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Indium chloride catalyzed intramolecular cyclization of *N*-aryl imines: synthesis of pyrrolo[2,3-*d*]pyrimidine annulated tetrahydroquinoline derivatives

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Abstract

The intramolecular aza Diels–Alder cyclization reaction of aldimines derived from aromatic amines and *N*-prenyl/cinnamyl derivatives of pyrrolo[2,3-*d*]pyrimidine were efficiently catalyzed by $InCl_3$ to afford the corresponding tetrahydroquinoline derivatives in good yields.
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Keywords: Imines; Tetrahydroquinoline; Pyrrolo[2,3-*d*]pyrimidine; Indium chloride

1. Introduction

The intramolecular aza Diels–Alder reaction is a useful synthetic tool for constructing N-containing six-membered heterocycles such as tetrahydroquinolines, octahydroacridines, tetrahydrochromanoquinolones and dihydro-4-pyridones.[1–5] Of these, the tetrahydroquinoline skeleton is found in a number of alkaloids and derivatives thereof and is found to exhibit a wide range of biological activities,[5–7] for example, indersine, oricine and veprisine and their derivatives exhibit psychotropic, anti-allergic, anti-inflammatory and estrogenic activities.[8–11]

Pyrrolo[2,3-*d*]pyrimidine derivatives are reported to possess various biological activities such as anti-HCV, anti-HIV type 1, anti-HSV, adenosine kinase inhibition, Aurora-A kinase inhibition and cAMP phosphodiesterase inhibition.[12–15] Many naturally occurring compounds such as mycalisine A, cadeguomycin and 2-deoxycadeguomycin are found to possess a pyrrolo[2,3-*d*]pyrimidine moiety.[16,17] Hence, new and efficient syntheses of such compounds are still important.

In continuation of our research[18–20] on the development of highly expedient methods for the synthesis of heterocyclic compounds of biological importance, we disclose here our preliminary investigations on the indium chloride promoted synthesis of novel pyrrolo[2,3-*d*]pyrimidine annulated tetrahydroquinoline derivatives through intramolecular aza Diels–Alder reaction of the *N*-alkenylimines of 1,3-dimethyl-1-pyrrolo[2,3-*d*]pyrimidine-2,4-dione-6-carbaldehyde **1**.

The substrate *N*-alkenyl 1,3-dimethyl-1-pyrrolo[2,3-*d*]-pyrimidine-2,4-dione-6-carbaldehydes **3a**–**b** were prepared in good yields (70–80%) from 1,3-dimethyl-1-pyrrolo[2,3-*d*]-pyrimidine-2,4-dione-6-carbaldehyde **1** by treatment with 1-bromo-3-methyl-but-2-ene **2a** or cinnamyl bromide **2b** in dry DMF in the presence of K_2CO_3 (Scheme 1).[21] The same reaction when carried out in 10% aqueous sodium hydroxide in the presence of a catalytic amount of PTC resulted in a lower yield of the products (40–58%).

Reaction of *N*-prenyl aldehyde **3a** with aromatic amines **4a**–**f** in the presence of indium trichloride generated the corresponding imine in situ which then underwent intramolecular aza Diels–Alder cycloaddition in one-pot

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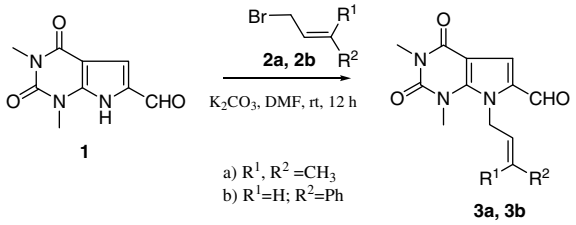


Scheme 1.

reaction to yield a mixture of *cis*- and *trans*-tetrahydroquinoline derivatives in moderate yield (55–65%) (route a).

However, in the absence of the catalyst reaction of aldehyde **3a** with aniline derivatives **4a–f** in refluxing ethanol yielded an isolable imine which could be cyclized in the presence of $InCl_3$ to give better yields of the products in short reaction times (85–93%) (route b) (Scheme 2).

The intermediate imines were characterized on the basis of ^1H NMR, ^{13}C NMR and elemental analysis. The structure of imine **5e** was further confirmed by X-ray crystal analysis[22] (Fig. 1).

In an effort to demonstrate the utility of the $InCl_3$ catalyzed aza Diels–Alder cyclization, the reaction was carried out with anilines with varied substituents and the results are summarized in Table 1.

In all cases the products were obtained as a mixture of cis- and trans-isomers, which were separated by column chromatography using silica gel. The ratios of the products were determined from the ^1H NMR spectra of the crude products.

The structures assigned to cycloadducts **6a–f** and **7a–f** were confirmed by the examination of their respective ^1H NMR spectra. The Ha proton of **6a** appeared as a doublet at δ 4.77 ($J = 6.3$ Hz). This small coupling constant is consistent with a cis-diaxial relationship for these two protons. Furthermore, the stereochemistry of H_a was confirmed by the observation of a strong NOE enhancement of H_a upon the irradiation of H_b (8.1%).

In a similar way, the Ha proton of **7a** exhibited a doublet at δ 4.63 ($J = 10.6$ Hz) indicating the trans stereochemistry of H_a with respect to H_b (Scheme 2).

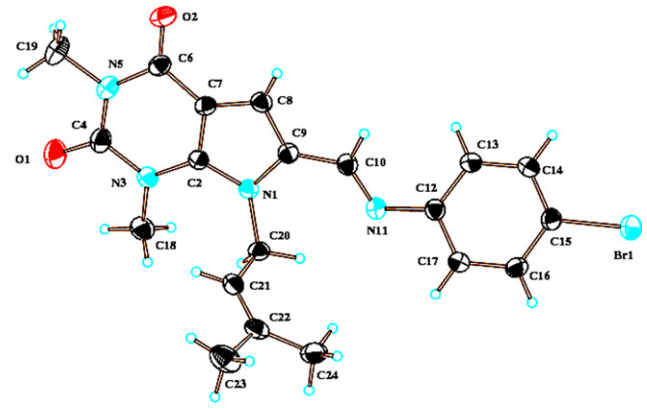


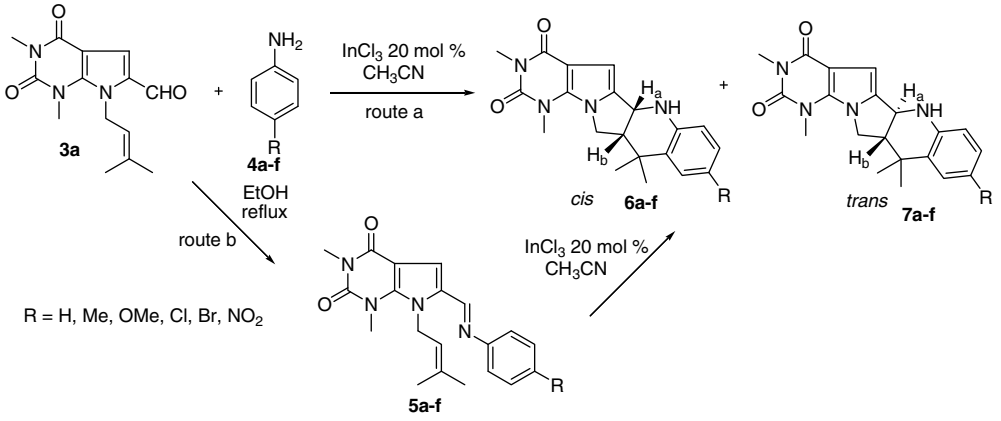
Fig. 1. Ortep diagram of compound **5e**.

Further, to examine the effect of substitution on the dienophile on the cycloaddition process, we prepared *N*-cinnamyl-pyrrolo[2,3-*d*]pyrimidine-6-carbaldehyde **3b** as previously described (Scheme 1). Aldehyde **3b** underwent intramolecular cycloaddition with **4a–f** in the presence of indium trichloride to afford the corresponding cis- and trans-cycloadducts **9a–f** and **10a–f** in good yields (87–90%).

The structures of cycloadducts **9a** and **10a** were established by the examination of their ^1H NMR spectra and NOE experiments. The enhanced yields and short reaction times for the formation of products **9a–f** and **10a–f** relative to the cycloaddition of **3a** with **4a–f** in acetonitrile, clearly showed the greater reactivity of the phenyl-substituted dienophile in **3b** (Scheme 3).

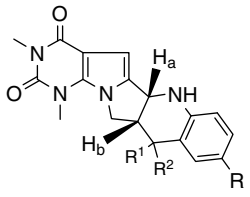
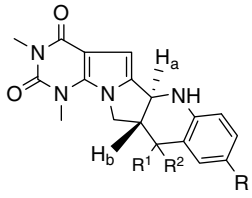
From the above results, it can be seen that the cyclization proceeds by a stepwise mechanism as shown in Scheme 4.[23–25] However, under thermal conditions without any Lewis acid, cyclization of the *N*-arylimines was not observed. This further confirms the stepwise mechanism.

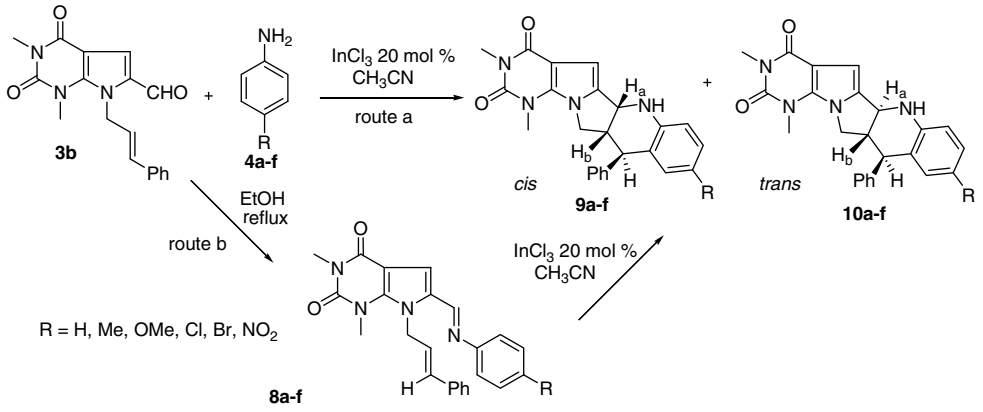
To study the scope and limitations of the cycloaddition reaction, the same reactions were carried out with the Lewis acid catalysts, namely, $BF_3{\cdot}OEt_2$, $Yb(OTf)_3$, $Sc(OTf)_3$ and $InCl_3$. Indium trichloride proved to be very efficient as we found the overall yield of the products was high (90%) when compared to the other Lewis acid catalysts. The results obtained for the cycloaddition of **3a**



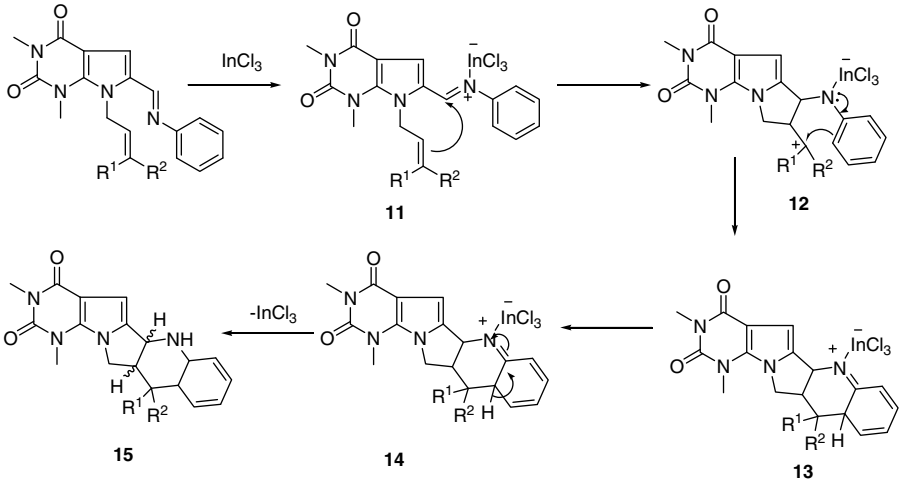
Scheme 2.

Table 1
Indium chloride catalyzed reaction of **3a/3b** with **4a–f** in the presence of $InCl_3$

Entry	R	R^1	R^2			Time (h)	Ratio cis:trans	Overall yield (%)
1	H	CH_3	CH_3	**6a**	**7a**	4.0	73:27	90
2	Me	CH_3	CH_3	**6b**	**7b**	3.0	80:20	85
3	OMe	CH_3	CH_3	**6c**	**7c**	2.5	90:10	87
4	Cl	CH_3	CH_3	**6d**	**7d**	3.5	84:16	92
5	Br	CH_3	CH_3	**6e**	**7e**	4.0	86:14	94
6	NO_2	H	CH_3	**6f**	**7f**	5.0	76:24	93
7	H	H	Ph	**9a**	**10a**	3.0	88:12	87
8	Me	H	Ph	**9b**	**10b**	2.5	84:16	91
9	OMe	H	Ph	**9c**	**10c**	3.0	82:18	85
10	Cl	H	Ph	**9d**	**10d**	3.0	90:10	93
11	Br	H	Ph	**9e**	**10e**	2.5	92:8	94
12	NO_2	H	Ph	**9f**	**10f**	3.5	90:10	90



Scheme 3.



Scheme 4. Proposed mechanism for the formation of the products.

and **4a** in the presence of various Lewis acid catalysts are summarized in Table 2.

The cis-isomer is prevalent in all of the cases studied. In the cycloaddition step of the reaction the cis products result

Table 2
Influence of Lewis acids on the reaction of **3a** with **4a**

Entry	Lewis acid	Reaction time (h)	Overall yield (%)
1	$BF_3{\cdot}OEt_2$	8	62
2	$Yb(OTf)_3$	5	78
3	$Sc(OTf)_3$	6	72
4	$InCl_3$	3	90

from the favourited *endo* transition states, imine is in the favoured *E*-configuration and the reaction is influenced by the bulky nature of the two alkyl groups.

Similarly, the yield proved to be strongly solvent dependent and with acetonitrile as solvent, the overall yields of the tetrahydroquinolines **6a**–**f** and **7a**–**f** were good.

In summary, this work describes our first attempt to use *N*-alkenyl pyrrolo[2,3-*d*] pyrimidine derivatives as useful precursors for the synthesis of pyrrolo[2,3-*d*]pyrimidine-annulated tetrahydroquinolines through $InCl_3$ mediated aza Diels–Alder reactions.

2. General procedure for the synthesis of imines 5a–f and 8a–f

A solution of **3a**,**b** (1 mmol) in ethanol (10 mL) was added dropwise to a solution of *p*-substituted aniline **4a**–**f** (1 mmol) in ethanol (5 mL). The mixture was heated at reflux for 4 h. The resulting solution was allowed to cool to room temperature and then was cooled in an ice-water bath for 0.5 h. Filtration provided the corresponding imines **5a**–**f** and **8a**–**f**.

2.1. 1,3-Dimethyl-7-(3-methylbut-2-enyl)-6-phenylimino-pyrrolo[2,3-d]pyrimidine-2,4-dione **5a**

Mp: 162 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 3H), 1.59 (s, 3H), 3.39 (s, 3H), 3.52 (s, 3H), 5.17 (d, $J = 5.0$ Hz, 2H), 5.59 (t, $J = 5.0$ Hz, 1H), 6.94–7.35 (m, 5H), 6.93 (s, 1H), 8.14 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.31, 24.52, 25.69, 29.31, 30.30, 104.84, 105.83, 112.52, 123.67, 123.78, 125.86, 130.37, 132.98, 133.00, 133.49, 136.85, 152.56, 158.24, 159.80. MS: *m*/*z*: 350.13 (M^+). Anal. Calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found: C, 68.68; H, 6.40; N, 15.86.

3. General procedure for the synthesis of tetrahydroquinoline derivatives

$InCl_3$ (20 mol %) was added to a mixture of substituted anilines (1 mmol) and **3a** or **3b** (1 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at 55–60 °C until the completion of the reaction as indicated by TLC; the mixture was then quenched with water and extracted with ethyl acetate. The organic layer was washed with water and dried over $MgSO_4$. The solvent was evaporated in vacuo and the crude product was chromatographed on silica gel (ethyl acetate–hexane) to afford *cis*- and *trans*-tetrahydroquinolines in good overall yields.

3.1. 7a,13b-cis-8,8-dimethyl pyrrolo[2,3-d]pyrimidine-[2,1-a]pyrrolo[4,3:2,3]-7a,8,13,13b-tetrahydroquinoline **6a**

Mp: 177 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 3H), 1.45 (s, 3H), 3.10 (dt, $J = 9.0$, 10.0 Hz, $1H_b$), 3.38 (s, 3H), 3.57 (s, 3H), 3.70 (t, $J = 10.0$ Hz, $1H_d$), 4.25 (dd, $J = 7.7$, 9.0 Hz, $1H_c$), 4.77 (d, $J = 6.3$ Hz, $1H_a$), 5.30 (s, 1H), 6.69 (dd, $J = 1.2$, 6.9 Hz, 1H), 7.00 (d, $J = 1.5$ Hz, 1H), 7.16 (dd, $J = 1.5$, 7.8 Hz, 1H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.62, 26.71, 29.51, 32.36, 35.16, 36.42, 55.69, 61.01, 100.52, 105.37, 120.13, 120.78, 123.95, 124.65, 131.39, 132.45, 138.19, 140.37, 154.52, 159.81 ppm. MS: *m*/*z*: 350 (M^+). Anal. Calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found: C, 68.76; H, 6.46; N, 15.81.

3.2. 7a,13b-trans-8,8-dimethylpyrrolo[2,3-d]pyrimidine-[2,1-a]pyrrolo[4,3:2,3]-7a,8,13,13b-tetrahydroquinoline **7a**

Mp: 174 °C, IR (KBr): 1678, 3394 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (s, 3H), 1.53 (s, 3H), 3.20 (td, $J = 9.7$, 10.4 Hz, $1H_b$), 3.41 (s, 3H), 3.52 (s, 3H), 3.55 (t, $J = 10.4$ Hz, $1H_d$), 4.11 (dd, $J = 7.5$, 9.7 Hz, $1H_c$), 4.63 (d, $J = 10.6$ Hz, $1H_a$), 5.20 (s, 1H), 6.49–7.10 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.72, 25.18, 27.82, 30.14, 34.59, 37.31, 52.77, 60.00, 99.32, 106.89, 121.15, 121.79, 122.13, 125.25, 130.30, 133.72, 139.33, 141.10, 152.77, 160.93 ppm. MS: *m*/*z*: 350 (M^+). Anal. Calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found: C, 68.71; H, 6.42; N, 15.84.

3.3. 7a,13b-cis-8,8-dimethyl-10-methylpyrrolo[2,3-d]-pyrimidine[2,1-a]pyrrolo[4,3:2,3]-7a,8,13,13b-tetrahydroquinoline **6b**

Mp: 178 °C, IR (KBr): 1689, 3389 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 3H), 1.41 (s, 3H), 2.24 (s, 3H), 3.10 (dt, $J = 9.7$, 10.0 Hz, $1H_b$), 3.27 (s, 3H), 3.32 (s, 3H), 3.47 (t, $J = 10.0$ Hz, $1H_d$), 4.17 (dd, $J = 7.8$, 9.7 Hz, $1H_c$), 4.63 (d, $J = 6.5$ Hz, $1H_a$), 5.20 (s, 1H), 6.27 (d, $J = 8.1$ Hz, 1H), 6.53 (s, 1H), 6.71 (d, $J = 8.1$ Hz, 1H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.39, 26.14, 26.75, 30.13, 31.32, 36.77, 37.40, 53.91, 62.76, 102.25, 107.53, 121.01, 121.75, 123.32, 124.81, 130.00, 131.05, 137.14, 141.52, 152.13, 160.34 ppm. MS: *m*/*z*: 364.19 (M^+). Anal. Calcd for $C_{21}H_{24}N_4O_2$: C, 69.21; H, 6.64; N, 15.37. Found: C, 68.39; H, 6.51; N, 15.48.

3.4. 7a,13b-trans-8,8-dimethyl-10-methylpyrrolo[2,3-d]-pyrimidine[2,1-a]pyrrolo[4,3:2,3]-7a,8,13,13b-tetrahydroquinoline **7b**

Mp: 180 °C, IR (KBr): 1673, 3381 cm^{-1} ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (s, 3H), 1.45 (s, 3H), 2.29 (s, 3H), 3.17 (td, $J = 9.6$, 10.1 Hz, $1H_b$), 3.30 (s, 3H), 3.35

(s, 3H), 3.51 (t, $J = 10.1$ Hz, $1H_d$), 4.20 (dd, $J = 7.8$, 9.6 Hz, $1H_c$), 4.55 (d, $J = 11.5$ Hz, $1H_a$), 5.25 (s, 1H), 6.31 (d, $J = 8.2$ Hz, 1H), 6.59 (s, 1H), 7.01 (d, $J = 8.2$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.14, 27.81, 28.65, 31.32, 31.98, 36.25, 36.93, 54.13, 60.27, 100.22, 102.75, 122.10, 123.17, 124.33, 124.48, 129.00, 130.10, 136.17, 143.15, 151.21, 159.03 ppm. Anal. Calcd for $C_{21}H_{24}N_4O_2$: C, 69.21; H, 6.64; N, 15.37. Found: C, 68.29; H, 6.48; N, 15.29.

References and notes

1. Boger, D. L. *Chem. Rev.* **1986**, *86*, 781.
2. Kiselyov, A. S.; Smith, L. S.; Armstrong, R. W. *Tetrahedron* **1998**, *54*, 5089.
3. Buonora, P.; Olsen, J. C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099.
4. Ma, Y.; Qian, C.; Xie, M.; Sun, J. *J. Org. Chem.* **1999**, *64*, 6462.
5. Kiselyov, A. S.; Smith, L. S.; Virgilio, A.; Armstrong, R. W. *Tetrahedron* **1998**, *54*, 7987.
6. Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357–7360.
7. Grieco, P. A.; Bahsas, A. *Tetrahedron Lett.* **1988**, *29*, 5855–5858.
8. Katritzky, A. R.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070. and references cited therein.
9. Yamada, N.; Kadowaki, S.; Takahashi, K.; Umezu, K. *Biochem. Pharmacol.* **1992**, *44*, 1211.
10. Faber, K.; Stueckler, H.; Kappe, T. *J. Heterocycl. Chem.* **1984**, *21*, 1177.
11. Johnson, J. V.; Rauckman, B. S.; Baccanari, D. P.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942.
12. Varaprasad, C. V. N. S.; Ramasamy, S. K.; Girardet, J. L.; Gunic, E.; Lai, V.; Zhong, Z.; An, H.; Hong, Z. *Bioorg. Chem.* **2007**, *35*, 25–34.
13. Srikanth, K.; Debnath, B.; Jha, T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 899–902.
14. Moriarty, K. J.; Koblish, H. K.; Garrabrant, T.; Maisuria, J.; Khalil, E.; Ali, F.; Petrounia, L. P.; Crysler, C. S.; Maroney, A. C.; Johnson, D. L.; Galemmo, R. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5778–5783.
15. Klumpp, S.; Frey, M.; Kleefeld, G.; Sauer, A.; Eger, K. *Biochem. Pharmacol.* **1989**, *38*, 949–953.
16. Wade, A. E.; Krawczyk, S. H.; Townsend, B. L. *Tetrahedron Lett.* **1988**, *29*, 4073–4076.
17. Edstrom, E. D.; Wei, Y. *Tetrahedron Lett.* **1994**, *35*, 8989–8990.
18. Rathna Durga, R.; Jayashankaran, J.; Raghunathan, R. *Tetrahedron Lett.* **2006**, *48*, 7571–7574.
19. Rathna Durga, R.; Jayashankaran, J.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 4139–4142.
20. Ramesh, E.; Elamparuthi, E.; Raghunathan, R. *Synth. Commun.* **2006**, *36*, 1431–1436.
21. *Experimental procedure for compounds* **3a/3b**: 1,3-Dimethyl-2,4-dioxo-1*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbaldehyde **1** (10 mmol) in DMF (20 mL) was treated with solid K_2CO_3 (16 mmol) and 3,3-dimethyl allylbromide/cinnamyl bromide (12 mmol). The mixture was stirred overnight at 20 °C, then water (50 mL) was added. The aqueous layer was extracted with ethyl acetate (4 × 20 mL), the combined organic layers were dried ($MgSO_4$) and the solvent was removed in vacuo and the crude product subjected to column chromatography (100–200 mesh) using hexane–ethyl acetate (8:2) as eluent. Compound **3a**: Pale yellow solid, mp: 152 °C; ^1H NMR (400 MHz, $CDCl_3$): 1.75 (s, 3H), 2.01 (s, 3H), 3.41 (s, 3H), 3.78 (s, 3H), 5.18 (d, $J = 4.5$ Hz, 2H), 5.33 (t, $J = 4.5$ 1H), 7.38 (s, 1H), 9.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2, 24.3, 30.4, 30.1, 32.4, 104.8, 117.7, 117.9, 130.9, 132.2, 150.4, 158.8, 147.5, 178.6; mass *m*/*z*: 275 (M^+); Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.09; H, 6.18; N, 15.27. Found: C, 60.77; H, 6.14; N, 15.23. Compound **3b**: Pale yellow solid, mp: 170 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.42 (s, 3H), 3.82 (s, 3H), 5.54 (d, $J = 4.8$ Hz, 2H), 6.22 (d, $J = 16.1$ Hz, 1H), 6.35 (dt, $J = 16.1$ Hz, 1H), 7.26–7.30 (m, 5H), 7.45 (s, 1H), 9.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 33.6, 31.5, 104.5, 117.7, 126.4 128.0, 128.7, 128.9, 130.5, 131.0, 133.2, 133.4, 135.2, 146.6, 150.1, 157.3, 178.3 ppm; mass *m*/*z*: 323 (M^+); Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.87; H, 5.26; N, 13.00. Found: C, 66.87; H, 5.26; N, 13.04.
22. Murugavel, S.; Ramesh, P.; Subbiah Pandi, A.; Ramesh, E.; Raghunathan, R. *Acta. Crystallogr., Sect. E* **2007**, *63*, o4108.
23. Linkert, F.; Laschat, S.; Kotila, S.; Fox, T. *Tetrahedron* **1996**, *52*, 955–970.
24. Magomedov, A. N. *Org. Lett.* **2003**, *5*, 2509–2512.
25. Spaller, M. R.; Thielemann, W. T.; Brennan, P. E.; Bartlett, P. A. *J. Comb. Chem.* **2002**, *4*, 516–522.