# Facile Methods for the Synthesis of 5-Aryl and 5-Iodo Pyrrolo[2,3-*d*] pyrimidines

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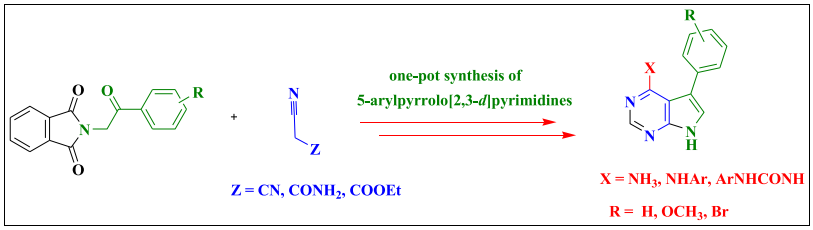


An efficient and environmentally benign one-pot method has been developed for the synthesis of 4-amino-5-arylpyrrolo[2,3-*d*]pyrimidines. Phthalimido acetophenones were reacted with cyanoacetamide to give 2-amino-4-phenyl-1*H*-pyrrole-3-carboxamides, which were further converted to 5-aryl-3*H*-pyrrolo [2,3-*d*]pyrimidin-4-ones. A novel method is also developed for the synthesis of 4-amino-5-iodopyrrolo [2,3-*d*]pyrimidines.

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## INTRODUCTION

The fused heterocyclic framework of pyrrolo[2,3-*d*] pyrimidine (**I**, Fig. 1) has been used as a prototype scaffold for the synthesis of a wide variety of analogs to study and improve their biological properties. Several of them have been reported to exhibit tyrosine kinase [1], adenosine kinase [2], and platelet-derived growth factor receptor inhibitor activities [3]. They were also reported to possess $A_1$-adenosine receptor antagonist activity [4] and anticancer activities [5,6]. A number of multistep methodologies have been reported to synthesize these compounds [6,7]. As shown in Figure 1, these target compounds are generally synthesized by two methods: initial synthesis of suitably substituted pyrrole nucleus followed by conversion to **I** (Method A, Fig. 1), and the latter is the other way round, that is, initial formation of pyrimidine skeleton followed by cyclization to **I** (Method B) [8].

In our drug discovery program, a variety of 5-aryl and 5-halopyrrolo[2,3-*d*]pyrimidin-4-amines revealed to be interesting for tyrosine kinase and adenosine kinase inhibitor activities. For generating new ligands with better pharmacological profiles, our structure-based drug design studies propose that hydrophobic substituent's such as phenyl and halogen at C-5 and amines at C-4 positions of pyrrolo[2,3-*d*]pyrimidine scaffold (**IV**, Fig. 2) can potentially improve the desired affinities towards the target. Contrary to this, any substituent bulkier than hydrogen at C-2 was indicated to be detrimental for the biological activity. Hence, it was felt worthwhile to synthesize a library of analogs without any substituent at C-2 of **IV**. Although literature shows a number of methods to synthesize pyrrolo[2,3-*d*]pyrimidines, most of them needed desulfurization of 2-thioxopyrrolo[2,3-*d*]pyrimidines (**II** or **III**, Fig. 1). This step involves the use of a large excess of raney nickel thereby making the methods environmentally unacceptable. Further, they also suffer from some practical disadvantages such as longer reaction times and inconsistent yields that are vital for process development [9,10]. On the basis of these observations, we sought to develop a method that is not only sufficiently facile and robust but also environment friendly.

During the course of our current research, two facile methods (Scheme 1 and 3) were developed to synthesize C-2 unsubstituted analogs of **IV**. These novel methods are highly efficient in synthesis of several 5-iodo and 5-aryl pyrrolo[2,3-*d*]pyrimidines. The details of the protocols are described in this communication.

## RESULTS AND DISCUSSION

As shown in Scheme 1 (Method 1), 4-amino-6-chloropyrimidine (**1**) was used as starting material to synthesize the target molecules. Compound **3** is utilized either from commercial sources or was synthesized by reported methods [11]. Iodination followed by Sonagashira cross-coupling reaction with TMS acetylene using $Pd(PPh_3)_2Cl_2$ as catalyst provided the alkyne **3** [12]. In the presence of iodine, base catalyzed cyclization of **3** gave

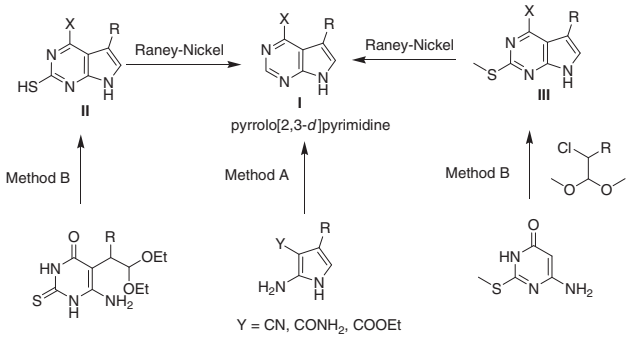



**Figure 1.** General methods for the synthesis of pyrrolo[2,3-*d*]pyrimidines.

5-iodopyrrolo[2,3-*d*]pyrimidine (**4**). Different inorganic bases were found to be suitable for this ring closure. However, reactions with $CsCO_3$, $K_2CO_3$ were found to be favorable not only in obtaining automatic TMS deprotection but also to give good yields of **4**.

Nucleophilic substitution of 4-chloro with different alkyl/aryl amines generated a library of 4-amino-5-iodopyrrolo[2,3-*d*]pyrimidines (**5**) in good yields [few of the synthesized compounds are depicted in Fig. 3(A): **4** and **5a–d**]. Similarly, Suzuki cross-coupling reaction of **5** with arylboronates provided 5-aryl analogs (**6**) in moderate yields. However, the necessity of involving different commercially inaccessible boronic acids hindered the utility of this method. Consequently, we decided to develop an alternative robust method to synthesize diverse analogs of **6**. It was envisaged that method A (Fig. 1) could be a facile process for the synthesis of target molecules (**6**). Therefore, Knorr pyrrole synthesis was adopted to synthesize key intermediates 2-amino-4-arylpyrrole-3-carboxamides/carbonitriles (**14**) [8,9]. Because several of the starting 2-aminoacetophenones (**12**) are either not commercially available or prohibitively expensive, an attempt was made to synthesize **12** from the respective 2-bromoacetophenones (**9**, Scheme 2). Heating of acetophenones under reflux with NBS and *p*-toluenesulfonic acid in acetonitrile resulted in quantitative yields of **9** [13].

Unusually conversion of **9** to **12** using known procedures resulted in poor yields in our hands. Synthesis of hexamine salts (**10**) followed by an acid-catalyzed hydrolysis resulted in low yields of **12**. In another attempt, synthesis

**Scheme 1.** General method for the synthesis of 5-iodopyrrolo[2,3-*d*] pyrimidines; reagents and conditions: (a) $I_2$ (2 equiv), $K_2CO_3$, DMF/$H_2O$, 45°C, 65%.; (b) TMS-acetylene, $Pd(PPh_3)_2Cl_2$, CuI, $Et_3N$, MeCN, RT, 2 h; (c) (i) $I_2$ (3 equiv), anhyd. $K_2CO_3$, MeCN; (ii) MeOH, $K_2CO_3$; (d) R-$NH_2$, $K_2CO_3$, DMF or Ar—$NH_2$, Pyridine, 80°C.; (e) $Pd(PPh_3)_2Cl_2$, $Ar(BOH)_2$, DME, 80°C, 8 h.

of azides (**11**) followed by reduction with Fe/$NH_4Cl$ was also low yielding. We surmise that rapid self-condensing nature of **12** could be responsible for these low yields. Thus, phthalimido acetophenones (**13**) were synthesized and used as synthetic equivalents of **12** (Scheme 3) [14,15]. Under basic reaction conditions, **13** readily produced **12** (Scheme 2) that was utilized *in situ* for the synthesis of **14** conveniently.

Because the pyrimidinone formation step requires strong base, such as sodium ethoxide, it was chosen as the base for the pyrrole formation as well. 2-Cyanoacetamide was treated with sodium ethoxide at ice-bath temperature, followed by **13** at 40–50°C. Upon consumption of **13**, triethyl orthoformate was added, and reaction continued for 4–8 h at 60–80°C; the reaction mixtures were then quenched with water, solvents evaporated, and 5-arylpyrrolo[2,3-*d*] pyrimidinones (**15**) were isolated by adjusting the pH to 7–8. Reactions with ethyl-2-cyanoacetate, instead of 2-cyanoacetamide, were also resulted in **14**; in such case, formamide is used to convert **14** to **15**. This one-pot method is highly efficient for the synthesis of several 5-aryl and 4,5-diarylpyrrolo[2,3-*d*]pyrimidines. Reflux of **15** with $POCl_3$ followed by nucleophilic substitution of 4-chloro with different amines resulted in 4-substituted-5-arylpyrrolo[2,3-*d*]pyrimidines (**6**) in good yields [some of the synthesized analogs are depicted in Fig. 3(B), **6a–b**, **15a–b**].

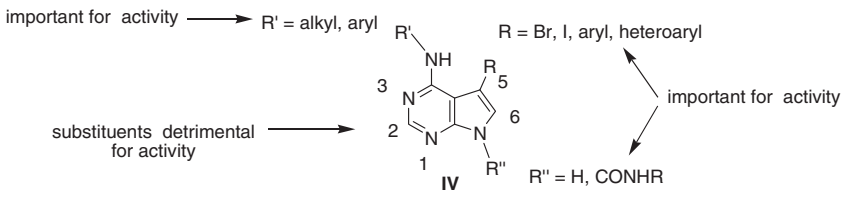



**Figure 2.** Pyrrolo[2,3-*d*]pyrimidine scaffold of medicinal interest.

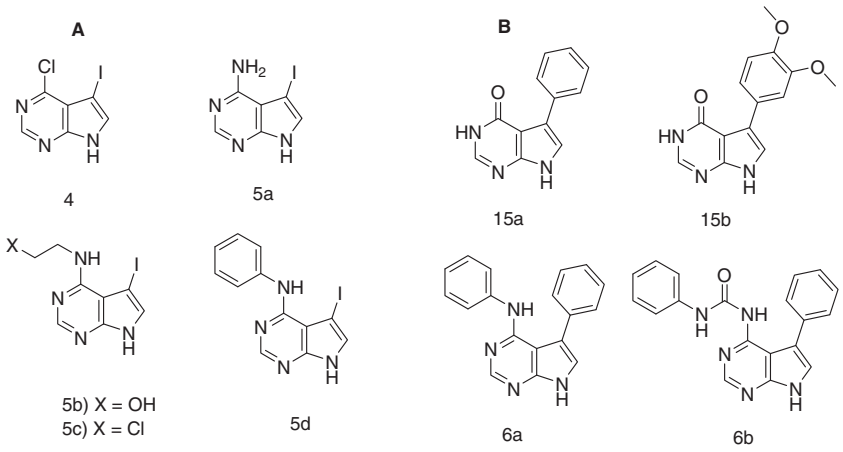
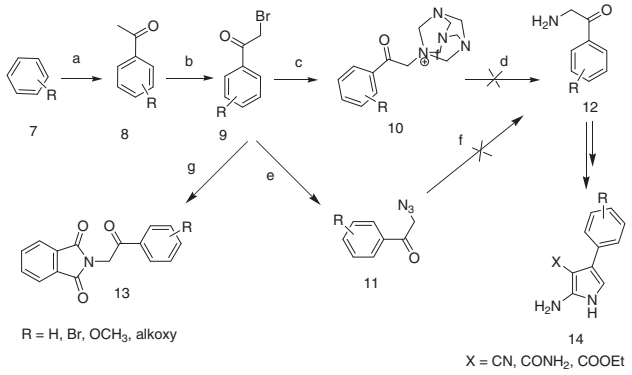
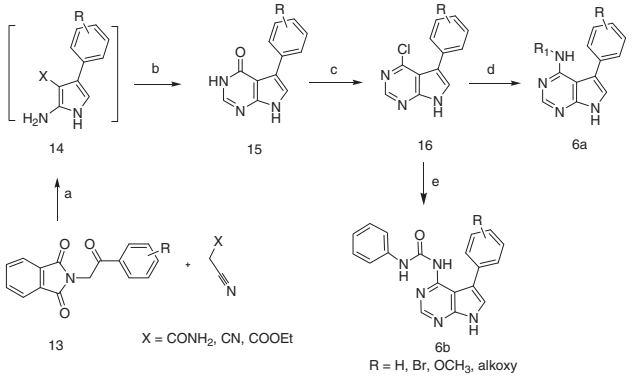



**Figure 3.** Few of the synthesized pyrrolo[2,3-*d*]pyrimidines.

**Scheme 2.** Synthesis of 2-aminoacetophenones and phthalimido acetophenones; reagents and conditions: (a) $ZnCl_2/Ac_2O$, RT; (b) NBS, *p*-toluenesulfonic acid, $CH_3CN$, 80°C; (c) hexamine, $CHCl_3$, RT; (d) HCl, 0°C – RT; (e) $NaN_3$, THF, RT; (f) $Fe/NH_4Cl$, THF/EtOH/$H_2O$ (4:1:0.5); (g) DMF, pot.phthalimide, RT.




**Scheme 3.** Synthesis of 5-arylpyrrolo[2,3-*d*]pyrimidines; reagents and conditions: (a) DMF, 3 equiv NaoEt/EtOH; (b) 5 equiv $CH(OEt)_3$ (if X = $CONH_2$), $HCONH_2$ (if X = COOEt), 60°C; (c) $POCl_3$, 4 h, 120°C; (d) R—$NH_2$, $K_2CO_3$, DMF; (e) $PhNHCONH_2$, 12 h, 80°C.




## CONCLUSION

The immense biological significance of pyrrolo[2,3-*d*] pyrimidine ring system generated considerable attention for the development of facile and environmental friendly methods. Although several multistep methodologies are existing for C-2 unsubstituted pyrrolo[2,3-*d*]pyrimidines, most of them involve use of large excess of raney nickel for desulfurization process making them environmentally unacceptable. The present study reveals two novel methods that are efficient to synthesize these analogs. Particularly, phthalimidoacetophenone method (Scheme 3) is highly useful for the synthesis of 5-aryl analogs of pyrrolo[2,3-*d*]pyrimidines. This one-pot method completely circumvents the use of metal catalysts thereby offers an environmental friendly protocol.

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