Tetrahedron Letters 54 (2013) 1160–1163

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Suzuki cross-coupling of 5-bromothieno[2,3-*b*]pyridines for the convenient synthesis of 8-arylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amines

Yvonnick Loidreau [a,b], Vincent Levacher [b,c], Thierry Besson [a,b,*]

[a] Université de Rouen, Place Emile Blondel, 76821 Mont-Saint-Aignan, France
[b] Laboratoire Chimie Organique et Bioorganique, Réactivité et Analyse (C.O.B.R.A.), CNRS UMR 6014 & FR 3038, Institut de Recherche en Chimie Organique Fine (I.R.C.O.F.) rue Tesnière, 76131 Mont-Saint-Aignan, France
[c] INSA de Rouen, Avenue de l'Université, 76801 Saint-Étienne-du-Rouvray Cedex, France

ARTICLE INFO

Article history:
Received 31 October 2012
Revised 12 December 2012
Accepted 18 December 2012
Available online 27 December 2012

Keywords:
Suzuki cross-coupling
Microwave-assisted chemistry
Thieno[2,3-*b*]pyridines
Pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines

ABSTRACT

For the first time, Suzuki cross-coupling reactions were used for introducing an aromatic group in position 8 of the pyridine ring of novel pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amines. This reliable and simple method may be extended to various boronic acids for allowing preparation of a larger library of these compounds in the hope of further structure–activity relationship investigations.

The main interests of our research group include the synthesis of C,N,S-containing heterocyclic precursors of bioactive molecules able to modulate the role of kinases in signal transduction.[1] As a part of this work, the synthesis of *N*-arylbenzothieno[3,2-*d*]pyrimidin-4-amines and their pyrido and pyrazino analogues was published.[2] The inhibitory potency of the final products against five protein kinases (CDK5/p25, CK1δ/ε, GSK3αβ, DYRK1A and CLK1) was evaluated. It was found that *N*-arylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amine series of compounds (see **I** in Scheme 1) turned out to be particularly promising for the development of new pharmacological inhibitors of CK1 and CLK1 kinases. Among these compounds, **II** (Scheme 1) has been considered as the most active product with submicromolar IC_{50} values for CK1 (31 nM) and CLK1 (680 nM). Pursuing our investigations in the design of potent kinase inhibitors we envisioned the synthesis of functionalized pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amines of general structure **1** (Scheme 1).

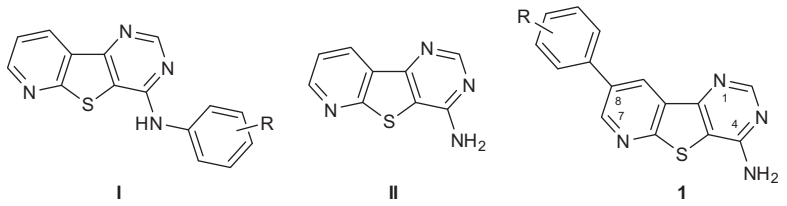
A literature survey revealed that the synthesis of 8-substituted-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amines (**1**) has been rarely described until now.[3] In contrast, synthetic routes and biological activity of some pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine analogues, substituted by various groups in position 7 of the pyrido moiety, were already studied and published.[4] We decided that it would be an interesting challenge to synthesize novel pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines which can be functionalized in position 8 of the pyridine ring for further structure–activity relationship investigations.[5] This Letter describes the development of a reliable and simple method that allows the preparation of a library of these compounds for which interesting biological properties can be expected. As a continuation of previous works, the main part of the chemistry performed in this study was realized under microwave irradiation for an efficient heating of the reaction mixtures and a good control of reaction parameters.[6]

The target compounds we studied were 8-arylpyrido [3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amines (**1**) which are substituted by an aromatic group in position 8 of the pyridine moiety. The route envisioned is described in the retro-synthetic pathway presented in Scheme 2. The multi-step synthetic pathway was inspired by our previous work on the utility of formamide to generate ammonia synthon for introducing a nitrogen atom into a pyrimidine ring from anthranilic acids,[7] anthranilonitrile[8] or its benzofuro or benzothieno analogues.[9]

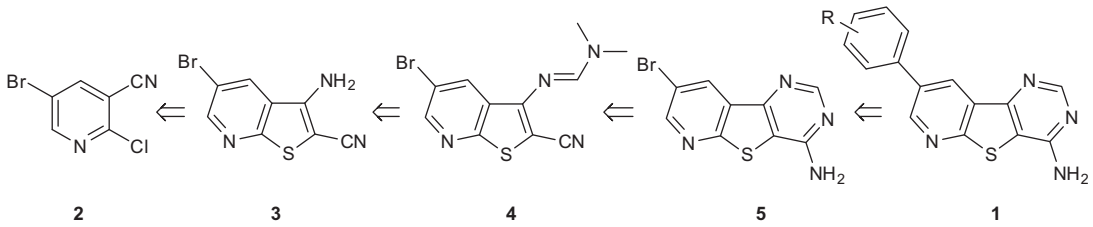
Our approach consisted of preparing a brominated enaminonitrile (**3**) from the commercial 5-bromo-2-chloronicotinonitrile (**2**) (Scheme 2). Transformation of thieno[2,3-*b*]pyridine (**3**) into its corresponding formamidine derivative (**4**) and nucleophilic attack by ammonia and cyclization will yield the expected brominated pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amine (**5**). At the end of this process, incorporation of the phenyl moiety was envisioned via a Suzuki cross-coupling reaction with various phenylboronic acids.

* Corresponding author. Tel.: +33 (0) 235522904; fax: +33 (0) 235522962.
E-mail address: thierry.besson@univ-rouen.fr (T. Besson).

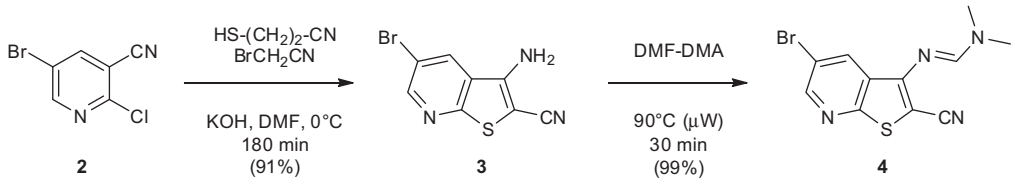
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.12.077



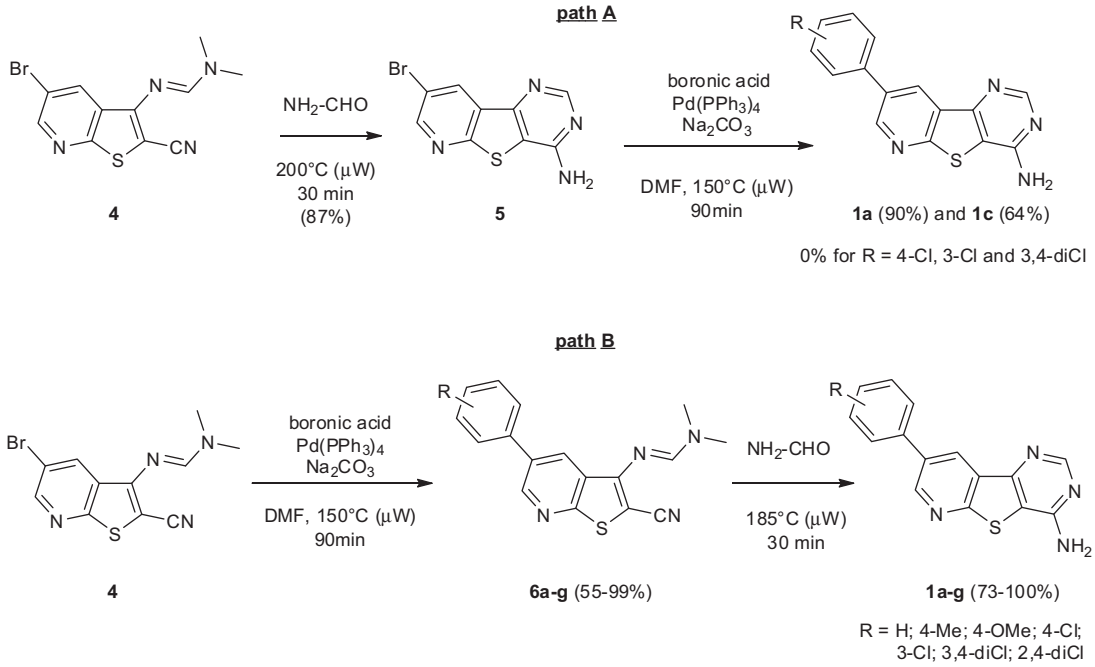
Scheme 1. Structure of target 8-arylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amines (**1**) and their pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amine congeners previously studied[2] (**I** and **II**).



Scheme 2. Synthetic routes envisioned for an access to the target products.



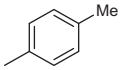
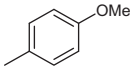
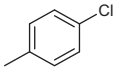
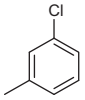
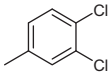
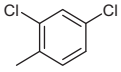
Scheme 3. Synthesis of 3-amino-5-bromothieno[2,3-*b*]pyridine-2-carbonitrile precursor (**3**) and its *N*,*N*-dimethylformimidamide derivative (**4**).



Scheme 4. Synthesis of 8-arylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amines (**1**); for reaction times and yields see Table 1.

The synthesis of the thieno[2,3-*b*]pyridine precursor (**3**) was inspired from a method previously described in the literature for the preparation of benzothiophene analogues.[9] 5-Bromo-2-chloronicotinonitrile (**2**) was firstly treated by freshly prepared 3-mercaptopropionitrile[10] in the presence of aqueous potassium hydroxide, in dimethylformamide (DMF) at 0 °C. After 1 h of stirring, the alkylating agent (bromoacetonitrile) was added to the cold reaction mixture to give the expected 3-amino-5-bromothieno

Table 1
Synthesis of *N*,*N*-dimethylformimidamides **6a–g** and final thieno[3,2-*d*]pyrimidines **1a–g**

Ar	Starting compound	Yield[a,b,c] (%)	Product	Yield[b,c,d] (%)
	**6a**	99	**1a**	87
	**6b**	99	**1b**	93
	**6c**	79	**1c**	85
	**6d**	94	**1d**	78
	**6e**	98	**1e**	92
	**6f**	55	**1f**	100
	**6g**	90	**1g**	73

[a] Reactions were performed for 90 min at 150 °C and at atmospheric pressure under microwave irradiation (800 W) on a 1.0 mmol scale from **4** with 1.5 equiv of appropriate boronic acid.
[b] Yield of isolated product.
[c] Microwave reactor: RotoSYNTH™ from Milestone S.r.l, Italy.
[d] Reactions were performed for 30 min at 185 °C and at atmospheric pressure under microwaves (200 W) on a 0.2 mmol scale from **6a–g** with 40 equiv of formamide.

[2,3-*b*]pyridine-2-carbonitrile (**3**) in high yield (91%). The synthesis of (*E*)-*N*′-(5-bromo-2-cyanothieno[2,3-*b*]pyridin-3-yl)-*N*,*N*-dimethylformimidamide intermediate (**4**) was performed in quantitative yield by reaction of cyanoenamine (**3**) with *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA) after 30 min of microwave irradiation (800 W) at 90 °C (Scheme 3).

As described in the retrosynthetic pathway (Scheme 2) the next step of the synthesis consisted of a nucleophilic attack of ammonia on the *N*,*N*-dimethylamidine **4** and cyclization of the intermediate amidine to yield the expected 8-bromopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amine (**5**) in a very good yield (87%). At this part of the work, the Suzuki cross-coupling reactions of five phenylboronic acids (Scheme 4) with **5** were investigated. Using freshly prepared $Pd(PPh_3)_4$ as the catalyst,[11] and applying usual conditions for the Suzuki cross-coupling, we noticed that reaction from 8-bromopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**5**) allowed the synthesis of only two of the expected derivatives in good to modest yields (90% for phenyl and 64% for *p*-methoxyphenyl derivatives, respectively) (Scheme 4, path A). At this stage of the study, we observed that the purification of the products obtained by reaction with halogenated boronic acids was difficult due to the high polarity of molecules. Whatever be the method of purification used, the process led to the expected product in very poor yields, or did not allow isolation of any compound. In view of these results we considered trying the introduction of phenyl substituents before cyclizing the pyrimidine ring via thermal decomposition of formamide (Scheme 4, path B).

Returning to the *N*,*N*-dimethylformimidamide intermediate (**4**), we observed that Suzuki cross-coupling of various phenyl boronic acids with **4** can be performed under usual conditions of temperature and time to give very good yields of (*E*)-*N*′-(5-aryl-2-cyano)thieno[2,3-*b*]pyridin-3-yl)-*N*,*N*-dimethylformimidamide series (**6a–g**) (Table 1). Strong heating (185 °C) of these intermediates in the presence of formamide allowed convenient formation of novel pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amines (**1a–g**) substituted in position 8 by a phenyl ring, itself substituted by various electro-donor or electro-withdrawing groups.[5] This second route can be considered more efficient and easier in practice. It allowed good overall yields of the target molecules and the operating conditions were easy to apply.

Some comments can be made concerning the microwave procedure as well as the technical and practical aspects. Microwave heating was realized at atmospheric pressure in a well-controlled multimode cavity[12] and not in pressurized vials as described in various papers, especially for Suzuki cross-coupling reactions.[13] The choice of a reactor able to work at atmospheric pressure was guided by our previous experience in the use of microwaves in organic synthesis.[14] It has some advantages, such as the possibility of easier work-up and the use of usual laboratory glassware. In the main steps of the synthetic pathway described in this Letter, irradiation power at 200 or 800 W, was enough to efficiently reach the programmed temperature with a short ramp time (3 min, not added to the reaction time indicated in schemes). Temperature was monitored via a contactless-infrared pyrometer which was calibrated by control experiments with a fibre-optic contact thermometer.

In conclusion, synthesis of functionalized pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amines was investigated with success. For the first time, Suzuki cross-coupling reactions were used for introducing an aromatic group in position 8 of the pyridine ring of the pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine core. This reliable and simple method may be extended to various boronic acids to allow the preparation of a larger library of these compounds in the hope of further structure–activity relationship investigations. In this point of view, the synthesis of the intermediate *N*,*N*-dimethylformimidamides (**6a–g**) is also promising for the synthesis of various derivatives which can be substituted in position 3 or 4 of the pyrimidine part of the tricyclic core.

Acknowledgement

This work was supported by a PhD grant from the *Région Haute-Normandie* (Y.L.) and the ISCE-CHEM program. We acknowledge Milestone S.r.l. (Italy) for providing the microwave reactors and financial and technical support. Y.L. also thank Charline Denneval for preparation of the $Pd(PPh_3)_4$ catalyst.

Supplementary data

Supplementary data (^1H and ^{13}C spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.077.

References and notes

1. (a) Logé, C.; Testard, A.; Thiéry, V.; Lozach, O.; Blairvacq, M.; Robert, J.-M.; Meijer, L.; Besson, T. *Eur. J. Med. Chem.* **2008**, *43*, 1469; (b) Beauchard, A.; Ferandin, Y.; Frère, S.; Lozach, O.; Blairvacq, M.; Meijer, M.; Thiéry, V.; Besson, T. *Bioorg. Med. Chem.* **2006**, *14*, 6434; (c) Testard, A.; Logé, C.; Léger, B.; Robert, J.-M.; Lozach, O.; Blairvacq, M.; Meijer, L.; Thiéry, V.; Besson, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3419; (d) Testard, A.; Picot, L.; Lozach, O.; Blairvac, M.; Meijer, L.; Murillo, L.; Piot, J.-M.; Thiéry, V.; Besson, T. *J. Enzyme Inhib. Med. Chem.* **2005**, *20*, 557.
2. Loidreau, Y.; Marchand, P.; Dubouilh-Benard, C.; Nourrisson, M.-R.; Duflos, M.; Lozach, O.; Loaëc, N.; Meijer, L.; Besson, T. *Eur. J. Med. Chem.* **2012**, *58*, 171.
3. The synthesis of some 8-bromo derivatives was described in: (a) Madkour, H. M. F.; Afify, A. A. E.; Abdalha, A. A.; Elsayed, G. A.; Salem, M. S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2009**, *184*, 719; The synthesis of 8-phenylpyrido [3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amine (**1a**) was described in: (b) Zhao, C.; Tovar, C.; Yin, X.; Xu, Q.; Todorov, I. T.; Vassilev, L. T.; Chen, L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 319.

4. (a) Sleebs, B. E.; Levit, A.; Street, I. P.; Flak, H.; Hammonds, T.; Ching Wong, A.; Charles, M. D.; Olson, M. F.; Baell, J. B. *Med. Chem. Commun.* **2011**, *2*, 977; (b) Sleebs, B. E.; Ganame, D.; Levit, A.; Street, I. P.; Gregg, A.; Flak, H.; Baell, J. B. *Med. Chem. Commun.* **2011**, *2*, 982; (c) Quintela, J. M.; peinador, C.; Veiga, C.; Gonzalez, L.; Bonata, L. M.; Alfonso, A.; Riguera, R. *Bioorg. Med. Chem.* **1998**, *6*, 1911.
5. Topliss, J. G. *J. Med. Chem.* **1972**, *15*, 1006. In this Letter, proposals are presented for the stepwise selection for synthesis of analogues of an active compound. The diagrams are based on a fundamental assumption of the Hansch method that a particular substituent may modify activity relative to the parent compound by virtue of resulting changes in hydrophobic, electronic and steric effects. In the case of our study, using the Topliss scheme allowed us to choose certain reagents to check the interest of our methodology, while starting to build a list of molecules with potential biological interest.
6. (a)For a book see: *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Whiley-VCH Gmbh & KGaA: Weinhein, 2006; For reviews see: (b) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325; (c) Kappe, C. O.; Dallinger, D. *Mol. Divers.* **2009**, *13*, 71; (d) Larhed, M.; Allberg, A. *Drug Discov. Today* **2001**, *6*, 406.
7. (a) Nouira, I.; Kostakis, I. K.; Dubouilh, C.; Chosson, E.; Iannelli, M.; Besson, T. *Tetrahedron Lett.* **2008**, *49*, 7033; (b) Kostakis, I. K.; Elomri, H.; Seguin, E.; Iannelli, M.; Besson, T. *Tetrahedron Lett.* **2007**, *48*, 6609.
8. Loidreau, Y.; Besson, T. *Tetrahedron* **2011**, *67*, 4852.
9. (a) Loidreau, Y.; Dubouilh-Benard, C.; Marchand, P.; Nourrisson, M.-R.; Duflos, M.; Buquet, C.; Corbière, C.; Besson, T. *J. Heterocycl. Chem.* **2013**. http://dx.doi.org/10.1002/jhet.1716; (b) Beck, J. R.; Yahner, J. A. *J. Org. Chem.* **1974**, *39*, 3440.
10. 3-Mercaptopropionitrile was prepared following the procedure described in: (a) Gerber, E.; Hasbun, C.; Dubenko, L. G.; King, M. F.; Bierer, D. E. *Org. Synth.* **2000**, *77*, 186; (b) Klose, J.; Reese, C. B.; Song, Q. *Tetrahedron* **1997**, *53*, 14411.
11. Tetrakis(triphenylphosphine)palladium(0) was prepared following the procedure described in: Coulson, D. R.; Satek, L. C.; Grim, S. O. *Inorg. Synth.* **2007**, *13*, 121.
12. Microwave experiments were conducted in a commercial microwave reactor especially designed for synthetic chemistry. RotoSYNTH™ (Milestone S.r.l. Italy) is a multi-mode cavity with a microwave power delivery system ranging from 0 to 1200 W. Open vessel experiments were carried out in 50, 100 or 250 mL round bottom flasks fitted with a reflux condenser. Temperature was monitored via a contactless-infrared pyrometer which was calibrated by control experiments with a fibre-optic contact thermometer. The vessel contents were stirred by means of an adjustable rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar inside the vessel. Temperature, pressure and power profiles were monitored in both cases through the EASY-control software provided by the manufacturer.
13. For recent examples see: (a) Kabri, Y.; Crozet, M. D.; Primas, N.; Vanelle, P. *Eur. J. Org. Chem.* **2012**, 5595; (b) Ng-Choi, T.; Soler, M.; Cerezo, V.; Badosa, E.; Montesinos, E.; Planas, M.; Feliu, L. *Eur. J. Org. Chem.* **2012**, 4321; (c) Bretéché, A.; Marchand, P.; Nourrisson, M.-R.; Hautefaye, P.; De Nanteuil, G.; Duflos, M. *Tetrahedron* **2011**, *67*, 4767.
14. For recent examples see: (a) Foucourt, A.; Dubouilh-Benard, C.; Chosson, E.; Corbière, C.; Buquet, C.; Iannelli, M.; Leblond, B.; Marsais, F.; Besson, T. *Tetrahedron* **2010**, *66*, 4495; (b) Besson, T.; Chosson, E. *Comb. Chem. High Throughput Screen* **2007**, *10*, 903; (c) Pereira, M. de F.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* **2007**, *48*, 7657.