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AN EFFICIENT ONE-POT AND SOLVENT-FREE SYNTHESIS OF CHROMENO[2,3-*d*]PYRIMIDINE DERIVATIVES: MICROWAVE ASSISTED REACTION

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Abstract – An efficient synthesis of some new chromeno[2,3-*d*]pyrimidine derivatives has been described by a solvent-free, multi-component reaction in fairly high yields.

Development of multi-component reaction (MCRs) is of great interests in recent years since MCRs have the advantages such as atom economy, high efficiency and selectivity as well as environmental friendliness.¹⁻³ On the other hand, microwave (MW) promoted reactions have shown environmentally friendly nature, greater selectivity and enhanced reaction rate.⁴⁻⁸ Fused pyrimidine derivatives are an important heterocyclic compounds which occur in many biological active products, useful as anticancer,⁹ antiplatelet,¹⁰ antimicrobial,¹¹ antitumor,¹² neuroprotective,¹³ DHFR inhibitory,¹⁴ antiviral¹⁵ and antifungal¹⁶ activities. Various methods for the synthesis of pyrimidine derivatives have been reported.¹⁷⁻²⁷ Most of these methods require prolonged reaction times, isolation of intermediates, complex synthetic pathways or generate moderate yields. Sakurai and coworker have already reported the condensation of hydroxybenzaldehyde and methylene compounds such as benzoylacetone, ethyl cyanoacetate and ethyl acetoacetate in the presence of ammonia or ammonium acetate to give benzoquinazoline derivatives in 28-35% yields.²⁸ Meyer has reported the synthesis of pyranopyrimidine derivatives by condensation of malonodiamidine dihydrochloride and aromatic aldehyde in 4-51% yields.²⁹

One of the key areas of green chemistry is the elimination of catalysts and solvents. In today's world, synthetic chemists in both academia and industry have a widespread current debate over the relative "greenness" of different procedures.³⁰ We have already reported multicomponent, one-pot synthetic procedures for some new heterocyclic compounds.³¹⁻³⁴ Now we wish to report multicomponent reaction of malononitrile **1**, salicylaldehydes **2**, and secondary amines **3** in a 1:2:2 molar ratio under heat or microwave irradiation (MWI) to afford a series of new chromeno[2,3-*d*]pyrimidines **4**.

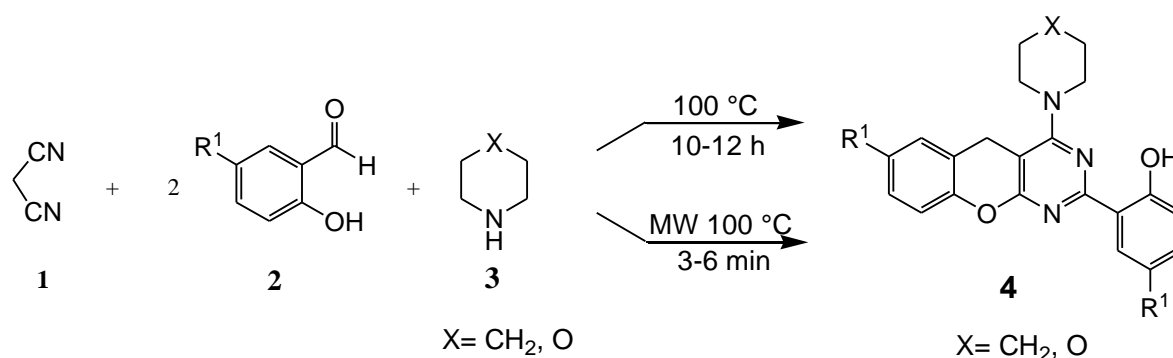


Table 1. Synthesis of products **4** under microwave irradiation and heat

Comp.	R ¹	Amine	Time (h)	Time (min)	Yield (%)	Yield (%)	MP
Entry 4			(Δ)	(MW)	(Δ)	(MW)	(°C)
a	H	piperidine	12	6	75	90	187
b	H	morpholine	11	6	78	92	210
c	Cl	piperidine	12	5	80	86	216
d	Cl	morpholine	12	5	82	88	250
e	Br	piperidine	11	4	81	91	226
f	Br	morpholine	10	4	83	89	219
g	MeO	piperidine	10	3	85	96	195
h	MeO	morpholine	10	3	85	95	231

X-Ray crystal structure of **4b** was preformed to confirm unambiguously its highly functionalized structure.³⁵ The X-ray crystal structure shows the intramolecular O-H---N hydrogen bonding and neighboring molecules are stabilized by intermolecular hydrogen bonds (Figure 1).

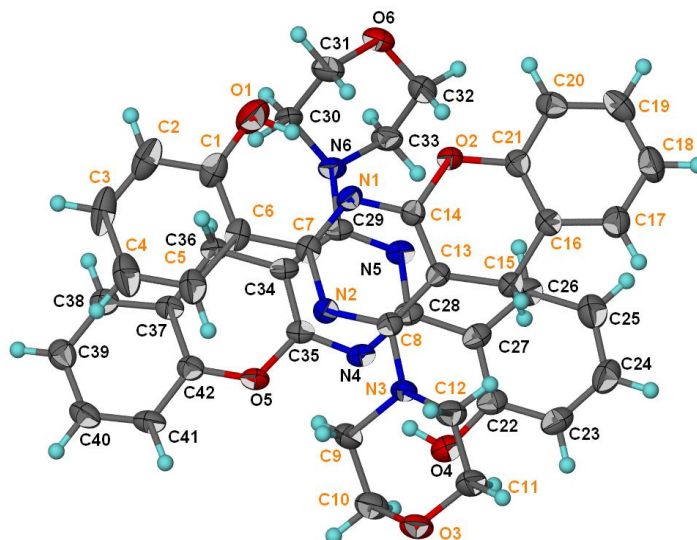


Figure 1. X-Ray crystal structure of **4b**

In this research initially 2-imino-2*H*-chromene-3-carbonitriles **5** (its synthesis and spectroscopic data has been already reported^{36,37}) was synthesized by one-pot reaction of malononitrile **1**, salicylaldehyde derivative **2**, and catalytic amounts of secondary amine **3** within a few minutes at room temperature under solvent-free condition. Addition of secondary amines **3** (~ 2 equiv.) and refluxing the reaction mixture for 10-12 h or microwave irradiation for 3-6 min by using microwave oven,³⁸ in this stage produced the chromeno[2,3-*d*]pyrimidines **4** as solid products. The products **4** can be purified by recrystallization from ethanol or methanol. Single crystals of **4b** were obtained from a mixture of methanol and acetone.

This procedure is optimized as following: Catalytic amounts of secondary amine **3** for preparation of iminocoumarin **5** is necessary in the first step. It is the major component to produce the final products **4** in the second step and help to carry out the reaction under solvent-free conditions. The second step was optimized by varying reaction time, temperature and molar ratio of secondary amines **3**. The best results were obtained when the secondary amines were used 1.7-2 equivalents and the reaction mixtures were heated at 100 °C (180 W) for 3-6 minutes under microwave irradiation.³⁸ For the best comparison we performed the reaction using conventional heating (oil bath), we kept the quantities of the reactant exactly the same as in the microwave-promoted reaction and performed the solvent less reaction in a 50 mL three-necked flask with a thermometer. The reaction mixture was heated at 100 °C for 10-12 h. Moderate yields (75-85%) of the final products were obtained. Clearly, the microwave irradiation has shortened the reaction times with yield enhancement.

In summary, we have reported here a new and effective methodology for the synthesis of some new chromeno[2,3-*d*]pyrimidines with potential biological activities.

This method has many dramatic advantages such as solvent-free synthesis, short reaction time, high yield and simple procedure for purification of the only one product. In this one-pot, solvent-free procedure, eight new bonds was formed and the new aromatic ring (pyrimidine) was produced. Microwave irradiation improved the yields and shortened the reaction times. Further investigations of this method are currently in progress to establish its scope and utility.

EXPERIMENTAL

Chemicals and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Microwave assisted reactions were carried out in microwave oven (ETHOS 1600, Milestone) with a power of 600 W specially designed for organic synthesis. Columns chromatography were performed on silica Gel (0.015-0.04 mm, mesh-size) and TLC on precoated plastic sheets (25 DC_{UV-254}), respectively. Melting points were measured on Barnstead Electrothermal melting point apparatus and were not corrected. Elemental analyses for C, H and N were performed using a Thermo Finnigan Flash EA1112 instrument. IR spectra were measured on a Shimadzu FT-IR-4300 spectrophotometer as KBr discs. ¹H NMR and ¹³C NMR spectra were determined in CDCl₃ on a Bruker 500 spectrophotometer and chemical shifts were expressed in ppm downfield from tetramethylsilane. Mass spectra were recorded on a Finnigan-MAT 8430 spectrometer at an ionization potential of 70 eV.

General Procedure:

To a magnetically stirred mixture of malononitrile **1** (1 mmol), salicylaldehyde derivatives **2** (2 mmol) and morpholine or piperidine (0.2 mmol) were added at 5 °C, the reaction mixture was stirred for 5 min then secondary amines **3** (~1.5 mmol) was added dropwise to the above mixture and stirred for 5-10 min at room temperature and placed in a open glass container. Irradiation in a microwave oven³⁸ at 100 °C for 3-6 min gave the solid products **4** were collected by filtration and recrystallized from EtOH or MeOH.

2-(4-(Piperidin-1-yl)-5H-chromeno[2,3-d]pyrimidin-2-yl)phenol (4a).

Light yellow crystals; mp 187 °C; ν_{\max} (KBr): 3043 (O-H), 1622, 1605 (C=N), 1257, 1151, 1110 (C-O) cm⁻¹; δ_{H} (500 MHz, CDCl₃): 1.77-1.81 (6H, m, 3CH₂ of piperidine), 3.45-3.47 (4H, m, 2CH₂ of piperidine), 3.93 (2H, s, CH₂), 6.94-6.97, 7.00-7.02, 7.11-7.14, 7.21-7.31, 7.36-7.40, 8.44-8.46 (8H, 6m, aromatic), 13.50 (1H, brs, OH); δ_{C} (125 MHz): 24.79, 26.36, 49.93, (CH₂ of piperidine), 26.04 (CH₂), 97.91, 117.47, 117.96, 119.02, 119.22, 119.97, 124.80, 128.59, 128.98, 129.62, 133.21, 151.01, 160.86, 162.39, 165.59 (aromatic); MS: m/z: 359, 331, 275, 181, 84; Anal. Calcd for C₂₂H₂₁N₃O₂: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.51; H, 5.88; N, 11.71.

2-(4-(Morpholino-5H-chromeno[2,3-d]pyrimidin-2-yl)phenol (4b).

Light yellow crystals; mp 210 °C; ν_{\max} (KBr): 3038 (O-H), 1630, 1609 (C=N), 1250, 1109, 1015 (C-O) cm⁻¹; δ_{H} (500 MHz, CDCl₃): 3.45-3.56, 3.94-3.96 (8H, 2t, *J* = 4.73 Hz, CH₂ of morpholine), 3.98 (2H, s,

CH₂), 6.96-6.98, 7.02-7.04, 7.16-7.18, 7.22-7.24, 7.29-7.30, 7.40-7.44, 8.43-8.45 (8H, 7m, aromatic), 13.38 (1H, brs, OH); δ_C (125 MHz): 26.04 (CH₂), 49.14, 67.11 (CH₂ of morpholine), 94.07, 117.62, 118.10, 119.38, 119.51, 125.03, 128.98, 128.84, 129.66, 133.51, 151.90, 160.81, 162.40, 165.92 (aromatic); MS: m/z: 361, 275, 268, 182, 95, 92, 86; Anal. Calcd for C₂₁H₁₉N₃O₃: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.77; H, 5.33; N, 11.65.

4-Chloro-2-(7-chloro-4-(piperidin-1-yl)-5H-chromeno[2,3-d]pyrimidin-2-yl)phenol (4c).

Light yellow crystals; mp 216 °C; ν_{\max} (KBr): 3074 (O-H), 1644, 1634 (C=N), 1250, 1208, 1180, 1097 (C-O), 871, 825 (C-Cl) cm⁻¹; δ_H (500 MHz, CDCl₃): 1.80-1.81 (6H, m, CH₂ of piperidine), 3.46-3.47 (4H, m, CH₂ of piperidine), 3.89 (2H, s, CH₂), 6.90-6.92, 7.12-7.14, 7.22-7.24, 7.28-7.31, 8.36-8.37 (6H, 5m, aromatic), 13.31 (1H, brs, OH); δ_C (125 MHz): 24.71, 26.34, 49.93 (CH₂ of piperidine), 25.96 (CH₂), 97.41, 118.76, 119.49, 119.92, 121.47, 124.15, 128.70, 128.73, 128.76, 129.82, 133.04, 149.45, 159.43, 161.40, 165.55 (aromatic); MS: m/z: 429, 427, 345, 343, 308, 229, 215, 127, 84; Anal. Calcd for C₂₂H₁₉Cl₂N₃O₂: C, 61.69; H, 4.47; N, 9.81. Found: C, 61.68; H, 4.47; N, 9.83.

4-Chloro-2-(7-chloro-4-(merpholin-4-yl)-5H-chromeno[2,3-d]pyrimidin-2-yl)phenol (4d).

Light yellow crystals; mp 250 °C; ν_{\max} (KBr): 3165 (O-H), 1656, 1648 (C=N), 1274, 1245, 1182, 1118 (C-O), 898, 906 (C-Cl) cm⁻¹; δ_H (500 MHz, CDCl₃): 3.52-3.54, 3.94-3.96 (8H, 2t, $J = 4.23$ Hz, 4CH₂ of morpholine), 3.91 (2H, s, CH₂), 6.91-6.93, 7.13-7.15, 7.23-7.27, 7.29-7.32, 8.33-8.34 (6H, 5m, aromatic), 13.00 (1H, brs, OH); δ_C (125 MHz): 25.92 (CH₂), 49.08, 67.04 (CH₂ of morpholine), 97.72, 118.85, 119.63, 119.74, 120.98, 124.27, 128.75, 128.95, 130.06, 133.28, 149.25, 159.38, 161.53, 165.26 (aromatic); MS: m/z: 431, 429, 345, 343, 301, 215, 127, 86; Anal. Calcd for C₂₁H₁₇Cl₂N₃O₃: C, 58.62; H, 3.98; N, 9.77. Found: C, 58.60; H, 3.97; N, 9.79.

4-Bromo-2-(7-bromo-4-(piperidin-1-yl)-5H-chromeno[2,3-d]pyrimidin-2-yl)phenol (4e).

Yellow crystals; mp 226 °C; ν_{\max} (KBr): 3068 (O-H), 1640, 1593 (C=N), 1249, 1181, 1089 (C-O), 900, 811 (C-Br) cm⁻¹; δ_H (500 MHz, CDCl₃): 1.79-1.81 (6H, m, CH₂ of piperidine), 3.46-3.47 (4H, m, CH₂ of piperidine), 3.92 (2H, s, CH₂), 6.87-6.89, 7.09-7.11, 7.38-7.40, 7.43-7.45, 8.52-8.53 (6H, 5m, aromatic), 13.36 (1H, brs, OH); δ_C (125 MHz): 24.70, 26.33, 49.96 (CH₂ of piperidine), 25.91 (CH₂), 95.06, 111.30, 117.30, 119.21, 119.97, 122.00, 131.68, 131.71, 131.75, 135.95, 159.94, 163.21, 166.57 (aromatic); MS: m/z: 519, 517, 515, 433, 431, 343, 259, 171, 84, 57; Anal. Calcd for C₂₂H₁₉Br₂N₃O₂: C, 51.09; H, 3.70; N, 8.12. Found: C, 51.11; H, 3.72; N, 8.15.

4-Bromo-2-(7-bromo-4-(merpholin-4-yl)-5H-chromeno[2,3-d]pyrimidin-2-yl)phenol (4f).

Yellow crystals; mp 219 °C; ν_{\max} (KBr): 3046 (O-H), 1618, 1603 (C=N), 1216, 1176, 1106, 1018 (C-O), 898, 867 (C-Br) cm⁻¹; δ_H (500 MHz, CDCl₃): 3.41-3.43, 3.81-3.83 (8H, 2t, $J = 4.55$ Hz, CH₂ of morpholine), 3.90 (2H, s, CH₂), 6.75-6.77, 6.97-6.99, 7.28-7.30, 7.31-7.33, 8.36-8.37 (6H, 5m, aromatic), 12.95 (1H, brs, OH); δ_C (125 MHz): 25.57 (CH₂), 48.86, 66.81 (CH₂ of morpholine), 97.79, 111.00,

117.22, 118.93, 119.91, 120.19, 121.56, 131.45, 131.58, 135.77, 149.57, 159.65, 160.97, 163.96 (aromatic); MS: m/z: 521, 519, 517, 433, 431, 345, 268, 171, 86, 57; Anal. Calcd for C₂₁H₁₇Br₂N₃O₃: C, 48.58; H, 3.30; N, 8.09. Found: C, 48.55; H, 3.32; N, 8.12.

4-Methoxy-2-(7-methoxy-4-(piperidin-1-yl)-5H-chromeno[2,3-d]pyrimidin-2-yl)phenol (4g).

Light yellow crystals; mp 195 °C; ν_{\max} (KBr): 3064 (O–H), 1643, 1616 (C=N), 1213, 1169, 1089, 1030 (C–O) cm⁻¹; δ_{H} (500 MHz, CDCl₃): 1.69–1.82 (6H, m, 3CH₂ of piperidine), 3.44–3.46 (4H, m, 2CH₂ of piperidine), 3.83, 3.89 (6H, 2s, 2OMe), 3.92 (2H, brs, CH₂), 6.74–6.75, 6.80–6.83, 6.93–6.95, 6.99–7.01, 7.12–7.15, 7.96–7.97 (6H, 6m, aromatic), 13.10 (1H, brs, OH); δ_{C} (125 MHz): 24.77, 26.36, 49.98 (CH₂ of piperidine), 26.30 (CH₂), 56.09, 56.47 (2CH₃O), 97.54, 112.24, 113.36, 114.22, 118.22, 118.73, 118.87, 120.68, 121.22, 144.91, 152.56, 155.27, 156.66, 162.19, 164.97 (aromatic); MS: m/z: 419, 404, 387, 357, 304, 182, 91, 84; Anal. Calcd for C₂₄H₂₅N₃O₄: C, 68.72; H, 6.01; N, 10.02. Found: C, 68.71; H, 6.00; N, 10.05.

4-Methoxy-2-(7-methoxy-4-(morpholin-4-yl)-5H-chromeno[2,3-d]pyrimidin-2-yl)phenol (4h).

Light yellow crystals; mp 231 °C; ν_{\max} (KBr): 3044 (O–H), 1631, 1612 (C=N), 1262, 1199, 1154, 1106, 1021 (C–O) cm⁻¹; δ_{H} (500 MHz, CDCl₃): 3.50–3.52, 3.93–3.95 (8H, 2t, $J = 4.49$ Hz, 4CH₂ of morpholine), 3.58, 3.87 (6H, 2s, 2OCH₃), 3.89 (2H, s, CH₂), 6.52–6.55, 6.72–6.74, 6.77–6.78, 7.12–7.14, 8.33–8.35 (6H, 5m, aromatic), 13.41 (1H, brs, OH); δ_{C} (125 MHz): 26.36 (CH₂), 49.11, 67.13 (CH₂ of morpholine), 55.79, 55.94 (2OCH₃), 96.72, 101.70, 102.52, 107.20, 111.37, 111.72, 128.25, 128.94, 129.46, 130.94, 151.57, 160.10, 162.32, 165.04 (aromatic); MS: m/z: 421, 406, 389, 335, 303, 298, 182, 92, 86; Anal. Calcd for C₂₃H₂₃N₃O₅: C, 65.55; H, 5.50; N, 9.97. Found: C, 65.54; H, 5.52; N, 10.01.

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35. Crystallographic data for the structure of compound **4b** reported in this paper have been deposited with the Cambridge Crystallographi Data Center as supplementary publication No. CCDC 747366. These data can be obtained free of charge via www.ccdc.com.ac.uk/data_request/cif
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38. The experiments were performed using a microwave oven (ETHOS 1600, Milestone) with a power of 600 W specially designed for organic synthesis.