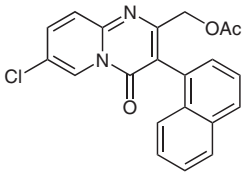
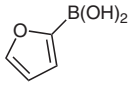
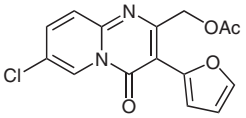
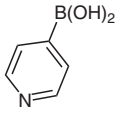
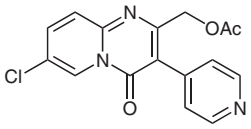
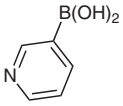
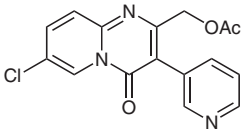
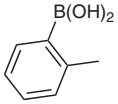
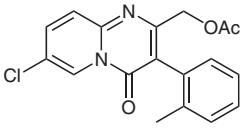
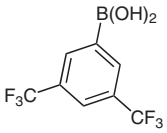
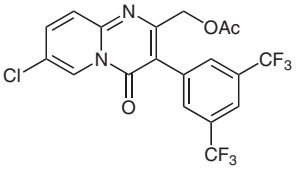
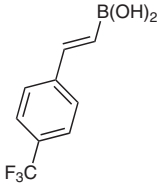
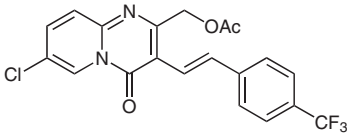
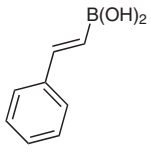
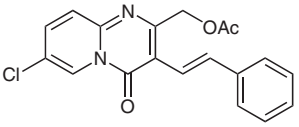
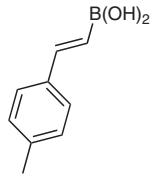
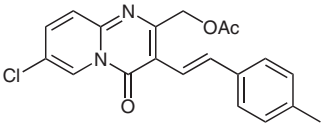
	Boronic acid	Product	Yield (%)	
1			**5**	79
2			**6**	73
3			**7**	70
4			**8**	82
5			**9**	84
6			**10**	63

Table 3 Suzuki–Miyaura Coupling Reaction of **3** with Aryl, Heteroaryl, and Styrylboronic Acid Derivatives under the Optimized Conditions[a] (continued)

	Boronic acid	Product	Yield (%)	
7			**11**	65
8			**12**	89
9			**13**	90
10			**14**	53
11			**15**	71
12			**16**	73
13			**17**	62
14			**18**	83
15			**19**	75
16			**20**	80

[a] Reaction conditions: boronic acid derivative (1.5 equiv), $[Pd(PPh_3)_4]$ (0.05 equiv), K_2CO_3 (3 equiv), DME–EtOH (9:1), MW, 100 °C, 2 h.

To conclude, we have developed a general operating procedure for an efficient synthesis of new 3-aryl, 3-heteroaryl, and 3-styryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives from the microwave-assisted palladium-mediated coupling reactions of aryl, heteroaryl, and styryl boronic acid derivatives with (7-chloro-3-iodo-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)methyl acetate (**3**). Finally, a wide array of electron-withdrawing, electron-donating, and sterically bulky groups has been shown to be well tolerated under these microwave-assisted conditions. These results constitute the first example of a Suzuki–Miyaura cross-coupling reaction of a 4*H*-pyrido[1,2-*a*]pyrimidin-4-one series under microwave irradiation. Furthermore, replacement of the acetyl group at the 2-position gave access to a large variety of analogues and also to derivatives that could, after hydrolysis of the acetyl group and chlorination, constitute promising candidates for $S_{RN}1$ reactions.

Melting points were determined with a Büchi B-540 and are uncorrected. Elemental and MS analyses were carried out at the Spectropole, Faculté des Sciences et Techniques de Saint-Jérôme. 200 MHz ^{1}H NMR ($CHCl_3$: δ = 7.26 ppm) and 50 MHz ^{13}C NMR ($CHCl_3$: δ = 76.9 ppm) spectra were recorded with a Bruker ARX 200 spectrometer in $CDCl_3$ solvent at the Faculté de Pharmacie de Marseille. Solvents were dried by conventional methods. Silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM) was used for column chromatography. TLC was performed with 5 × 10 cm aluminum plates coated with silica gel 60F-254 (Merck) in an appropriate solvent. MS spectra were recorded with a QStar Elite (Applied Biosystems SCIEX) spectrometer; PEG was used as the matrix for HRMS.

Microwave-assisted reactions were performed in a multimode microwave oven of a ETHOS Synth Lab station and MicroSYNTH Lab terminal 1024 (Ethos start, Milestone Inc.) or a Biotage Initiator Microwave oven. The multimode microwave was fitted with a twin magnetron (2 × 800 W, 2.45 GHz) with a maximum delivered power of 1000 W in 10 W increments (pulsed irradiation). Built-in magnetic stirring (Teflon-coated stirring bar) was used in all operations. During experiments, the time, temperature and power were measured with the "easy WAVE" software package. The temperature was measured throughout the reaction and recorded with either an infrared detector or an optical fiber (ATC-FO 300). The microwave reactions were performed with a Biotage Initiator Microwave oven using 10–20 mL sealed vials; temperatures were measured with an IR-sensor and reaction times are given as hold times.

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

To a solution of 5-chloropyridin-2-amine (5 g, 38.9 mmol, 1 equiv) in ethyl 4-chloroacetoacetate (7.4 mL, 54.5 mmol, 1.4 equiv), PPA (25 g) was added. The reaction mixture was heated at 110 °C for 3 h. After cooling, H_2O (500 mL) was added and the solution was neutralized with Na_2CO_3. A precipitate appeared and was filtered, washed with H_2O (3 × 100 mL) and dried in a vacuum drying oven (desiccator cabinet). Recrystallization from propan-2-ol gave pure **1**.

Yield: 8.0 g (90%); brown solid; mp 155 °C (Lit.[23] 156 °C).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.50 (s, 2 H), 6.65 (s, 1 H), 7.56–7.71 (m, 2 H), 9.04 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 44.9, 102.7, 123.8, 124.5, 126.5, 137.3, 148.8, 156.4, 161.7.

7-Chloro-2-(chloromethyl)-3-iodo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (2)

A mixture of 7-chloro-2-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1**; 1 g, 4.36 mmol, 1 equiv) and NIS (1.08 g, 5.24 mmol, 1.2 equiv) was heated at reflux in MeCN (60 mL) for 16 h. At this time, the solution was cooled and evaporated under reduced pressure. Flash chromatography (silica gel; CH_2Cl_2–EtOAc, 9:1) provided, after recrystallization from propan-2-ol, pure **2**.

Yield: 1.16 g (75%); yellow solid; mp 190 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.78 (s, 2 H), 7.66 (d, *J* = 9.4 Hz, 1 H), 7.76 (dd, *J* = 9.4, 2.2 Hz, 1 H), 9.05 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 50.1, 79.2, 125.5, 125.6, 127.1, 138.2, 148.6, 155.2, 163.2.

Anal. Calcd for $C_9H_5Cl_2IN_2O$: C, 30.45; H, 1.42; N, 7.89. Found: C, 30.97; H, 1.35; N, 7.74.

(7-Chloro-3-iodo-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)methyl Acetate (3)

A solution of 7-chloro-2-(chloromethyl)-3-iodo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**2**; 1 g, 2.82 mmol, 1 equiv) and potassium acetate (0.33 g, 3.38 mmol, 1.2 equiv) in DMF (70 mL) was stirred at r.t. for 5 h. At this point, the DMF was evaporated under reduced pressure. Flash chromatography (silica gel; CH_2Cl_2–EtOAc, 9.5:0.5) provided, after recrystallization from propan-2-ol, pure **3**.

Yield: 0.81 g (76%); yellow solid; mp 156 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.23 (s, 3 H), 5.24 (s, 2 H), 7.62 (d, *J* = 9.4 Hz, 1 H), 7.73 (dd, *J* = 9.4, 2.2 Hz, 1 H), 9.06 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.8, 68.8, 76.6, 125.3, 125.6, 127.2, 137.9, 148.4, 154.7, 162.3, 170.5.

Anal. Calcd for $C_{11}H_8ClIN_2O_3$: C, 34.90; H, 2.13; N, 7.40. Found: C, 35.09; H, 2.10; N, 7.42.

Suzuki–Miyaura Reaction; General Procedure

A solution of (7-chloro-3-iodo-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)methyl acetate (**3**; 0.3 g, 0.79 mmol, 1 equiv), boronic acid (1.5 equiv, 1.19 mmol), and $[Pd(PPh_3)_4]$ (45 mg, 39 μmol, 0.05 equiv), and a 1N solution of K_2CO_3 (2.37 mL, 2.37 mmol, 3 equiv) in a DME–EtOH mixture (9:1, 15 mL) was heated at 100 °C under microwave irradiation for 2 h. At this time, H_2O (100 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 60 mL). The organic layer was washed with H_2O (3 × 100 mL), dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography (silica gel; CH_2Cl_2–EtOAc, 9:1) and recrystallized from propan-2-ol.

(7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)methyl Acetate (4) (Table 2, Entry 1)

Yield: 58%; yellow solid; mp 137 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.21 (s, 3 H), 5.10 (s, 2 H), 6.51 (s, 1 H), 7.56 (d, *J* = 9.5 Hz, 1 H), 7.69 (dd, *J* = 9.5, 2.3 Hz, 1 H), 9.05 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.8, 65.1, 101.3, 124.2, 125.1, 127.1, 137.8, 149.5, 157.0, 162.5, 170.2.

Anal. Calcd for $C_{11}H_9ClN_2O_3$: C, 52.29; H, 3.59; N, 11.09. Found: C, 52.50; H, 3.56; N, 10.87.

[7-Chloro-3-(4-methoxyphenyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]methyl Acetate (5)

Yield: 79%; yellow solid; mp 126 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.10 (s, 3 H), 3.84 (s, 3 H), 5.00 (s, 2 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 7.28 (d, *J* = 8.7 Hz, 2 H), 7.62–7.64 (m, 2 H), 9.04–9.06 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.7, 55.3, 64.4, 114.1, 114.1, 117.5, 124.3, 124.6, 125.2, 127.5, 131.3, 131.3, 136.9, 148.0, 156.9, 157.3, 159.6, 170.5.

Anal. Calcd for $C_{18}H_{15}ClN_2O_4$: C, 60.26; H, 4.21; N, 7.81. Found: C, 60.27; H, 4.34; N, 7.65.

7-Chloro-2-(hydroxymethyl)-3-(4-methoxyphenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (5′) (Table 2, Entry 7)
Yield: 33%; yellow solid; mp 163 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.86 (s, 3 H), 4.55 (s, 2 H), 7.00 (d, *J* = 8.7 Hz, 2 H), 7.26 (d, *J* = 8.7 Hz, 2 H), 7.66–7.77 (m, 2 H), 9.12 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 55.3, 61.8, 114.3, 114.3, 114.7, 123.9, 124.6, 125.6, 126.6, 131.1, 131.1, 137.7, 147.8, 156.3, 159.6, 160.7.

Anal. Calcd for $C_{16}H_{13}ClN_2O_3$: C, 60.67; H, 4.14; N, 8.84. Found: C, 60.32; H, 4.18; N, 8.57.

(7-Chloro-4-oxo-3-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)methyl Acetate (6)
Yield: 73%; beige solid; mp 110 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.09 (s, 3 H), 5.00 (s, 2 H), 7.34–7.47 (m, 5 H), 7.66–7.67 (m, 2 H), 9.07 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.7, 64.4, 117.7, 124.5, 125.3, 127.5, 128.4, 128.7, 128.7, 130.1, 130.1, 132.6, 137.3, 148.2, 156.7, 157.4, 170.4.

Anal. Calcd for $C_{17}H_{13}ClN_2O_3$: C, 62.11; H, 3.99; N, 8.52. Found: C, 62.27; H, 3.99; N, 8.42.

[7-Chloro-3-(3-nitrophenyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]methyl Acetate (7)
Yield: 70%; beige solid; mp 167 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.09 (s, 3 H), 4.95 (s, 2 H), 7.61–7.79 (m, 4 H), 8.24–8.29 (m, 2 H), 9.07–9.08 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.5, 64.5, 115.3, 123.3, 125.1, 125.3, 125.4, 127.6, 129.5, 134.6, 136.5, 138.0, 148.3, 148.6, 156.4, 157.9, 170.2.

Anal. Calcd for $C_{17}H_{12}ClN_3O_5$: C, 54.63; H, 3.24; N, 11.24. Found: C, 54.86; H, 3.30; N, 11.04.

[7-Chloro-3-(4-fluorophenyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]methyl Acetate (8)
Yield: 82%; yellow solid; mp 132 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.07 (s, 3 H), 4.96 (s, 2 H), 7.08–7.19 (m, 2 H), 7.29–7.38 (m, 2 H), 7.59–7.71 (m, 2 H), 9.03–9.04 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.6, 64.2, 115.7 (d, J_{C-F} = 21.6 Hz, 2 × CHCF), 116.6, 124.5, 125.2, 127.4, 128.5 (d, J_{C-F} = 3.7 Hz, C-CF), 131.9 (d, J_{C-F} = 8.1 Hz, 2 × CHCF), 137.3, 148.2, 156.6, 157.6, 162.6 (d, J_{C-F} = 248.1 Hz, CF), 170.3.

Anal. Calcd for $C_{17}H_{12}ClFN_2O_3$: C, 58.89; H, 3.49; N, 8.08. Found: C, 58.81; H, 3.61; N, 7.95.

[7-Chloro-3-(4-chlorophenyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]methyl Acetate (9)
Yield: 84%; beige solid; mp 136 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.09 (s, 3 H), 4.98 (s, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.44 (d, *J* = 8.4 Hz, 2 H), 7.61–7.73 (m, 2 H), 9.07 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.7, 64.3, 116.5, 124.7, 125.3, 127.5, 128.9, 128.9, 131.1, 131.5, 131.5, 134.5, 137.5, 148.3, 156.6, 157.6, 170.4.

Anal. Calcd for $C_{17}H_{12}Cl_2N_2O_3$: C, 56.22; H, 3.33; N, 7.71. Found: C, 56.26; H, 3.30; N, 7.58.

[7-Chloro-4-oxo-3-(3,4,5-trimethoxyphenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]methyl Acetate (10)
Yield: 63%; yellow solid; mp 186 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.13 (s, 3 H), 3.86 (s, 6 H), 3.90 (s, 3 H), 5.02 (s, 2 H), 6.59 (s, 2 H), 7.61–7.73 (m, 2 H), 9.08–9.09 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.7, 56.1, 56.1, 60.8, 64.4, 77.2, 107.2, 107.2, 117.6, 124.5, 125.3, 127.5, 128.0, 137.3, 148.2, 153.4, 153.4, 156.7, 157.7, 170.4.

Anal. Calcd for $C_{20}H_{19}ClN_2O_6$: C, 57.35; H, 4.57; N, 6.69. Found: C, 57.24; H, 4.54; N, 6.71.

{7-Chloro-4-oxo-3-[3-(trifluoromethyl)phenyl]-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl}methyl Acetate (11)
Yield: 65%; yellow solid; mp 141 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.08 (s, 3 H), 4.96 (s, 2 H), 7.57–7.75 (m, 6 H), 9.09 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.5, 64.5, 116.3, 123.9 (q, J_{C-F} = 273.0 Hz, CF_3), 124.9, 125.2 (q, J_{C-F} = 3.7 Hz, $CHCF_3$), 125.3, 127.1 (q, J_{C-F} = 3.7 Hz, $CHCF_3$), 127.6, 129.2, 131.0 (q, J_{C-F} = 32.1 Hz, CCF_3), 133.5, 133.6, 137.7, 148.5, 156.5, 157.8, 170.3.

Anal. Calcd for $C_{18}H_{12}ClF_3N_2O_3$: C, 54.49; H, 3.05; N, 7.06. Found: C, 54.16; H, 3.17; N, 6.89.

{7-Chloro-3-(naphthalen-1-yl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl}methyl Acetate (12)
Yield: 89%; yellow solid; mp 160 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.90 (s, 3 H), 4.85 (s, 2 H), 7.41–7.60 (m, 4 H), 7.68–7.78 (m, 3 H), 7.90–7.96 (m, 2 H), 9.11 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.4, 64.4, 115.7, 124.6, 124.8, 125.5, 125.6, 126.1, 126.6, 127.6, 128.1, 128.7, 129.2, 130.2, 131.9, 133.9, 137.5, 148.8, 156.5, 159.3, 170.3.

HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}ClN_2O_3$: 379.0844; found: 379.0843.

[7-Chloro-3-(furan-2-yl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]methyl Acetate (13)
Yield: 90%; brown solid; mp 147 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.17 (s, 3 H), 5.51 (s, 2 H), 6.59 (m, 1 H), 7.28 (d, *J* = 3.4 Hz, 1 H), 7.56–7.68 (m, 3 H), 9.12 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.8, 65.3, 106.8, 111.8, 113.4, 124.9, 125.1, 127.6, 136.8, 142.5, 146.7, 146.8, 154.6, 156.4, 170.8.

Anal. Calcd for $C_{15}H_{11}ClN_2O_4$: C, 56.53; H, 3.48; N, 8.79. Found: C, 55.83; H, 3.52; N, 8.66.

[7-Chloro-4-oxo-3-(pyridin-4-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]methyl Acetate (14)
Yield: 53%; yellow solid; mp 140 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.06 (s, 3 H), 4.99 (s, 2 H), 7.34 (d, *J* = 5.7 Hz, 2 H), 7.64–7.78 (m, 2 H), 8.72 (d, *J* = 5.7 Hz, 2 H), 9.07–9.08 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.6, 64.2, 114.7, 125.0, 125.1, 125.1, 125.4, 127.6, 138.0, 141.3, 148.7, 150.1, 150.1, 156.1, 157.9, 170.3.

HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{12}ClN_3O_3$: 330.0640; found: 330.0642.

[7-Chloro-4-oxo-3-(pyridin-3-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]methyl Acetate (15)
Yield: 71%; yellow solid; mp 145 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.05 (s, 3 H), 4.96 (s, 2 H), 7.35 (dd, *J* = 4.8, 7.8 Hz, 1 H), 7.62–7.70 (m, 2 H), 7.72–7.78 (m, 1 H), 8.59 (d, *J* = 1.6 Hz, 1 H), 8.62 (dd, *J* = 1.6, 4.8 Hz, 1 H), 9.05–9.06 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.5, 64.3, 114.1, 123.3, 124.8, 125.3, 127.5, 129.0, 137.7, 137.7, 148.5, 149.4, 150.7, 156.6, 158.1, 170.2.

HRMS-FAB: *m/z* [M + H]$^+$ calcd for $C_{16}H_{12}ClN_3O_3$: 330.0640; found: 330.0641.

(7-Chloro-4-oxo-3-*o*-tolyl-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)methyl Acetate (16)
Yield: 73%; yellow solid; mp 148 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.07 (s, 3 H), 2.17 (s, 3 H), 4.86 (s, 2 H), 7.11–7.15 (m, 1 H), 7.31–7.33 (m, 3 H), 7.62–7.72 (m, 2 H), 9.09 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 19.6, 20.7, 63.9, 117.2, 125.0, 125.5, 126.3, 127.0, 129.0, 130.0, 130.5, 131.7, 137.5, 138.0, 148.3, 155.6, 157.4, 170.4.

HRMS-FAB: *m/z* [M + H]$^+$ calcd for $C_{18}H_{15}ClN_2O_3$: 343.0844; found: 343.0843.

{3-[3,5-Bis(trifluoromethyl)phenyl]-7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl}methyl Acetate (17)
Yield: 62%; yellow solid; mp 139 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.06 (s, 3 H), 4.93 (s, 2 H), 7.68–7.81 (m, 2 H), 7.90–7.92 (m, 3 H), 9.09–9.10 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.4, 64.7, 114.9, 122.3 [sept, J_{C-F} = 3.7 Hz, $CH(CF_3)_2$], 123.2 (q, J_{C-F} = 272.6 Hz, 2 × CF_3), 125.3, 125.4, 127.7, 130.7 (q, J_{C-F} = 3.3 Hz, 2 × $CHCCF_3$), 132.0 (q, J_{C-F} = 33.7 Hz, 2 × CCF_3), 135.2, 138.3, 148.7, 156.4, 158.2, 170.1.

Anal. Calcd for $C_{19}H_{11}ClF_6N_2O_3$: C, 49.10; H, 2.39; N, 6.03. Found: C, 49.34; H, 2.35; N, 6.34.

(*E*)-{7-Chloro-4-oxo-3-[4-(trifluoromethyl)styryl]-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl}methyl Acetate (18)
Yield: 83%; yellow solid; mp 209 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.18 (s, 3 H), 5.40 (s, 2 H), 7.23 (d, *J* = 16.0 Hz, 1 H), 7.60–7.72 (m, 6 H), 8.10 (d, *J* = 16.0 Hz, 1 H), 9.14 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.8, 64.1, 112.1, 118.8 (q, J_{C-F} = 271.5 Hz, CF_3), 121.1, 125.2, 125.5, 125.7 (q, J_{C-F} = 4.0 Hz, 2 × $CHCF_3$), 126.8, 126.8, 127.1, 129.7 (q, J_{C-F} = 32.5 Hz, CCF_3), 133.8, 137.7, 141.2, 146.6, 155.2, 156.6, 170.5.

Anal. Calcd for $C_{20}H_{14}ClF_3N_2O_3$: C, 56.82; H, 3.34; N, 6.63. Found: C, 56.45; H, 3.45; N, 6.58.

(*E*)-(7-Chloro-4-oxo-3-styryl-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)methyl Acetate (19)
Yield: 75%; yellow solid; mp 188 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.19 (s, 3 H), 5.39 (s, 2 H), 7.14 (d, *J* = 16.0 Hz, 1 H), 7.28–7.42 (m, 3 H), 7.53–7.62 (m, 4 H), 8.04 (d, *J* = 16.0 Hz, 1 H), 9.12–9.14 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.8, 64.7, 112.9, 118.9, 124.8, 125.0, 126.8, 126.8, 127.6, 128.1, 128.7, 128.7, 135.3, 136.5, 137.8, 146.6, 155.5, 156.7, 170.6.

Anal. Calcd for $C_{19}H_{15}ClN_2O_3$: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.45; H, 4.32; N, 7.87.

(*E*)-[7-Chloro-3-(4-methylstyryl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]methyl Acetate (20)
Yield: 80%; yellow solid; mp 205 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.18 (s, 3 H), 2.37 (s, 3 H), 5.38 (s, 2 H), 7.08 (d, *J* = 16.0 Hz, 1 H), 7.18 (d, *J* = 8.1 Hz, 2 H), 7.44 (d, *J* = 8.1 Hz, 2 H), 7.60 (m, 2 H), 8.01 (d, *J* = 16.0 Hz, 1 H), 9.11–9.12 (m, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.8, 21.3, 64.7, 113.1, 117.9, 124.7, 124.9, 126.7, 126.7, 127.5, 129.4, 129.4, 135.1, 135.4, 136.4, 138.1, 146.4, 155.5, 156.3, 170.6.

Anal. Calcd for $C_{20}H_{17}ClN_2O_3$: C, 65.13; H, 4.65; N, 7.60. Found: C, 65.13; H, 4.69; N, 7.72.

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