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$AlCl_3$-induced (hetero)arylation of thienopyrimidine ring: a new synthesis of 4-substituted thieno[2,3-*d*]pyrimidines

K. Shiva Kumar [a], Srinivas Chamakuri [a], Peddy Vishweshwar [b], Javed Iqbal [a,*], Manojit Pal [a,*]

[a] *Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, India*
[b] *Pharmaceutical Development, Aurigene Discovery Technologies Ltd., Miyapur, Hyderabad 500 049, India*

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ABSTRACT

$AlCl_3$ facilitated C–C bond forming reaction between 4-chloro-thieno[2,3-*d*]pyrimidines and (hetero)arenes affording a direct and single-step method for the synthesis of 4-(hetero)aryl substituted thieno[2,3-*d*]pyrimidines. A number of novel thienopyrimidines were prepared in good to excellent yields using this methodology. The molecular structure of a representative compound was established unambiguously by single crystal X-ray diffraction.

Pyrimidine nucleus fused with another heterocycle has been found to be an integral part of many natural products, agrochemicals and veterinary products.[1,2] This class of compounds has also found wide applications in the design and discovery of novel bioactive compounds and drugs.[3] Recently, thienopyrimidine that belongs to this class have attracted considerable interest because of their remarkable pharmacological properties.[4–7] For example, 2-alkoxy and 2-alkyl-subsituted thienopyrimidinones have shown significant antifungal and antibacterial activities,[4a–d] whereas some other derivatives exhibited promising anticonvulsant, angiotensin II or H_1 receptor antagonistic activities.[4e–h] Among thieno[2,3-*d*]pyrimidine derivatives, 3-amino-5,6-dimethyl-2-[4-(1-phenylmethyl)-1-piperazinyl]thieno[2,3-*d*]pyrimidin-4(3*H*)-one[5] **A** and 4-(4-methyl-1-piperazinyl)-2-methylthio-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidine[6] **B** (Fig. 1) exhibited remarkable affinity and selectivity for the 5-HT3 receptor.

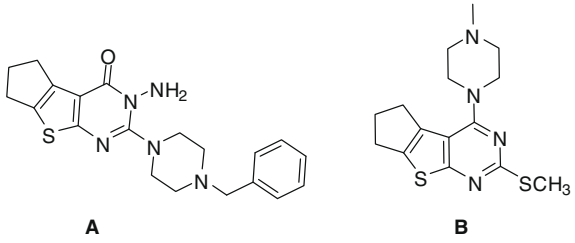


Figure 1. Examples of biologically active thieno[2,3-*d*]pyrimidin-2-ylmethan amines.

In pursuance of our research under the new drug discovery program, we became interested in the generation of a small-molecule library based on thieno[2,3-*d*]pyrimidine scaffold. Our library model is shown in Figure 2, which has three positions for the introduction of diversity into this framework. Since the C-4 substituent played a key role in displaying the pharmacological activities of thienopyrimidine derivatives[5–7] hence we focused on the C-4 position to introduce a range of diverse groups for the generation of a library of compounds. While a

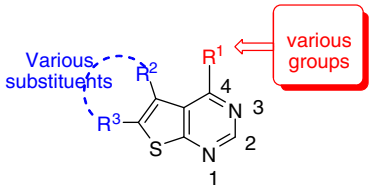
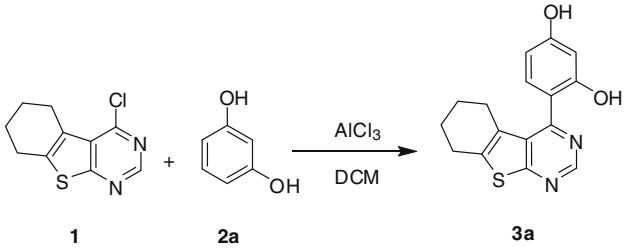


Figure 2. Diversity-based thieno[2,3-*d*]pyrimidine scaffold.



Scheme 1. $AlCl_3$-induced heteroarylation of resorcinol (**2a**) with 4-chloro thieno[2,3-*d*]pyrimidine (**1**).

* Corresponding authors. Tel.: +91 40 6657 1500; fax: +91 40 6657 1581.
E-mail addresses: manojitpal@rediffmail.com, palmanojit@yahoo.co.uk (M. Pal).

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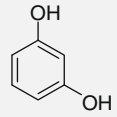
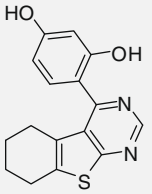
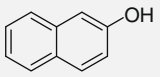
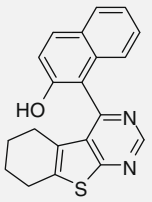
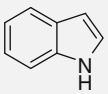
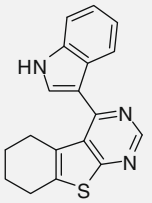
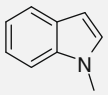
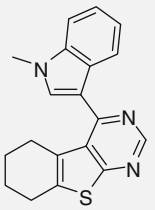
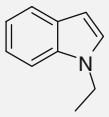
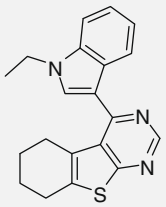
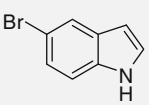
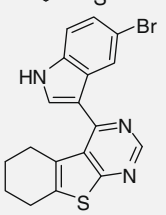
Table 1
Heteroarylation of **2a** with **1** under various conditions

Entry	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	CH_2Cl_2	rt	14	78
2	CH_2Cl_2	rt	48	73
3	CH_2Cl_2	40	8	75
4	$CHCl_3$	60	18	65
5	CH_3CN	60	12	60
6	EtOAc	60	15	60
7	THF	60	15	55

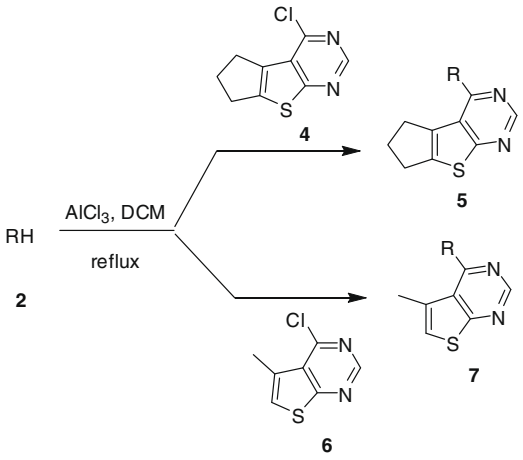
[a] Isolated yields after column chromatography.

number of reports are available on the introduction of aliphatic and aromatic amines at the C-4 position[8] of thieno[2,3-*d*]pyrimidine ring introduction of an aryl or heteroaryl moiety at the same position via C–C bond forming reaction is not common in the literature. Only one method based on Suzuki coupling reaction involving the use of palladium catalysts and boronic acids at 75–80 °C for 24 h has been reported recently.[9] The methodology required the use of degassed solvent to prepare the expected C–C coupled product. Moreover, the preparation of boronic acids is often cumbersome while we required a simple and straightforward method to prepare our target compounds. Herein, we describe our recent studies on the $AlCl_3$-induced C–C bond forming reaction[10] between thieno[2,3-*d*]pyrimidines and various (hetero)arenes leading to a direct and new synthesis of 4-(hetero)aryl substituted thieno[2,3-*d*]pyrimidines. To the best of our knowledge, this demonstration represents the first $AlCl_3$-induced

Table 2
Synthesis of 4-(hetero)aryl substituted 5,6,7,8 tetrahydrobenzothieno[2,3-*d*]pyrimidines (**3**) via $AlCl_3$-mediated C–C bond forming reaction between **1** and (hetero)arenes (**2**)[a]

Entry	Reactant (**2**)	Product (**3**)	Time (h)	Yield[b] (%)
1	 **2a**	 **3a**	8.0	75
2	 **2b**	 **3b**	12.0	75
3	 **2c**	 **3c**	8.0	75
4	 **2d**	 **3d**	7.0	73
5	 **2e**	 **3e**	7.0	72
6	 **2f**	 **3f**	7.0	74

[a] All the reactions were carried out using compound **1** (1.0 equiv), an appropriate arene or heteroarene **2** (1.0 equiv) and $AlCl_3$ (1.2 equiv) in dichloromethane (5 mL) at refluxing temperature.
[b] Isolated yields after column chromatography.



Scheme 2. $AlCl_3$-induced heteroarylation of **2** with **4** and **6**.

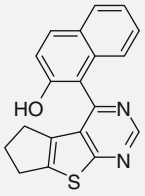
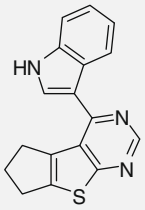
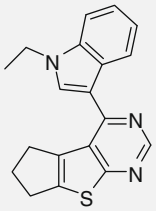
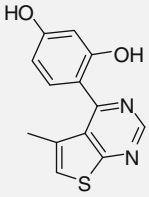
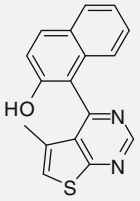
(hetero)arylation of a thienopyrimidine ring via C–C bond formation.

Initially, we decided to use 4-chloro thieno[2,3-*d*]pyrimidine[11a] (**1**) as a key starting material, which was reacted with resorcinol **2a** in the presence of $AlCl_3$ (Scheme 1).

The results of this study are summarized in Table 1. A mixture of **1** (1.0 equiv), **2a** (1.0 equiv) and $AlCl_3$ (1.2 equiv) in dichloromethane (5 mL) was stirred at room temperature for 14 h when both the reactants were consumed (monitored by TLC). After usual work-up the desired compound **3a** was isolated in 78% yield (Table 1, entry 1). Encouraged by this result, we then decided to examine the effect of time, temperature and solvents on this heteroarylation process. It was observed that the longer reaction time, for example, 48 h did not improve the product yield (Table 1, entry 2), whereas the reaction was completed within 8 h when carried out at reflux (Table 1, entry 3). Though the reaction was carried out initially in dichloromethane, a number of other solvents were examined (Table 1, entries 4–7). Despite the longer time allowed for the reaction to proceed, none of these solvents provided a better yield of **3a**.

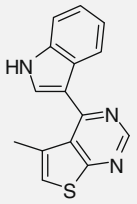
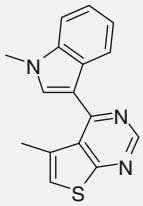
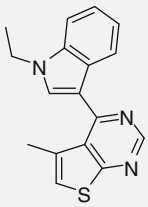
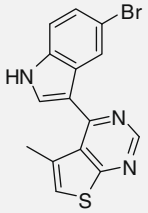
To test the generality and scope of this $AlCl_3$-mediated C–C bond forming process we then examined the reaction of chloro derivative **1** with a range of arene and heteroarenes **2** (Table 2).

Table 3
$AlCl_3$-mediated synthesis of 6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidine (**5**) and 6-methylthieno[2,3-*d*]pyrimidine (**7**)[a]

Entry	Reactant (**2**)	Product (**5** or **7**)	Time (h)	Yield[b] (%)
1	**2b**	 **5b**	12.0	72
2	**2c**	 **5c**	8.0	75
3	**2e**	 **5d**	7.0	74
4	**2a**	 **7a**	8.0	75
5	**2b**	 **7b**	12.0	70

(*continued on next page*)

Table 3 (*continued*)

Entry	Reactant (**2**)	Product (**5** or **7**)	Time (h)	Yield[b] (%)
6	**2c**	 **7c**	8.0	74
7	**2d**	 **7d**	7.0	75
8	**2e**	 **7e**	7.0	75
9	**2f**	 **7f**	7.0	73

[a] All the reactions were carried out using compound **4** or **6** (1.0 equiv), an appropriate arene or heteroarene **2** (1.0 equiv) and $AlCl_3$ (1.2 equiv) in dichloromethane (5 mL) at refluxing temperature.
[b] Isolated yields after column chromatography.

The reaction of chloro derivatives of other thieno[2,3-*d*]pyrimidine such as 4-chloro-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidine[11b] (**4**) and 4-chloro-5-methylthieno[2,3-*d*]pyrimidine[11c] (**6**) with various (hetero)arenes (**2**) (Scheme 2) was also investigated (Table 3). Based on the results summarized in Tables 2 and 3 it was evident that the heteroarylation of **2** proceeded well to give the desired products **3**, **5** and **7** in good yields. All the compounds synthesized were well characterized by spectral data (NMR, MS and IR). Additionally, the molecular structure of a representative compound **3d** was established unambiguously by single crystal X-ray diffraction (Fig. 3).[12]

All the chloro compounds, for example, **1**, **4** and **6** used in the present $AlCl_3$-mediated C–C bond forming reaction were prepared via a three-step method as shown in Scheme 3.[11] Thus construction of the appropriately substituted thiophene ring (**8**) in the first step followed by the fused pyrimidine ring in second step provided the desired thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivative **9**. Chlorination of compound **9** using $POCl_3$ provided the required chloro derivatives.

Mechanistically the present C–C bond forming reaction proceeds via (i) complexation of the azometine nitrogen of 4-chloro thieno[2,3-*d*]pyrimidine with $AlCl_3$ followed by (ii) nucleophilic attack by arenes or heteroarenes at the chlorine bearing carbon atom and finally and (iii) release of $AlCl_3$ affording the desired product (Fig. 4). It is evident that the complexation step is facilitated by the resonance stabilization of the complex formed (e.g., **X** and **Y**, Fig. 4). Nucleophilicity of the reacting arenes or heteroarenes is crucial in the present reaction, and therefore, the reaction proceeds

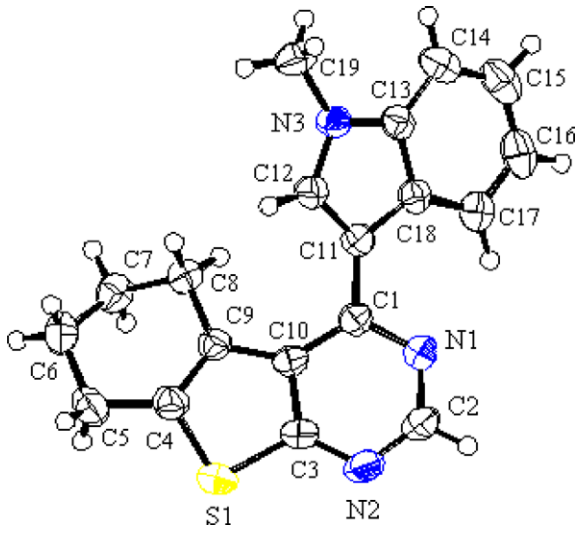
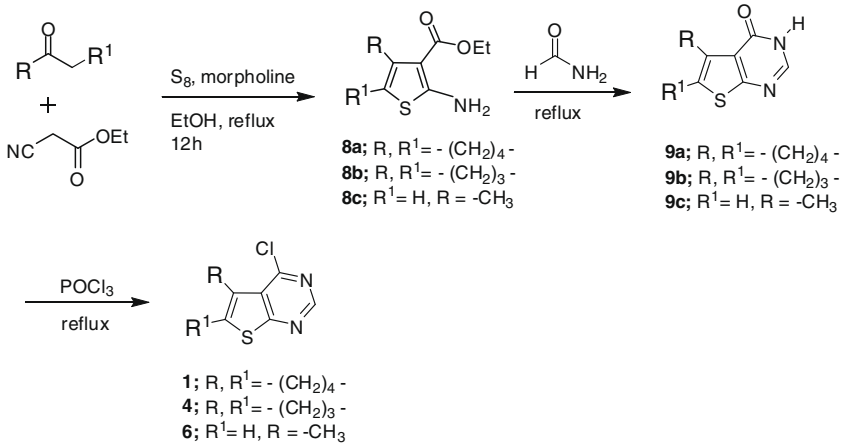


Figure 3. ORTEP of compound **3d**. The displacement ellipsoids are drawn at the 50% probability level. H atoms are shown by small circles of arbitrary radii.

smoothly with electron-rich arenes or heteroarenes, leading to the formation of desired compound. Notably, though a variety of heteroaryl chlorides containing the =C–C(Cl)=N– moiety have been utilized successfully earlier,[10] the reactivity of –C(Cl)=N–C=N– moiety fused with a thiophene ring towards an $AlCl_3$-induced C–C bond forming reaction has not been examined. Here, we have



Scheme 3. Preparation of 4-chloro thieno[2,3-*d*]pyrimidine (**1**), 4-chloro-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidine (**4**) and 4-chloro-5-methylthieno[2,3-*d*]pyrimidine (**6**).

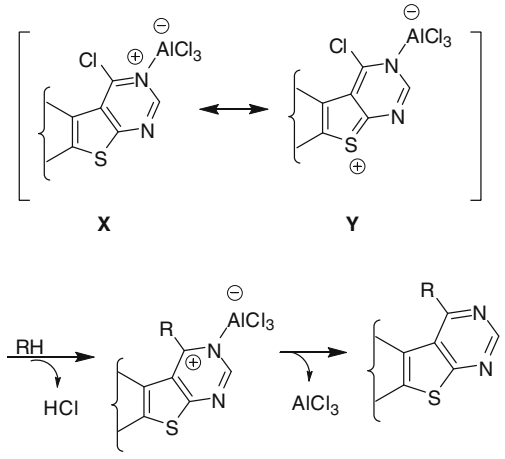


Figure 4. Proposed mechanism of the heteroarylation reaction.

shown that the chloro group of a thienopyrimidine (i.e., –C(Cl)=N–C=N– moiety) ring participated smoothly in the (hetero)arylation reaction affording a variety of novel heterocyclic compounds in good yields.

In conclusion, we have developed a new, operationally simple and direct method for the preparation of 4-(hetero)aryl substituted thieno[2,3-*d*]pyrimidines using readily available raw materials and $AlCl_3$. A variety of novel thienopyrimidines have been prepared by using this single-step methodology. Though the methodology works well only with electron-rich arenes or heteroarenes, the reaction however can be carried out at lower temperature for a shorter period of time.[9] Moreover, the methodology does not require the use of expensive transition metal catalysts or organometallic reagents, and therefore has potential to become a useful alternative towards the direct synthesis of diversity based thienopyrimidines of potential pharmacological interest.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.057.

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