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New Efficient Route to Dissymmetric 2,4-Di(het)aryl-pyrido[3,2-*d*]pyrimidines via Regioselective Cross-Coupling Reactions

Abdellatif Tikad,[†,‡] Sylvain Routier,*[,†] Mohamed Akssira,[‡] Jean-Michel Leger,[§] Christian Jarry,[§] and Gérald Guillaumet[†]

ICOA UMR 6005 CNRS, Université d'Orléans, F-45067, Orléans, France, LCBA Université Hassan II-Mohammedia, BP 146, 20650 Mohammedia, Morocco, and EA 2962, Pharmacochimie, Universite Victor Segalen Bordeaux II, France

sylvain.routier@univ-orleans.fr

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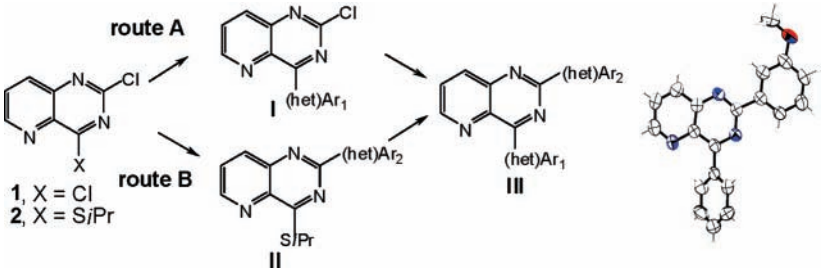
ABSTRACT



The first access to dissymmetric 2,4-di(het)aryl-pyrido[3,2-*d*]pyrimidines III is reported. Two mild alternative routes led to the rarely targeted compounds from 2,4-dichloro- and 2-chloro-4-isopropylsulfanyl-pyrido[3,2-*d*]pyrimidine by two successive palladium-catalyzed reactions involving an original regioselective chlorine discrimination. Alternatively, type III compounds were elaborated from 2 by C-2 chlorine further displacement of the C-4 isopropylsulfanyl group, which acted as a temporary C-4 protecting group. These results open the way to innovative synthesis strategies of various bis-functionalized pyrimidine series.

Palladium-catalyzed cross-coupling reactions represent an important method for carbon−carbon bond formation of heterocycles.[1] In recent years, the regioselectivity of polyhaloheteroaromatics as starting materials in such reactions has been extensively studied.[2] Some pyrido[*d*]pyrimidine derivatives were recently developed as anticancer agents and described as very promising PDGFs,[3] MAP kinase inhibitors,[4] and adenosine kinase inhibitors.[5] Hence, synthesis of pyridopyrimidine derivatives provides an interesting challenge in medicinal chemistry, but the synthesis of pyrido-[3,2-*d*]pyrimidines remains very complicated and is poorly cited in the literature. In our group, we recently showed that S_NAr and palladium insertion occurred regioselectively at the C-4 position of the 2,4-dichloro-pyrido[3,2-*d*]pyrimidine **1** giving access to the literature unknown 4-(*O*,*S*,*N*,*H*)-alkyl- and 4-*H*-2-chloro-pyrido[3,2-*d*]pyrimidines.[6]

[†] University of Orléans.
[‡] University of Mohammedia.
[§] University of Bordeaux.

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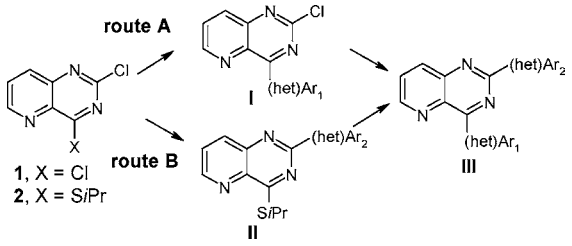
These results prompted us to explore selective and sequential palladium-catalyzed reactions to prepare, by either pathway A or B, compounds **III** from **1** and **2** (Scheme 1).

Scheme 1. Routes A and B to Design Derivatives **I**−**III**



So we performed a chlorine discrimination on **1** leading first to 4-(het)Ar$_1$-2-chloro derivatives **I** followed by dissymmetric 2,4-di(het)aryl compounds **III**.[7] As an alternative, two different (het)aryl moieties on **III** were introduced from **2** by sequential release of the 4-chlorine atom prior to the 2-S^{i}Pr group, which acted as a C-2 temporary protective group during the palladium-catalyzed reactions. Those two interesting, convergent, and efficient synthetic pathways offered numerous dissymmetric 2,4-di(het)aryl-pyrido[3,2-*d*]pyrimidines.

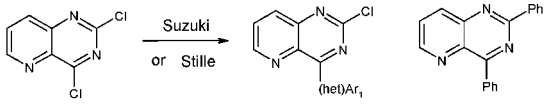
The first synthetic route A was achieved from **1** and the 2-chloro-4-(het)aryl-pyrido[3,2-*d*]pyrimidines **I** (Table 1). The Suzuki reactions were first achieved with a near stoichiometric amount of phenylboronic acid and only 5 mol % of $Pd(PPh_3)_4$ and K_2CO_3 (1.5 equiv) in toluene at 100 °C. After only 2 h, the regioselective C-4 arylation occurred, and **3** was isolated in 84% yield (Table 1, entry 1). The replacement of the catalyst with $Pd(OAc)_2/PPh_3$ tandem affected neither the selectivity nor the reaction time, but the yield of **3** slightly decreased to 79% (Table 1, entry 2). With a near stoichiometric amount of reagents, no trace of biphenyl compound **4** was observed, indicating the lack of reactivity of the 2-Cl vs 4-Cl atom. On the other hand, treatment of compound **1** with 2 equiv of phenylboronic acid and K_2CO_3 (3 equiv) afforded a separable mixture of products from which monocoupled product **3** and dicoupled product **4** could be isolated in 55 and 12% yield, respectively (Table 1, entry 4). $Pd(PPh_3)_4$ replacement with $Pd(OAc)_2/PPh_3$ gives in 1 h the dicoupled product with 88% yield (Table 1, entry 5), as the only compound.

To rationalize this unexpected result, we decided to study the influence of diverse structural parameters. The chlorine discrimination was then investigated using the bulk naphthalene ring and two electron-rich phenyl boronic acids in the presence of the best catalyst $Pd(PPh_3)_4$, without any lack of selectivity (entries 6−8).

The reaction time increased slightly to 24 h; however, selectivity was preserved and compounds **5**−**7** were then isolated in 72−89% yield as sole products.

To maintain the selectivity, the 2-thiophene boronic acid afforded after 24 h the attempted compound **8** in only 50% yield, and starting material **1** subsisted. Change of the catalytic system led to identical results (entries 9 and 10). The lack of reactivity of the boronic acid and its degradation were the main reasons for the decrease of yield.

Table 1. Selective Suzuki and Stille Reactions on **1**[a]



1 **3, 5-10** **4**

entry	conditions	(het)Ar$_1$	time	product (yield)
1	(a)		2 h	**3** (84%)
2	(b)		2 h	**3** (79%)
3	(c)		12 h	**3** (83%)
4	(a) $PhB(OH)_2$ (2.1 equiv)		24 h	**3** (55%) **4** (12%)
5	(b) $PhB(OH)_2$ (2.1 equiv)		1 h	**4** (88%)
6	(a)		3 h	**5** (72%)
7	(a)		8 h	**6** (89%)
8	(a)		24 h	**7** (75%)
9	(a)		24 h	**8** (50%)
10	(b)		18 h	**8** (48%)
11	(c)		12 h	**8** (72%)
12	(c)		8 h	**9** (71%)
13	(d)		24 h	**10** (34%)
14	(c)		22 h	-----

[a] Yields are given in isolated products. Reagents and conditions: (a) (het)Ar$_1$B(OH)$_2$, 1.05 equiv; K_2CO_3, 1.5 equiv; $Pd(PPh_3)_4$, 0.05 equiv; toluene, 100 °C. (b) Idem with $Pd(OAc)_2$, 0.05 equiv; PPh_3, 0.1 equiv. (c) (het)Ar$_1$SnBu$_3$, 1.05 equiv; $Pd(PPh_3)_4$, 0.05 equiv; LiCl, 2.8 equiv; toluene, 100 °C. (d) Idem with (het)Ar$_1$SnMe$_3$.

As an alternative to Suzuki, Stille reactions were then investigated with near stoichiometric amounts of tributylstannylbenzene and **1**, but the base was switched for LiCl (2.8 equiv).[8] The reaction afforded the 2-chloro-4-phenyl-pyrido[3,2-*d*]pyrimidine **3** in 83% yield with no trace of **4** (entry 3). Interestingly, this selective Stille cross-coupling was also successfully employed with other heteroaryls (entries 11 and 12). Starting from the more bulky 2-trimethylstannyl-*N*-benzene-sulfonylindole, the selective heteroarylation yielded **10** in 34% yield (Table 1, entry 13). The only inefficient assay was found with the unstable and versatile 2-tributylstannylpyridine (Table 1, entry 14).

From type **I** compounds, the family **III** was immediately attainable indiscriminately via a Suzuki or a Stille cross-coupling, by the C-2 chlorine insertion of several aromatic

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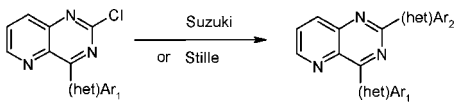
or heteroaromatic moieties. The Suzuki procedure was achieved with a slight excess of boronic acids and Na_2CO_3 in a mixture of toluene/EtOH at 100 °C.[5] The Stille reactions were performed with a stoichiometric amount of stannanes and required 2.8 equiv of LiCl in DMF at 90 °C.[8] Each reaction needed only 5 mol % of $Pd(PPh_3)_4$ and was stopped as soon as starting material completely disappeared to afford the expected products **11**−**21** (Table 2).

Table 2. First Synthesis of Compounds of Type **III** from Type **I**[a]



I III

entry	SM	conditions	(het)Ar_1	(het)Ar_2	product (yield)
1	**3**	(a), 4 h (b), 3 h			**11** (98%) **11** (87%)
2	**3**	(a), 5 h			**12** (98%)
3	**3**	(a), 5 h			**13** (98%)
4	**3**	(a), 4 h			**14** (89%)
5	**7**	(a), 5 h			**15** (89%)
6 7	**8**	(a), 4 h (b), 16 h			**16** (94%) **16** (67%)
8	**5**	(a), 6 h			**17** (96%)
9	**3**	(b), 1 h			**18** (88%)
10	**3**	(b), 14 h			**19** (77%)
11	**9**	(b), 24 h			**20** (52%)
12	**10**	(b), 24 h			**21** (58%)

[a] SM: Starting Material. Yields are given in isolated products. Reagents and conditions: (a) (het)$Ar_2B(OH)_2$, 1.2 equiv; Na_2C0_3, 2 equiv; $Pd(PPh_3)_4$, 0.05 equiv; toluene, EtOH, 100 °C. (b) (het)Ar_2SnBu_3, 1.25 equiv; LiCl, 2.8 equiv; $Pd(PPh_3)_4$, 0.05 equiv; DMF, 90 °C.

All Suzuki reactions were achieved in 4−6 h and led to the attempted products in excellent yields (89−98%). Conversely, individual variations in yield (52−97%) or reaction time (1−24 h) appeared under Stille conditions. Fortunately, the reaction with the versatile 2-tributylstannylpyridine was achieved in 14 h and yielded **19** from **3** in a 77% yield. Compounds **3** and **14**, resulting, respectively, from the chlorine differentiation and dissymmetrical bisarylations were clearly elucidated by X-ray analysis (Figure 1).

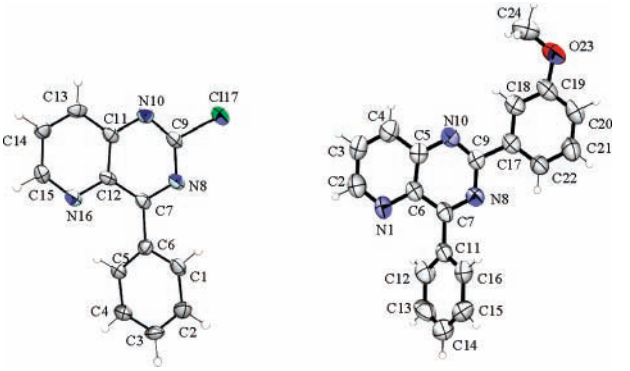
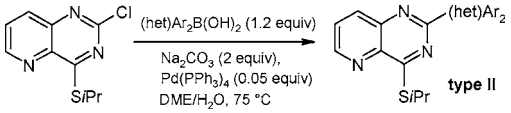


Figure 1. ORTEP view of compound **3** (left) and **14** (right).

The second synthetic route B offered alternative solutions during the synthetic challenge designing compounds **III**. Alternatively, such dissymmetric derivatives could be obtained by the sequential use of the C-2 chlorine atom followed by the elimination of the C-4 isopropylsulfanyl group during palladium-catalyzed (het)arylations. The three representative compounds **22**−**24** of type **II** were also prepared from **2** under basic Suzuki conditions[5] without coupling in the C-4 position (Scheme 2).[9]

Scheme 2. Preparation of Derivatives of Type **II**[a]



2 **22-24**

[a] For **22**: (het)Ar_2 = Ph, 1 h, 90%. For **23**: (het)Ar_2 = 3-MeOPh, 3 h, 81%. For **24**: (het)Ar_2 = 2-thienyl, 3 h, 73%.

The second palladium cross-coupling reaction, which was reported by Liebeskind et al.,[10] required the presence of copper(I) cofactors. On the basis of our knowledge,[11] we applied this strategy to our electron-deficient pyridopyrimidines **22**−**24**. Suzuki related conditions were also first

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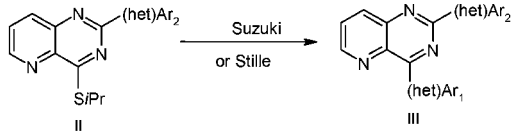
Table 3. Synthesis of Compounds of Type **III** from Type **II**[a]



II III

entry	SM	conditions	(het)Ar$_1$	(het)Ar$_2$	product (yield)
1	**22**	(a), 30 min			**15** (99%)
2	**22**	(a), 1 h			**17** (91%)
3	**24**	(a), 3 h			**11** (90%)
4	**23**	(a), 1 h			**14** (86%)
5	**22**	(b), 10 min			**16** (95%)
6	**22**	(b), 10 min			**20** (96%)
7	**24**	(b), 10 min			**11** (89%)
8	**23**	(b), 10 min			**14** (85%)
9	**22**	(c), 30 min			**21** (75%)
10	**22**	(b), 24 h			----

[a] SM: Starting Material. Reagents and conditions: (a) (het)Ar$_1$B(OH)$_2$, 2.2 equiv; CuTC, 2.2 equiv; Pd(PPh$_3$)$_4$, 0.05 equiv; THF, 50 °C. (b) (het)Ar$_1$SnBu$_3$, 2.2 equiv; CuBr·Me$_2$S, 2.2 equiv; Pd(PPh$_3$)$_4$, 0.05 equiv; DME, reflux. (c) Idem with (het)Ar$_1$SnMe$_3$.

carried out with a slight excess of (het)aryl boronic acids and 2-thiophene copper(I) carboxylate[12] as a cofactor. Each reaction required only 5 mol % of Pd(PPh$_3$)$_4$ and the THF temperature limited to 50 °C (Table 3).

All aromatic Suzuki arylations were completed in a few hours and with excellent yields (entries 1−4). Encouraged by this result, similar sulfur releases were then achieved following a Stille related procedure by using the organostannane in the presence of CuBr·Me$_2$S as a soluble copper(I) source and Pd(PPh$_3$)$_4$ in boiling DME. All examples were achieved in only a few minutes in either aromatic or heteroaromatic series (entries 5−8). The yields in isolated products ranged between 89 and 96%.

Interestingly, the cross-coupling reaction using 2-trimethylstannyl-*N*-benzenesulfonylindole was carried out in only 30 min, and **21** was isolated in 75% yield (Table 3, entry 9), as a supplementary proof of the efficiency of the reaction. As described in Table 3, the use of the versatile 2-tributylstannylpyridine was again and inexplicably unsuccessful (entry 10).

In this report, we developed two efficient palladium-catalyzed routes A and B to design new and rare dissymmetrical 2,4-bis(het)aryl-pyrido[3,2-*d*]pyrimidines. Suzuki- and Stille-type reactions were accurately adapted to perform each step with high selectivity and originality.

In the first route A, we showed that the first (het)arylation occurred selectively in the C-4 position of the 2,4-dichloropyrido[3,2-*d*]pyrimidine **1**. The two chlorine atoms could also be fully discriminated. The second route B involved two sequential (het)aryl transfers from the 2-chloro-4-isopropylsulfanyl-pyrido[3,2-*d*]pyrimidine **2** by palladium insertion first in the C−Cl bond and then in the C−S bond. The two original methods opened the way to a general synthesis of bis-functionalized pyridopyrimidines, major skeletons for designing biologically active compounds. Further studies are currently in progress in our laboratory.

Supporting Information Available: Characterization data for new compounds and experimental procedures are included. Full crystallographic results have been deposited as Supporting Information at the Cambridge Crystallographic Data Centre, University Chemical Lab, 12 Union Road, Cambridge CB2 1EZ, U.K., e-mail: deposit@ccdc.cam.ac.uk. This material is available free of charge via the Internet at http://pubs.acs.org.

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