A "Neat" Synthesis of Substituted 2-Hydroxy-pyrido[1,2-a]pyrimidin-4-ones

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Abstract:

We report the synthesis of a series of substituted 2-hydroxy-pyrido[1,2-a]pyrimidin-4-ones through solvent-free condensation of of 2-aminopyridines and diethyl malonate. This method is contrasted with three reported general procedures for the preparation of these compounds, revealing the simple, "neat" synthesis conditions are suitable for a number of derivatives. Environmental, safety, and economic factors were considered in exploring this effective and robust synthetic method.

Keywords: Pyridopyrimidinones, Organic Synthesis, Heterocycles,

Introduction

Nitrogen-containing heterocycles are an indispensable component of many functional organic compounds.[1–3] Both saturated and unsaturated nitrogen-containing hetereocycles are not only ubiquitous in agrochemicals,[4] and natural products,[5] but they are critical moieties in many biologically active compounds for anticancer,[6] antibacterial,[7] and antiviral purposes,[8,9] conferring significant pharmacological value.[10] This is reflected in the number of FDA approved small molecule pharmaceuticals that contain *N*-heterocycles. A 2014 review stated that 59% of FDA approved pharmaceuticals contained at least one *N*-heterocycle,[11] with a more recent 2020 review revealing a significant jump to 75%.[12] Thus, methods to prepare and functionalize *N*-heterocycles remain an important part of organic synthesis research.

Pyrido[1,2-a]pyrimidin-4-ones (PPDs) are a specific class of *N*-heterocycle, with an aromatic bicyclic structure containing nitrogens at the 1 and 5 positions, as well as a carbonyl at the 4 position. They were first synthesized in 1924,[13] but have only been recognized as an important scaffold more recently.[14–18] Specific examples of approved active pharmaceutical ingredients based on a PPD pharmacophore include permirolast,[19] an anti-allergen medication, and risdiplam,[20] a treatment for spinal muscular atrophy (Figure 1). Additional studies indicate PPDs have potential as compounds for cancer treatment,[21] and diabetes.[22]

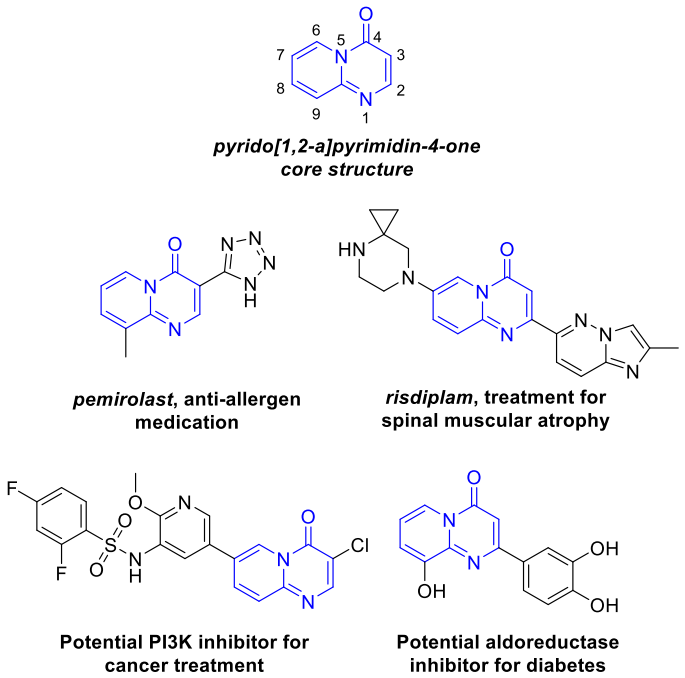


Figure 1: Current and potential active pharmaceutical ingredients containing a pyrido[1,2-a]pyrimidin-4-one subunit (highlighted in blue).[19–22]

Herein we evaluate three literature syntheses for substituted 2-hydroxy-PPDs, and report a simple and generally applicable solvent-free synthesis of these compounds using commercially available substituted 2-aminopyridines and diethyl malonate without any further purification. While numerous methods have been reported in the literature for a target 2-hydroxy-PPD, there remains few reports detailing procedures applicable to the synthesis of multiple 2-hydroxy-PPD molecules. In addition, the poor solubility and high polarity of these compounds means typical purification methods are often unsuitable. The method reported herein proceeds without the need for additional purification, providing substituted 2-hydroxy-PPDs with potential for further functionalization.

Materials and Methods

General Considerations: All reactions were performed using standard Schlenk techniques under N_2. All starting materials were purchased from commercial suppliers and used without further purification. All NMR spectra were acquired on either a Bruker AVANCE 300 MHz spectrometer or a Bruker AVANCE Neo 500 MHz spectrometer. All ^{1}H and ^{13}C NMR chemical shifts are calibrated to residual protio-solvents. All NMR spectroscopic data is processed using Bruker TopSpin 4.10. High-resolution mass spectrometry (HRMS) were obtained using a Bruker maXis Impact Quadrupole Time-of-Flight LC/MS System.

General procedure for synthesis of substituted 2-hydroxy-PPDs: A round bottom flask is charged with diethyl malonate (5 equiv) and the desired 2-aminopyridine derivative (1 equiv). A condenser fitted to an N_2 line was attached to the reaction flask. The reaction mixture was then brought to reflux using an aluminum heat block (T_{block} = 230 °C) and stirred for 3 h. At this point, the condenser was replaced with a distillation apparatus, and excess diethyl malonate was distilled from the flask at ambient pressure. The residual solid was suspended in refluxing hexanes for 1 h. The resulting solid was filtered, washed with diethyl ether, and dried *in vacuo*, giving the desired 2-hydroxy-PPD product as a solid. All NMR spectroscopy was conducted in d-DMSO.

Poor solubility of these compounds hindered the acquisition of ^{13}C NMR spectra with acceptable signal-to-noise in several cases. Notably, this is a common issue with 2-hydroxy-PPDs, with only one known compound reporting ^{13}C NMR chemical shifts.[23]

2-Hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (2a). 2-Aminopyridine **1a** (2.00 g, 21.25 mmol), was coupled with diethyl malonate (17.0 g, 106.25 mmol) to form **2a** as a brown solid. Isolated yield: 1.69 g, 49%. ^{1}H NMR (300MHz, $(CD_3)_2SO$, 292 K, ppm): δ 12.03 (s, 1H), 8.93 (dd, *J*

= 6.9, 0.7 Hz, 1H), 8.09 (dtd, *J* = 8.7, 6.9, 1.6 Hz, 1H), 7.41 (dt, *J* = 8.8, 1.3, 0.8 Hz, 1H), 7.33 (td, *J* = 6.9, 1.3 Hz, 1H), 4.97 (s, 1H).[24] HRMS: Cal'd for $C_8H_7N_2O_2$ [M+H]+: 163.05020; found: 163.04973.

2-Hydroxy-9-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (2b). 2-Amino-3-methylpyridine **1b** (2.00 g, 18.49 mmol), was coupled with diethyl malonate (14.8 g, 92.46 mmol) to form **2b** as a brown solid. Isolated yield: 1.34 g, 41%. ^{1}H NMR (500MHz, $(CD_3)_2SO$, 292 K, ppm): δ 11.48 (s, 1H), 8.80 (d, *J* = 7.0, 1.6 Hz, 1H), 7.84 (d, *J* = 6.9 Hz, 1H), 7.17 (t, *J* = 7.0 Hz, 1H), 5.40 (s, 1H), 2.44 (s, 3H). HRMS: Cal'd for $C_9H_9N_2O_2$ [M+H]+: 177.06585; found: 177.06539.

2-Hydroxy-8-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (2c). 2-Amino-4-methylpyridine **1c** (2.00 g, 18.49 mmol), was coupled with diethyl malonate (14.8 g, 92.46 mmol) to form **2c** as a brown solid. Isolated yield: 1.50 g, 46%. ^{1}H NMR (300MHz, $(CD_3)_2SO$, 292 K, ppm): δ 11.97 (s, 1H), 8.85 – 8.77 (d, 1H), 7.24 – 7.13 (m, 2H), 4.84 (s, 1H), 2.46 (s, 3H).[25] ^{13}C NMR (126 MHz, $(CD_3)_2SO$, 292 K, ppm): δ162.9, 155.8, 154.1, 147.3, 128.3, 117.7, 115.0, 80.8, 21.1. HRMS: Cal'd for $C_9H_9N_2O_2$ [M+H]+: 177.06585; found: 177.06602.

6-Methyl-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (2d). 2-amino-6-methylpyridine **1d** (2.00 g, 18.49 mmol), was coupled with diethyl malonate (14.8 g, 92.46 mmol) to form **2d** as a brown solid. Isolated yield: 1.05 g, 32%. ^{1}H NMR (300MHz, $(CD_3)_2SO$, 292 K, ppm): δ 10.59 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.67 (t, *J* = 7.9 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 1H), 3.60 (s, 1H), 2.41 (s, 3H). HRMS: Cal'd for $C_9H_9N_2O_2$ [M+H]+: 177.06585; found: 177.06559.

6-Chloro-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (2e). 2-Amino-6-chloropyridine **1e** (2.00 g, 15.56 mmol), was coupled with diethyl malonate (12.46 g, 77.78 mmol) to form **2e** as a brown solid. Isolated yield: 1.07 g, 35%. ^{1}H NMR (300MHz, $(CD_3)_2SO$, 292 K, ppm): δ 10.98 (s, 1H),

8.04 (d, *J* = 8.2 Hz, 1H), 7.86 (t, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 7.8, 0.7 Hz, 1H), 3.63 (s, 1H). HRMS: Cal'd for $C_8H_6ClN_2O_2$ [M+H]+: 197.01123; found: 197.01049.

8-Chloro-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (2f). 2-amino-4-chloropyridine **1f** (2.00 g, 15.56 mmol), was coupled with diethyl malonate (12.46 g, 77.78 mmol) to form **2f** as a brown solid. Isolated yield: 1.43 g, 47%. ^{1}H NMR (300MHz, $(CD_3)_2SO$, 292 K, ppm): δ 12.02 (s, 1H), 8.87 (d, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 2.2 Hz, 1H), 7.36 (dd, *J* = 7.5, 2.3 Hz, 1H), 5.15 (s, 1H). ^{13}C NMR (126 MHz, $(CD_3)_2SO$, 292 K, ppm): δ 165.3, 156.5, 149.1, 145.4, 130.0, 118.3, 116.1, 82.3. HRMS: Cal'd for $C_8H_6ClN_2O_2$ [M+H]+: 197.01123; found: 197.01035.

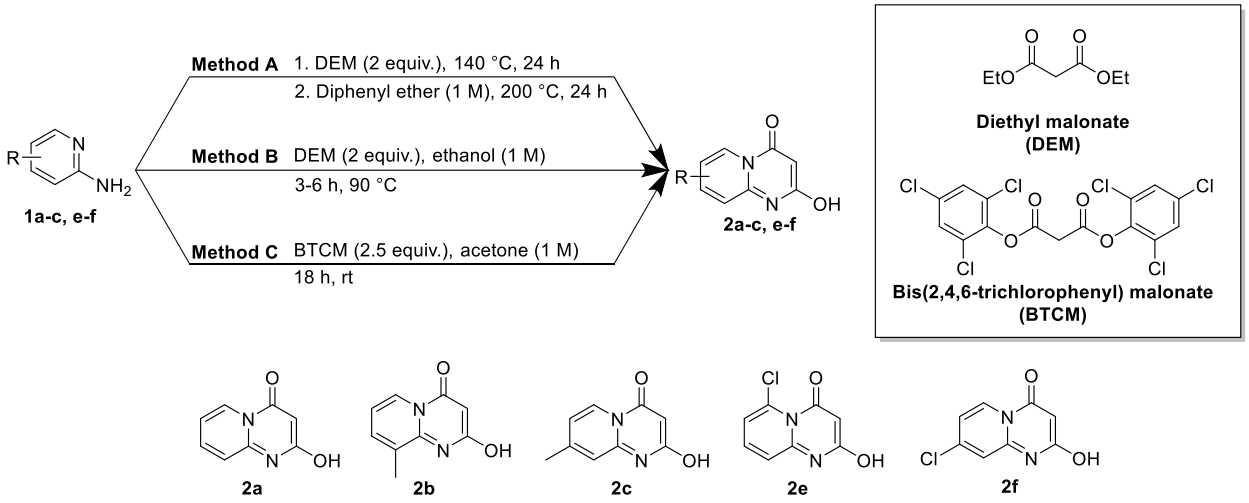
8-Bromo-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (2g). 2-amino-4-bromopyridine **1g** (1.00 g, 5.78 mmol), was coupled with diethyl malonate (4.63 g, 28.90 mmol) to form **2g** as a brown solid. Isolated yield: 0.78 g, 56%. ^{1}H-NMR (300MHz, $(CD_3)_2SO$, 292 K, ppm): δ 12.00 (s, 1H), 8.77 (d, *J* = 7.4 Hz, 1H), 7.64 (d, *J* = 2.1 Hz, 1H), 7.47 (dd, *J* = 7.4, 2.1 Hz, 1H), 5.15 (s, 1H). HRMS: Cal'd for $C_8H_6BrN_2O_2$ [M+H]+: 240.96072; found: 240.96112.

6-Fluoro-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (2h). 2-Amino-6-fluoropyridine **2h** (1.00 g, 8.92 mmol), was coupled with diethyl malonate (7.14 g, 44.60 mmol) to form **2h** as a brown solid. Isolated yield: 0.42 g, 26%. ^{1}H-NMR (500MHz, $(CD_3)_2SO$, 292 K, ppm): δ 10.85 (s, 1H), 8.16 – 7.72 (m, 2H), 7.04 – 6.65 (m, 1H), 3.64 (s, 1H). HRMS: Cal'd for $C_8H_6FN_2O_2$ [M+H]+: 181.04078; found: 181.04141.

Results and Discussion

As part of our efforts to develop new catalytic methods for heterocycle functionalization, we sought a versatile and robust method to access various 2-hydroxy-PPDs. When synthesizing

the otherwise unsubstituted 2-hydroxy-PPD **2a**, literature reports are consistent that using 2-aminopyridine and a malonate derivative to effect two successive amidation reactions is an efficient method.[21,24–28] However, in our hands we found inconsistent results when we applied these methods to access 2-hydroxy-PPDs beyond the scope explored in the original report. With a goal to establish conditions that could be broadly applied to a library of commercially available 2-aminopyridine building blocks, we began by evaluating three methods (**A**-**C**) to access five 2-hydroxy-PPDs (**2a**-**c**, **2e**, **2f**; Figure 2).



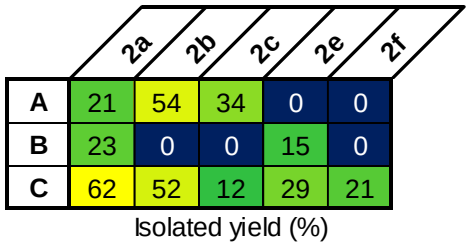


Figure 2: Three reported methods (**A**-**C**) applied to the synthesis of five substituted 2-hydroxy-PPDs; reactions performed at 2.0 g scale (mass of 2-aminopyridine substrate).

Initially, we explored a reported two-step method for the formation of **2a**, similar to **Method A** shown above (step 2 reaction temperature = 160 °C, and open to atmosphere);[24] however, we observed inconsistent results with respect to yield of desired product. A consistent issue when performing the second step is little/no cyclization to generate **2a**. To overcome this, we modified the procedure to run under N_2 (Figure S4 in Supplementary Info) and then also at an elevated reaction temperature. We only observe appreciable cyclization when performing the second step ≥200 °C (Figure S5 in Supplementary Info). With these modifications, **Method A** was then applied to convert all five 2-aminopyridines. While this method provided sufficient yield for the unsubstituted (**2a**) and tolyl derivatives (**2b**-**2c**), no halide containing species (**2e**-**2f**) was successfully synthesized using this method. Furthermore, the use of high-boiling diphenyl ether as solvent (b.p. = 258 °C) complicated isolation once the reaction was complete.

Method B, which uses ethanol as a polar protic solvent at reflux, was then attempted.[26] However, we again observed incomplete or no cyclization, with the initial monoamidation product as the major/sole species. While we were able to successfully isolate the unsubstituted (**2a**) and the 6-chloro product (**2e**), **Method B** was not able to furnish the other three 2-hydroxy-PPD products.

Method C, which employs a more elaborate malonate ester substrate bis(2,4,6-trichlorophenyl)malonate (BTCM), was the most broadly successful approach.[17] Originally reported by Kappe,[29] this procedure enables the difficult second amidation by replacing the ethyl esters with activated 2,4,6-trichlorophenol esters; the higher reactivity of BTCM also enables the cyclization to occur at room temperature. However, BTCM is considerably more expensive and mass inefficient compared to diethyl malonate. Its synthesis uses phosphorus oxychloride ($POCl_3$)

to activate malonic acid. $POCl_3$ is highly hazardous, with safety incidents involving reaction quenching reported in the literature.[30] While **Method C** does provide the best results across the five 2-hydroxy-PPD targets, we sought a more economical and safe method to access these compounds that is consistent with the principles of green chemistry.[31]

Our experience with **Methods A**-**C** inspired us to explore an alternative pathway for preparation of 2-hydroxy-PPDs. With respect to **Method A**, elevated temperatures (>200 °C) were required to facilitate the second amidation. Rather than use diphenyl ether as a solvent for the second amidation, we simply used a larger excess of diethyl malonate (5 equiv) and directly heated the reaction mixture to high temperature. Notably, the original synthesis of **2a**, reported by Chichibabin, employed a similar approach of using malonate esters as both reactant and solvent.[13]

With reactor block temperatures of 230 °C (diethyl malonate b.p. = 199 °C), we standardized the reaction time to 3 h to compare reactivity across the set of 2-aminopyridines (**1a**-**h**). This also enabled reaction set-up, execution, and clean-up to be completed within a single day, and avoided the need to run high temperature reactions unattended (i.e. overnight). We do observe improved yield of **2a** with a longer reaction time of 18 h (78% versus 49%). Diethyl malonate proves to be an effective solvent as well as reactant, providing synthetically useful yields of 2-hydroxy-PPDs **2a**-**h** on (multi)gram scale (Figure 3). This includes halogenated derivatives **2e**-**h**, which provide synthetic handles for further functionalization via S_NAr or metal-catalyzed coupling. Notably, we do observe diminished yield in the case of **2d**, **2e**, and **2h**, all of which have a substituent at the 6 position. This is likely due to increased steric hindrance adjacent to the pyridyl nitrogen slowing the rate of cyclization. Importantly, on larger scale the excess diethyl

malonate distilled at the end of the reaction could potentially be reused in future experiments, significantly improving the overall mass efficiency of this process.

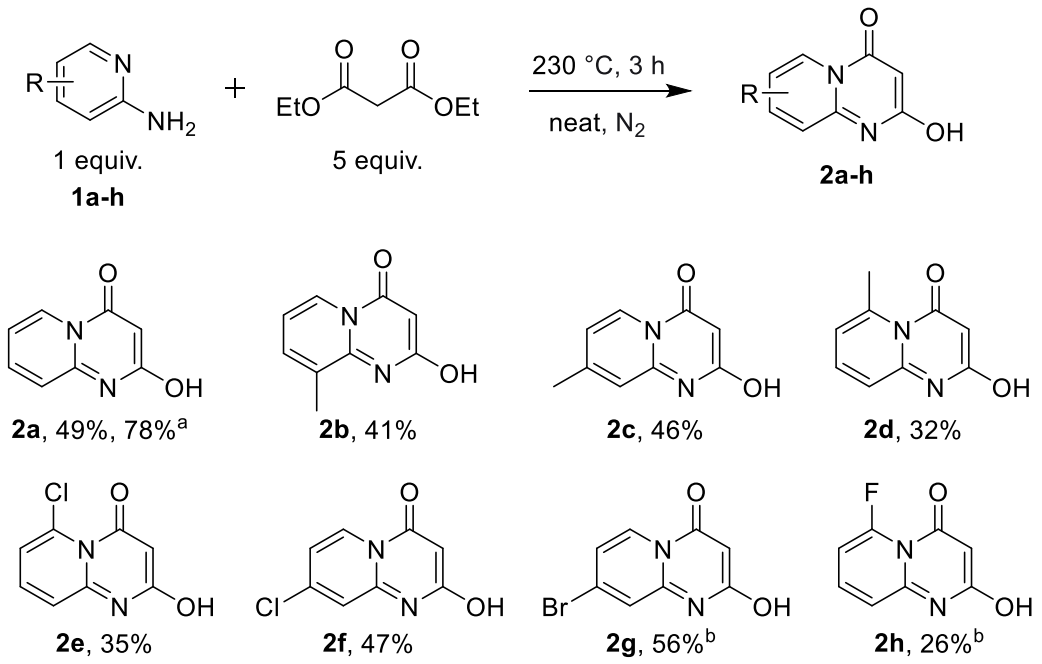
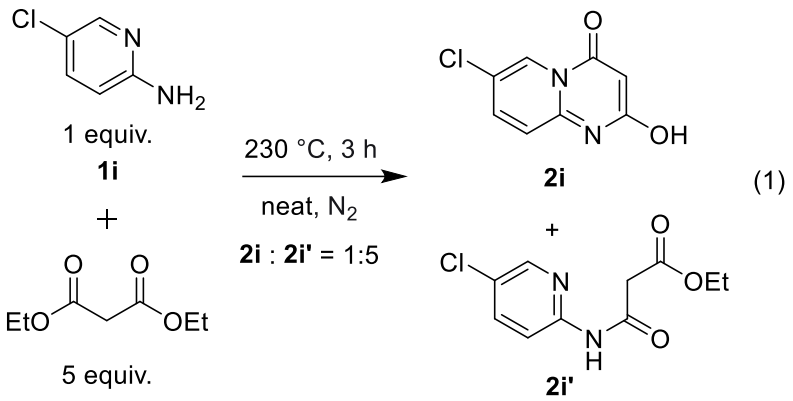


Figure 3: Synthesis of **2a**-**h** from **1a**-**h** using diethyl malonate. All reactions performed at 2.0 g, scale relative to (substituted) 2-aminopyridine, isolated yields. [a]18 h reaction time. [b]1.0 g scale.

Finally, we do observe some limitations of the current method. In an attempt to prepare 7-chloro-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**2i**) from the corresponding 2-amino-5-chloropyridine (**1i**), we observe an incomplete reaction and isolation of a mixture of **2i** and the intermediate amide **2i'** in a 1:5 molar ratio (eq. 1). Attempts to separate these materials was unsuccessful.



(1)

Conclusions

By exploiting the use of diethyl malonate as both solvent and reactant, we have realized the synthesis of substituted 2-hydroxy-PPDs, several of which are new compounds. By evaluating three reported methods and taking inspiration from Chichibabin's original preparation, we have demonstrated that neat reaction conditions are suitable as a generally applicable method. This procedure provides synthetically useful yields in a short turnaround time, and is highly mass efficient. As the importance of nitrogen-containing heterocycles and PPDs in particular continues to grow, robust methods to access key scaffolds will remain critical.

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