One-pot Synthesis of 2,4-Diamino-substituted Thieno[3,2-*d*]pyrimidines

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An efficient one-pot synthetic approach to 2,4-diamino-substituted thieno[3,2-*d*]pyrimidines from 2,4-dichlorothieno[3,2-*d*]pyrimidine was described.

Keywords privileged structure, 2,4-dichlorothieno[3,2-*d*]pyrimidine, one-pot

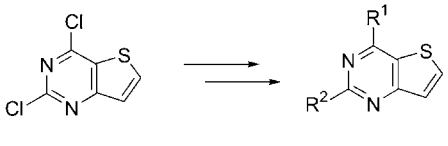
Introduction

As an ideal source for lead discovery, privileged structures refer to a single molecular framework that is able to provide ligands for diverse receptors. Since it was first addressed by Evans *et al.* in 1988,[1] many skeletons have been identified as privileged structures and this concept has attracted much attention of medicinal chemists. Nowadays, the construction of compounds libraries based on privileged structures followed by diverse screening has evolved into a practical strategy to obtain lead compounds with more efficiency.

Thienopyrimidine skeletons are typical privileged structures with occurrence in a variety of biological active compounds. For example, some 2-alkoxy or 2-alkyl-subsituted thienopyrimidinones show significant antifungal and antibacterial activities.[2a-2d] Modification on 5- and 6-position of thienopyrimidine has led to a series of *N*,*N*-diaryl ureas which potently inhibit both vascular-growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinases.[3] As a continuous work to our previous synthetic methodology study on selective dechlorination of 2,4-dichloropyrimidines, we intend to develop an efficient synthetic approach to introduce diverse functional groups through selective nucleophilic substitution of the chlorine at 2- and 4-position, so as to explore their chemical space. Our preliminary study results are described here.

In our research, 2,4-dichlorothieno[3,2-*d*]pyrimidine was chosen since it was readily prepared by literature method as starting material for 2,4-disubstitued thieno-[3,2-*d*]pyrimidine. Traditionally 2,4-disubstitued thieno-[3,2-*d*]pyrimidines were prepared in a stepwise way.[4] In our previous work, we have reported that the two chlorine atoms in 2- and 4-position showed different reactivity and chloride at 4-position can be removed under mild hydrogenation condition in the presence of $NaHCO_3$.[5] Considering this reactivity difference of the two chlorine atoms, we propose that various organic amines will attack these two chlorine atoms sequentially, therefore, introduction of two different amino groups in a one-pot way would be feasible. To our delight, this approach turned out to be a good alternative method to 2,4-diamino-substituted thieno[3,2-*d*]pyrimidines, which is much more efficient than traditional stepwise manner, which requires chromatographic purification upon each reaction step (Scheme 1).

Scheme 1 One-pot synthesis of 2,4-diamino-substitued thieno[3,2-*d*]pyrimidines



A1 **A2**

In a typical procedure, 2,4-dichlorothieno[3,2-*d*]-pyrimidine was dissolved in a suitable aprotic solvent [dimethylsulphoxide (DMSO), *N*-methyl-2-pyrrolidine (NMP) or *N*,*N*-dimethylformamide (DMF)]. To this solution, arylamines (1.5 equiv.) and $NaHCO_3$ (2 equiv.) were added and the mixture was heated to 100 ℃. It usually took 3—4 h to complete the replacement of 4-chlorine atom. Then, without intermediate separation, a variety of aliphatic amines (5—10 equiv.) was added directly and the mixture was heated again to 100 ℃ for

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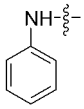
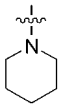
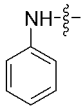
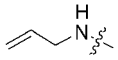
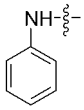
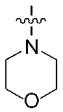
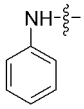
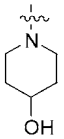
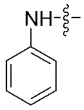
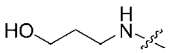
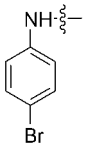
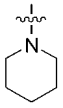
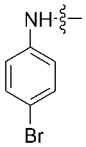
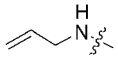
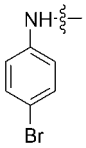
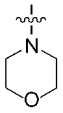
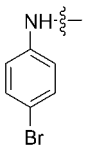
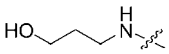
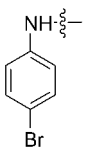
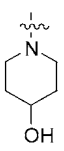
5—10 h. After routine workup and silica-gel chromatographic purification, 2,4-diamine-substituted thieno-[3,2-*d*]pyrimidines were obtained in moderate to good yields (38%—94%). The results are summarized in Table 1.

Table 1 One-pot synthesis of 2,4-diamine-substituted thieno[3,2-*d*]pyrimidines

Entry	R^1	R^2	Solvent	Time/h		Product	Yield/% (isolated)
				Step 1	Step 2		
1			DMSO	3	5	**A2-1**	88
2			DMF	3	10	**A2-2**	49
3			DMSO	3	5	**A2-3**	83
4			DMSO	3	5	**A2-4**	71
5			NMP	3	10	**A2-5**	75
6			DMSO	3	5	**A2-6**	79
7			DMF	3	10	**A2-7**	38
8			DMSO	3	5	**A2-8**	58
9			DMSO	3	5	**A2-9**	78
10			NMP	3	10	**A2-10**	38

Continued

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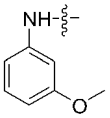
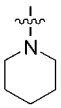
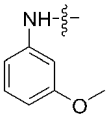
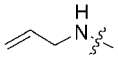
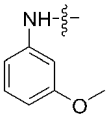
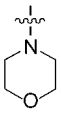
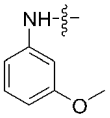
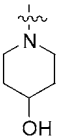
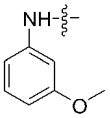
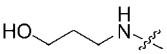
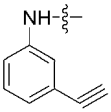
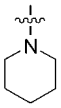
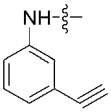
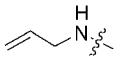
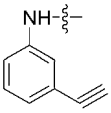
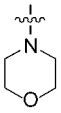
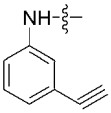
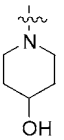
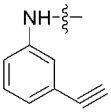
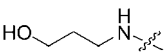
				Step 1	Step 2		
11			DMSO	3	5	**A2-11**	58
12			DMF	3	10	**A2-12**	65
13			DMSO	3	5	**A2-13**	72
14			DMSO	3	5	**A2-14**	90
15			NMP	3	10	**A2-15**	41
16			DMSO	3	5	**A2-16**	43
17			DMF	3	10	**A2-17**	94
18			DMSO	3	5	**A2-18**	90
19			DMSO	3	5	**A2-19**	93
20			NMP	3	10	**A2-20**	58

Because 4-chlorine atom is much more reactive than 2-chlorine atom, 2,4-dichlorothieno[3,2-*d*]pyrimidine reacted with various anilines to give mono-substituted compounds within 3 h, regardless of the electron-donating or -withdrawing substitutes at the aromatic rings. However, particularly in the cases of anilines bearing electron-withdrawing groups, excess anilines (1.5 equiv.) were necessary to prevent side-products formation. Boiling point of the second amine is an important parameter in step 2 reactions. Amines with low boiling point usually lead to low yields (Entries 2, 7 and 12) even large excess of amines (10 equiv.) are employed, while amines with high boiling points usually lead to satisfying yields. In the case of piperidine, low yield was usually resulted from the difficult products separation by flash silica-gel chromatography. For 3-aminopropan-1-ol, solvent seemed to be critical. NMP is the solvent of choice, the reaction did not proceed at all in DMSO or DMF, which was in accordance with literature reports.[6] Many functional groups (halogen, hydroxy and alkyne) at aromatic rings are tolerable, and this permits further derivation possible from these

2,4-diamino-substituted thieno[3,2-*d*]-pyrimidines via cross-coupling reaction, click reaction, ester- or amide-formation reaction.

In conclusion, a practical and efficient one-pot approach to 2,4-diamino-substituted thieno[3,2-*d*]-pyrimidines was developed. The obtained diamino-substituted products with more functional groups make it easy for further structure modifications through simple known reactions.

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