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Efficient Synthesis of Uracil-Derived Hexa- and Tetrahydropyrido[2,3-*d*]pyrimidines

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A reaction of 6-amino-1,3-dimethyluracil with 3-(hetero)-aroylacrylic acids and their methyl esters leads to hexahydropyrido[2,3-*d*]pyrimidine-5-carboxylic acids or the corresponding methyl esters in high to excellent yields. One-pot oxidation of the acid derivatives with CAN is accompanied by decarboxylation to give tetrahydropyrido[2,3-*d*]pyrimidines, while oxidation with bromine resulted in the formation of tetrahydropyrido[2,3-*d*]pyrimidine-5-carboxylic acids. The aromatization of methyl hexahydropyrido[2,3-*d*]pyrimidine-5-carboxylates was achieved by K_2CO_3-mediated air oxidation under ambient conditions.

Introduction

In recent decades, heteroannulated pyrimidines have received considerable attention. This interest is a result of their various pharmacological activities. For example, uracil-derived pyrido[2,3-*d*]pyrimidines have a range of biological properties, such as phosphodiesterase 2 (PDE 2) inhibition,[1a] or antihypertensive,[1b,1c] cardiotonic,[2] analgesic,[3a] antiviral,[3b] anti-inflammatory,[4] antimicrobial,[5,6] or anticancer activities[7,8] (Figure 1). Therefore, the synthesis of diverse structures belonging to this class of compounds is important.

Several synthetic approaches for the construction of the pyrido[2,3-*d*]pyrimidine scaffold have been reported in which 6-aminouracils react with different types of 1,3-dielectrophiles, such as α,β-unsaturated carbonyl compounds,[9–12] electron-rich enamines,[13] Meldrum's acid derivatives,[14] compounds with a reactive methylene group, or Mannich adducts.[15] They have also been synthesized by multicomponent reactions.[16–20]

3-(Hetero)aroylacrylic acids or esters are reactive 1,3-dielectrophiles that are commonly used as versatile building blocks for diversity-oriented synthesis.[21–27] They are commercially available, or can be easily obtained by a recently reported procedure.[28] However, to the best of our knowledge, they have never been used for the synthesis of uracil-derived pyrido[2,3-*d*]pyrimidine-5-carboxylic acids or their esters.[29]

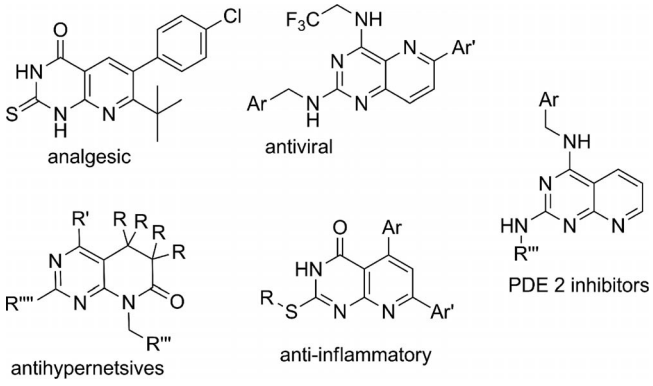

Figure 1. Various biologically active pyrido[2,3-*d*]pyrimidines.

In this paper, we report the synthesis of tetra- and hexahydro-7-arylpyrido[2,3-*d*]pyrimidines bearing a 5-carboxylic acid or ester moiety, by condensation of 3-aroylacrylic acids with 1,3-dimethyl-6-aminouracil. This approach is straightforward, metal-free, and atom-efficient.

Results and Discussion

Initially, *p*-methoxybenzoylacrylic acid (**1a**) was treated with an equimolar amount of 1,3-dimethyl-6-aminouracil (**2**) in DMF at room temp. for 12 h (Table 1, Entry 1) and, to our delight, a new compound was formed. NMR spectroscopic analysis of the crude mixture showed remaining

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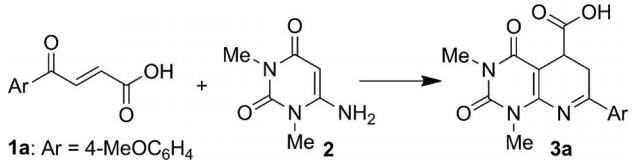
starting materials and also a new hexahydropyrido[2,3-*d*]-pyrimidine derivative **3a**, formed in 35% yield.

Table 1. Optimization of the reaction conditions.[a]



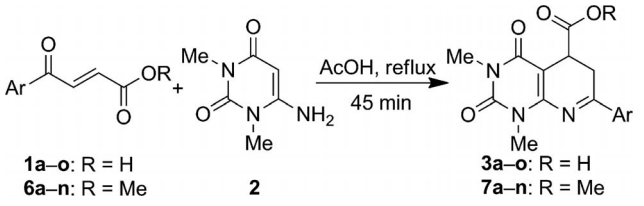
Entry	Solvent	*T*/*t*	Yield [%][b]
1	DMF	r.t./12 h	35
2	DMF	60 °C/5 h	42
3	EtOH	60 °C/5 h	50
4	MeOH	60 °C/5 h	54
5	CH_3CN	60 °C/5 h	44
6	1,4-dioxane	60 °C/5 h	40
7[c]	DMF	r.t./12 h	<5
8[d]	DMF	r.t./12 h	<5
9[e]	DMF	r.t./30 min	71
10	AcOH	reflux/45 min	99 (95)[f]

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), solvent (0.5 mL). [b] Yields based on NMR spectroscopy using mesitylene as internal standard. [c] Et_3N (1 equiv.) was used. [d] K_2CO_3 (1 equiv.) was used. [e] HCl (1 M aq.; 20 mol-%) was used. [f] Isolated yield.

Inspired by this result, different reaction conditions were screened. Altering the reaction temperature in the same solvent gave no appreciable improvements in the outcome of the reaction (Table 1, Entry 2). Heating in polar protic solvents, such as alcohols, or in polar aprotic solvents, such as acetonitrile or 1,4-dioxane, resulted in the formation of the target compound, but only in moderate yields (Table 1, Entries 3–6). Additionally, NMR spectroscopic analysis indicated the formation of the dehydrogenated product, presumably because of air present under the reaction conditions. The use of bases such as Et_3N and K_2CO_3 (Table 1, Entries 7 and 8) was totally unsuccessful, due to salt formation with the aroylacrylic acids. On the other hand, when we used aqueous HCl as a catalyst in DMF, after 3 h at room temperature, we obtained hexahydropyrido[2,3-*d*]pyrimidine derivative **3a** in 71% yield (Table 1, Entry 9). However, many by-products were formed under these conditions, which made purification of the target molecule problematic. These results suggested that acetic acid could be used as a solvent. This idea was also supported by studies of the Bohlmann–Rahtz reaction,[11d] which were extended by Bagley and co-authors[12b,12c] for the formation of related pyrido[2,3-*d*]pyrimidines. Surprisingly, under these conditions, the desired hexahydropyrido[2,3-*d*]pyrimidine derivative **3a** was formed in 95% isolated yield (Table 1, Entry 10). The product was isolated as a single compound requiring no further purification by simple dilution of the reaction mixture with ice-cold water and filtration of the resulting solid.

Subsequently, these optimized conditions were used for a series of reactions of 3-(het)aroylacrylic acids **1b**–**o** with 1,3-dimethyl-6-aminouracil, and target compounds **3b**–**o** were formed in high to excellent yields (Table 2).

Table 2. Synthesis of 1,3-dimethyl-2,4-dioxo-7-aryl-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyrimidine-5-carboxylic acids **3a**–**o** and methyl esters **7a**–**n**.[a]

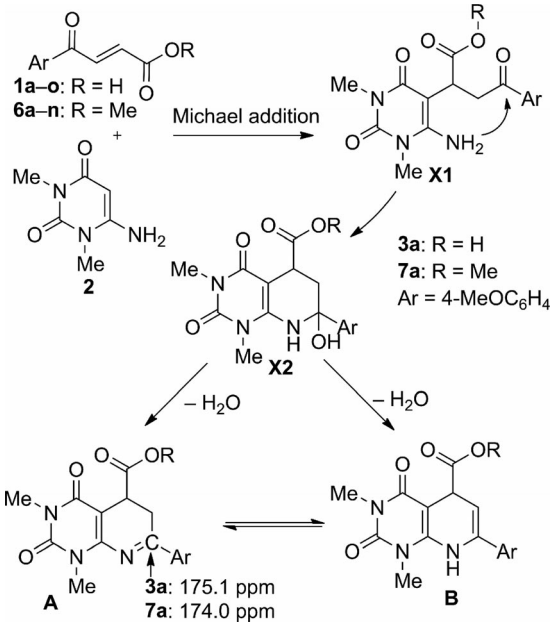


Entry	Ar	Product	Yield [%][b]
1	4-methoxyphenyl-	**3a**	95
2		**7a**	90
3	phenyl-	**3b**	94
4		**7b**	80
5	4-fluorophenyl-	**3c**	98
6		**7c**	89
7	4-bromophenyl-	**3d**	98
8		**7d**	86
9	5-bromothienyl-	**3e**	95
10		**7e**	95
11	2-bromophenyl-	**3f**	90
12		**7f**	92
13	3,4,5-trimethoxyphenyl-	**3g**	94
14		**7g**	90
15	4-MeS-phenyl-	**3h**	93
16		**7h**	84
17	2,4-difluorophenyl-	**3i**	95
18		**7i**	90
19	perfluorophenyl-	**3j**	89
20		**7j**	95
21	3-methoxyphenyl-	**3k**	90
22		**7k**	85
23	4-$MeSO_2$-phenyl-	**3l**	97
24		**7l**	96
25	2,4-dichlorophenyl-	**3m**	95
26		**7m**	89
27	3,4-difluorophenyl-	**3n**	87
28		**7n**	87
29	3-CF_3-phenyl-	**3o**	85

[a] Reaction conditions: **1** (1 equiv., 1 mmol), **2** (1 equiv., 1 mmol), AcOH (1 mL). [b] Isolated yields.

To expand the scope of our method, we also used the methyl esters of the 3-aroylacrylic acids, synthesized by esterification of acids **1a**–**o**. The corresponding hexahydropyrido[2,3-*d*]pyrimidines (i.e., **7a**–**n**) were smoothly obtained in high yields under the optimized conditions (Table 2). The comparable yields of the methoxycarbonyl products (i.e., **7a**–**n**) show that there is no significant difference between the reactivity of the acids and the esters.

The proposed mechanism is shown in Scheme 1. Based on literature data, we propose that the α-position is the most electrophilic center of the 3-aroylacrylic acids, and that C-5 is the most nucleophilic position in 6-aminouracil. Most probably, an initial Michael-type addition leads to adduct **X1**, and then nucleophilic attack of the 6-amino group onto the carbonyl group results in the formation of intermediate **X2**. Finally, two possible pathways of dehydration could give the product either in imine form **A** or enamine form **B**.



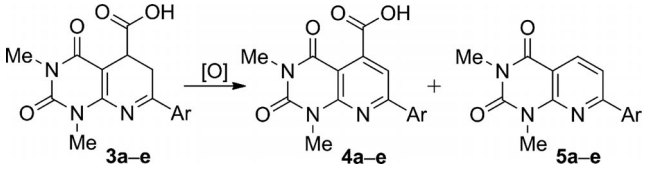
Scheme 1. Plausible mechanism for the formation and imine/enamine tautomerism of hexahydropyrido[2,3-*d*]pyrimidines **3** and **7**.

For the structural elucidation of previously unknown hexahydropyrido[2,3-*d*]pyrimidines **3a**–**o** and **7a**–**n**, a full assignment of their ^{1}H and ^{13}C NMR spectra was performed by using DEPT, HSQC, and HMBC in $CDCl_3$. Hexahydropyrido[2,3-*d*]pyrimidines **3a**–**o** and **7a**–**n** exist mainly as their imine forms (i.e., **A**) in $CDCl_3$, whereas in [D_6]DMSO, their enamine form (i.e., **B**) predominates (Scheme 1). This was clear from the correlation of the key carbon signal of C-7 with the neighboring aliphatic -CH_2- and -CH- protons, as well as with protons of the aromatic ring.

The imino form could easily be identified by a ^{13}C NMR DEPT experiment, due to the presence of a 6-CH_2 carbon signal (at δ = 26.0 ppm for compound **3a**). For the enamine form, a pair of doublets due to protons 5-H and 6-H (δ = 4.2 and 5.2 ppm, respectively, J = 5.0 Hz for compound **3b**) was observed in the ^{1}H NMR spectrum. It was found that the the tautomeric ratio is determined by the substituent. For example, phenyl derivative **3b** is present in form **B** in both solvents, whereas compound **3h** exists in [D_6]DMSO as a tautomeric mixture of **A** and **B** forms in a ratio of 1:4 (see Supporting Information for 2D NMR spectra). A similar observation was made for ester derivatives **7b** and **7h**.

For the purposes of further functionalization, we investigated the ease of oxidation of hexahydropyrido[2,3-*d*]pyrimidine **3a** into its tetrahydro analog **4a** (Scheme 2).

An initial attempted oxidation with air by using *N*-hydroxyphthalimide (NHPI) and $Co(OAc)_2$ in refluxing MeCN[30] led only to the recovery of starting material **3a**. When *N*-bromosuccinimide (NBS) or bromine was used in refluxing AcOH or $CHCl_3$, a mixture of the desired compound (i.e., **4a**) and decarboxylated derivative **5a** was obtained. Conversely, when bromine was used in refluxing dichloromethane, and the reaction was worked up with KOH and HCl (aq.), pure acid **4a** was isolated in 75% yield.

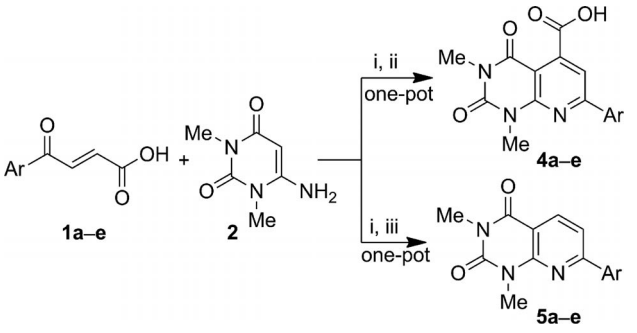


Scheme 2. Oxidation products of hexahydropyrido[2,3-*d*]pyrimidines **3**.

For complete decarboxylation, cerium ammonium nitrate (CAN) was successfully used in water/acetone (1:9) under ambient conditions to give decarboxylated product **5a** exclusively in 74% yield. The use of iodine pentoxide in water also led to oxidative decarboxylation, but gave a much lower yield.

Having found optimized reaction conditions, we developed a one-pot synthesis of two arrays of compounds **4a**–**e** and **5a**–**e**, which were obtained in good to excellent isolated yields (Table 3).

Table 3. Synthesis of 7-aryl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-5-carboxylic acids **4a**–**e** and 1,3-dimethyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **5a**–**e**.[a]



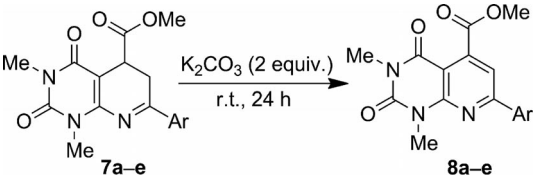
Entry	Ar	Product	Yield [%][b]
1	4-methoxyphenyl	**4a**	75
2		**5a**	74
3	phenyl	**4b**	67
4		**5b**	75
5	4-fluorophenyl	**4c**	76
6		**5c**	96
7	4-bromophenyl	**4d**	75
8		**5d**	94
9	5-bromothienyl	**4e**	73
10		**5e**	86

[a] Reaction conditions: (i) **1** (1 equiv., 1 mmol), **2** (1 equiv., 1 mmol), AcOH (1 mL), reflux, 45 min; (ii) Br_2 (1.2 mmol)/CH_2Cl_2, reflux, 3 h; KOH (4 mmol), *i*PrOH, reflux, 30 min, then HCl (aq.). (iii) CAN (2.5 mmol), acetone/water (9:1; 15 mL), room temp., 3 h. [b] Isolated yields.

In an attempt to stabilize the enamine form we performed alkylation at the N-8 position of the (methoxycarbonyl)hexahydropyrido[2,3-*d*]pyrimidine derivative **7a** with benzyl bromide. We used K_2CO_3 (2.0 equiv.) as a base, and conducted the reaction in acetone at room temperature for 24 h. To our great surprise, we obtained no alkylation product, but only aromatic tetrahydropyrido[2,3-*d*]pyrimidine derivative **8a**, which was formed in excellent yield. To be certain, we repeated this reaction without benzyl bromide

and with other esters **7b**–**e**, and we obtained only oxidized products **8a**–**e** in high yields (Table 4, Entries 1–5).

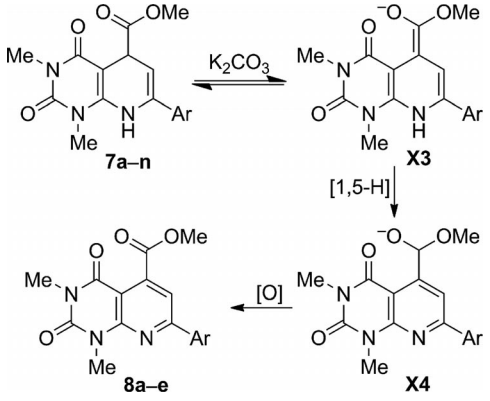
Table 4. Synthesis of methyl 7-aryl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-5-carboxylates **8a**–**e**.[a]



Entry	Ar	Product	Yield [%][b]
1	4-methoxyphenyl	**8a**	94
2	phenyl	**8b**	92
3	4-fluorophenyl	**8c**	96
4	4-bromophenyl	**8d**	94
5	5-bromothienyl	**8e**	90

[a] Reaction conditions: (i) **7** (1 equiv., 1 mmol), K_2CO_3 (2 equiv., 2 mmol), acetone (5 mL). [b] Isolated yields.

We believe that this process occurs by a sequence of α-deprotonation, formation of intermediate **X3**, which is stabilized by conjugation, a 1,5-hydrogen shift promoted by aromatization, and finally air oxidation of the resulting hemiacetal **X4** to give the product (Scheme 3). This protocol appears to be superior to other typically used conditions, and deserves further investigation.



Scheme 3. Plausible mechanism for the K_2CO_3-mediated aerial oxidation of hexahydropyrido[2,3-*d*]pyrimidines **7**.

Finally, to demonstrate the utility of our method, we prepared compound **5b**, which has been described as a herbicide agent for the selective control of unwanted plant growth.[31] Pyrido[2,3-*d*]pyrimidine derivative **5b** can be easily accessed from readily available starting materials in a one-pot approach with an overall yield of 75%.

Conclusions

We have developed a new approach for the synthesis of pyrido[2,3-*d*]pyrimidine-5-carboxylic acids and their corresponding methyl esters. The reaction of 3-(hetero)aroylacrylic acids or their methyl esters with 6-amino-1,3-dimethyluracil leads to the formation of hexahydropyrido[2,3-*d*]-pyrimidines in high to excellent yields. The further oxidation of these acid products in a one-pot fashion gives the aromatized compounds or the products of oxidative decarboxylation, depending on the oxidative system used. Remarkably, efficient air oxidation of the corresponding esters was demonstrated to occur in the presence of K_2CO_3 in acetone at room temperature.

Experimental Section

General Methods: 3-(het)aroylacrylic acids **1a**–**o** were prepared by a slightly modified previously published procedure.[28] Methyl esters **6a**–**o** were prepared by an unmodified previously published procedure.[32] All other chemicals were obtained from commercial sources and used without further purification. All solvents were used as received. Mass spectra were recorded with a Varian 1200 L GC–MS instrument by using the direct exposure probe (DEP) method with EI at 70 eV. High-resolution mass spectrometry was performed with a KRATOS MS50TC instrument. NMR spectra were recorded with Varian Mercury VX 200, Bruker AMX 300, Bruker AMX 400, or Bruker AMX 600 spectrometers by using [D_6]-DMSO or $CDCl_3$ as solvent and TMS as an internal standard. All 2D NMR experiments were performed by using a Bruker AMX 400 spectrometer. Microwave-assisted reactions were carried out in a Milestone MicroSYNTH Labstation apparatus in 35 mL vials. Melting points were determined with a Kofler apparatus.

General Procedure for the Microwave-Assisted Synthesis of 3-(Het)-aroylacrylic Acids 1a–o: Glyoxylic acid monohydrate (37 mmol), acetic anhydride (39 mmol), and ytterbium triflate (0.57 g, 0.925 mmol) were mixed, and 20 mL of this mixture was put into a microwave reaction vial and stirred at room temperature for 10 min. Then, an acetophenone (37 mmol) and glacial acetic acid (6 mL) were added. The reaction vial was sealed, and the mixture was subjected to microwave irradiation under the conditions specified in Table 1 (initial power 150 W). The internal pressure was not higher than 5–6 bar during the experiment. After cooling, the solvent was evaporated. The residue was washed with ice-cold water (50 mL) by decantation or on a filter. The crude product was dissolved in K_2CO_3 (25% aq.) and washed with CH_2Cl_2 (5 × 60 mL). Then, the aqueous phase was cooled in an ice-bath and acidified with HCl (concentrated aq.). The solid product was filtered off, washed with water, and dried in air at 50 °C for 24 h. The acids were checked by ^{1}H NMR spectroscopy, and then used for further reaction without any additional purification; however, in some cases (**1g**, **1h**, **1k**), recrystallization from EtOH/H_2O was carried out.

General Procedure for the Preparation of 3-(Het)aroylacrylic Acid Methyl Esters 6a–n: 3-(Het)aroylacrylic acid **1a**–**n** (10 mmol) and dimethyl sulfate (12 mmol) were dissolved in DMF (5 mL), and then K_2CO_3 (10 mmol) was added to the stirred mixture. The resulting mixture was stirred at room temp. (it is important to prevent overheating to temperatures above 25 °C) for 8 h. Then the mixture was poured into ice-cold water, and the solid precipitate was filtered off and dried in air at 50 °C for 24 h to obtain a crude product (95–97%).

General Procedure for the Preparation of 7-Aryl-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyrimidine-5-carboxylic Acids 3a–o: A mixture of 6-amino-1,3-dimethyluracil (1.0 mmol) and a 3-aroylacrylic acid (1.0 mmol) in acetic acid (1 mL) was stirred at reflux for 45 min. The solvent was removed under reduced pressure, and the solid residue was suspended in cold water (50 mL), filtered, washed with cold water, and dried in air at 50 °C for 24 h to give

dihydropyridine derivatives **3a**–**o**. No additional purification was required.

General Procedure for the Preparation of Methyl 1,3-Dimethyl-2,4-dioxo-7-aryl-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyrimidine-5-carboxylates 7a–n: The same procedure as for compounds **3a**–**o** was used. Crude products **7a**–**n** were recrystallized from *i*PrOH/hexane mixtures.

General Procedure for the One-Pot Preparation of 7-Aryl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-5-carboxylic Acids 4a–e: A mixture of 6-amino-1,3-dimethyluracil (1.0 mmol) and a 3-aroylacrylic acid (1.0 mmol) in acetic acid (1 mL) was stirred at reflux for 45 min. The solvent was removed under reduced pressure, and then CH_2Cl_2 (10 mL) and Br_2 (1.2 mmol) were added sequentially. The resulting mixture was stirred at reflux for 3 h. The CH_2Cl_2 was removed under reduced pressure. 1-Propanol (4 mL) and KOH (3.00 mmol) were added sequentially to the residue, and the resulting mixture was heated at reflux for 30 min. The reaction mixture was allowed to cool, then the solid precipitate was filtered off and washed with 1-propanol (10 mL). The salt was dried on the filter, then it was mixed with brine (10 mL), and the mixture was acidified with HCl (10% aq.) until neutral pH was reached. A precipitate formed, which was filtered off, washed with cold water (2× 5 mL), and dried in air at 50 °C for 24 h. No additional purification was required.

General Procedure for the One-Pot Preparation of 1,3-Dimethyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones 5a–e: A mixture of 6-amino-1,3-dimethyluracil (**2**) (1.0 mmol) and a 3-aroylacrylic acid (1.0 mmol) in acetic acid (1 mL) was stirred at reflux for 45 min. Then the acetic acid was removed under reduced pressure. The residue was stirred with CAN (2.5 mmol) in water/acetone (1:9; 15 mL) at room temp. for 3 h. The solvent was removed under reduced pressure, and the residue was washed with water (50 mL) and methanol, and dried in air at 50 °C for 24 h to give pyridine derivatives **5**. No additional purification was required.

General Procedure for the Preparation of Methyl 7-Aryl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-5-carboxylates 8a–e: A methyl 7-aryl-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyrimidine-5-carboxylate **7a**–**n** (1.0 mmol) and K_2CO_3 (1.0 mmol) were stirred in acetone (5 mL) at room temp. for 24 h. The solvent was removed, and the solid residue was suspended in cold water (50 mL), filtered, and washed with cold water to give a crude product, which was dried in air for 24 h. No additional purification was required.

Supporting Information (see footnote on the first page of this article): Characterization of all new compounds, including m.p., MS, and IR data, correlation investigation, and ^1H and ^{13}C NMR spectra.

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