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An efficient synthesis of 4,6-substituted pyrrolo[3,2-*d*]pyrimidines by silver-catalyzed cyclization of acetylene amine

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ABSTRACT

A silver catalyzed cyclization of acetylene amine was developed to synthesize 4,6-substituted pyrrolo[3,2-*d*]pyrimidine, a bioactive isosteric scaffold of purine. Starting from simple commercially available acetylenes and pyrimidines, the method was found to be compatible with wide chemical functionalities, leading to a series of pyrrolo[3,2-*d*]pyrimidines in 84–91% yields.

Pyrrolo[3,2-*d*]pyrimidine (**1**) is a privileged heterocyclic framework and can be considered as a 9-carbon surrogate of purine. Consequently, these isosteric molecules containing pyrrolo[3,2-*d*]pyrimidine are widely recognized as purine nucleoside phosphorylase (PNP) inhibitors,[1] HER2/EGFR dual inhibitors,[2] antivirus reagents,[3] human 5′-methylthioadenosine phosphorylase (MTAP) inhibitors,[4] and DPP-IV inhibitors for the treatment of diabetes.[5] This scaffold also exhibits extensive biological activities,[6] such as dihydrofolate reductase inhibitors, neuropeptide Y5 receptor antagonists, and antitubulin agents.

Since the pyrrolo[3,2-*d*]pyrimidine structure does not occur in nature, a number of synthetic methods have been reported (Fig. 1). For example, (1) the most common methods utilized condensation of the 2,3-di-substituted pyrrole to form the pyrimidine ring;[7] (2) Madelung indole synthetic strategy was also conducted on the *ortho*-methyl-*N*-acyl pyrimidine to prepare the pyrrole moiety;[8] (3) alternatively starting from 6-methyl-5-nitropyrimidin, pyrrolo[3,2-*d*]pyrimidine was achieved by a Leimgruber–Batcho indole synthesis including sequential DMF formylation and reductive cyclization;[9] (4) and Sonogashira coupling was recently introduced to *ortho*-halogen aminopyrimidine, which was followed by a cyclization of the acetylene amine intermediate.[2b,10]

In our effort to prepare a new type of HER2/EGFR dual inhibitors, the pyrrolo[3,2-*d*]pyrimidine (**1**) with 4,6-substitution was highly needed (Fig. 2). Although the post 6-position functionalization on pyrrolo[3,2-*d*]pyrimidine scaffold is a direct choice, it always involved an aromatic hydrogen subtraction coupled with expensive and sensitive organolithium reagents.[11,12] Among the existing strategies mentioned above, Sonogashira coupling is the most convenient strategy to introduce the 6-substitution by varying the R_1 group on acetylene, however, such a coupling method was never reported on 4-phenylamino pyrimidine substrates. The only 4,6-substituted pyrrolo[3,2-*d*]pyrimidine example has to deploy a phenylether group as a placeholder and then a nucleophilic substituted by the specific 4-phenylamino groups.[2b] Herein, we wish to develop an efficient coupling method that can assemble 4,6-substituted pyrrolo[3,2-*d*]pyrimidines directly from 4-phenylamino pyrimidine and various acetylenes.

The initial preparation of substrates **5** was started from a commercially available pyrimidine **2** (Scheme 1). Nucleophilic aromatic substitution with aniline produced 4-phenylamino pyrimidine intermediate **3**, which showed lower Sonogashira reactivity to acetylene. Further halogen exchange to iodides **4** enhanced the yields of the desired acetylene amines **5.** Having various acetylene amines in hand, we first chose substrate **5a** to investigate the cyclization condition (Table 1). To our surprise, the most used

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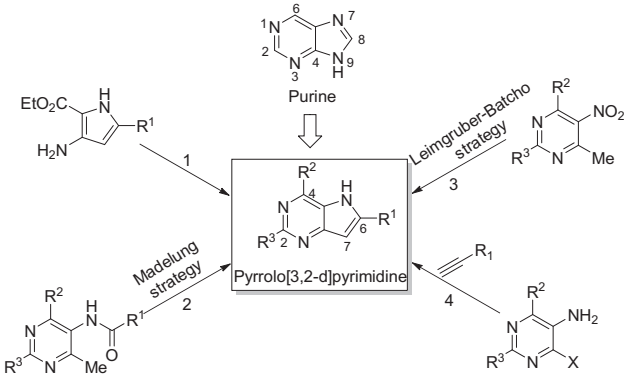


Figure 1. Representative synthetic methods to pyrrolo[3,2-*d*]pyrimidine.

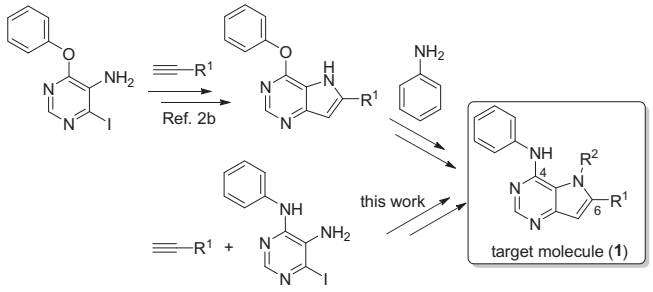
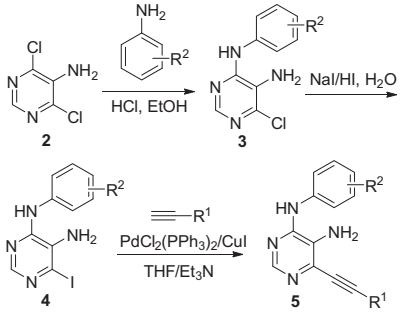


Figure 2. Synthetic strategy to 4,6-substituted pyrrolo[3,2-*d*]pyrimidine.

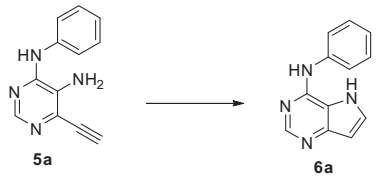


Scheme 1. Preparation of substrates **5**.

palladium catalysts in this cyclization gave a little amount of the 4,6-substituted pyrrolo[3,2-*d*]pyrimidine (entries 1–4, Table 1). Next examination of other transition metal catalysts found Cu(I) and Ag(I) led to the product in good yields (entries 5–9, Table 1), and $AgNO_3$ gave the best yield up to 82% (entries 10 and 11, Table 1). Further tuning of the reaction temperature showed raising the temperature to 90 °C marginally improved the yield to 88% (entries 12–14, Table 1). Although most solvents screened here generated similar results, we considered DMF as the optimal condition due to its good solubility of pyrimidine substrates (entries 15–17, Table 1).

To explore the scope of electronic and steric substituents on the 4-phenylamino moiety, various substituents were exposed to the

Table 1
The cyclization optimization of **5a** to **6a**[a]



Entry	Catalyst	Solvent	*T* (°C)	Time (h)	Yield (%)
1	$PdCl_2$	DMF	80	30	3
2	$Pb(OAc)_2$	DMF	80	30	2
3	$Pd(PPh_3)_2Cl_2$	DMF	80	30	5
4	$Pb(OAc)_2 + PPh_3$	DMF	80	30	7
5	$RhCl_3$	DMF	80	30	0
6	$RuCl_3$	DMF	80	30	0
7	AuCl	DMF	80	30	0
8	CuI	DMF	80	30	67
9	Ag_2O	DMF	80	30	80
10	$AgNO_3$	DMF	80	30	82
11	AgOAc	DMF	80	30	77
12	$AgNO_3$	DMF	70	40	81
13	$AgNO_3$	DMF	90	24	88
14	$AgNO_3$	DMF	100	20	85
15	AgNO3	Toluene	90	24	87
16	AgNO3	CH_3CN	90	24	81
17	AgNO3	THF	90	24	85

[a] To a solution of compound **5a** (0.3 mmol) in DMF (5 mL) was added catalyst (0.06 mmol, 20 mol %). The resulting mixture was stirred at a specific temperature until the reaction was completed and monitored by TLC.

optimized reaction condition (entries 1–10, Table 2). The position of substituents on the 4-phenylamino moiety was well tolerated; while the electron properties were also compatible in the cyclization reaction and gave comparable yields ranging from 84% to 91%. We also investigated the use of different acetylenes as coupling partners to 4-phenylamino pyrimidines. The results showed that both aliphatic and aromatic acetylenes are favorable in this reaction. All the reactions examined gave exclusive high yields of the desired 4,6-substituted pyrrolo[3,2-*d*]pyrimidines (entries 11–20, Table 2).

To demonstrate the robustness of the silver-catalyzed cyclization of acetylene amine, we selected some representative and interesting substrates, such as **6a** and **6k**, for scale-up experiments (20 mmol). The total yields (56% for **6a** and 59% for **6k** from the starting material **2**, see Supplementary data) were similar to those of the small-scale results listed in Scheme 1 and Table 2.

4,6-Substituted pyrrolo[3,2-*d*]pyrimidines **6** can undergo further transformations to add substituent diversity (Scheme 2). For example, a Mannich reaction occurred at 7-position of **6k** when it was treated with HCHO and $HNMe_2$, and a useful dimethylamino methyl group was introduced. In addition, an esterification of **6k** followed by methylation at 4-position gave ester **9** as a product.

In summary, an efficient synthesis of 4,6-substituted pyrrolo [3,2-*d*]pyrimidines was developed. Silver nitrite was found to be the robust catalyst to enable the cyclization of acetylene amine intermediates possessing diverse functionalities, leading to an efficient preparation of a series of potential bioactive molecules. This method would enrich our combinatorial library construction of HER2/EGFR dual inhibitors, which is undergoing in our laboratory.