# A FACILE SYNTHESIS OF NEW 4-(PHENYLAMINO)THIENO[3,2-*d*]PYRIMIDINES USING 3-AMINOTHIOPHENE-2-CARBOXAMIDE

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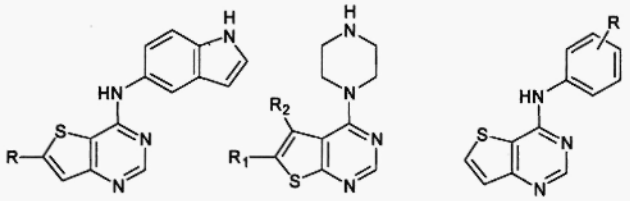
**Abstract:** Several new 4-(phenylamino)thieno[3,2-*d*]pyrimidine derivatives **3** were synthesized in high yield by the reaction of aniline derivatives and 4-chlorothieno[3,2-*d*]pyrimidine that can be easily prepared using 3-aminothiophene-2-carboxamide.

## Introduction

Thienopyrimidine derivatives have been found to have good medicinal and biological activities.[1] Recently, a novel class of thieno[3,2-*d*]pyrimidine **1** has been identified as potent inhibitors of VEGF receptor-2 kinase, which is a key component of the signaling pathway responsible for the sprouting and maturation of new blood vessels from tumors.[2] New thieno[2,3-*d*]pyrimidine derivatives **2** were also prepared and investigated as selective and potent ligands for the 5-$HT_3$ receptor.[3] 5-$HT_3$ receptor ligands have potential therapeutic applications in the treatment of psychosis, memory impairment, and drugs abuse.[4]



1 2 3

Since a variety of thienopyrimidine derivatives are needed for their biological importance, we herein wish to report a facile method for the preparation of new 4-(phenylamino)thieno[3,2-*d*]pyrimidine derivatives **3** using 3-aminothiophene-2-carboxamide **4**[5] in stead of methyl 3-aminothiophene-2-carboxylate.

## Results and Discussion

The cyclization reaction of methyl 3-aminothiophene-2-carboxylate with formic amide was not efficient in forming **5** by previous known method.[6] Yield of the product does not exceed 50% and the reaction needs two steps, a very high temperature and longer reaction time. We found a facile synthetic route to **3** started from the condensation reaction of 3-aminothiophene-2-carboxamide **4**[5] with excess

boiling formic acid for 4 h to give thieno[3,2-*d*]pyrimidin-4(3*H*)-one **5** (mp 222-223°C)[6] in 90% yield. The resultant **5** was easily converted in 2h to 4-chlorothieno[3,2-*d*]pyrimidine **6** (mp 123-124°C)[6] using excess $POCl_3$. The conversion of **6** to the new 4-(phenylamino)thieno[3,2-*d*]pyrimidine derivatives **3** was accomplished by treatment with the appropriate aniline for 3-5 h in a mixture of 2-propanol/THF/ HCl(trace) in high yields (85-95%) as shown Table-1.

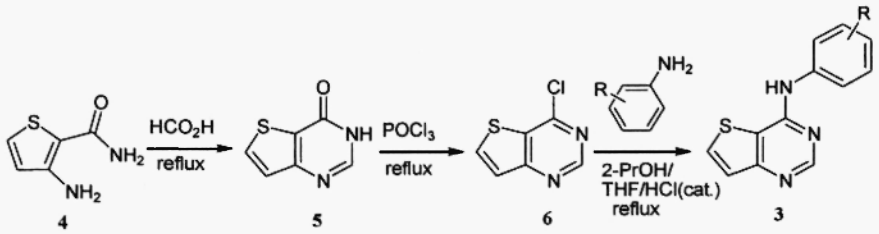



**Table-1**: 4-(Phenylamino)thieno[3,2-*d*]pyrimidine **3**[a]

| | R | isolated yield(%) | mp(°C) |
|---|---|---|---|
| **3a**[7] | 3'-Br | 92 | 201-202 |
| **3b** | H | 88 | 186-188 |
| **3c** | 2'-$CH_3$ | 90 | 220-221 |
| **3d** | 4'-Cl | 95 | 101-102 |
| **3e** | 3'-I | 85 | 139-140 |
| **3f** | 4'-OMe | 91 | 155-157 |
| **3g** | 3',5'-diCl | 92 | 167-169 |
| **3h** | 2,6'-diEt | 90 | 65-67 |
| **3i** | 4'-*i*Pr | 88 | 121-122 |

[a] Satisfactory spectra for all new compounds were obtained in measurements of $^1H$ and $^{13}C$ NMR and MS

**References**

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7. Compound **3a**: yield 92%; mp 201-202°C; $^1H$ NMR(300MHz, DMSO-$d_6$): δ 9.80(s, 1H, NH), 8.64(s, 1H, pyrimidine), 8.24(d, *J*=6.0 Hz, 1H, thiophene), 8.18(s, 1H, H-2'), 7.82(dd, 1H, H-4'), 7.48(d, *J*=6.0 Hz, 1H, thiophene), 7.30(t, 1H, H-5'), 7.25(dd, 1H, H-6'); $^{13}C$ NMR: δ 115.8, 120.1, 121.2, 123.6, 124.4, 125.6, 130.6, 134.6, 141.0, 153.8, 154.8, 160.5; MS(m/z):306($M^+$).

Received on August 12, 2006.