DOI: 10.1002/ejoc.201101065

BF_3·OEt_2-Mediated 1,3-Hydride Shift Followed by 6π Electrocyclization: An Efficient Route for the Synthesis of Pyridopyrimidine, Pyranoquinoline, and Phenanthroline Derivatives

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Keywords: Imines / Rearrangement / Cyclization / Fused-ring systems / Nitrogen heterocycles

The synthesis of pyridopyrimidine, pyranoquinoline, and phenanthroline derivatives can be easily and efficiently accomplished by the direct reaction of a 1-aminopenta-1,4-diene fragment, an aromatic aldehyde, and BF_3·OEt_2 in the absence of any metal catalyst. The notable features of this procedure are mild reaction conditions, good to high yields, and operational simplicity.

Introduction

Among the small organic molecules, simple nitrogen-containing heterocycles receive much attention in the literature as a consequence of their exciting biological properties and role as pharmacophores of considerable historical importance. Among these nitrogen-containing heterocycles, the synthesis, reactions, and biological activities of pyridine-containing molecules is an ever-expanding area of research in heteroaromatic chemistry, and this structural motif appears in a large number of pharmaceutical agents and natural products.[1–8] Recently, the importance of pyridopyrimidine derivatives has increased dramatically because of their biological and medicinal applications such as antibacterials,[9] antiallergic,[10] CNS stimulants,[11] and inhibitors of enzyme adenosine kinase (AK)[12] or dihydrofolatereductase (DHFR).[13] Among the nitrogen heterocycles, quinoline represents an important class of alkaloids and is often found as structural framework in a large number of biologically active natural products and pharmaceuticals.[14] Quinoline has also found applications in drug development. Pyrano[3,2-*f*]quinolines, which contain both a quinoline ring and pyran moiety, display unique biological activities, such as psychotropic,[15] antiallergic,[16] anti-inflammatory,[17] and estrogenic activities.[18] They are also used as potential pharmaceuticals.[19] Helietidine, dutadrupine, and geibalansine[20] are examples of natural products containing pyranoquinoline as a core structure. 4,7-Phenanthroline derivatives and their analogs exhibit high antibacterial activity and are used for the treatment of gastrointestinal diseases.[21–26] This makes the synthesis of pyridopyrimidine and pyranoquinoline derivatives from easily accessible precursors interesting and significant.

As a part of continuing efforts in our laboratory towards the development of new protocols for the expeditious synthesis of biologically relevant heterocyclic compounds,[27] we became interested in exploring the possibility of developing newer methodologies for the synthesis of highly bioactive pyridopyrimidine derivatives. A number of reports in the literature for the synthesis of pyridopyrimidine derivatives[28] usually require forcing conditions, long reaction times, and complex synthetic pathways. We have previously reported the synthesis of pyrido[3,2-*d*]pyrimidine derivatives by the palladium-catalyzed intramolecular arylation of pyrimidines[29] and the silver-catalyzed 6-*endo-dig* mode of cycloisomerization from various *N*-propargylated heterocyclic compounds[30] that require harsh reaction conditions and expensive metal catalysts. This prompted us to undertake a study on the synthesis of these heterocycles by the BF_3·OEt_2-mediated reaction of a 1-aminopenta-1,4-diene fragment and aromatic aldehydes. Herein we report the results of our study.

Results and Discussion

The starting material, 6-allyl-5-amino-1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)-dione (**1**), for this study was prepared according to our earlier published procedure.[31] A mixture of substrate **1** and **2a** was heated in refluxing toluene in the presence of BF_3·OEt_2 for 12 h. Two products were obtained, that is, 6-(4-chlorophenyl)-1,3,7-trimethylpyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**3a**, 86%) along with a small amount of 1,3,6-trimethylpyrrolo[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione derivative **4** as a side product,

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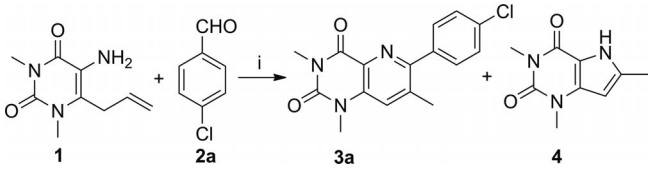
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101065.

which is also potentially bioactive[32,33] (Scheme 1). Compound **4** can also be obtained as a side product during the formation of the starting material from 5-(allylamino)-1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)-dione by aza-Claisen rearrangement using BF_3·OEt_2 as a catalyst. The final products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry. The optimized reaction conditions were established by carrying out several experiments by changing the nature and amount of the Lewis acid catalyst used (Table 1). Among the various Lewis acid catalysts screened, coinage metal-based catalysts like $AuCl_3$, $AgSbF_6$, and CuI did not give satisfactory results (Table 1, Entries 12, 16, 15). The reaction was also carried out in the presence of $AlCl_3$ and $Yb(OTf)_3$ but these also did not give results as satisfactory as those obtained with the use of BF_3·OEt_2 (Table 1, Entries 13 and 14). On examining the role of the solvents for improving the efficiency of this reaction, we found that toluene gave better results than CH_3CN, CH_2Cl_2, THF, benzene, or xylene (Table 1, Entries 4–9). The reaction did not proceed at all at room temperature (Table 1, Entry 10). The yield of the product increased by increasing the amount of catalyst (Table 1, Entry 1–4): 40 mol-% BF_3·OEt_2 gave an excellent yield, but the use of greater amounts of catalyst resulted in the formation of side products such as **4** (Table 1, Entry 11). Variation of the catalyst and solvent showed that running the reaction in toluene using BF_3·OEt_2 (40 mol-%) under refluxing conditions for 12 h provided the highest yield of the product (Table 1, Entry 4). The optimized reaction conditions were then applied to other substrates to examine the scope of this protocol to synthesize a range of pyridopyrimidine derivatives (Table 2).



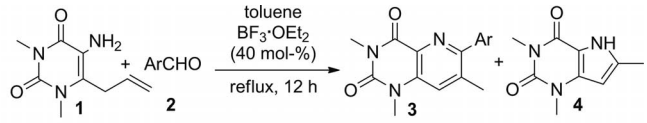
Scheme 1. Reagent and conditions: (i) BF_3·OEt_2, toluene, reflux, 12 h.

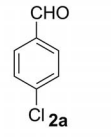
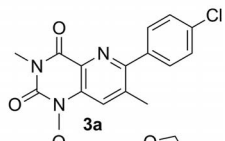
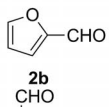
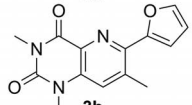
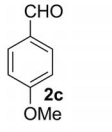
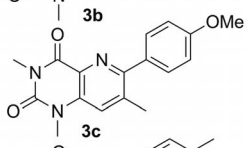
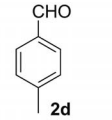
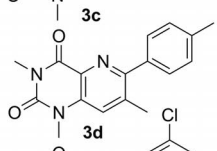
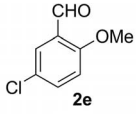
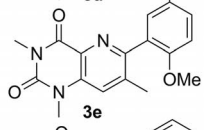
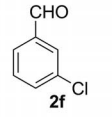
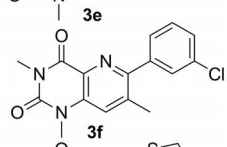
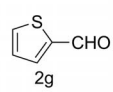
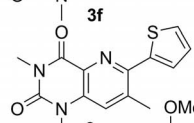
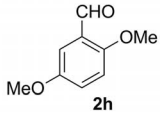
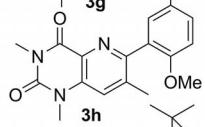
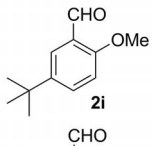
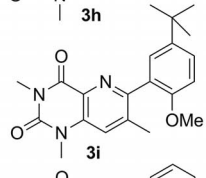
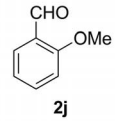
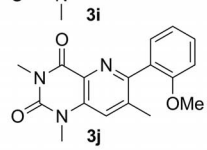
Table 1. Screening of different catalysts and conditions in the formation of pyridopyrimidine derivatives.

Entry	Catalyst	Conditions	% Yield **3a**/**4**[f]
1	BF_3·OEt_2[a]	toluene, reflux	32:2
2	BF_3·OEt_2[b]	toluene, reflux	39:5
3	BF_3·OEt_2[c]	toluene, reflux	54:7
4	BF_3·OEt_2[d]	toluene, reflux	86:12
5	BF_3·OEt_2[d]	CH_3CN, reflux	72:9
6	BF_3·OEt_2[d]	CH_2Cl_2, reflux	42:5
7	BF_3·OEt_2[d]	THF, reflux	38:3
8	BF_3·OEt_2[d]	benzene, reflux	35:6
9	BF_3·OEt_2[d]	xylene, reflux	43:7
10	BF_3·OEt_2[d]	toluene, r.t., stirring	0:0
11	BF_3·OEt_2[e]	toluene, reflux	81:17
12	$AuCl_3$[d]	toluene, reflux	68:7
13	$AlCl_3$[d]	toluene, reflux	47:3
14	$Yb(OTf)_3$[d]	toluene, reflux	52:4
15	CuI[d]	toluene, reflux	39:3
16	$AgSbF_6$[d]	toluene, reflux	49:3

[a] 5 mol-% of catalyst. [b] 10 mol-% of catalyst. [c] 20 mol-% of catalyst. [d] 40 mol-% of catalyst. [e] 50 mol-% of catalyst. [f] Isolated yield.

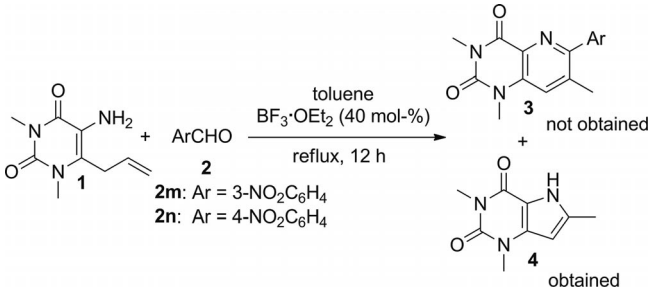
Table 2. Scope of BF_3·OEt_2-mediated synthesis of substituted pyridopyrimidine derivatives.



Entry	Aldehyde **2**	Product **3**	% Yield **3**/**4**
1.			86:12
2.			83:13
3			84:11
4			81:15
5			79:17
6			82:15
7			76:20
8			80:14
9			83:14
10			83:12

Various substituted benzaldehydes and heterocyclic aldehydes give desired products **3** uniformly in high yields. The reaction is mostly unaffected by the substituents on the aro-

matic ring of aldehydes **2a**–**j**, as products **3a**–**j** were obtained in excellent yields of 76–86% (Table 2, Entries 1–10). For heterocyclic aldehydes such as furfuraldehyde and thiophene aldehyde, desired products **3b** and **3g** were obtained in 83 and 76% yield, respectively (Table 2, Entries 2 and 7). Both electron-donating and electron-withdrawing groups on the aromatic ring of the aldehyde give the desired derivatives in high yields. However, in case of substrates with NO_2 substitution on the aromatic ring of the aldehyde (i.e., **2m**, **2n**), the exclusive formation of pyrrolo[3,2-*d*]pyrimidine[20] derivative **4** (83 and 81% yield, respectively) was observed, and this product was also the side product in other cases (Scheme 2).



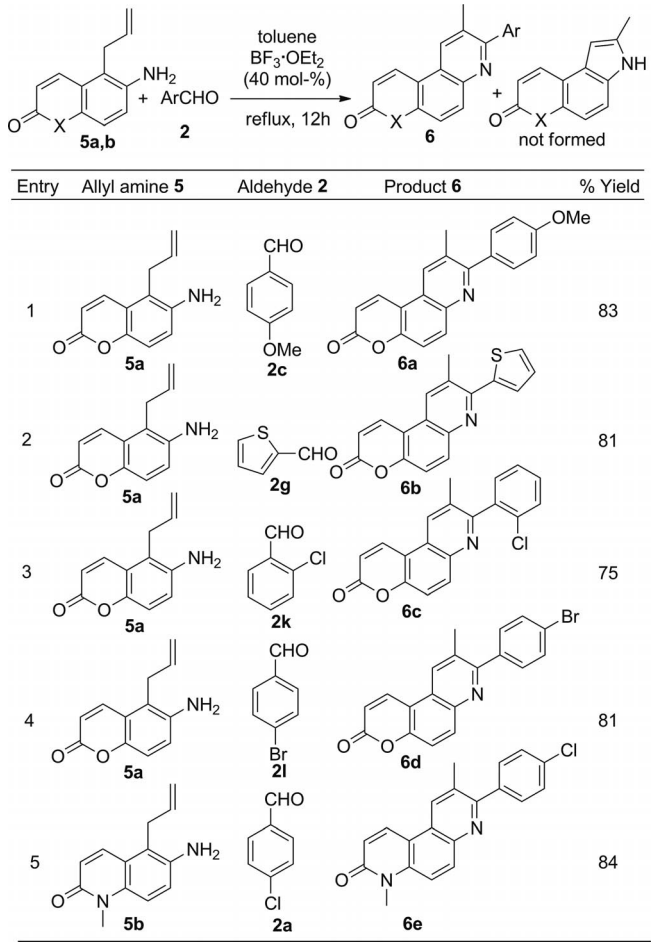
Scheme 2. Synthesis of pyrrolo[3,2-*d*]pyrimidine derivatives.

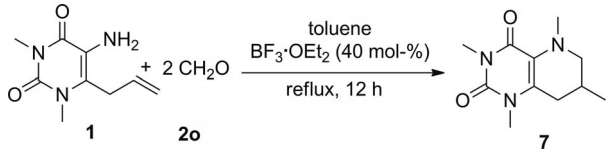
This methodology has also been applied for the synthesis of bioactive pyranoquinoline and phenanthroline derivatives **6a**–**d** in 75–83% yield (Table 3). Phenanthroline derivative **6e** has also been synthesized from the reaction of **5b** and aldehyde **2a** under the same conditions as those stated earlier. Compounds **5a** and **5b** can be prepared according to our previously published procedure.[34] Interestingly, substrate **1** reacts with aliphatic aldehydes such as formaldehyde (**2o**) to give 1,3,5,7-trimethyl-5,6,7,8-tetrahydropyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**7**) in 82% yield under the same reaction conditions (Scheme 3).

It is observed from the examples described earlier that various pyridopyrimidine, pyranoquinoline, and phenanthroline derivatives can easily be synthesized by the application of this methodology. A survey of the literature reveals that several methods have been developed for the synthesis of quinolines,[35] pyranoquinolines,[27b,30] and pyridopyrimidines,[28] but this present methodology is simple, facile, and novel for the construction of these derivatives from a 1-aminopenta-1,4-diene fragment and aldehydes.

The formation of the pyridine ring may be rationalized by the initial BF_3-catalyzed formation of imine **A** from the reaction of the 1-aminopenta-1,4-diene fragment and **2** through a simple condensation reaction (Scheme 4). The electron-dense olefin can then attack the nucleophilic nitrogen to form intermediate **B**, which under acid catalysis rearranges to isomer **D** via intermediate **C** obtained through 1,3-H shift. Intermediate **D** undergoes cyclization through a simple 6π electrocyclization process to form intermediate **E**, which can undergo further rearrangement and aromatization to give the desired products. Formation of **D** from **C** is unfavorable when R = $NO_2C_6H_4$ due to the strong electron-withdrawing properties of the NO_2 group. This might be the reason why nitrobenzaldehydes fail to give the final product. So, the formation of compounds **4** is rationalized by the participation of the lone pair of electrons on the nitrogen atom (intermediate **G**) that attack the double bond coordinated by the Lewis acid. Removal of the acid may give intermediate **I**, which may then isomerize to give products **4**.

Table 3. BF_3·OEt_2-mediated synthesis of various pyranoquinoline and phenanthroline derivatives.

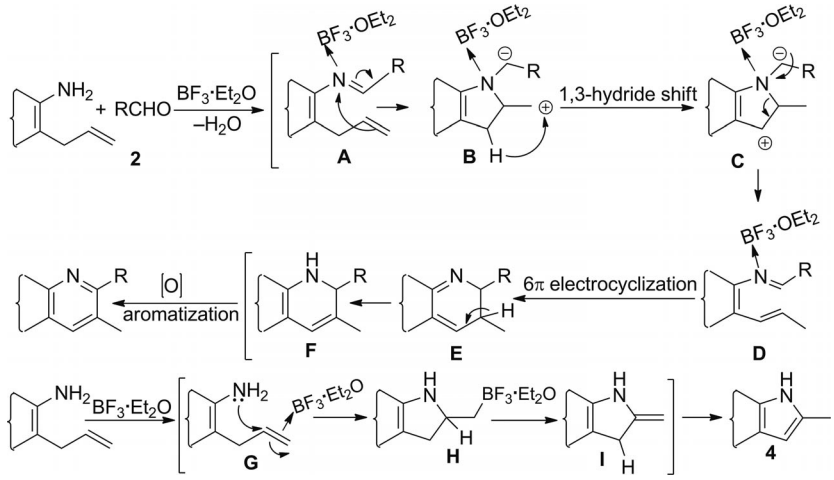




Scheme 3. Synthesis of 1,3,5,7-tetramethyl-5,6,7,8-tetrahydropyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione.

Conclusions

In conclusion, we have developed an efficient, rapid, and high-yielding procedure for the construction of potentially bioactive pyridopyrimidine, pyranoquinoline, and phen-



Scheme 4. The proposed mechanism for the synthesis of quinoline derivatives and product **4**.

anthroline derivatives from easily available starting materials. This method is simple, easy to handle, and does not require a transition-metal catalyst. This methodology will be readily applicable to the synthesis of various substituted quinoline derivatives and heterocyclic systems.

Experimental Section

General Methods: Melting points were determined in open capillaries. IR spectra were run for KBr discs with a Perkin–Elmer 120–000A apparatus, and NMR spectra were determined for solutions in $CDCl_3$ with TMS as an internal standard with Bruker DPX-300 and Bruker DPX-400 instruments. ^{13}C NMR spectra were determined for solutions in $CDCl_3$ with a Bruker DPX-400 spectrometer. CHN analyses were recorded with a 2400 series II CHN analyzer by Perkin–Elmer. Mass spectra were recorded with a QTOF Micro instrument. Silica gel (60–120 mesh and 230–400 mesh) was used for chromatographic separation. Silica gel-G [E-Mark (India)] was used for TLC. Petroleum ether refers to the fraction between 60 and 80 °C.

General Procedure for the Preparation of Compounds 3a–j: A mixture of 6-allyl-5-amino-1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)-dione (**1**, 1.0 equiv.) and aromatic aldehyde **2a**–**j** (1.0 equiv.) was stirred in toluene (5 mL) at room temperature for 10 min. After the addition of $BF_3{\cdot}OEt_2$ (40 mol-%, mol-% calculated relative to **1**) the reaction mixture was heated at reflux for 12 h. After completion of the reaction as monitored by TLC, the reaction mixture was cooled and diluted with a saturated $NaHCO_3$ solution (50 mL). This was extracted with ethyl acetate (3 × 25 mL). The combined organic extract was washed with brine (50 mL) and dried (Na_2SO_4). The solvent was distilled off. The resulting crude product was purified by column chromatography over silica gel (230–400 mesh, petroleum ether/ethyl acetate) and recrystallized (CH_3CN) to give compounds **3a**–**j**.

6-(4-Chlorophenyl)-1,3,7-trimethylpyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (3a): Using the general procedure, **1** (200 mg, 1.02 mmol), **2a** (143.3 mg, 1.02 mmol), and $BF_3{\cdot}OEt_2$ (57.9 mg, 0.05 mL, 0.408 mmol) gave compound **3a** (280.8 mg) as a white powder. Yield: 86%. M.p. 228–230 °C. IR (KBr): $\tilde{\nu}$ = 2951, 1707, 1663 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 3.53 (s, 3 H, NCH_3), 3.63 (s, 3 H, NCH_3), 7.41 (d, J = 8.0 Hz, 2 H, ArH), 7.49 (d, J = 8.4 Hz, 2 H, ArH), 7.51 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (CH_3), 29.0, 30.6, 123.8, 128.5, 130.0, 130.7, 134.6, 136.7, 137.3, 137.7, 150.7, 153.9, 160.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{14}ClN_3O_2$ $[M + Na]^+$ 338.0672; found 338.0691.

6-(Furan-2-yl)-1,3,7-trimethylpyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (3b): Using the general procedure, **1** (200 mg, 1.02 mmol), **2b** (98 mg, 1.02 mmol), and $BF_3{\cdot}OEt_2$ (57.9 mg, 0.05 mL, 0.408 mmol) gave **3b** (230.7 mg) as a grayish solid. Yield: 83%. M.p. 222–224 °C. IR (KBr): $\tilde{\nu}$ = 3114, 1712, 1667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.71 (s, 3 H, -CH_3), 3.53 (s, 3 H, NCH_3), 3.61 (s, 3 H, NCH_3), 6.56 (t, J = 1.6 Hz, 1 H, ArH), 7.12 (d, J = 3.2 Hz, 1 H, ArH), 7.40 (s, 1 H, ArH), 7.59 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (CH_3), 28.9, 30.6, 111.7, 112.2, 124.3, 129.6, 135.9, 136.7, 143.5, 144.5, 150.6, 152.6, 160.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{13}N_3O_3$ $[M + Na]^+$ 294.0885; found 294.0836.

6-(4-Methoxyphenyl)-1,3,7-trimethylpyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (3c): Using the general procedure, **1** (200 mg, 1.02 mmol), **2c** (139.5 mg, 1.02 mmol), and $BF_3{\cdot}OEt_2$ (57.9 mg, 0.05 mL, 0.408 mmol) gave **3c** (268 mg) as a white powder. Yield: 84%. M.p. 250–252 °C IR (KBr): $\tilde{\nu}$ = 2841, 1704, 1662 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 3.54 (s, 3 H, NCH_3), 3.63 (s, 3 H, NCH_3), 3.86 (s, 3 H, OCH_3), 6.97 (d, J = 8.8 Hz, 2 H, ArH), 7.46 (s, 1 H, ArH), 7.51 (dd, J = 2, 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (CH_3), 28.9, 30.6, 55.4, 113.6, 114.2, 123.7, 128.3, 129.7, 130.6, 131.4, 136.3, 137.8, 150.8, 154.9, 159.8, 160.6 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}N_3O_3$ $[M + H]^+$ 312.1328; found 312.1343.

1,3,7-Trimethyl-6-*p*-tolylpyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (3d): Using the general procedure, **1** (200 mg, 1.02 mmol), **2d** (122.4 mg, 1.02 mmol), and $BF_3{\cdot}OEt_2$ (57.9 mg, 0.05 mL, 0.408 mmol) gave **3d** (245 mg) as a white powder. Yield: 81%. M.p. 218–220 °C. IR (KBr): $\tilde{\nu}$ = 2919, 1710, 1665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 2.51 (s, 3 H, CH_3), 3.54 (s, 3 H, NCH_3), 3.63 (s, 3 H, NCH_3), 7.24 (d, J = 7.2 Hz, 2 H, ArH), 7.45 (m, 3 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (CH_3), 21.3 (CH_3), 29.0, 30.6, 123.6, 128.9, 129.2, 129.8, 136.0, 136.4, 137.9, 138.3, 150.8, 155.4, 160.6 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}N_3O_2$ $[M + H]^+$ 296.1406; found 296.1393.

6-(5-Chloro-2-methoxyphenyl)-1,3,7-trimethylpyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (3e): Using the general procedure, **1** (200 mg, 1.02 mmol), **2e** (173.9 mg, 1.02 mmol), and $BF_3{\cdot}OEt_2$(57.9 mg, 0.05 mL, 0.408 mmol) gave **3e** (280 mg) as a white powder. Yield: 79%. M.p. 240–242 °C. IR (KBr): $\tilde{\nu}$ = 2835, 1704, 1667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, CH_3), 3.53 (s, 3 H, NCH_3), 3.63 (s, 3 H, NCH_3), 3.72 (s, 3 H, OCH_3), 6.85 (d, J = 8.8 Hz, 1 H, ArH), 7.29 (d, J = 2.8 Hz, 1 H, ArH), 7.32 (dd, J = 2.4, 8.8 Hz, 1 H, ArH), 7.46 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7 (CH_3), 29.0, 30.6, 55.8, 111.9, 122.6, 125.9, 129.7, 129.8, 130.9, 137.1, 139.9, 150.8, 152.3, 155.5, 160.5 ppm. HRMS (ESI): calcd. for $C_{17}H_{16}ClN_3O_3$ $[M + H]^+$ 346.0938; found 346.0953.

6-(3-Chlorophenyl)-1,3,7-trimethylpyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (3f): Using the general procedure, **1** (200 mg, 1.02 mmol), **2f** (143.3 mg, 1.02 mmol), and $BF_3{\cdot}OEt_2$(57.9 mg, 0.05 mL, 0.408 mmol) gave **3f** (267.7 mg) as a white powder. Yield: 82%. M.p. 232–234 °C. IR (KBr): $\tilde{\nu}$ = 2954, 1707, 1663 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 3.54 (s, 3 H, NCH_3), 3.64 (s, 3 H, NCH_3), 7.36–7.41 (m, 3 H, ArH), 7.49 (s, 1 H, ArH) 7.55 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0 (CH_3), 29.0, 30.7, 123.8, 127.4, 128.6, 129.4, 129.5, 129.9, 134.2, 136.8, 137.9, 140.5, 150.7, 153.7, 160.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{14}ClN_3O_2$ $[M + H]^+$ 316.0859; found 316.0847.

1,3,7-Trimethyl-6-(thiophen-2-yl)pyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (3g): Using the general procedure, **1** (200 mg, 1.02 mmol), **2g** (114.2 mg, 1.02 mmol), and $BF_3{\cdot}OEt_2$(57.9 mg, 0.05 mL, 0.408 mmol) gave **3g** (223.7 mg) as a white powder. Yield: 76%. M.p. 221–223 °C. IR (KBr): $\tilde{\nu}$ = 2952, 1710, 1666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.72 (s, 3 H, CH_3), 3.53 (s, 3 H, NCH_3), 3.62 (s, 3 H, NCH_3), 7.13 (t, J = 3.6 Hz, 1 H, ArH), 7.43 (s, 1 H, ArH), 7.45 (dd, J = 0.8, 5.2 Hz, 1 H, ArH), 7.52 (d, J = 3.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2 (CH_3), 28.9, 30.6, 124.3, 127.6, 128.2, 129.5, 135.9, 136.6, 143.0, 148.1, 150.6, 160.1 ppm. HRMS (ESI): calcd. for $C_{14}H_{13}N_3O_2S$ $[M + H]^+$ 288.0781; found 288.0801.

6-(2,5-Dimethoxyphenyl)-1,3,7-trimethylpyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (3h): Using the general procedure, **1** (200 mg, 1.02 mmol), **2h** (169.3 mg, 1.02 mmol), and $BF_3{\cdot}OEt_2$(57.9 mg, 0.05 mL, 0.408 mmol) gave **3h** (280 mg) as a white powder. Yield: 80%. M.p. 194–196 °C. IR (KBr): $\tilde{\nu}$ = 2941, 1704, 1663 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, CH_3), 3.53 (s, 3 H, NCH_3), 3.62 (s, 3 H, NCH_3), 3.72 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 6.50 (d, J = 2.0 Hz, 1 H, ArH), 6.57 (dd, J = 2, 8 Hz, 1 H, ArH) 7.25 (d, J = 8.4 Hz, 2 H, ArH), 7.43 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0 (CH_3), 29.0, 30.6, 55.4, 55.5, 98.4, 104.7, 121.4, 122.5, 129.6, 131.7, 136.7, 140.3, 150.9, 153.8, 157.8, 160.7, 161.4 ppm. HRMS (ESI): calcd. for $C_{18}H_{19}N_3O_4$ $[M + Na]^+$ 364.1273; found 364.1264.

6-(5-*tert*-Butyl-2-methoxyphenyl)-1,3,7-trimethylpyrido[3,2-*d*]-pyrimidine-2,4-(1*H*,3*H*)-dione (3i): Using the general procedure, **1** (200 mg, 1.02 mmol), **2i** (196.9 mg, 1.02 mmol), and $BF_3{\cdot}OEt_2$(57.9 mg, 0.05 mL, 0.408 mmol) gave **3i** (313.2 mg) as a white powder. Yield: 83%. M.p. 234–236 °C. IR (KBr): $\tilde{\nu}$ = 2959, 1712, 1667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 [s, 9 H, $C(CH_3)_3$], 2.30 (s, 3 H, CH_3), 3.54 (s, 3 H, NCH_3), 3.64 (s, 3 H, NCH_3), 3.71 (s, 3 H, OCH_3), 6.85 (d, J = 8.8 Hz, 1 H, ArH), 7.25 (s, 1 H. ArH), 7.37 (dd, J = 2.4, 8.8 Hz, 1 H, ArH), 7.44 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1 (CH_3), 29.0, 30.6, 31.5, 34.2, 55.5, 110.3, 122.4, 126.7, 127.7, 129.5, 136.8, 140.1, 143.5, 150.9, 154.6, 160.7 ppm. HRMS (ESI): calcd. for $C_{21}H_{25}N_3O_3$ $[M + H]^+$ 368.1953; found 368.1969.

6-(2-Methoxyphenyl)-1,3,7-trimethylpyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (3j): Using the general procedure, **1** (200 mg, 1.02 mmol), **2j** (139.5 mg, 1.02 mmol), and $BF_3{\cdot}OEt_2$(57.9 mg, 0.05 mL, 0.408 mmol) gave **3j** (264.7 mg) as a white powder. Yield: 83%. M.p. 240–242 °C. IR (KBr): $\tilde{\nu}$ = 2833, 1708, 1659 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, CH_3), 3.53 (s, 3 H, NCH_3), 3.64 (s, 3 H, NCH_3), 3.74 (s, 3 H, OCH_3), 6.93 (d, J = 8.4 Hz, 1 H, ArH), 7.05 (t, J = 7.6 Hz, 1 H, ArH), 7.31 (dd, J = 1.6, 7.2 Hz, 1 H, ArH), 7.39 (td, J = 1.6, 9.6 Hz, 1 H, ArH) 7.44 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8 (CH_3), 28.9, 30.6, 55.4, 110.6, 120.9, 122.5, 128.3, 129.5, 130.0, 130.9, 136.9, 140.0, 150.8, 153.9, 156.7, 160.7 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}N_3O_3$ $[M + H]^+$ 312.1328; found 312.1341.

1,3,5,7-Tetramethyl-5,6,7,8-tetrahydropyrido[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (7): Using the general procedure, **1** (200 mg, 1.02 mmol), **2o** (61.2 mg, 2.04 mmol), and $BF_3{\cdot}OEt_2$(57.9 mg, 0.05 mL, 0.408 mmol) gave **7** (187.5 mg) as a white powder. Yield: 82%. M.p. 240–242 °C. IR (KBr): $\tilde{\nu}$ = 2951, 1684, 1637 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.07 (d, J = 5.2 Hz, 3 H, CH_3), 2.03–2.05 (m, 2 H, CH_2), 2.54–2.64 (m, 2 H, CH_2), 2.76 (s, 3 H, NCH_3), 2.91 (d, J = 12.8 Hz, 1 H, CH), 3.37 (s, 6 H, NCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6 (CH_3), 21.9, 28.2, 30.6, 33.5, 41.2, 57.7, 122.7, 137.9, 151.2, 160.2 ppm. MS: m/z = 246.13 $[M + Na]^+$. $C_{11}H_{17}N_3O_2$ (223.27): calcd. C 59.17, H 7.67, N 18.82; found C 59.39, H 7.58, N 18.71.

8-(4-Methoxyphenyl)-9-methyl-3*H*-pyrano[3,2-*f*]quinolin-3-one (6a): Using the general procedure, **5a** (200 mg, 0.995 mmol), **2c** (135.3 mg, 0.995 mmol), and $BF_3{\cdot}OEt_2$ (56.5 mg, 0.05 mL, 0.398 mmol) gave **6a** (261.8 mg) as a white powder. Yield: 83%. M.p. 226–228 °C. IR (KBr): $\tilde{\nu}$ = 2917, 2849, 1726 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.60 (s, 3 H, CH_3), 3.89 (s, 3 H, OCH_3), 6.61 (d, J = 9.6 Hz, 1 H, ArH), 7.04 (d, J = 8.8 Hz, 2 H, ArH), 7.58 (d, J = 8.8 Hz, 2 H, ArH), 7.62 (d, J = 9.2 Hz, 1 H, ArH), 8.25 (d, J = 8.8 Hz, 1 H, ArH), 8.37 (s, 1 H, ArH), 8.44 (d, J = 10 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (CH_3), 55.4, 112.0, 113.9, 116.0, 119.7, 123.13, 130.4, 130.8, 131.4, 132.4, 134.3, 138.5, 143.8, 153.5, 159.9, 159.9, 160.7 ppm. HRMS (ESI): calcd. for $C_{20}H_{15}NO_3$ $[M + H]^+$ 318.1136; found 318.1184.

9-Methyl-8-(thiophen-2-yl)-3*H*-pyrano[3,2-*f*]quinolin-3-one (6b): Using the general procedure, **5a** (200 mg, 0.995 mmol), **2g** (111.4 mg, 0.995 mmol), and $BF_3{\cdot}OEt_2$ (56.5 mg, 0.05 mL, 0.398 mmol) gave **6b** (236.1 mg) as a white powder. Yield: 81%. M.p. 236–238 °C. IR (KBr): $\tilde{\nu}$ = 2922, 2853, 1691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.82 (s, 3 H, CH_3), 6.60 (d, J = 10 Hz, 1 H, ArH), 7.19 (t, J = 4.8 Hz, 1 H, ArH), 7.51 (d, J = 5.2 Hz, 1 H, ArH), 7.61 (d, J = 9.2 Hz, 1 H, ArH), 7.65 (d, J = 3.2 Hz, 1 H, ArH), 8.21 (d, J = 9.2 Hz, 1 H, ArH), 8.33 (s, 1 H, ArH), 8.40 (d, J = 9.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4 (CH_3), 116.2, 120.1, 127.9, 128.2, 128.8, 130.2, 131.6, 134.0, 138.3, 153.5, 160.6 ppm. HRMS (ESI): calcd. for $C_{17}H_{11}NO_2S$ $[M + H]^+$ 294.0547; found 294.0583.

8-(2-Chlorophenyl)-9-methyl-3*H*-pyrano[3,2-*f*]quinolin-3-one (6c): Using the general procedure, **5a** (200 mg, 0.995 mmol), **2k** (139.8 mg.0.995 mmol), and $BF_3{\cdot}OEt_2$ (56.5 mg, 0.05 mL, 0.398 mmol) gave **6c** (240 mg) as a white powder. Yield: 75%. M.p. 206–208 °C. IR (KBr): $\tilde{\nu}$ = 2920, 2851, 1717 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 6.63 (d, J = 9.6 Hz, 1 H, ArH), 7.42 (m, 3 H, ArH), 7.52 (m, 1 H, ArH), 7.66 (d, J = 9.2 Hz, 1 H, ArH), 8.26 (d, J = 9.2 Hz, 1 H, ArH), 8.42 (s, 1 H, ArH), 8.46 (d, J = 10 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7 (CH_3), 112.2, 116.2, 119.9, 123.9, 127.3, 129.7, 130.0, 130.1, 132.4, 132.6, 134.3, 138.4, 139.0, 143.4, 153.8, 158.8,

160.6 ppm. HRMS (ESI): calcd. for $C_{19}H_{12}ClNO_2$ $[M + H]^+$ 322.0625; found 322.0629.

8-(4-Bromophenyl)-9-methyl-3*H*-pyrano[3,2-*f*]quinolin-3-one (6d): Using the general procedure, **5a** (200 mg, 0.995 mmol), **2l** (184 mg, 0.995 mmol), and $BF_3{\cdot}OEt_2$ (56.5 mg, 0.05 mL, 0.398 mmol) gave **6d** (287.7 mg) as a white powder. Yield: 81%. M.p. 264–266 °C. IR (KBr): $\tilde{\nu}$ = 2923, 1753, 1741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.57 (s, 3 H, CH_3), 6.62 (d, J = 10.0 Hz, 1 H, ArH), 7.50 (d, J = 8.4 Hz, 2 H, ArH), 7.64 (d, J = 8.4 Hz, 3 H, ArH), 8.24 (d, J = 9.6 Hz, 1 H, ArH), 8.40 (s, 1 H, ArH), 8.43 (d, J = 9.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0 (CH_3), 77.2, 112.1, 116.3, 120.1, 123.1, 123.4, 130.6, 131.0, 131.7, 134.3, 138.3, 138.9, 143.7, 153.7, 159.0, 160.5 ppm. MS: m/z = 365.93 $[M + H]^+$, 367.92 $[M + H + 2]^+$. $C_{19}H_{12}BrNO_2$ (366.21): calcd. C 62.32, H 3.30, N 3.82; found C 62.18, H 3.39, N 3.94.

8-(4-Chlorophenyl)-4,9-dimethyl-4,7-phenanthrolin-3(4*H*)-one (6e): Using the general procedure, **5b** (200 mg, 0.934 mmol), **2a** (131.3 mg, 0.934 mmol), and $BF_3{\cdot}OEt_2$ (53.02 mg, 0.048 mL, 0.373 mmol) gave **6e** (262.6 mg) as a white powder. Yield: 84%. M.p. 246–248 °C. IR (KBr): $\tilde{\nu}$ = 2918, 1658 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.57 (s, 3 H, CH_3), 3.90 (s, 3 H, NCH_3), 6.93 (d, J = 9.6 Hz, 1 H, ArH), 7.48 (m, 2 H, ArH), 7.58 (d, J = 8.4 Hz, 2 H, ArH), 7.79 (d, J = 9.6 Hz, 1 H, ArH), 8.26 (d, J = 9.2 Hz, 1 H, ArH), 8.49 (s, 1 H, ArH), 8.52 (m, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (CH_3), 30.3, 77.2, 113.6, 117.7, 121.4, 128.7, 130.4, 130.8, 131.2, 133.0, 133.2, 134.6, 138.6, 139.1, 142.6, 158.2 ppm. HRMS (ESI): calcd. for $C_{20}H_{15}ClN_2O$ $[M + H]^+$ 335.0938; found 335.0946.

1,3,6-Trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (4): The general procedure was used with **1** (200 mg, 1.02 mmol) and 3-nitrobenzaldehyde or 4-nitrobenzaldehyde (154 mg, 1.02 mmol). The mixture was stirred in toluene at room temperature for 10 min. After the addition of $BF_3{\cdot}OEt_2$ (57.9 mg, 0.05 mL, 0.408 mmol), the reaction mixture was heated at reflux for 12 h. After completion of the reaction as monitored by TLC, the reaction mixture was cooled and diluted with a saturated $NaHCO_3$ solution (50 mL). This was extracted with ethyl acetate (3 × 25 mL). The combined organic extract was washed with brine (50 mL) and dried (Na_2SO_4). The solvent was distilled off. The resulting crude product was purified by column chromatography over silica gel (230–400 mesh; petroleum ether/ethyl acetate, 80:20) to give **4** as a colorless solid.[20] M.p. 268–270 °C. IR (KBr): $\tilde{\nu}$ = 2929, 1694, 1637 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 3.47 (s, 6 H, NCH_3), 5.74 (s, 1 H, ArH), 11.42 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (CH_3), 27.9, 32.1, 93.7, 109.3, 136.8, 139.3, 151.7, 155.7 ppm.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra.

Acknowledgments

We thank the Council of Scientific and Industrial Research (CSIR) (New Delhi) and the Department of Science and Technology (DST) (New Delhi) for financial assistance. S. P and R. K. N are grateful to CSIR (New Delhi) for their Research Fellowships. We also thank the DST (New Delhi) for providing the NMR spectrometer (400 MHz), CHN analyzer, and FTIR spectrophotometer.

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Received: July 21, 2011
Published Online: September 28, 2011

