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# First synthesis of 4-aminopyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidines

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ABSTRACT

This Letter describes for the first time the synthesis of pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidines substituted by a primary or secondary amino group on position 4 of the pyrimidine ring. Application of microwave irradiation technology allowed fast and convenient procedures.



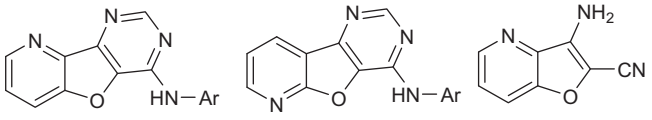
The main interests of our research groups include the synthesis of C,N,S- or C,N,O-containing heterocyclic precursors of bioactive molecules able to modulate the role of kinases in signal transduction.[1,2] Recent synthesis of 3-amino-6-bromofuro[3,2-*b*]pyridine-2-carbonitrile[3] prompted us to use similar novel poly-functionalized heterocyclic precursors for the preparation of 4-amino-substituted pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidines (**1** in Scheme 1). A literature survey revealed that pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidines were only once described in a recent patent in which this original heterocyclic ring was introduced into more complex molecules that were able to inhibit the activity of HCV (Hepatitis C Virus) protease, and then, can be useful for the treatment of C hepatitis.[4] In contrast, synthetic routes and biological activity of some pyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidine isosters (see **2** in Scheme 1) were more extensively described in the literature. Various 4-morpholino-substituted derivatives were considered as potential anti-cancer agents because of their capacity to inhibit phosphatidylinositol 3-kinase (PI3K), a specific target in cancer treatment.[5]

We decided that it would be an interesting challenge to start from a 3-aminofuro[3,2-*b*]pyridine-2-carbonitrile precursor (**3** in Scheme 1) and to explore the possibilities offered by the thermal-sensitive Dimroth rearrangement.[6,7]

For these reasons, the use of microwave heating may allow efficient synthesis of target pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidines (**1**) where traditional thermal procedures may require forcing conditions and prolonged reaction times. This paper describes the development of a reliable and simple method that allows the preparation of a library of these compounds which can serve as precursors to various bioactive molecules.

The target compounds we studied were pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidines (**1**) which are substituted by an aromatic amine in position 4 of the pyrimidine moiety. Two routes were envisioned and are described in the retro-synthetic pathways presented in Scheme 2. The multi-step synthetic pathway usually described for the synthesis of bicyclic or tricyclic fused pyrimidines[8] suggests the use of a 3-amino-2-enoic acid or its corresponding ester as starting material (route A, Scheme 2). Thermal cyclization in the presence of formamide in a Niementowski reaction gives pyrimidin-4-ones which can react with thionyl chloride, phosphoryl chloride or oxalyl chloride, yielding unstable 4-chloropyrimidines. In the final step, nucleophilic substitution, using various aromatic or aliphatic amines, will lead to the expected products.

The second route is shorter, starting from an enaminonitrile analog (route B, Scheme 2). Generally in this reaction the starting




**Scheme 1.** Structure of target pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidines (**1**) and precursor (**3**).

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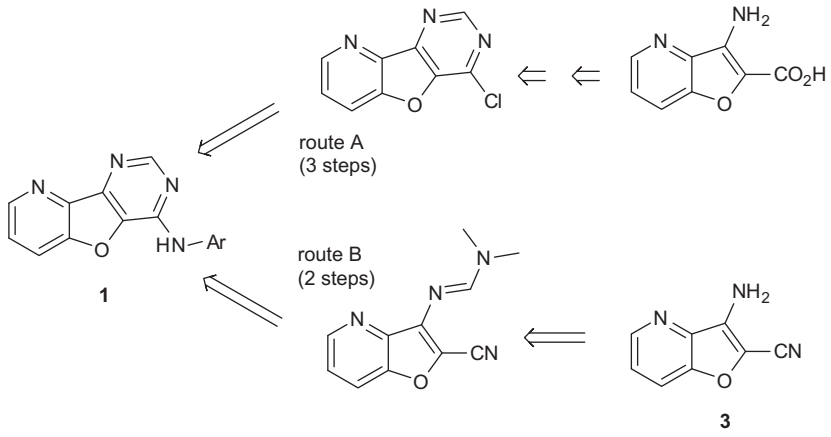



**Scheme 2.** Synthetic routes envisaged for an access to the target products.

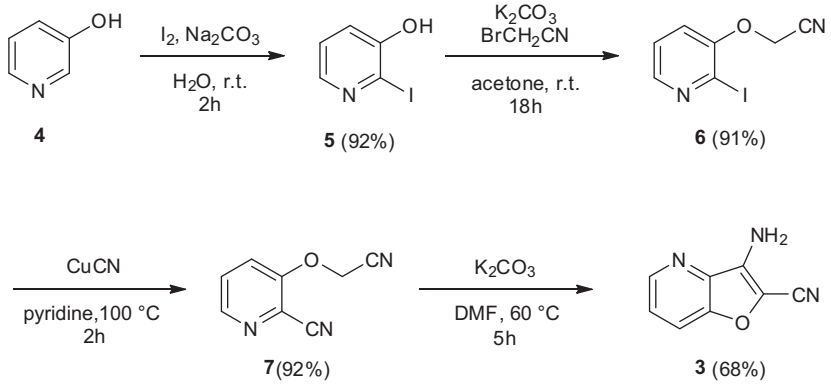
cyanoenamine derivative is first transformed into its corresponding formamidine. Subsequent nucleophilic attack by an amine and cyclization yield 3-substituted pyrimidine derivatives in which exocyclic and endocyclic nitrogen atoms can switch place via a Dimroth rearrangement.[6,7] The thermodynamically stable product obtained is then substituted on position 4 of the pyrimidine moiety.

Taking into account that thermal effects usually observed in microwave experiments may favor the appearance of thermodynamic products,[9] we decided to prepare the target pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidines (**1**) via the second route. It involved starting the synthesis from the novel 3-aminofuro[3,2-*b*]pyridine-2-carbonitrile (**3**), itself obtained by the strategy previously described for its 6-bromo-substituted analog.[3] The synthetic route used for preparation of the starting enaminonitrile (**3**) is outlined in Scheme 3.

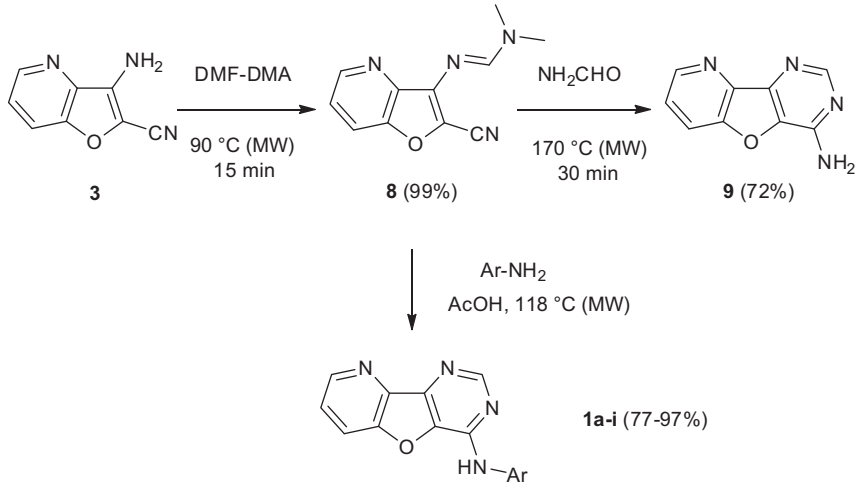
Selective iodination in position 2 of the pyridine ring was carried out by the action of iodine in the presence of sodium carbonate in water at room temperature.[3] Subsequent alkylation of the 2-iodo-3-hydroxypyridine (**5**) was obtained in good yield by formation of the potassium salt using potassium carbonate, followed by its reaction with bromoacetonitrile at room temperature.[10] The corresponding nitrile (**7**) was synthesized by heating [(2-iodopyridin-3-yl)oxy]acetonitrile (**6**) at 100 °C with copper cyanide (CuCN) in pyridine. Finally, heteroannulation of (**7**) under basic conditions produced 3-aminofuro[3,2-*b*]pyridine-2-carbonitrile (**3**). The use of potassium carbonate as a base in DMF instead of sodium hydride allowed increasing the cyclization yield from 41 to 68%.

With starting compound (**3**) now available, the second step in our synthesis consisted of the formation of *N*′-(2-cyanofuro[3,2-*b*]pyridin-3-yl)-*N*,*N*-dimethylformimidamide intermediate (**8**). It was realized by the reaction of the cyanoenamine (**3**) with *N*,*N*-dimethylformamide dimethylacetal (DMF–DMA). After various attempts to optimize the reaction parameters (time, temperature and microwave power applied), the expected product (**8**) was obtained in quantitative yields after 15 min of irradiation (800 W) at 90 °C (Scheme 4). Note that microwave heating was realized at atmospheric pressure in a controlled multimode cavity[11] and not in pressurized vials in order to avoid the appearance of methanol and formamide by thermal decomposition of excess DMF–DMA. This reaction can generate a high pressure level and may lead to explosion of the reaction vessel. Irradiation wattage at 800 W was the best compromise between on one hand, a lower power which involved longer reaction times (because of its lack of efficiency to heat the flask in a convenient period) and on the other hand a too high power (we were able to reach 1200 W) which generated problems, mainly in the control of temperature. It should be noted that such a process allows scale-up of the reaction to a multi-gram scale.

Before introducing a substituted amino group on the skeleton of the targeted products, synthesis of the non-alkylated 4-aminopyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidine (**9**) was realized in good yield by strong heating of compound (**8**) in the presence of formamide which played the dual role of solvent and reactant. Its temperature dependent ability to generate ammonia, synthon, and its intrinsic properties of heating under microwave irradiation (its loss dissipation factor, tan $\delta$, is greater than 0.5) were combined in a comfortable

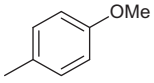
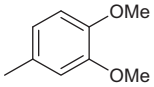
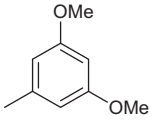
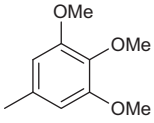
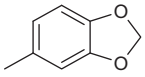
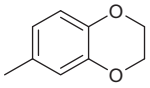
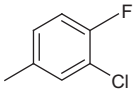
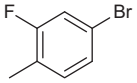



**Scheme 3.** Synthesis of 3-aminofuro[3,2-*b*]pyridine-2-carbonitrile **3**.




**Scheme 4.** Synthesis of pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidines (**1a**–**h** and **9**); for reaction times and yields see Table 1; microwave irradiation: 800 W at atmospheric pressure.

**Table 1**
Synthesis of 4-aminosubstituted pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidines (**1a**–**h**)[a]

| Ar | Product | Time (min) | Yield[b] (%) |
|---|---|---|---|
|  | **1a** | 5 | 84 |
|  | **1b** | 5 | 78 |
|  | **1c** | 5 | 77 |
|  | **1d** | 5 | 83 |
|  | **1e** | 5 | 83 |
|  | **1f** | 10 | 84 |
|  | **1g** | 10 | 82 |
|  | **1h** | 15 | 80 |
|  | **1i** | 60 | 97 |

[a] Reactions were performed under microwave (800 W) on a 0.5 mmol scale from **8** with 1 equiv of aniline derivative (Start S™ from Milestone S.r.l, Italy).
[b] Yield of isolated product.

process constituting a safe alternative to the extreme conditions usually described in the literature.[12]

According to various procedures previously described for the synthesis of quinazolines,[13] the next step consisted of heating the formimidamide derivative (**8**) with 1 equiv of various anilines in the presence of acetic acid. For this reaction, other solvents (e.g., acetonitrile or NMP) have already been tried in our group but their main drawback was a more difficult work-up. The starting mixture was irradiated at 400 W in a multimode cavity. After 3 min., the temperature at which the solvent could be refluxed (118 °C) was reached. This time is not added to the reaction time described in Table 1. A library of nine original pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidines was prepared using similar experimental conditions.[14] Obviously the time and yield of the reaction depended on the nucleophilicity of starting aniline, as well as the presence of electron-attracting groups on the benzene ring. Steric hindrance due to the position of the substituents may also play a role and caused an increase in the reaction time (e.g., **1i** in Table 1). To obtain good yields, the irradiation time was prolonged for those reactions that were affected by the steric and electronic effects mentioned above.

In conclusion, we described for the first time the synthesis of new pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidines substituted by a primary or secondary amino group in position 4 of the pyrimidine ring. The fast and convenient procedure described in this Letter is explored for a general use to access to pyrimidine-condensed heterocyclic scaffolds which can be useful in the design of novel bioactive compounds.

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## Supplementary data

Supplementary data ($^{1}$H and $^{13}$C spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.042.

## References and notes

1. (a) Testard, A.; Picot, L.; Lozach, O.; Blairvac, M.; Meijer, L.; Murillo, L.; Piot, J.-M.; Thiéry, V.; Besson, T. *J. Enzym. Inhib. Med. Chem.* **2005**, *20*, 557–568; (b) 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*, 3419–3423; (c) Logé, C.; Testard, A.; Thiéry, V.; Lozach, O.; Blairvacq, M.; Robert, J.-M.; Meijer, L.; Besson, T. *Eur. J. Med. Chem.* **2008**, *43*, 1469–1477.
2. (a) Antoine, M.; Czech, M.; Gerlach, M.; Günther, E.; Schuster, T.; Marchand, P. *Synthesis* **2011**, *5*, 794–806; (b) Bretéché, A.; Marchand, P.; Nourrisson, M.-R.; Hautefaye, P.; De Nanteuil, G.; Duflos, M. *Tetrahedron* **2011**, *67*, 4767–4773.

3. Bretéché, A.; Marchand, P.; Nourrisson, M.-R.; De Nanteuil, G.; Duflos, M. *Tetrahedron* **2010**, *66*, 4490–4494.
4. Wang, C. –C.; Liu, C. –F.; Lee, K. –Y.; Lin, M. –C.; Wang, S. –H.; Yen, C. –F.; Wang, Y. –H.; King, R. C. –H. U.S. 20110178107 A1, 2011; *Chem. Abstr.* **2011**, *155*, 212110.
5. (a) Hayakawa, M.; Kaizawa, H.; Morimoto, H.; Koizumi, T.; Ohishi, T.; Yamano, M.; Okada, M.; Ohta, M.; Tsukamato, S.; Raynaud, F. I.; Workman, P.; Waterfield, M. D.; Paker, P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2438–2442; (b) Hayakawa, M.; Kaizawa, H.; Morimoto, H.; Kawaguchi, K.; Koizumi, T.; Yamano, M.; Matsuda, K.; Okada, M.; Ohta, M.; WO 2001083456 A1;*Chem. Abstr.* **2001**, *135*, 344500.; (c) Wagner, G.; Prantz, J.; Leistner, S. *Pharmazie* **1992**, *47*, 825–828; (d) Shuttleworth, S. S.; Cecil, A. R. L.; Hill, T. J.; Silva, F. A. WO 2011,021,038 A1; *Chem. Abstr.* **2011**, *154*, 284313.
6. Dimroth, O. *Liebigs Ann. Chem.* **1909**, *364*, 183–226. This paper is considered as the first paper of Otto Dimroth reporting the translocation of endocyclic and exocyclic nitrogen atoms with certain 1,2,3-triazoles..
7. For two very complete reviews on Dimroth rearrangement see: (a) El Ashry, E. S. H.; Nadeem, S.; Raza Shah, M.; El Kilany, Y. *Adv. Heterocycl. Chem.* **2010**, *101*, 161–229; (b) El Ashry, E. S. H.; El Kilany, Y.; Rashed, N.; Assafir, H. *Adv. Heterocycl. Chem.* **1999**, *75*, 79–165.
8. Hurley, L. H.; Mahadevan, D.; Han, H.; Bearss, D. J.; Vankayalapati, H.; Bashyam, S.; Munoz, R. M.; Warner, S. L.; Della Croce, K.; Von Hoff, D. D.; Grand, C. L.; Welsh, J. (a) U.S. 20090099165 A1; *Chem. Abstr.* **2009**, *150*, 414245; (b) U.S. Patent 20090143399 A1; *Chem. Abstr.* **2009**, *151*, 8539.
9. Microwave experiments were conducted in a commercial microwave reactor especially designed for synthetic chemistry. Start SYNTH™ (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 a 250 mL round bottomed flask fitted with a reflux condenser. The temperature can be monitored via a fibre-optic contact thermometer protected in a Teflon coated ceramic well inserted directly in the reaction mixture or via contact-less infrared pyrometer. 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.
10. Koch, V.; Schnatterer, S. *Synthesis* **1990**, 497–498.
11. For a paper on the thermal effect of microwaves see: Obermayer, D.; Guttmann, B.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 8321–8324.
12. Lost dissipation factor (tan $\delta$) expresses the capacity of a molecule or a material to transform electromagnetic energy into thermal energy. A high susceptibility to microwaves is characterized by a high value (>0.5) of tan $\delta$. For more details see: (a) Gabriel, C.; Gabriel, S.; Grant, E. J.; Halstead, B. S.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213–223; (b) Loidreau, Y.; Besson, T. *Tetrahedron* **2011**, *67*, 4852–4857.
13. (a) Tsou, H. R.; Mamuya, N.; Johnson, B. D.; Reich, M. F.; Gruber, B. C.; Ye, F.; Nilakantan, R.; Shen, R.; Discafani, C.; DeBlanc, R.; Davis, R.; Koehn, R. E.; Greenberger, L. M.; Wang, Y. F.; Wissner, A. *J. Med. Chem.* **2001**, *44*, 2719–2734; (b) Yoon, D. S.; Han, H.; Stark, T. M.; Haber, J. C.; Gregg, B. T.; Stankovich, S. B. *Org. Lett.* **2004**, *6*, 4775–4778; (c) Foucourt, A.; Dubouilh-Benard, C.; Chosson, E.; Corbière, C.; Buquet, C.; Iannelli, M.; Leblond, B.; Marsais, F.; Besson, T. *Tetrahedron* **2010**, *66*, 4495–4502.
14. Typical procedure for the synthesis of *N*-arylpyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidin-4-amines (**1a**–**i**): A mixture of *N*′-(2-cyanofuro[3,2-*b*]pyridin-3-yl)-*N*,*N*-dimethyl formimidamide **8** (0.1 g, 0.47 mmol) and appropriate aniline (1.0 equiv) in acetic acid (2 mL) was irradiated at 118 °C (400 W, 3 min ramp). On completion (followed by thin-layer chromatography), the reaction was cooled to room temperature and water was added. The powder was filtered off, washed with water and dried. The crude powder was purified by column chromatography over silica gel using a gradient of petroleum ether/ethyl acetate (100:0 to 0:100, v/v) as the eluent to give the desired compounds.