Tetrahedron Letters 51 (2010) 3597–3598

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient formation of 4,6-disubstituted pyrrolo[2,3-*d*]pyrimidines: a novel route to TWS119, a glycogen synthase kinase-3β inhibitor

Anand Mayasundari, Naoaki Fujii *

Medicinal Chemistry Center, Department of Chemical Biology and Therapeutics, St. Jude Children's Research Hospital, Memphis, TN 38105, United States

ARTICLE INFO

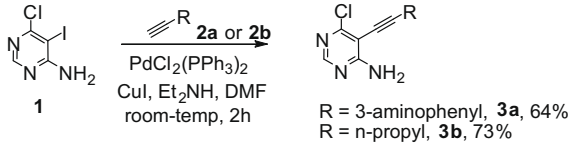
Article history:
Received 12 April 2010
Revised 3 May 2010
Accepted 7 May 2010
Available online 12 May 2010

ABSTRACT

A concise synthesis of 4,6-disubstituted pyrrolo[2,3-*d*]pyrimidines is described. The key step involves the formation of an ether or thioether linkage along with concurrent ring closure in one-pot to yield the desired product in only two steps from a common intermediate. The reaction is chemoselective to incorporate phenol, thiophenol, and thiol. This method enabled efficient production of TWS119, a glycogen synthase kinase-3β inhibitor.

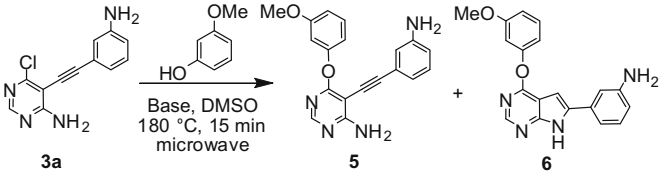
Pyrrolo[2,3-*d*]pyrimidine is a deazapurine chemical scaffold commonly used to create many bioactive compounds and drug candidates such as antifolates[1] and antitumor agents.[2] While numerous examples of the 4-amino-substituted pyrrolo[2,3-*d*]pyrimidine are reported, those of 4-ether or 4-thioether-substituted pyrrolo[2,3-*d*]pyrimidines are rather limited.[3] This is presumably due to the lack of reliable and efficient synthetic method for the latter two. TWS119 is a glycogen synthase kinase-3β inhibitor of the 4-ether-substituted pyrrolo[2,3-*d*]pyrimidine scaffold that induces neuronal differentiation in pluripotent murine embryonal carcinoma and embryonic stem cells.[4] It activates the canonical Wnt pathway in cultured hepatic stellate cells[5] and suppresses alveolar rhabdomyosarcoma.[6] Only one patented method[7] has been disclosed for the synthesis of TWS119. However, the preparation of starting material for this method is tedious and in low yield; key reaction step for the 4-ether formation in this method is extremely sluggish and also in low yield; and this method was used to produce only pyrrolo[2,3-*d*]pyrimidines in which 6-position is substituted with an aromatic group (Scheme S1, Supplementary data). To improve the productivity and generality, we developed a new method for efficiently producing 4,6-disubstituted pyrrolo[2,3-*d*]pyrimidines including TWS119.

The first step is conventional Sonogashira coupling[8] of 6-amino-4-chloro-5-iodopyrimidine (**1**, prepared from commercially available 6-amino-4-chloropyrimidine in 50% yield, Scheme S2, Supplementary data) affording alkyne **3** (Scheme 1). The reaction was chemoselective to the 5-iodo and no bisalkynylated products were formed. We expected that converting electron-withdrawing 4-chloro to electron-donating 4-ether group increases the nucleophilicity of the 6-amino group and could facilitate the cyclization forming the fused pyrrolo moiety. Indeed, when the reaction of **3a** and 3-methoxy phenol was carried out at 150 °C in the presence of potassium *tert*-butoxide to obtain 4-ether compound **5**, we have observed that small amount of the TWS119 precursor pyrrolo[2,3-*d*]pyrimidine **6** is formed (isolated mixture of **5**:**6** = 80:20 in 64% yield). This suggests that the ether formation and cyclization can be performed in one-pot under appropriate temperature and base. Indeed, compound **6** was the major product when the reaction temperature was 180 °C. Among tested, cesium carbonate was the most effective base to obtain **6** as the single product in good yield (Table 1). As no



Scheme 1. Synthesis of alkynes **3a** and **3b**.

Table 1
Effect of base on the pyrrolo[2,3-*d*]pyrimidine formation



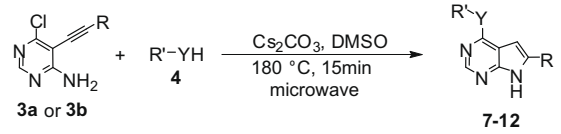
Entry	Base	Isolated yield% (**5**+**6**)	Ratio* (**5**:**6**)
1	DMAP	30	100:0
2	DBU	65	85:15
3	KO^{t}Bu	60	5:95
4	NaH	49	8:92
5	NaOH	53	0:100
6	Cs_2CO_3	74	0:100

* Ratio determined by HPLC.

* Corresponding author. Tel.: +1 901 595 5854; fax: +1 901 595 5715.
E-mail address: naoaki.fujii@stjude.org (N. Fujii).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.05.032

Table 2
Synthesis of 4,6-disubstituted pyrrolo[2,3-*d*]pyrimidines



Product	Alkyne	R′	Y	Isolated yield%
7	**3a**	Phenyl	O	77
8	**3a**	Phenyl	S	85
9	**3a**	Cyclohexyl	S	64
10	**3b**	Phenyl	O	79
11	**3b**	Phenyl	S	87
12	**3b**	Cyclohexyl	S	71

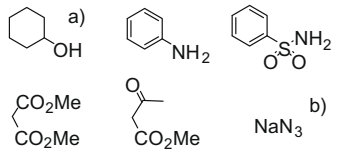
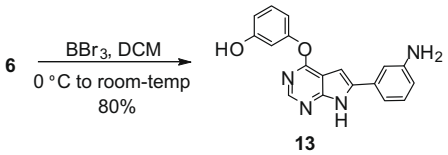


Figure 1. Substrates (**4**, R′-YH) that do not afford the objective coupled pyrrolo[2,3-*d*]pyrimidines. (a) Using KO^{t}Bu or NaH instead of Cs_2CO_3 either did not afford the objective product. (b) Cs_2CO_3 was omitted from the reaction mixture.



Scheme 2. Synthesis of TWS119 (**13**).

self-condensation products of **3a** (in which the aniline amino was intermolecularly substituted to 4-position) was formed, the *m*-aniline moiety of **3a** did not need to be protected. This suggests that this one-pot reaction is chemoselective to phenol over aniline.

We also validated the general applicability of the optimized conditions (Table 1, entry 6) for producing other pyrrolo[2,3-*d*]pyrimidines (Table 2). Both aromatic (**7–9**) and aliphatic substituents (**10**–**12**) can be incorporated on the 6-position. Phenol (**7**, **10**), thiophenol (**8**, **11**), and thiol (**9**, **12**) were efficiently used. Meanwhile, alcohol, aniline, sulfonamide, malonate, acetoacetate, and azide did not afford the desired coupling product (Fig. 1), showing chemoselectivity of this reaction toward the building blocks (R′-YH) for diversifying the 4-position.

Compound **6** was deprotected to afford TWS119 in 38% overall yield from **1** (Scheme 2). NMR spectra of TWS119 obtained by this route were identical to those of the batch obtained by the literature method[7] (Supplementary data).

In summary, we have developed a convenient method to synthesize pyrrolo[2,3-*d*]pyrimidines in which the 4-position is substituted by an ether or a thioether, and demonstrated this method efficiently produces TWS119. The key steps involving the formation of an ether or thioether linkage along with concurrent ring closure were accomplished in single step to yield 4,6-disubstituted pyrrolo[2,3-*d*]pyrimidines, in only two steps from the common starting material **1**.

Acknowledgment

This work was supported by the American Lebanese and Syrian Associated Charities (ALSAC).

A. Supplementary data

Supplementary data (experimental procedures and NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.032.

References and notes

1. Gangjee, A.; Jain, H. D.; Queener, S. F.; Kisliuk, R. L. *J. Med. Chem.* **2008**, *51*, 4589–4600.
2. Gangjee, A.; Kurup, S.; Ihnat, M. A.; Thorpe, J. E.; Shenoy, S. S. *Bioorg. Med. Chem.* **2010**, in press.
3. CAS registration entry of query = 4-X, 6-C, 5,7-*H*-pyrrolo[2,3-*d*]pyrimidine: 1345 for X = N, 117 for X = O, 8 for X = S, on January 2010.
4. Ding, S.; Wu, T. Y.; Brinker, A.; Peters, E. C.; Hur, W.; Gray, N. S.; Schultz, P. G. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 7632–7637.
5. Kordes, C.; Sawitza, I.; Haussinger, D. *Biochem. Biophys. Res. Commun.* **2008**, *367*, 116–123.
6. Zeng, F. Y.; Dong, H.; Cui, J.; Liu, L.; Chen, T. *Biochem. Biophys. Res. Commun.* **2010**, *391*, 1049–1055.
7. Ding, S.; Wu, T. Y.; Gray, N. S.; Schultz, P. G. In WO2004093812A2, 2004.
8. Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis-Stuttgart* **1980**, 627–630.