

Microwave-assisted one-pot synthesis of 2-amino-6,7-disubstituted-5-methyl-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-one without catalyst

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Abstract

A series of 2-amino-6,7-disubstituted-5-methyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-one derivatives were synthesized through one-pot condensation of 2,6-diaminopyrimidin-4-one, aldehyde and acyclic 1,3-dicarbonyl compounds in glycol under microwave irradiation without catalyst. The protocol in the absence of catalyst has the advantage of good yield (89-95%), short reaction time and being environmentally friendly.

Keywords: Dihydropyridopyrimidine derivatives, microwave irradiation, environmentally friendly

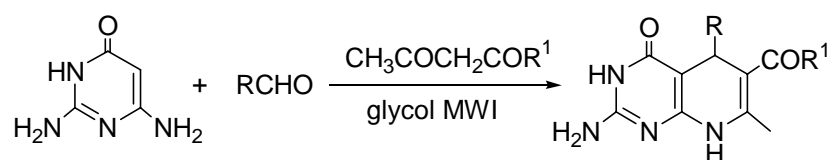
Introduction

Pyrimidine and its derivatives have been studied for over a century due to a variety of important chemical and biological applications. They have been reported as antibacterial, antiviral and antitumor agents.¹ A number of heterocyclic compounds fused with pyrimidines are known for their varied biological activities.²⁻⁶

Microwave activation as a non-conventional energy source has been adapted to the assembly of a library of compounds; this protocol has the advantage of short reaction time, high yield and environmentally friendliness. Mark⁷ et al have prepared dihydropyridopyrimidine derivatives via three-component cyclocondensation reaction under microwave-assisted conditions. However, this method suffers from a longer reaction time (20 min) and the use of zinc(II) bromide as a catalyst and DMSO as a solvent which may be hazardous to environment.

In our previous work,⁸ we have prepared pyrimidoquinoline derivatives via the reaction of 2,6-diaminopyrimidin-4-one with the cyclic 1,3-dicarbonyl compound and appropriate aldehyde in glycol under microwave irradiation without catalyst. In order to investigate the scope of this method, we carried out the reaction using the acyclic 1,3-dicarbonyl compound instead of the cyclic 1,3-dicarbonyl compound to afford dihydropyridopyrimidin derivatives under microwave

irradiation (Scheme1). The reaction was complete within 4-7 min and the target compounds were obtained with high yields. Herein, we report the details of this simple and efficient method.



Scheme 1. Synthesis of dihydropyridopyrimidine derivatives.

Results and Discussion

The mixture of aldehyde (2 mmol), 1,3-dicarbonyl compound (2 mmol) and 2,6-diaminopyrimidin-4-one (2 mmol) in glycol (1 ml) was irradiated for 4-7 min, and the dihydropyridopyrimidin derivatives were obtained in excellent yields. Besides, compared with the traditional heating methodology in similar condition, we found that the reaction could complete within 7 min under microwave irradiation and at 100°C within 2 h using standard thermal conditions. The results are listed in Table 1.

Table 1. Synthesis of dihydropyridopyrimidine **3** under MWI

Entry	R	R ¹	Time(min)	Yield (%)	Mp (°C)
3a	4-ClC ₆ H ₄	CH ₃	4	95	>300
3b	2-ClC ₆ H ₄	CH ₃	6	95	>300
3c	4-BrC ₆ H ₄	CH ₃	7	94	>300
3d	3-NO ₂ C ₆ H ₄	CH ₃	6	93	>300
3e	4-NO ₂ C ₆ H ₄	CH ₃	6	95	>300
3f	4-OCH ₃ C ₆ H ₄	CH ₃	7	92	>300
3g	2,4-Cl ₂ C ₆ H ₃	CH ₃	6	90	>300
3h	CH ₃ CH ₂	CH ₃	5	89	>300
3i	4-ClC ₆ H ₄	OCH ₃	5	94	>300
3j	4-NO ₂ C ₆ H ₄	OCH ₃	5	92	>300
3k	4-BrC ₆ H ₄	OCH ₃	6	92	>300
3l	3,4-Cl ₂ C ₆ H ₃	OCH ₃	7	91	>300
3m	3-NO ₂ C ₆ H ₄	OCH ₃	6	93	>300
3n	4-OCH ₃ C ₆ H ₄	OCH ₃	5	89	>300
3o	CH ₃ CH ₂ CH ₂ CH ₂	OCH ₃	6	92	>300

It is noteworthy that the glycol as an energy transfer agent plays a critical role in the success of the reaction. Owing to its high boiling point and good activity of dehydration, it can accelerate dehydration, which makes the reaction proceed smoothly in the absence of catalyst.

Conclusions

In conclusion, we have disclosed a facile method for the preparation of 2-amino-6,7-disubstituted-5-methyl-5,8-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-one in glycol under microwave-assisted condition without catalyst. This present one-pot synthesis of dihydropyridopyrimidin derivatives is a simple, time saving, high yield, and environmentally friendly process. Furthermore, the protocol can be applied not only for the aromatic aldehyde but also for aliphatic aldehyde.

Experimental Section

General Procedure. Microwave irradiation was carried out in a modified commercial microwave oven under atmospheric pressure. Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Shimadzu spectrometer. ¹H NMR spectra were measured on a DPX 400 spectrometer, using DMSO-*d*₆ as solvent and TMS as internal standard. Elemental analyses were determined by using a Perkin-Elmer 240c elemental analysis instrument.

Typical procedure for the preparation of 3. The mixture of aldehyde (2 mmol), 1,3-dicarbonyl compound (2 mmol) and 2,6-diaminopyrimidin-4-one (2 mmol) in glycol (1 ml) was irradiated for 4-7 min with power 300 W. The achieved temperature in the mean reaction time was about 198 °C. The reaction mixture was cooled to room temperature and poured into water (50 mL), filtered and washed with ethanol (5 mL) to give the product. All products were characterized by IR and ¹H NMR spectral data as well as the elemental analyses.

2-Amino-4-oxo-6-aceto-7-methyl-5-(4-chlorophenyl)pyrido[2,3-*d*]pyrimidine (3a). Yellow crystals (0.627g, 95%); mp >300°C. IR (KBr): ν 3338 (NH₂), 3230 and 3170 (NH), 1652 (COCH₃), 1613 (CONH) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.37 (s, 1H, NH) 9.13 (s, 1H, NH), 7.27 (d, 2H, J=8.8 Hz, ArH), 7.23 (d, 2H, J=8.8 Hz, ArH), 6.28 (s, 2H, NH₂), 4.90 (s, 1H, CH), 2.32 (s, 3H, COCH₃), 2.03 (s, 3H, CH₃). Anal. Calcd for C₁₆H₁₅ClN₄O₂: C, 58.10; H, 4.57; N, 16.94. Found: C, 58.01; H, 4.49; N, 16.87.

2-Amino-4-oxo-6-aceto-7-methyl-5-(2-chlorophenyl)pyrido[2,3-*d*]pyrimidine (3b). Yellow crystals (0.627g, 95%); mp >300°C. IR (KBr): ν 3334 (NH₂), 3251 and 3178 (NH), 1650 (COCH₃), 1612 (CONH) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.20 (s, 1H, NH), 9.08 (s, 1H, NH), 7.08-7.30 (m, 4H, ArH), 6.27 (s, 2H, NH₂), 5.23 (s, 1H, CH), 2.22 (s, 3H, COCH₃), 2.07 (s, 3H, CH₃). Anal. Calcd for C₁₆H₁₅ClN₄O₂: C, 58.10; H, 4.57; N, 16.94. Found: C, 58.00; H, 4.50; N, 16.95.

2-Amino-4-oxo-6-aceto-7-methyl-5-(4-bromophenyl)pyrido[2,3-*d*]pyrimidine (3c). Yellow crystals (0.703g, 94%); mp >300°C. IR (KBr): ν 3337 (NH₂), 3250 and 3168 (NH), 1661 (COCH₃), 1611 (CONH) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.38 (s, 1H, NH), 9.13 (s,

1H, NH), 7.40 (d, 2H, $J=8.4$ Hz, ArH), 7.17 (d, 2H, $J=8.4$ Hz, ArH), 6.29 (s, 2H, NH₂), 4.89 (s, 1H, CH), 2.32 (s, 3H, COCH₃), 2.04 (s, 3H, CH₃). Anal. Calcd for C₁₆H₁₅BrN₄O₂: C, 51.22; H, 4.03; N, 14.93. Found: C, 51.18; H, 3.98; N, 14.87.

2-Amino-4-oxo-6-aceto-7-methyl-5-(3-nitrophenyl)pyrido[2,3-d] pyrimidine (3d). Yellow crystals (0.634g, 93%); mp >300°C. IR (KBr): ν 3335 (NH₂), 3251 and 3179 (NH), 1653 (COCH₃), 1610 (CONH) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.42 (s, 1H, NH), 9.26 (s, 1H, NH), 7.50-8.05 (m, 4H, ArH), 6.35 (s, 2H, NH₂), 5.05 (s, 1H, CH), 2.37 (s, 3H, COCH₃), 2.09 (s, 3H, CH₃). Anal. Calcd for C₁₆H₁₅N₅O₅: C, 53.78; H, 4.23; N, 19.60. Found: C, 53.69; H, 4.21; N, 19.58.

2-Amino-4-oxo-6-aceto-7-methyl-5-(4-nitrophenyl)pyrido[2,3-d] pyrimidine (3e). Yellow crystals (0.648g, 95%); mp >300°C. IR (KBr): ν 3336 (NH₂), 3250 and 3167 (NH), 1654 (COCH₃), 1612 (CONH) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.48 (s, 1H, NH), 9.28 (s, 1H, NH), 8.11 (d, 2H, $J=8.8$ Hz, ArH), 7.48 (d, 2H, $J=8.4$ Hz, ArH), 6.37 (s, 2H, NH₂), 5.04 (s, 1H, CH), 2.37 (s, 3H, COCH₃), 2.09 (s, 3H, CH₃). Anal. Calcd for C₁₆H₁₅N₅O₅: C, 53.78; H, 4.23; N, 19.60. Found: C, 53.72; H, 4.18; N, 19.49.

2-Amino-4-oxo-6-aceto-7-methyl-5-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine (3f). Yellow crystals (0.559g, 92%); mp >300°C. IR (KBr): ν 3336 (NH₂), 3268 and 3171 (NH), 1659 (COCH₃), 1610 (CONH) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.39 (s, 1H, NH), 9.07 (s, 1H, NH), 7.14 (d, 2H, $J=8.8$ Hz, ArH), 6.77 (d, 2H, $J=8.4$ Hz, ArH), 6.27 (s, 2H, NH₂), 4.84 (s, 1H, CH), 3.68 (s, 3H, OCH₃), 2.32 (s, 3H, COCH₃), 2.03 (s, 3H, CH₃). Anal. Calcd for C₁₇H₁₈N₄O₃: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.48; H, 5.51; N, 17.20.

2-Amino-4-oxo-6-aceto-7-methyl-5-(2,4-dichlorophenyl)pyrido[2,3-d]pyrimidine (3g). Yellow crystals (0.655g, 90%); mp >300°C. IR (KBr): ν 3334 (NH₂), 3267 and 3184 (NH), 1655 (COCH₃), 1612 (CONH) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.25 (s, 1H, NH), 9.15 (s, 1H, NH), 7.17-7.29 (m, 3H, ArH), 6.33 (s, 2H, NH₂), 5.20 (s, 1H, CH), 2.25 (s, 3H, COCH₃), 2.09 (s, 3H, CH₃). Anal. Calcd for C₁₆H₁₄Cl₂N₄O₂: C, 52.62; H, 3.86; N, 15.34. Found: C, 52.48; H, 3.78; N, 15.21.

2-Amino-4-oxo-6-aceto-7-methyl-5-ethyl-pyrido[2,3-d]pyrimidine (3h). Yellow crystals (0.441g, 89%); mp >300°C. IR (KBr): ν 3341 (NH₂), 3260 and 3178 (NH), 1664 (COCH₃), 1613 (CONH) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.46 (s, 1H, NH), 8.83 (s, 1H, NH), 6.27 (s, 2H, NH₂), 3.83 (t, 1H, $J=4.8$ Hz, CH), 2.19 (s, 3H, COCH₃), 2.17 (s, 3H, CH₃), 1.15-1.48 (m, 2H, CH₂), 0.64 (t, 3H, $J=7.6$ Hz, CH₃). Anal. Calcd for C₁₂H₁₆N₄O₂: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.10; H, 6.48; N, 22.49.

2-Amino-4-oxo-6-methoxycarbonyl-7-methyl-5-(4-chlorophenyl)-pyrido[2,3-d] pyrimidine (3i). Yellow crystals (0.650g, 94%); mp >300°C. IR (KBr): ν 3465 (NH₂), 3317 and 3197 (NH), 1658 (COOCH₃), 1619 (CONH) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.35 (s, 1H, NH), 9.11 (s, 1H, NH), 7.18-7.26 (m, 4H, ArH), 6.28 (s, 2H, NH₂), 4.85 (s, 1H, CH), 3.32 (s, 3H, OCH₃), 2.31 (s, 3H, CH₃). Anal. Calcd for C₁₆H₁₅ClN₄O₃: C, 55.42; H, 4.36; N, 16.16. Found: C, 55.34; H, 4.30; N, 16.10.

2-Amino-4-oxo-6-methoxycarbonyl-7-methyl-5-(4-nitrophenyl)-pyrido[2,3-*d*]pyrimidine

(3j). Yellow crystals (0.657g, 92%); mp >300°C. IR (KBr): ν 3454 (NH₂), 3329 and 3193 (NH), 1660 (COOCH₃), 1602 (CONH) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.54 (s, 1H, NH), 9.23 (s, 1H, NH), 8.10 (d, 2H, *J*=8.8 Hz, ArH), 7.45 (d, 2H, *J*=8.8 Hz, ArH), 6.42 (s, 2H, NH₂), 4.98 (s, 1H, CH), 3.32 (s, 3H, OCH₃), 2.35 (s, 3H, CH₃). Anal. Calcd for C₁₆H₁₅N₅O₆: C, 51.48; H, 4.05; N, 18.76. Found: C, 51.37; H, 3.98; N, 18.71.

2-Amino-4-oxo-6-methoxycarbonyl-7-methyl-5-(4-bromophenyl)-pyrido[2,3-*d*]pyrimidine

(3k). Yellow crystals (0.718g, 92%); mp >300°C. IR (KBr): ν 3465 (NH₂), 3317 and 3186 (NH), 1657 (COOCH₃), 1600 (CONH) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.35 (s, 1H, NH), 9.11 (s, 1H, NH), 7.36 (d, 2H, *J*=8.4 Hz, ArH), 7.15 (d, 2H, *J*=8.4 Hz, ArH), 6.28 (s, 2H, NH₂), 4.85 (s, 1H, CH), 3.31 (s, 3H, OCH₃), 2.32 (s, 3H, CH₃). Anal. Calcd for C₁₆H₁₅BrN₄O₃: C, 49.12; H, 3.86; N, 14.32. Found: C, 49.02; H, 3.77; N, 14.22.

2-Amino-4-oxo-6-methoxycarbonyl-7-methyl-5-(3,4-dichlorophenyl)-pyrido[2,3-*d*]pyrimidine

(3l). Yellow crystals (0.691g, 91%); mp >300°C. IR (KBr): ν 3460 (NH₂), 3292 and 3183 (NH), 1644 (COOCH₃), 1602 (CONH) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.38 (s, 1H, NH), 9.19 (s, 1H, NH), 7.14-7.48 (m, 3H, ArH), 6.34 (s, 2H, NH₂), 4.85 (s, 1H, CH), 3.31 (s, 3H, OCH₃), 2.33 (s, 3H, CH₃). Anal. Calcd for C₁₆H₁₄Cl₂N₄O₃: C, 50.41; H, 3.70; N, 14.70. Found: C, 50.31; H, 3.65; N, 14.58.

2-Amino-4-oxo-6-methoxycarbonyl-7-methyl-5-(3-nitrophenyl)-pyrido[2,3-*d*]pyridine (**3m**).

Yellow crystals (0.664g, 93%); mp >300°C. IR (KBr): ν 3414 (NH₂), 3316 and 3202 (NH), 1655 (COOCH₃), 1613 (CONH) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.39 (s, 1H, NH), 9.21 (s, 1H, NH), 7.49-8.03 (m, 4H, ArH), 6.35 (s, 2H, NH₂), 5.00 (s, 1H, CH), 3.31 (s, 3H, OCH₃), 2.35 (s, 3H, CH₃). Anal. Calcd for C₁₆H₁₅N₅O₆: C, 51.48; H, 4.05; N, 18.76. Found: C, 51.41; H, 3.92; N, 18.68.

2-Amino-4-oxo-6-methoxycarbonyl-7-methyl-5-(4-methoxyphenyl)-pyrido[2,3-*d*]pyrimidine

(3n). Yellow crystals (0.608g, 89%); mp >300°C. IR (KBr): ν 3600 and 3436 (NH₂), 3324 and 3210 (NH), 1665 (COOCH₃), 1600 (CONH) cm⁻¹. ¹H NMR (400MHz, DMSO-*d*₆): δ 10.28 (s, 1H, NH), 9.02 (s, 1H, NH), 7.08 (d, 2H, *J*=8.4 Hz, ArH), 6.75 (d, 2H, *J*=8.4 Hz, ArH), 6.22 (s, 2H, NH₂), 4.80 (s, 1H, CH), 3.67 (s, 3H, OCH₃), 3.31 (s, 3H, OCH₃), 2.30 (s, 3H, CH₃). Anal. Calcd for C₁₇H₁₈N₄O₄: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.59; H, 5.26; N, 16.28.

2-Amino-4-oxo-6-methoxycarbonyl-7-methyl-5-butyl-pyrido[2,3-*d*]pyrimidine (**3o**).

Yellow crystals (0.537g, 92%); mp >300°C. IR (KBr): ν 3410 (NH₂), 3314 and 3175 (NH), 1647 (COOCH₃), 1619 (CONH) cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.33 (s, 1H, NH), 8.76 (s, 1H, NH), 6.22 (s, 2H, NH₂), 4.80 (s, 1H, CH), 3.59 (s, 3H, OCH₃), 2.21 (s, 3H, CH₃), 1.06-1.24 (m, 6H, CH₂), 0.86 (t, 3H, *J*=6.1 Hz, CH₃). Anal. Calcd for C₁₄H₂₀N₄O₃: C, 57.52; H, 6.90; N, 19.17. Found: C, 57.48; H, 4.78; N, 19.11.

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