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L-Proline catalyzed synthesis of densely functionalized pyrido[2,3-*d*]pyrimidines via three-component one-pot domino Knoevenagel aza-Diels–Alder reaction

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ABSTRACT

Highly functionalized hitherto unreported pyrido[2,3-*d*]pyrimidines have been concisely synthesized in good yields via L-proline catalyzed one-pot three-component domino coupling of 6-amino-1,3-dimethyluracil, aldehydes, and dialkyl acetylenedicarboxylates under mild conditions for the first time. The MCR process involves Knoevenagel condensation followed by [4+2] cycloaddition reaction. No co-catalyst or activator is required for this MCR. The molecular structures of two representative pyrido[2,3-*d*]pyrimidines **4a** and **4h** were confirmed by single crystal X-ray diffraction.

1. Introduction

Organic compounds containing pyrimidine scaffold as a core unit are known to exhibit various biological and pharmaceutical activities,[1a–c] such as antiviral,[1d] antibacterial,[1e,f] antitumor,[1g] anti-inflammatory,[1h] antifungal,[1i,j] and antileishmanial agent.[1k] Consequently, the synthesis of such heterocyclic scaffolds is assigned as one of the most fertile areas for both synthetic and medicinal chemists. Uracil derivatives[2] are versatile building blocks for the synthesis of nitrogen-containing heteroaromatic species of biological importance.[3] Pyrido[2,3-*d*]pyrimidines are a class of naturally occurring fused uracils occupying a special place in synthetic organic as well as in medicinal chemistry. They have received enormous interest over the past years due to their wide range of pharmacological activities, such as antibacterial,[4a] antitumor,[4b,c] antihypertensive,[4d] cardiotonic,[4d,e] bronchiodilator,[4f] vasodilator,[4g] antialergic,[4h] antimalarial,[4i] analgesic,[4j,k] antifungal,[4l] and CNS depressant[4m] properties. Moreover, appropriately functionalized pyrido[2,3-*d*]pyrimidines (Chart 1) exhibit variety of promising pharmacological activities, such as potent inhibitor of dihydrofolate reductase(**I**),[5a] in treatment of diarrhea (**II**),[5b] specific inhibitor of cyclin dependent kinase 4 (**III**),[5c] and induces apoptosis of K562 cells.[5d] Compounds having pyrido[2,3-*d*]pyrimidine as a central core unit have also been identified as a new class of fibroblast growth factor receptor (FGFR3) tyrosine kinase inhibitors.[5e,f] 4-Amino-5,7-disubstituted pyridopyrimidines are potent non-nucleoside inhibitors of adenosine kinase (AK).[6] Therefore, much effort has been directed toward the synthetic manipulation of uracil for the preparation of these bioactive molecules.

Due to environmental and economically positive implications, one-pot multicomponent coupling reactions[7] (MCRs) have been proven to be a very elegant and rapid way to access complex structures in a single synthetic operation from simple building blocks. They also address fundamental principles of synthetic efficiency and reaction design, and show atom-economy and selectivity. MCRs are important tools for both combinatorial chemistry and diversity-oriented synthesis (DOS), and thus play a significant role in the development of methodology for drug discovery.[8,9] MCRs can be considered as an interesting topic for academic research, which also satisfies a practical interest of applied science. Among the variety of methods documented in the literature, the widely exploited Diels–Alder (DA) reaction[10] is the most favorite protocol to synthesize six-membered carbocycles and/or heterocycles. The hetero-Diels–Alder (HAD) reaction represents one of the most effective methods for the synthesis of six-membered heterocycles,[10i,11] because of their atom economical and stereocontrolled nature.[12] Among catalytic asymmetric hetero-Diels–Alder reactions,[12] the aza-Diels–Alder version[12m] has received much less attention, despite its potential utility to afford optically active dihydropyridines.

The synthesis of pyrido[2,3-*d*]pyrimidines is mainly by two ways, i.e., annulation of pyrimidine ring over pyridine or vice versa.[13a] In spite of the importance of pyrido[2,3-*d*]pyrimidines, exemplified by the derivatives (Chart 1), there are limited methods[13] that allow

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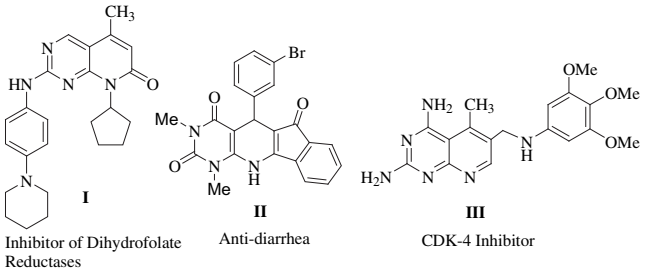


Chart 1. Some biologically active pyrido[2,3-*d*]pyrimidine frameworks.

their preparation. Further, they suffer from drawbacks, such as long reaction time, relatively expensive or harmful catalysts, cumbersome experimental procedures, and lacking generality. Therefore, more general, efficient, and viable routes are very much desirable in view of their broad array of biological activity, and would be of great relevance to both synthetic and medicinal chemists. L-Proline has drawn much interest in different organic reactions due to its experimental simplicity, non toxicity, ease of handling, cost effectiveness, and excellent solubility in water and organic solvents. L-Proline being bifunctional molecule, has been found to be very effective in direct catalytic asymmetric reactions,[14] including the synthesis of 1,4-dihydropyridines.[15] Recently, we reported L-proline catalyzed synthesis of highly substituted imidazoles via multicomponent one-pot reaction.[16] In the course of our research aimed at the synthesis of bioactive heterocycles utilizing multicomponent reactions,[17] in this paper, we report the first example of L-proline catalyzed efficient synthesis of highly functionalized pyrido[2,3-*d*] pyrimidines via one-pot three-component domino Knoevenagel aza-Diels–Alder reaction.

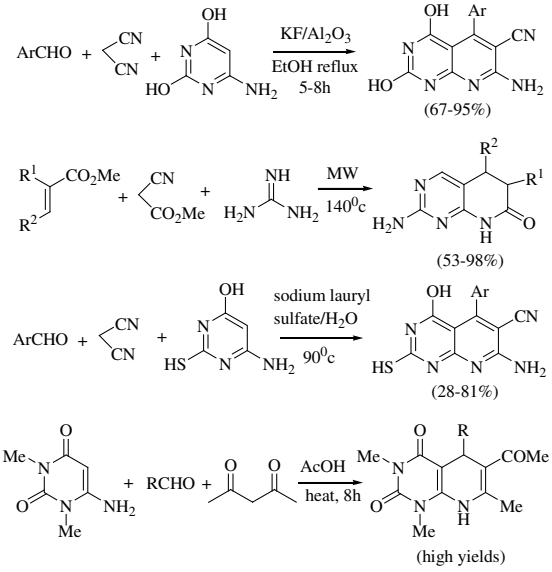
2. Results and discussion

Our literature survey at this stage revealed that, despite the potent and diverse biological activities of pyrido[2,3-*d*]pyrimidines, there are only limited publications[13] devoted to the synthesis of pyrido[2,3-*d*]pyrimidines (Scheme 1). However, to the best of our knowledge, there was no report yet available on the synthesis of pyrido[2,3-*d*]pyrimidines in one-pot via three-component coupling reaction utilizing 6-amino-1,3-dimethyluracil, aldehyde, and dialkyl acetylenedicarboxylate as the versatile templates in the presence of L-proline as catalyst. We therefore became interested in devising more general synthetic strategy for the construction of pyrido[2,3-*d*]pyrimidines (Scheme 1).

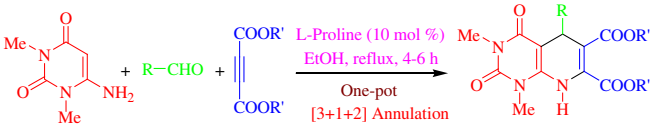
In our initial studies, 6-amino-1,3-dimethyluracil (1.0 mmol), benzaldehyde (1.0 mmol), and diethyl acetylenedicarboxylate (1.3 mmol) were refluxed in ethanol for 24 h without catalyst. The reaction gave an unexpected Knoevenagel condensation product **5** as the major one in 78% yield, while the expected cascade HDA cycloadduct **4** was detected in the trace amount only (Table 1, entry 1). TLC of the above reaction mixture showed the non-consumption of diethyl acetylenedicarboxylate. Subsequently, various acid catalysts, such as $InCl_3$, SiO_2–H_2SO_4, SiO_2–$HClO_4$, and *p*-TSA were tested for the above reaction to promote condensation and cycloaddition. $InCl_3$ could not trigger the reaction, while SiO_2–H_2SO_4, SiO_2–$HClO_4$, and *p*-TSA gave a mixture of **4** and **5** in almost equal amounts (Table 1, entries 3–5). Encouraged by this result, various organocatalysts, such as L-proline, *trans*-4-hydroxyproline, L-leucine, and phenyl glycine were used, and to our delight L-proline provided satisfactory results (Table 1, entries 6–11).

Confident that the method would tolerate structural diversity, focus then shifted to optimization. To optimize the catalyst loading, above model reaction was carried out under different L-proline

Earlier works:[13]



This work:



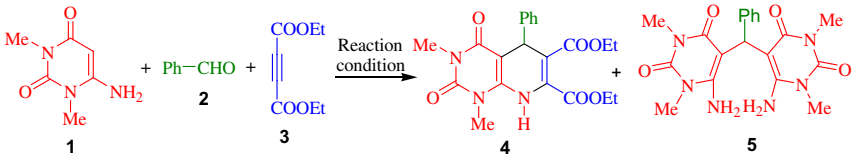
Scheme 1. Synthesis of pyrido[2,3-*d*]pyrimidines.

percentages (5 mol %, 10 mol %, and 15 mol %, Table 1, entries 6–8). It was observed that 10 mol % loading of the L-proline provided the maximum yield (Table 1, entry 7). Higher percentage loading of the catalyst neither increased the yield nor reduced the reaction time (Table 1, entry 8). Secondly, to find the most suitable solvent for L-proline, various non-polar (CH_2Cl_2, $CHCl_3$, toluene), polar-aprotic (CH_3CN, DMF, DMSO), and polar-protic (MeOH, EtOH, and *i*-PrOH) solvents were used but the best result was obtained in ethanol (Table 1, entry 7). Finally, the reaction temperature was also examined and 80 °C was found to be the optimum temperature. Reducing the temperature from 80 °C led to a significant decrease in the yield of the desired product **4**. The reactions usually completed within 4–6 h (monitored by TLC).

Subsequently, with optimal condition in hand, the generality and synthetic scope of this coupling protocol was demonstrated by synthesizing a series of pyrido[2,3-*d*]pyrimidines **4a**–**r**. A wide range of aldehydes (aromatic, heteroaromatic, and aliphatic) and methyl/ethyl acetylenedicarboxylates were well tolerated under the reaction conditions and furnished the corresponding pyrido[2,3-*d*] pyrimidines in good yields (Table 2). However, in comparison to aromatic aldehydes, aliphatic aldehydes gave lower yields (Table 2, entries 4l–n) thus, limiting the scope of this reaction to some extent.

The structures of all the compounds were ascertained by their satisfactory elemental analyses and spectral (IR, ^1H, ^{13}C NMR, and MS) studies. The ^1H NMR spectra showed the absence of C-5 proton of the uracil moiety in all the synthesized compounds, which supported the involvement of a cycloaddition process. The dihydropyridine ring exhibited a sharp singlet for the chiral 5-CH about 4.98–5.29 ppm when aromatic ring was attached to this chiral carbon, while it appeared around 3.90–4.00 ppm when aliphatic substituent was attached to this carbon. The sharp singlet around 6.66–6.90 ppm for the NH proton (D_2O exchangeable) was observed. ^{13}C NMR spectra showed distinct resonances in agreement

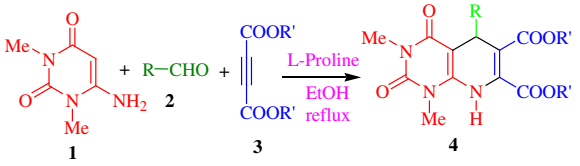
Table 1
Optimization of the reaction conditions for the synthesis of **4**[a]



Entry	Solvent	Catalyst (mol %)	Time (h)	Yield[b] (%) **4**	Yield[c] (%) **5**
1	EtOH	No catalyst	24	Trace	78
2	EtOH	$InCl_3$ (10)	4	Nil	90
3	EtOH	SiO_2–H_2SO_4	4	42	44
4	EtOH	SiO_2–$HClO_4$	4	40	45
5	EtOH	*p*-TSA (10)	4	35	40
6	EtOH	L-Proline (5)	4	62	14
7	EtOH	L-Proline (10)	4	84	7
8	EtOH	L-Proline (15)	4	84	8
9	EtOH	*trans*-4-Hydroxyproline (10)	4	58	16
10	EtOH	L-Leucine (10)	4	55	16
11	EtOH	Phenylglycine (10)	4	46	14
12	MeOH	L-Proline (10)	4	52	30
13	*i*-PrOH	L-Proline (10)	4	65	19
14	CH_2Cl_2	L-Proline (10)	4	20	52
15	$CHCl_3$	L-Proline (10)	4	18	62
16	Toluene	L-Proline (10)	4	24	51
17	CH_3CN	L-Proline (10)	4	29	44
18	DMF	L-Proline (10)	4	36	16
19	DMSO	L-Proline (10)	4	32	12

[a] Reaction of 6-amino-1,3-dimethyluracil **1** (1.0 mmol), benzaldehyde **2** (1.0 mmol), and diethyl acetylenedicarboxylate **3** (1.3 mmol).
[b] Isolated yields.
[c] Yields based upon the starting material aldehyde.

Table 2
Synthesis of pyrido[2,3-*d*]pyrimidines **4**



Entry	R	R′	Time (h)	Yield[a] (%)
4a	C_6H_5	Et	4	84
4b	4-MeC_6H_4	Et	4	74
4c	4-ClC_6H_4	Et	4.5	75
4d	4-$NO_2C_6H_4$	Et	4	76
4e	4-$OMeC_6H_4$	Et	4	74
4f	2-Furyl	Et	4	85
4g	2-Thienyl	Et	4	78
4h	2,4-$Cl_2C_6H_3$	Et	4	88
4i	4-BrC_6H_4	Et	4	69
4j	4-FC_6H_4	Et	4	70
4k	3-ClC_6H_4	Et	5	80
4l	CH_3	Et	5.5	48
4m	Cyclohexyl	Et	6	54
4n	CH_3CH_2	Et	6	46
4o	C_6H_5	Me	4	76
4p	2-ClC_6H_4	Me	5	70
4q	4-MeC_6H_4	Me	5	72
4r	2-Furyl	Me	4.5	70

[a] Isolated yields.

with the proposed structures. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values. Finally, the single crystal X-ray diffraction analyses of two representative compounds **4a** and **4h** were used unambiguously to corroborate the formation of racemic mixture, which was supported by X-ray diffraction data of compound **4h**, where both the optical isomers have co-crystallized in the same lattice (Fig. 1, Table 3). The CCDC numbers are available in the website.[18]

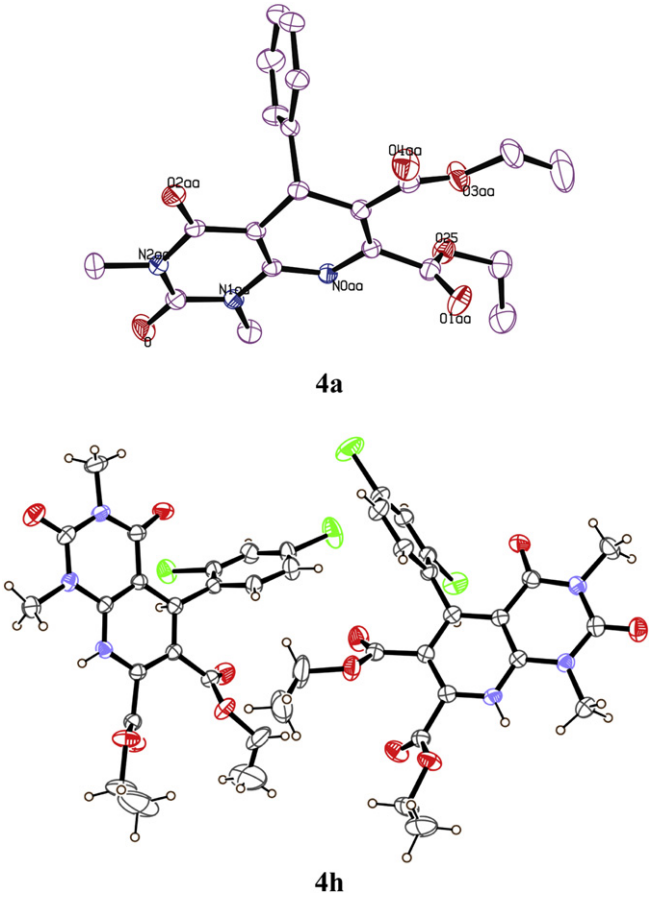
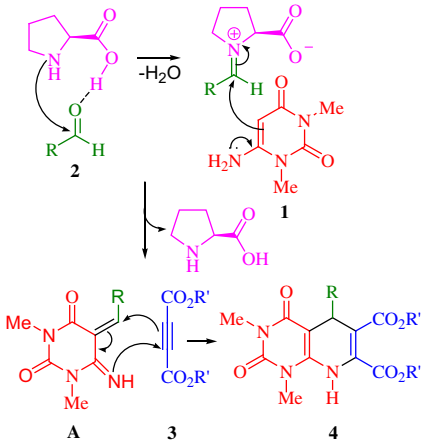


Fig. 1. ORTEP diagrams for **4a** and **4h**.

Table 3
Crystal data of compounds **4a** and **4h**

	4a	4h
Empirical formula	$C_{21}H_{23}N_3O_6$	$C_{21}H_{21}Cl_2N_3O_6$
Formula weight	413.42	482.31
Crystal system, space group	Monoclinic	Triclinic
a/Å	7.8659 (5)	8.9113 (7)
b/Å	19.4927 (15)	11.8263 (10)
c/Å	12.9732 (9)	23.2535 (13)
β/°	91.237 (9)	92.442 (5)
Volume/Å^3	1988.7 (2)	2270.8 (3)
Z	4	4
Calculated density/g cm^{-3}	1.1381	1.411
Absorption coefficient/mm^{-1}	0.103	0.328
F(000)	872	1000



Scheme 2. A plausible mechanism for the synthesis of pyrido[2,3-*d*]pyrimidines.

The preceding examples nicely highlight how adduct obtained from three-component reaction involving aldehydes, 1,3-dimethyl-6-amino uracil, and dialkyl acetylenedicarboxylate can be readily transformed by cascade reactions to generate heterocycles that are endowed with useful functionality for further manipulation and diversification. This new pyrido[2,3-*d*]pyrimidine synthesis can be viewed as an alternative to some previously known pyrido[2,3-*d*] pyrimidine synthesis. One of the benefits of this class of transformations is that it takes advantage of the large number of commercially available aldehyde derivatives. The economical factors (time, money, waste etc.) for these three-component reactions hold promise for the future of organic synthesis.

A tentative mechanistic rationale portraying the probable sequence of events is given in Scheme 2. It is conceivable that initially the 1,3-dimethyl-6-amino uracil **1** undergoes proline catalyzed Knoevenagel condensation with aldehyde **2** to give the *ortho*-iminemethide intermediate **A**. Once the intermediate **A** is formed, it underwent spontaneous [4+2] cycloaddition with dialkyl acetylenedicarboxylate **3** to form the desired pyrido[2,3-*d*]pyrimidine **4**. The intermediate **A** is quite reactive and not isolable, although its intermediacy has been confirmed by the formation of product **5** via the attack of second molecule of 1,3-dimethyl-6-amino uracil (Table 1). The condensation and cycloaddition proceeded well without the electronic and steric effect of the substituents. Thus, by this strategy, two new carbon–carbon bonds and one carbon–nitrogen bond could be formed in a single stroke with the efficient assembly of two rings from readily available starting materials.

3. Conclusion

In conclusion, we have devised a versatile, convenient, and efficient approach to construct the structurally diverse pyrido[2,3-*d*] pyrimidines via three-component one-pot reaction of 1,3-dimethyl-6-amino uracil, aldehydes, and dialkyl acetylenedicarboxylates through domino Knoevenagel condensation/[4+2] cycloaddition in the presence of L-proline for the first time. The advantages of operational simplicity, economic viability, generality, atom-economy, together with ecologically benign nature make this protocol a very efficient alternative to literature methods, which could be directly used for biological assays. Further, library generation and biological evaluation of these compounds is currently under investigation in our research group.

4. Experimental section

4.1. General

All the chemicals used were reagent grade purchased from Merck, Aldrich, CDH, and Fluka, and were used as received without further purification. The products were purified by column chromatography over silica gel. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, on JEOL AL 300 FT-NMR spectrometer. Chemical shifts are given as δ (ppm) values with reference to tetramethylsilane (TMS) as the internal standard. IR spectra (KBr) were recorded on Varian 3100 FT-IR spectrophotometer in the range of 400–4000 cm^{-1}. Mass spectra were recorded at 70 eV ionizing voltage on a JEOL-D300 MS instrument. The CHN analyses were performed from microanalytical laboratory with an Exeter Analytical Inc. 'Model CE-400 CHN Analyzer'. X-ray diffraction was measured on Xcalibur Oxford CCD Diffractometer. All the reactions were monitored by TLC using precoated sheets of silica gel G/UV-254 of 0.25 mm thickness (Merck 60F$_{254}$). Melting points were determined with Büchi B-540 melting point instrument and are uncorrected.

4.2. General procedure for the synthesis of 1,3-dimethyl-2,4-dioxo-5-aryl/alkyl-1,2,3,4,5,8-hexadihydro[2,3-*d*]pyrimidine-6,7-dicarboxylic acid dimethyl/diethylester (4)

In a 50 mL round bottom flask 6-amino-1,3-dimethyluracil (1.0 mmol), aldehyde (1.0 mmol), and ethyl or methyl acetylenedicarboxylate (1.3 mmol) were taken in 4 mL ethanol, and 11.5 mg (10 mol %) of L-proline was added to it. The reaction mixture was stirred at reflux temperature for the stipulated period of time. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The residue was diluted with water and extracted with diethyl ether (3×15 mL). The combined organic phase was washed with brine and dried over anhydrous MgSO$_4$. The solvent was removed under vacuum and the crude product was purified by silica gel column chromatography using methanol and dichloromethane (1:49) as eluent to afford the desired product in excellent purity. The physical and spectral data of the synthesized compounds are as follows:

*4.2.1. 1,3-Dimethyl-2,4-dioxo-5-phenyl-1,2,3,4,5,8-hexahydro pyrido [2,3-d]pyrimidine-6,7-dicarboxylic acid diethylester (**4a**).* Colorless solid; mp 224–225 °C; IR (KBr, ν_{max}, cm^{-1}): 3191, 1743, 1704, 1660, 1610; ^{1}H NMR (300 MHz, CDCl$_3$, δ ppm): 7.32–7.20 (m, 5H), 6.76 (s, 1H), 5.01 (s, 1H), 4.33 (q, J=5.1 Hz, 2H), 4.12 (q, J=7.2 Hz, 2H), 3.51 (s, 3H), 3.25 (s, 3H), 1.33 (t, J=7.2 Hz, 3H), 1.12 (t, J=7.8 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$, δ ppm): 166.3, 162.3, 161.0, 150.8, 143.3, 143.1, 128.4, 127.9, 127.2, 126.5, 118.0, 88.4, 63.1, 61.2, 40.7, 28.6, 28.0, 13.7; ESI-MS: m/z=436.2 (M$^+$+23); Anal. Calcd for $C_{21}H_{23}N_3O_6$: C, 61.01; H, 5.61; N, 10.16. Found: C, 61.29; H, 5.85; N, 10.02.

*4.2.2. 1,3-Dimethyl-2,4-dioxo-5-p-tolyl-1,2,3,4,5,8-hexahydro pyrido [2,3-d]pyrimidine-6,7-dicarboxylic acid diethylester (**4b**).* Pale yellow solid; mp 236–237 °C; IR (KBr, ν_{max}, cm^{-1}): 3266, 1744, 1707,

1617; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.21 (d, J=7.8 Hz, 2H), 7.09 (d, J=7.5 Hz, 2H), 6.90 (s, 1H), 4.97 (s, 1H), 4.34 (q, J=7.2 Hz, 2H), 4.13 (q, J=7.5 Hz, 2H), 3.47 (s, 3H), 3.25 (s, 3H), 2.27 (s, 3H), 1.33 (t, J=7.2 Hz, 3H), 1.16 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 166.8, 162.5, 161.0, 150.2, 142.7, 140.4, 137.0, 129.3, 127.4, 126.8, 118.1, 88.5, 63.6, 62.4, 40.0, 29.6, 28.6, 13.8; ESI-MS: m/z=428.2 (M^++1); Anal. Calcd for $C_{22}H_{25}N_3O_6$: C, 61.82; H, 5.90; N, 9.83. Found: C, 61.59; H, 6.23; N, 9.98.

*4.2.3. 5-(4-Chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6,7-dicarboxylic acid diethylester (**4c**).* White solid; mp 234–235 °C; IR (KBr, ν_{max}, cm^{-1}): 3219, 1747, 1702, 1640, 1607; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.41 (d, J=8.1 Hz, 2H), 7.21 (d, J=8.1 Hz, 2H), 6.76 (s, 1H), 4.98 (s, 1H), 4.37 (q, J=7.2 Hz, 2H), 4.13 (q, J=7.2 Hz, 2H), 3.51 (s, 3H), 3.25 (s, 3H), 1.34 (t, J=7.2 Hz, 3H), 1.15 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 166.2, 162.0, 160.9, 150.7, 143.0, 141.7, 133.1, 129.3, 128.6, 126.0, 118.2, 87.9, 63.3, 61.4, 40.5, 28.6, 28.1, 14.0, 13.7; ESI-MS: m/z=448.3 (M^++1); Anal. Calcd for $C_{21}H_{22}ClN_3O_6$: C, 56.32; H, 4.95; N, 9.38. Found: C, 56.10; H, 5.20; N, 9.65.

*4.2.4. 1,3-Dimethyl-5-(4-nitrophenyl)-2,4-dioxo-1,2,3,4,5.8-hexahydropyrido[2,3-d]pyrimidine-6,7-dicarboxylic acid diethylester (**4d**).* White solid; mp 275–276 °C; IR (KBr, ν_{max}, cm^{-1}): 3220, 1742, 1702, 1635, 1619, 1378; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.16 (d, J=8.4 Hz, 2H), 7.52 (d, J=8.4 Hz, 2H), 6.84 (s, 1H), 5.14 (s, 1H), 4.39 (q, J=7.2 Hz, 2H), 4.11 (q, J=7.5 Hz, 2H), 3.54 (s, 3H), 3.25 (s, 3H), 1.35 (t, J=7.2 Hz, 3H), 1.14 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 165.8, 161.9, 160.9, 150.6, 150.2, 147.0, 143.2, 129.0, 127.2, 123.7, 116.6, 87.4, 63.5, 61.6, 40.9, 28.7, 28.1, 13.8, 13.7; ESI-MS: m/z=459.2 (M^++1); Anal. Calcd for $C_{21}H_{22}N_4O_8$: C, 55.02; H, 4.84; N, 12.22. Found: C, 55.29; H, 5.17; N, 12.45.

*4.2.5. 5-(4-Methoxyphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6,7-dicarboxylic acid diethylester (**4e**).* Pale yellow solid; mp 241–242 °C; IR (KBr, ν_{max}, cm^{-1}): 3225, 1745, 1701, 1609; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.24 (d, J=8.7 Hz, 2H), 6.82 (d, J=8.7 Hz, 2H), 6.75 (s, 1H), 4.96 (s, 1H), 4.32 (q, J=5.7 Hz, 2H), 4.13 (q, J=7.2 Hz, 2H), 3.74 (s, 3H), 3.49 (s, 3H), 3.25 (s, 3H), 1.33 (t, J=7.2 Hz, 3H), 1.15 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 166.5, 162.2, 161.0, 158.7, 150.8, 142.9, 135.5, 129.0, 125.4, 119.0, 113.8, 88.4, 63.1, 61.3, 55.1, 40.3, 28.6, 28.1, 13.8, 13.7; ESI-MS: m/z=444.1 (M^++1); Anal. Calcd for $C_{22}H_{25}N_3O_7$: C, 59.59; H, 5.68; N, 9.48. Found: C, 59.80; H, 5.36; N, 9.72.

*4.2.6. 5-Furan-2-yl-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6,7-dicarboxylic acid diethylester (**4f**).* White solid; mp 175–176 °C; IR (KBr, ν_{max}, cm^{-1}): 3207, 1746, 1703, 1656, 1612; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.27 (s, 1H), 7.00 (s, 1H), 6.26–6.19 (m, 2H), 5.18 (s, 1H), 4.33 (q, J=7.2 Hz, 2H), 4.20 (q, J=6.9 Hz, 2H), 3.50 (s, 3H), 3.30 (s, 3H), 1.34 (t, J=7.2 Hz, 3H), 1.24 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 166.1, 162.1, 160.9, 154.1, 150.8, 143.5, 142.0, 127.0, 115.2, 110.5, 106.7, 85.3, 63.2, 61.4, 34.3, 28.6, 28.1, 13.9, 13.7; ESI-MS: m/z=404.2 (M^++1); Anal. Calcd for $C_{19}H_{21}N_3O_7$: C, 56.57; H, 5.25; N, 10.42. Found: C, 56.80; H, 5.02; N, 10.19.

*4.2.7. 1,3-Dimethyl-2,4-dioxo-5-thiophen-2-yl-1,2,3,4,5.8-hexahydropyrido[2,3-d]pyrimidine-6,7-dicarboxylic acid diethylester (**4g**).* Pale yellow solid; mp 181–182 °C; IR (KBr, ν_{max}, cm^{-1}): 3193, 1746, 1704, 1660, 1612; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.15 (d, J=8.1 Hz, 1H), 6.95 (s, 1H), 6.90–6.85 (m, 2H), 5.36 (s, 1H), 4.37 (q, J=6.9 Hz, 2H), 4.20 (q, J=7.2 Hz, 2H), 3.50 (s, 3H), 3.30 (s, 3H), 1.35 (t, J=7.2 Hz, 3H), 1.23 (t, J=7.2 Hz, 3H); ^{13}C NMR(75 MHz, $CDCl_3$, δ ppm): 165.8, 162.6, 161.0, 150.7, 147.0, 142.9, 128.4, 126.7, 124.8, 124.5, 115.5, 88.5, 63.2, 61.4, 34.7, 28.7, 27.2, 13.9, 13.7; ESI-MS: m/z=442.2 (M^++23); Anal. Calcd for $C_{19}H_{21}N_3O_6S$: C, 54.41; H, 5.05; N, 10.02. Found: C, 54.66; H, 5.27; N, 9.86.

*4.2.8. 5-(2,4-Dichlorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6,7-dicarboxylic acid diethylester (**4h**).* Colorless solid; mp 237–238 °C; IR (KBr, ν_{max}, cm^{-1}): 3222, 1746, 1705, 1643, 1619; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.33 (s, 1H), 7.23–7.17 (m, 2H), 6.80 (s, 1H), 5.50 (s, 1H), 4.32 (q, J=6.9 Hz, 2H), 4.14 (q, J=6.9 Hz, 2H), 3.54 (s, 3H), 3.24 (s, 3H), 1.32 (t, J=6.9 Hz, 3H), 1.17 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 165.9, 161.6, 160.8, 150.7, 143.7, 139.4, 133.8, 133.6, 131.6, 129.2, 127.5, 124.9, 118.0, 86.9, 63.3, 61.6, 38.5, 28.7, 28.0, 13.7; ESI-MS: m/z=482.0 (M^++1); Anal. Calcd for $C_{21}H_{21}Cl_2N_3O_6$: C, 52.29; H, 4.39; N, 8.71. Found: C, 52.01; H, 4.65; N, 8.56.

*4.2.9. 5-(4-Bromophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6,7-dicarboxylic acid diethylester (**4i**).* White solid; mp 266–267 °C; IR (KBr, ν_{max}, cm^{-1}) 3207, 1742, 1706, 1610; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.41 (d, J=8.1 Hz, 2H), 7.21 (d, J=8.1 Hz, 2H), 6.75 (s, 1H), 4.98 (s, 1H), 4.37 (q, J=7.2 Hz, 2H), 4.13 (q, J=7.5 Hz, 2H), 3.51 (s, 3H), 3.25 (s, 3H), 1.34 (t, J=7.2 Hz, 3H), 1.15 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 166.2, 162.0, 160.9, 150.7, 143.0, 142.2, 131.5, 129.7, 126.1, 121.3, 118.1, 87.9, 63.3, 61.4, 40.6, 28.6, 28.1, 13.8, 13.7; ESI-MS: m/z=492.1 (M^++1); Anal. Calcd for $C_{21}H_{22}BrN_3O_6$: C, 51.23; H, 4.50; N. 8.54. Found: C, 51.40; H, 4.25; N, 8.22.

*4.2.10. 5-(4-Fluorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6,7-dicarboxylic acid diethylester (**4j**).* White solid; mp 254–255 °C; IR (KBr, ν_{max}, cm^{-1}): 3212, 1746, 1704, 1612; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.30–7.28 (m, 1H), 6.99–6.93 (m, 3H), 6.78 (s, 1H), 5.00 (s, 1H), 4.34 (q, J=6.9 Hz, 2H), 4.12 (q, J=7.2 Hz, 2H), 3.53 (s, 3H), 3.25 (s, 3H), 1.35 (t, J=7.2 Hz, 3H), 1.14 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 165.8, 161.9, 160.9, 150.2, 147.0, 143.2, 133.7, 129.0, 127.2, 123.7, 116.6, 87.4, 63.5, 61.6, 40.9, 28.7, 28.1, 13.8, 13.7; ESI-MS: m/z=454.2 (M^++23); Anal. Calcd for $C_{21}H_{22}FN_3O_6$: C, 58.46; H, 5.14; N, 9.74. Found: C, 58.22; H, 5.36; N, 9.40.

*4.2.11. 5-(3-Chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6,7-dicarboxylic acid diethylester (**4k**).* White solid; mp 188–1 89 °C; IR (KBr, ν_{max}, cm^{-1}): 3196, 1746, 1709, 1664, 1611; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.25–7.20 (m, 4H), 6.76 (s, 1H), 5.00 (s, 1H), 4.37 (q, J=7.2 Hz, 2H), 4.14 (q, J=6.9 Hz, 2H), 3.53 (s, 3H), 3.26 (s, 3H), 1.34 (t, J=6.9 Hz, 3H), 1.15 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 166.1, 162.1, 160.9, 150.7, 145.2, 143.2, 134.3, 129.5, 128.0, 127.5, 126.7, 126.3, 117.4, 87.8, 63.2, 61.3, 40.6, 28.6, 28.1, 13.8, 13.7; ESI-MS: m/z=448.3 (M^++1); Anal. Calcd for $C_{21}H_{22}ClN_3O_6$: C, 56.32; H, 4.95; N, 9.38. Found: C, 56.19; H, 4.89; N, 9.50.

*4.2.12. 1,3,5-Trimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido [2,3-d] pyrimidine-6,7-dicarboxylic acid diethylester (**4l**).* Yellow jelly; IR (KBr, ν_{max}, cm^{-1}): 1740, 1702, 1661, 1597; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 6.66 (s, 1H), 4.36–4.22 (m, 4H), 3.94 (q, J=6.6 Hz, 1H), 3.47 (s, 3H), 3.42 (s, 3H), 1.35–1.28 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 166.8, 161.8, 161.1, 150.8, 143.5, 125.7, 120.5, 88.3, 62.9, 61.4, 30.1, 28.4, 28.0, 21.2, 14.0, 13.8; ESI-MS: m/z=352.2 (M^++1); Anal. Calcd for $C_{16}H_{21}N_3O_6$: C, 54.69; H, 6.02; N, 11.96. Found: C, 54.52; H, 5.90; N, 11.80.

*4.2.13. 5-Cyclohexyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6,7-dicarboxylic acid diethylester (**4m**).* Yellow jelly; IR (KBr, ν_{max}, cm^{-1}): 1743, 1707, 1662, 1599; ^{1}H NMR (300 MHz, CDCl3, δ ppm): 6.73 (s, 1H), 4.33 (q, J=7.2 Hz, 2H), 4.27 (q, J=7.2 Hz, 2H), 3.94 (s, 1H), 3.48 (s, 3H), 3.35 (s, 3H),

1.41–1.25 (m, 17H); ^{13}C NMR (75 MHz, CDCl3, δ ppm): 165.8, 163.4, 160.1, 151.0, 140.5, 119.1, 110.4, 83.1, 62.6, 62.1, 30.0, 29.6, 28.7, 25.6, 23.6, 14.1, 13.9; ESI-MS: m/z=420.2 (M^++1); Anal. Calcd for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 60.30; H, 6.70; N, 10.28.

*4.2.14. 5-Ethyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido [2,3-d]pyrimidine-6,7-dicarboxylic acid diethylester (**4n**).* Yellow jelly; IR (KBr, ν_{max}, cm^{-1}): 1747, 1706, 1660, 1612; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 6.59 (s, 1H), 4.35–4.23 (m, 4H), 4.02 (t, J=3.3 Hz, 1H), 3.47 (s, 3H), 4.34 (s, 3H), 1.34–1.20 (m, 8H), 0.88 (t, J=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 166.9, 161.7, 161.3, 150.9, 144.5, 126.6, 119.1, 85.9, 62.9, 61.4, 35.7, 28.5, 28.1, 26.8, 13.9, 8.8; ESI-MS: m/z=366.2 (M^++1); Calcd for $C_{21}H_{23}N_3O_6$: C, 55.88; H, 6.34; N, 11.50. Found: C, 55.94; H, 6.12; N, 11.57.

*4.2.15. 1,3-Dimethyl-2,4-dioxo-5-phenyl-1,2,3,4,5,8-hexahydropyrido [2,3-d]pyrimidine-6,7-dicarboxylic acid dimethylester (**4o**).* Yellow solid; mp 234–235 °C; IR (KBr, ν_{max}, cm^{-1}): 3195, 1746, 1702, 1656, 1607; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.30–7.20 (m, 5H), 6.78 (s, 1H), 5.03 (s, 1H), 3.88 (s, 3H), 3.64 (s, 3H), 3.50 (s, 3H), 3.25 (s, 3H); ^{13}C (75 MHz, $CDCl_3$, δ ppm): 166.8, 162.7, 161.0, 150.8, 143.2, 142.9, 128.5, 127.8, 127.4, 127.2, 117.7, 88.6, 53.6, 52.3, 40.6, 28.6, 28.1; ESI-MS: m/z=386.2 (M^++1); Anal. Calcd for $C_{19}H_{19}N_3O_6$: C, 59.22; H, 4.97; N, 10.90. Found: C, 59.07; H, 4.70; N, 10.68.

*4.2.16. 5-(2-Chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6,7-dicarboxylic acid dimethylester (**4p**).* White solid; mp 224–225 °C; IR (KBr, ν_{max}, cm^{-1}): 3226, 1747, 1704, 1654, 1612; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.33–7.28 (m, 2H), 7.20–7.14 (m, 2H) 6.83 (s, 1H), 5.54 (s, 1H), 3.84 (s, 3H), 3.65 (s, 3H), 3.53 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 166.5, 162.3, 160.8, 150.8, 143.7, 140.7, 135.1, 133.3, 129.8, 117.6, 87.5, 53.6, 52.4, 29.6, 29.3; ESI-MS: m/z=420.3 (M^++1); Anal. Calcd for $C_{19}H_{18}ClN_3O_6$: C, 54.36; H, 4.32; N, 10.01. Found: C, 54.20; H, 4.58; N, 10.28.

*4.2.17. 1,3-Dimethyl-2,4-dioxo-5-p-tolyl-1,2,3,4,5,8-hexahydropyrido [2,3-d]pyrimidine-6,7-dicarboxylic acid dimethylester (**4q**).* Pale yellow solid; mp 220–221 °C; IR (KBr, ν_{max}, cm^{-1}): 3260, 1746, 1704, 1629; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.21 (d, J=8.1 Hz, 2H), 7.09 (d, J=7.8 Hz, 2H), 6.80 (s, 1H), 4.98 (s, 1H), 3.87 (s, 3H), 3.65 (s, 3H), 3.49 (s, 3H), 3.25 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 166.8, 162.7, 161.0, 150.8, 142.8, 140.3, 137.0, 129.2, 127.6, 126.8, 118.0, 88.7, 53.6, 52.3, 40.0, 28.6, 28.1, 21.1; ESI-MS: m/z=400.1 (M^++1); Anal. Calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52. Found: C, 60.39; H, 5.14; N, 10.69.

*4.2.18. 5-Furan-2-yl-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6,7-dicarboxylic acid dimethylester (**4r**).* Pale brown solid; mp 188–189 °C; IR (KBr, ν_{max}, cm^{-1}): 3197, 1702, 1656, 1596; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.27 (d, J=4.2 Hz, 1H), 6.92 (s, 1H), 6.20–6.19 (m, 2H), 5.18 (s, 1H), 3.87 (s, 3H), 3.72 (s, 3H), 3.50 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 166.4, 162.7, 160.9, 154.1, 150.8, 143.4, 142.0, 128.5, 113.9, 110.5, 106.6, 85.6, 53.6, 52.4, 33.7, 28.7, 28.2; ESI-MS: m/z=398.2 (M^++23) Anal. Calcd for $C_{17}H_{17}N_3O_7$: C, 54.40; H, 4.57; N, 11.20. Found: C, 54.65; H, 4.32; N, 11.42.

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Supplementary data

X-ray structures and crystallographic information files (CIF) for compounds **4a** and **4h** have been attached. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.051.

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18. Crystallographic data for compounds **4a** and **4h** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 794380 and CCDC 794336, respectively. These data can be obtained free of charge at www.ccdc.cam.ac.uk.