Indium(III) Chloride Catalyzed Convergent, Regioselective Synthesis of Annulated Quinoline and Pyridine Derivatives

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Abstract: A direct convergent two-component regioselective synthesis of annulated pyridine motif from 1-aminopenta-1,4-diene fragment and aromatic aldehyde by indium(III) chloride catalyzed reaction has been developed through a concerted pathway. A series of potentially bioactive pyranoquinoline, phenanthroline, and pyridopyrimidine derivatives has been synthesized in high yields by this protocol.

Key words: indium(III) chloride, imine, Lewis acid, concerted reaction, electrocyclization, pyranoquinoline, phenanthroline, pyridopyrimidine

The pyridine and quinoline derivatives play a central role as versatile building blocks of many natural products.[1] Many methods are available for the synthesis of quinoline and pyridine scaffolds containing derivatives due to their broad spectrum of biological activities with antiasthmatic, antibacterial, antimicrobial, anti-inflammatory, antipyretic, antidiabetic, cytotoxic, and also having tyrosine kinase inhibition properties.[2] Recently, it has been found that substituted pyridines efficiently inhibit HMG-CoA reductase and cholesterol transport proteins.[3] It was also shown that quinoline derivatives can be used as a functional material for the preparation of nano and meso structures with enhanced photonic and electronic properties.[4] On the other hand natural products possessing coumarin, quinolone, and uracil subunits show a wide range of bioactivity.[5] Among them pyranoquinoline and phenanthroline are main scaffolds of many bioactive alkaloids[6] viz. amphimedine, dutadrupin, helietidine, and geibalansine.[7] Again pyranoquinoline derivatives are used as potential pharmaceuticals for their psychotropic, antiallergic, and estrogenic activity.[8] Recently, the pyridopyrimidine derivatives has gained enhanced importance because of their biological and medicinal applications such as antibacterial,[9] antiallergic,[10] and CNS stimulants,[11] and inhibitors of enzyme adenosine kinase (AK)[12] or dihydrofolatereductase (DHFR).[13] Moreover, due to bioactivities these low-molecular-weight heterocycles have received considerable attention in pharmaceutical and agrochemical sectors.[14] These biodynamic properties associated with pyridopyrimidine, pyranoquinoline, and phenanthroline derivatives have made the synthesis of these molecules more demanding.

As a part of our program aiming at developing selective and environmentally friendly methods for the synthesis of biodynamic heterocycles[15] we explored novel synthetic strategies for the synthesis of annulated pyridine and quinoline, that is, pyridopyrimidine, pyranoquinoline, and phenanthroline derivatives. Besides traditional approaches,[16] the last two decades have seen the development of a number of useful methods for the synthesis of quinoline and pyridine derivatives, which include metal-catalyzed reaction, radical-mediated cyclization, iodine-mediated reaction, or Lewis acid catalyzed reaction.[17] These are certainly improvements over traditional approaches, but also have some limitations. Some are time consuming, not environmentally benign, required harsh reaction conditions or multistep reaction. In recent years, enormous progress has been made in expanding the scope of the direct addition of carbon–carbon double bonds to carbon–nitrogen double bonds either from prepared imines or from aldehydes and amines in a one-pot procedure by several transition-metal catalyst or Lewis acids.[18] During the last decade indium(III) chloride has emerged as a powerful Lewis acid catalyst imparting high regio- and chemoselectivity in various chemical reactions and also has attracted a great deal of interest due to its relatively low toxicity, stability in air and water, operational simplicity, strong tolerance to oxygen- and nitrogen-containing substrates and functional groups, and also recyclability.[19] Its potential as a Lewis acid catalyst for fundamental reactions, such as the Diels–Alder,[20] Friedel–Crafts,[21] Mukaiyama aldol,[22] and Sakurai–Hosomi allylation reactions,[23] has been extensively investigated.[24] Literature search reveals that addition of carbon–carbon double bond to imine bond by indium(III) catalyst[25] is quite rare.

We indeed recently demonstrated the synthesis of pyridine derivatives from 1-aminopenta-1,4-diene fragment and aromatic aldehyde by $BF_3{\cdot}OEt_2$-mediated reaction,[26] where the yield of product varied with catalyst loading, and better results were achieved only by using as high as 40 mol% $BF_3{\cdot}OEt_2$ along with pyrrole derivatives as side product (Scheme 1).

These results prompted us to search for an improved and efficient protocol to access the potentially bioactive pyridine-annulated scaffolds exclusively. Indium-catalyzed,

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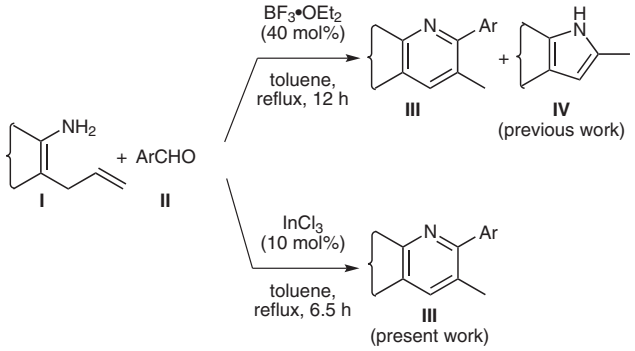
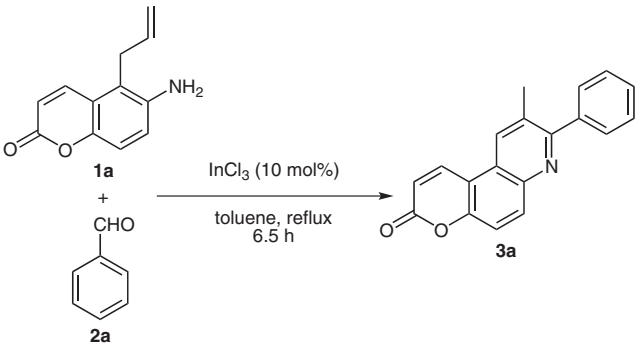


Scheme 1 Comparison between present and previous work

two-component convergent reaction of aldehydes and 1-aminopenta-1,4-diene fragment has not been explored so far for the synthesis of the aforesaid heterocyclic scaffolds. Herein we report the results of our investigation.

The required precursor **1a–c** were prepared according to our earlier published procedure.[15c] When the substrate **1a** was refluxed with aromatic aldehyde **2a** in the presence of indium(III) chloride (0.1 equiv with respect to substrate **1a**) in toluene for 6.5 hours, exclusively a new product **3a** was obtained (mp 240 °C, Scheme 2).The product **3a** has been characterized as 9-methyl-8-phenyl-3*H*-pyrano[3,2-*f*]quinolin-3-one from its spectral and analytical data.[27]



Scheme 2 Two-component synthesis of pyranoquinoline from 5-allyl-6-aminocoumarin and benzaldehyde

To optimize the reaction conditions, in order to obtain a maximum yield of the cyclized product, a set of experiments were carried out with the substrate **1a** by changing different parameters like nature of catalyst, solvent, and catalyst loading (Table 1). Among the various catalyst used coinage metal catalyst $AgSbF_6$, $AuCl_3$, and CuI gave the corresponding cyclized product in moderate yield (43–62%, Table 1, entries 9, 11, and 16).

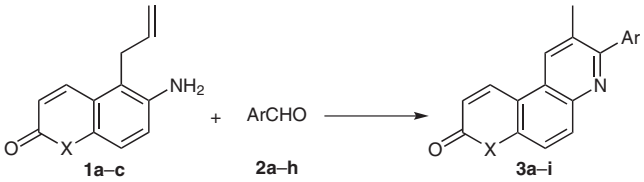
Other metal-based Lewis acids like $Yb(OTf)_3$, $AlCl_3$, $ZnCl_2$, and $FeCl_3$ also showed poor results (13–26%, Table 1, entries 12–15). When the reaction was performed in the presence of $InCl_3$ (0.1 equiv) in toluene, an excellent yield of the compound **3a** was obtained in 6.5 hours (Table 1, entry 2). On examining the role of the solvents for improving the efficiency of this reaction, it was found that the reaction in toluene gave better results compared to H_2O, EtOH, benzene, MeCN, and xylene as shown in Table 1 (entries 3–7). The reaction did not proceeded at all in the presence of Brønsted acid or in the absence of a catalyst (Table 1, entries 21 and 22), the reaction also failed at room temperature (Table 1, entry 8). To our delight, the two-component cyclization reaction proceeded smoothly and generated the desired product pyranoquinoline **3a** in 93% yield, giving the best results when 10 mol% of $InCl_3$ was used as a catalyst in the absence of any co-catalyst or activator (Table 1, entry 2). Other indium(III) salts InI_3, $InBr_3$, $In(OAc)_3$, and $In(OTf)_3$ also gave the same products (57–74% yields, Table 1, entries 17–20) but none gave better results than indium(III) chloride. Decrease in catalyst loading of $InCl_3$ to 5 mol% resulted in lowering the yield of the product even when the reaction was allowed to continue for a longer reaction time (Table 1, entry 1). The reaction was also examined by using 10 mol% $BF_3{\cdot}OEt_2$ as a catalyst which afforded only 35% yield of **3a** (Table 1, entry 10).

Table 1 Optimization Reaction Conditions for the Formation of Pyranoquinoline Derivatives

Entry	Catalyst	Solvent and conditions	Time (h)	Yield (%)[c]
1	$InCl_3$[a]	toluene, reflux	10	64
2	$InCl_3$[b]	toluene, reflux	6.5	93
3	$InCl_3$[b]	H_2O, reflux	6.5	32
4	$InCl_3$[b]	EtOH, reflux	6.5	39
5	$InCl_3$[b]	benzene, reflux	6.5	53
6	$InCl_3$[b]	MeCN, reflux	6.5	74
7	$InCl_3$[b]	xylene, reflux	6.5	68
8	$InCl_3$[b]	toluene, r.t.	6.5	–
9	$AgSbF_6$[b]	toluene, reflux	6.5	62
10	$BF_3{\cdot}OEt_2$[b]	toluene, reflux	6.5	35
11	$AuCl_3$[b]	toluene, reflux	6.5	43
12	$AlCl_3$[b]	toluene, reflux	6.5	26
13	$Yb(OTf)_3$[b]	toluene, reflux	6.5	13
14	$ZnCl_2$[b]	toluene, reflux	6.5	23
15	$FeCl_3$[b]	toluene, reflux	6.5	17
16	CuI[b]	toluene, reflux	6.5	46
17	InI_3[b]	toluene, reflux	6.5	82
18	$InBr_3$[b]	toluene, reflux	6.5	57
19	$In(OAc)_3$[b]	toluene, reflux	6.5	79
20	$In(OTf)_3$[b]	toluene, reflux	6.5	74
21	TfOH[b]	toluene, reflux	6.5	–
22	–	toluene, reflux	6.5	–

[a] Conditions: 5 mol%.
[b] Conditions: 10 mol% of catalyst used.
[c] Isolated yield of **3a**.

Table 2 $InCl_3$-Catalyzed Synthesis of Various Pyranoquinoline Derivatives and Phenanthroline Derivative



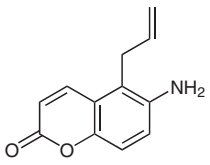
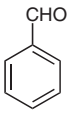
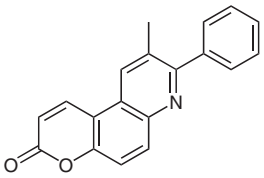
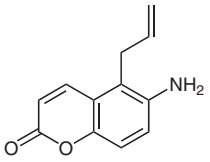
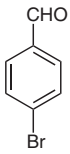
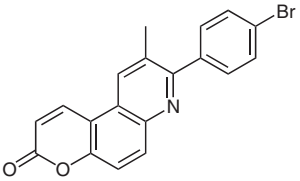
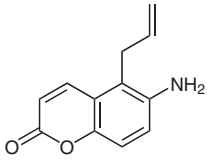
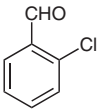
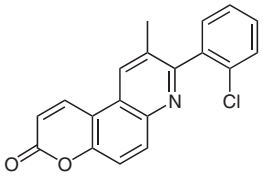
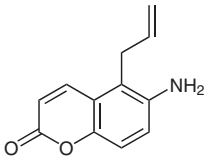
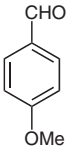
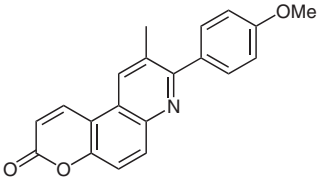
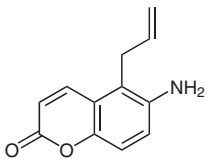
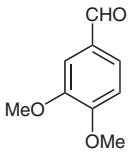
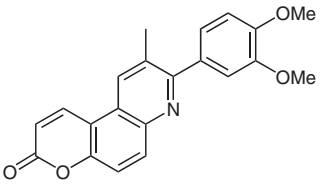
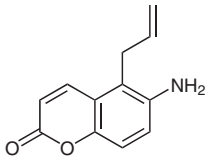
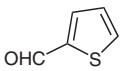
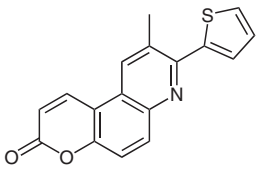
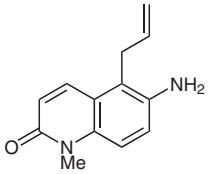
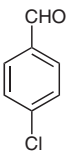
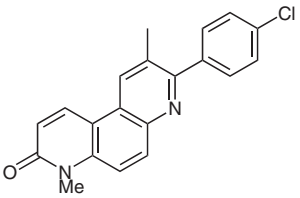
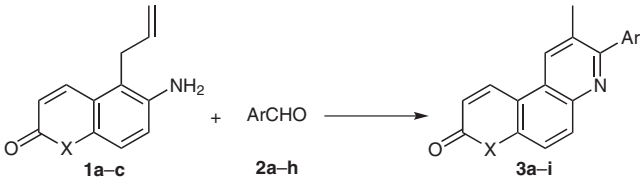
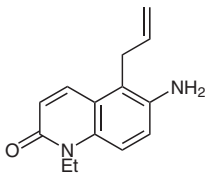
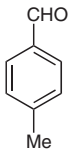
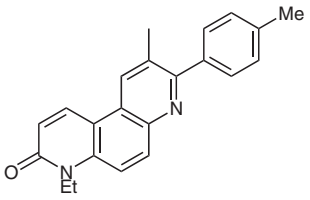
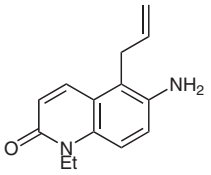
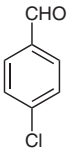
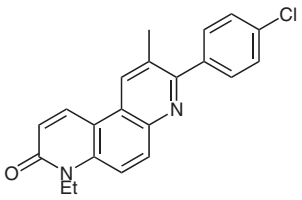
Entry	2-Allyl amine **1**	Aldehyde **2**	Product **3**	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**[27]	93
2	 **1a**	 **2b**	 **3b**	84
3	 **1a**	 **2c**	 **3c**	89
4	 **1a**	 **2d**	 **3d**	94
5	 **1a**	 **2e**	 **3e**	90
6	 **1a**	 **2f**	 **3f**	88
7	 **1b**	 **2g**	 **3g**	89

Table 2 $InCl_3$-Catalyzed Synthesis of Various Pyranoquinoline Derivatives and Phenanthroline Derivative (continued)



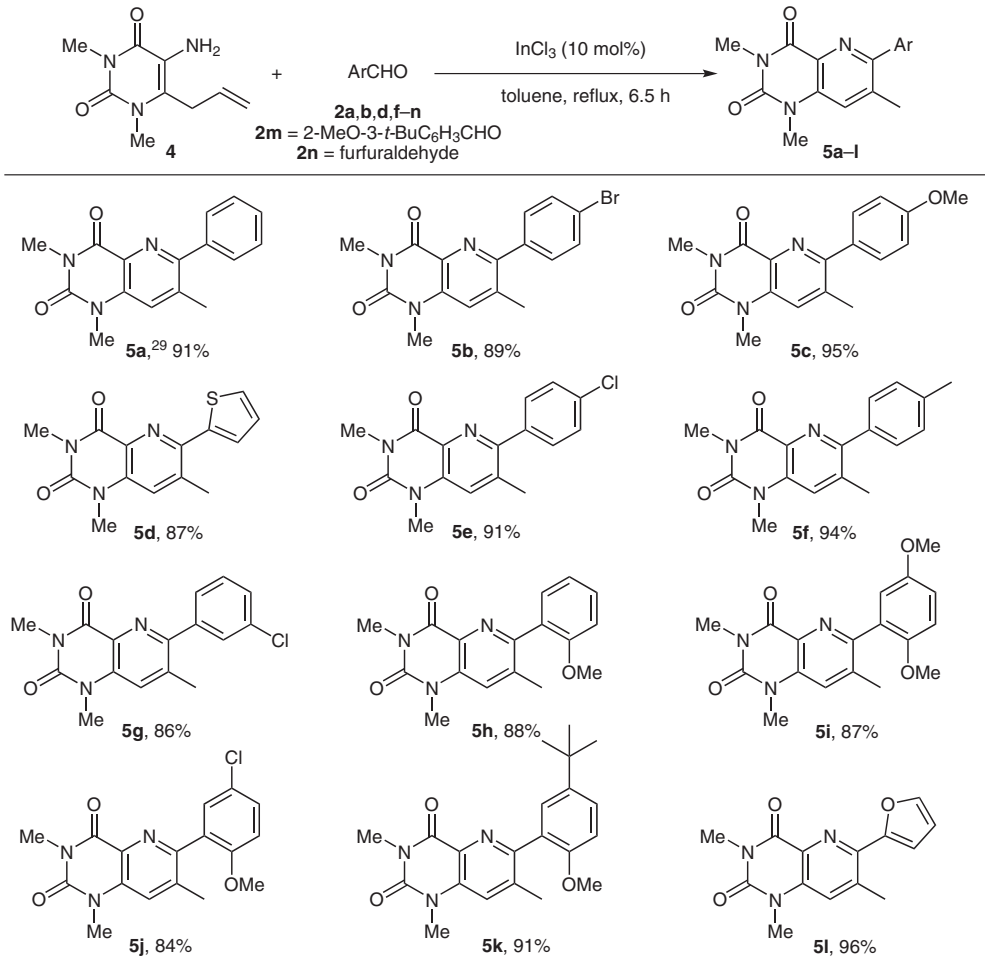
Entry	2-Allyl amine **1**	Aldehyde **2**	Product **3**	Yield (%)[a]
8	 **1c**	 **2h**	 **3h**	94
9	 **1c**	 **2g**	 **3i**	83

[a] Isolated yield.

The optimized reaction conditions were then applied to other substrates to examine the scope of this protocol to synthesize a range of pyranoquinoline derivatives (Table 2). When the substrate **1a** was treated with different aromatic aldehydes **2b–e** under the optimized reaction conditions, that is, 10 mol% $InCl_3$, toluene, under reflux for 6.5 hours, the corresponding cyclized products **3b–e** were obtained in 84–94% yield (Table 2. entries 2–5). In case of heterocyclic aldehyde like thiophene-2-carbaldehyde the desired product **3f** was obtained in 88% yield (Table 2, entry 6). The reaction does not seem to be affected by the substituents present in the aromatic ring of the aldehydes. We have also examined the application of this methodology for the synthesis of phenanthroline derivatives with the substrates **1b**,**c**. The reaction of various substituted benzaldehyde with **1b**,**c** under the optimized reaction conditions gave the corresponding phenanthroline derivatives in 83–94% yield (Table 2, entries 7–9).

As a part of our continuing efforts towards the synthesis of bioactive pyridopyrimidine derivatives[28] we have also tested this protocol with the substrate 6-allyl-5-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione.[15d] Various pyridopyrimidine derivatives **5a–l**[29] have been similarly synthesized in 84–96% yield from the corresponding aromatic and heteroaromatic aldehydes **2a**,**b**,**d**,**f–n** (Scheme 3). It should be noted that 1-aminopenta-1,4-diene fragment, that is, **1a–c** and **4** failed to give the corresponding expected cyclized product (annulated pyridine derivatives) with the reaction of nitro-substituted aromatic aldehyde viz. 3-$O_2NC_6H_4CHO$ and 4-$O_2NC_6H_4CHO$. The reaction of aliphatic aldehydes gave inseparable mixtures showing very close spots on TLC.

The formation of the pyridine derivatives **3** and **5** from the substrates **1** and **4**, respectively, can be rationalized by the initial formation of imine **A** from the reaction of 1-aminopenta-1,4-diene fragment and **2** by a simple condensation reaction. This intermediate **A** is not isolable under these reaction conditions, so the reaction may occur via a concerted pathway involving a sequence of steps viz. isomerization of the olefinic double bond simply catalyzed by Lewis acid $InCl_3$ or through tandem [1,5]-H and [1,7]-H shifts to generate the intermediate **C**, followed by a 6π-electrocyclization and [1,5]-hydrogen shift leading to the intermediate **E**, which may then undergo aromatization to give the desired products. Formation of **D** from **C** is somewhat unfavorable if R = $O_2NC_6H_4$, due to the strong electron-withdrawing property of the NO_2 group which may decrease the electron density of one of the interacting orbital of **B** for electrocyclization. Perhaps this may explain the failure of the reaction of **1** or **4** with NO_2-substituted aromatic aldehydes to give the expected cyclized products **3** and **5**. Earlier, pyridopyrrole derivatives were isolated as a side product from the reaction of **4** and **2** when $BF_3{\cdot}OEt_2$ was used in place of $InCl_3$.[26] This pyrrole derivative was obtained exclusively when nitro-group-containing aldehydes were used. But in our present work pyridopyrimidine derivatives are obtained exclusively by the indium(III) chloride catalyzed reaction. This is probably due to the greater Lewis acid character and complexation ability of In(III) than $BF_3{\cdot}OEt_2$. To form pyrrole derivatives, In(III) should coordinate with the olefinic π-bond

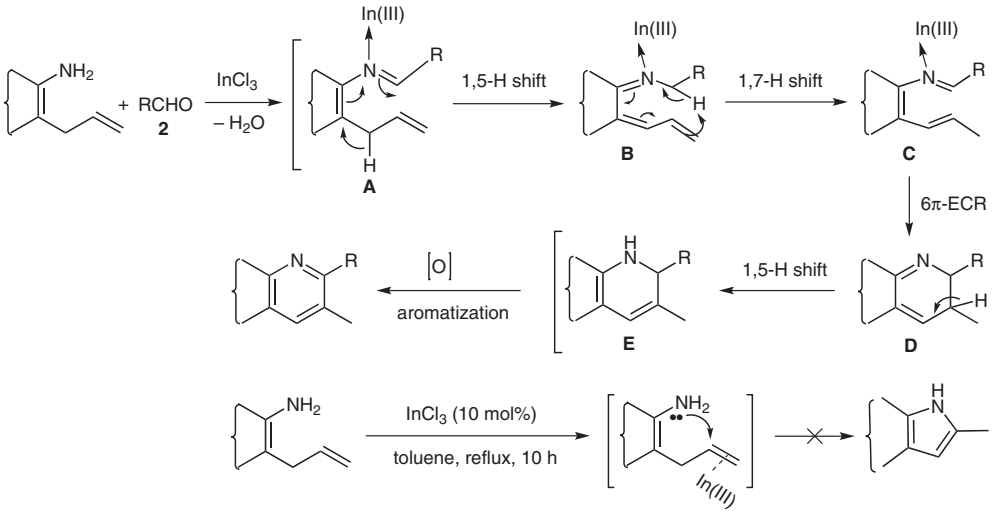


Scheme 3 Indium(III) chloride catalyzed synthesis of pyridopyrimidine derivatives

followed by a nucleophilic attack of the lone pair of the nitrogen. In(III) is very much prone to coordinate with the nitrogen lone pair rather than the olefinic double bond due to its greater Lewis acidity (Scheme 4).

To our knowledge this is the first report of a direct convergent, two-component regioselective synthesis of annulated pyridine derivatives from the 1-aminopenta-1,4-diene fragment and an aromatic aldehyde by the indium(III) chloride catalyzed reaction through a concerted pathway.

In conclusion, we have developed an efficient, rapid, and high-yielding procedure. Notable features of this protocol are mild reaction conditions, greater selectivity, improved



Scheme 4 The proposed mechanism for the synthesis of pyridine derivative

yields, cleaner reaction profiles, enhanced rates, and operational simplicity which make it a useful and attractive method for the construction of exclusively potentially bioactive pyranoquinoline, phenanthroline, and pyridopyrimidine derivatives of biological relevance from easily available starting materials.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(27) **Procedure for the Preparation of Compound 3a**
A mixture of 5-allyl-6-amino-2*H*-chromen-2-one (**1a**, 200 mg, 0.995 mmol, 1.0 equiv) and benzaldehyde (**2a**, 105.5 mg, 0.995 mmol, 1.0 equiv) was stirred in toluene at r.t. for 10 min. After addition of $InCl_3$ (21.9 mg, 0.0995 mmol, 0.1 equiv), the reaction mixture was refluxed for 6.5 h (completion of the reaction was monitored by TLC). The reaction mixture was cooled and to avoid any further workup, the mixture was directly dry packed over a silica gel (230–400 mesh) column. The pure product was obtained by eluting the column with PE–EtOAc mixture (4:1). The pure product thus obtained was recrystallized from MeCN to give compound **3a** as white powder with an isolated yield of 93%; mp 240 °C. IR (KBr): 2924, 2853, 1728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.57 (s, 3 H, CH_3), 6.63 (d, 1 H, *J* = 10.0 Hz, ArH), 7.47–7.54 (m, 3 H, ArH), 7.60–7.66 (m, 3 H, ArH), 8.28 (d, 1 H, *J* = 9.2 Hz, ArH), 8.40 (s, 1 H, ArH), 8.46 (d, 1 H, *J* = 9.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 112.1, 116.2, 119.8, 123.4, 128.5, 128.6, 128.9, 130.8, 131.4, 134.4, 138.4, 140.0, 143.7, 153.6, 160.3, 160.7 ppm. HRMS (ES^+): *m/z* calcd for $C_{19}H_{13}NO_2$ [M + H]: 288.0017; found: 287.9302.
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(29) **Procedure for the Preparation of Compound 5a**
A mixture of 6-allyl-5-amino-1,3-dimethylpyrimidine-2,4 (1*H*,3*H*)-dione **4** (200 mg, 1.02 mmol), benzaldehyde (**2a**, 108.1 mg, 1.02 mmol) was stirred in toluene at r.t. for 10 min. After addition of indium(III) chloride (22.5 mg, 0.102 mmol), the reaction mixture was refluxed for 6.5 h (the completion of the reaction was monitored by TLC). The reaction mixture was cooled and to avoid any further workup, the mixture was dry packed over a silica gel (230–400 mesh) column. The pure product was obtained by eluting the column with a PE–EtOAc mixture (1:1). The product thus obtained was recrystallized from MeCN to give compound **5a** as white powder. Yield: 91%; mp 218–220 °C. IR (KBr): 2948, 1714, 1666, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.51 (s, 3 H, CH_3), 3.54 (s, 3 H, NCH_3), 3.64 (s, 3 H, NCH_3), 7.41–7.48 (m, 4 H, ArH), 7.45–7.56 (m, 2 H, ArH), ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (CH_3), 29.0, 30.6, 123.6, 128.2, 128.4, 129.3, 129.8, 136.6, 137.9, 138.8, 150.8, 155.3, 160.7 ppm. ESI-HRMS: *m/z* calcd for $C_{16}H_{15}N_3O_2$ $[M + H]^+$: 282.1250; found: 282.1237.