

Efficient and regioselective functionalization of imidazo[1,2-*b*]pyridazines via palladium-catalyzed cross-coupling reaction and S_NAr

A. El Akkaoui^{a,b}, J. Koubachi^{a,b}, S. El Kazzouli^{a,b}, S. Berteina-Raboin^{a,*},
A. Mouaddib^b, G. Guillaumet^a

^a *Institut de Chimie Organique et Analytique, UMR CNRS 6005, Université d'Orléans, BP 6759, 45067 ORLEANS Cedex 2, France*

^b *Faculté des Sciences et Techniques de Beni-Mellal, Université Cadi-Ayyad, BP 523, 23000 Beni-Mellal, Morocco*

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Abstract

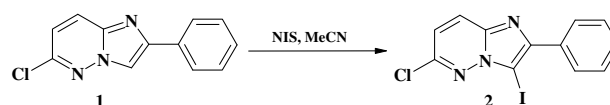
The synthesis of 3,6-disubstituted-2-phenylimidazo[1,2-*b*]pyridazine derivatives by palladium cross-coupling and S_NAr reactions is described. Sonogashira and Stille cross-coupling reactions were investigated to introduce alkynyl, alkenyl, and aryl at the 3-position of imidazo[1,2-*b*]pyridazines. Then, at the 6-position, palladium-catalyzed N-arylation and direct S_NAr were used to introduce amines and alcohols.

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1. Introduction

Imidazo[1,2-*b*]pyridazines are useful compounds in biological and therapeutic areas.^{1–12} Despite these significant and interesting potentials, their reactivity toward palladium-mediated cross-coupling was poorly investigated. Whereas, preliminary studies on the functionalization of imidazo[1,2-*b*]pyridazines by Suzuki coupling are available,¹³ Sonogashira, Stille and Buchwald reactions have never been described for this heterocyclic system.

As part of our ongoing interest in the development of heterocycles with a bridgehead nitrogen atom,^{14,15} herein we report a regioselective functionalization of imidazo[1,2-*b*]pyridazines using Sonogashira and Stille cross-coupling reactions. Afterwards, the 6-position was also functionalized by nucleophilic aromatic substitution and palladium-catalyzed N-arylation (Scheme 1).



Scheme 1. Preparation of 6-chloro-3-iodo-2-phenylimidazo[1,2-*b*]pyridazine **2**.

To reduce the number of halogenation/coupling steps, we first decided to explore the regioselective coupling by Sonogashira, and Stille reactions at the 3-position of 6-chloro-2-phenylimidazo[1,2-*b*]pyridazine **2**. Then, the displacement of the chloro group at the 6-position would permit the access to a large number of derivatives using either N-arylation by palladium cross-coupling or S_NAr (Scheme 1).

We started by the preparation of 6-chloro-3-iodo-2-phenylimidazo[1,2-*b*]pyridazine **1**, which was obtained in 89% yield by condensation between 3-amino-6-chloropyridazine and 2-bromoacetophenone in refluxing ethanol.⁸ Then, in analogy to the procedure described on imidazo[1,2-*a*]pyridines,¹⁶ 6-chloro-2-phenylimidazo[1,2-*b*]pyridazine **1** was iodinated at the 3-position using

* Corresponding author. Tel.: +33 2 38 49 4856; fax: +33 2 38 41 7281.
E-mail address: sabine.berteina-raboin@univ-orleans.fr (S. Berteina-Raboin).

N-iodosuccinimide in acetonitrile to give 3-iododerivative **2** in 92% yield (Scheme 1).

2. Sonogashira cross-coupling

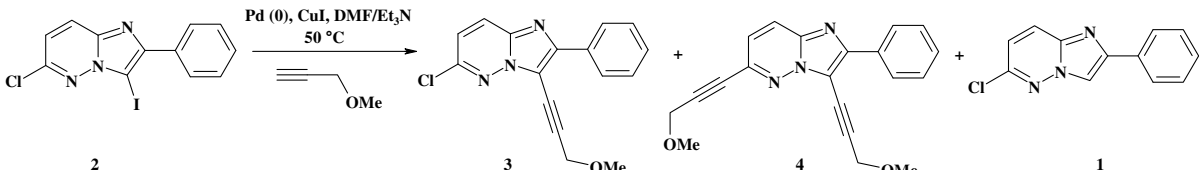
The Sonogashira cross-coupling has been used extensively in organic synthesis.¹⁷ To explore the potential of the regioselective Sonogashira reaction, 6-chloro-3-iodo-2-phenylimidazo[1,2-*b*]pyridazine **2** was first treated under standard conditions with 3-methoxypropyne (1.5 equiv) in the presence of PdCl₂(PPh₃)₂ (0.5 equiv) and CuI (0.05 equiv) in a mixture of DMF/Et₃N at 50 °C for 48 h.^{14c} Unfortunately, these conditions gave the expected compound **3** in a modest yield of 33%, 20% of starting material **1** was recovered (Table 1, entry 1). When 2 equiv of 3-methoxypropyne were used, under the same reaction conditions, compound **3** was isolated in only 36% yield (Table 1, entry 2).

To optimize the reaction conditions, we decided to investigate the reactivity of **2** by increasing the amount of CuI and/or 3-methoxypropyne. Thus, when 2.2 equiv of 3-methoxypropyne and 0.2 equiv of CuI were used, the desired monocoupled compound **3** and byproduct **4** were isolated in 74% and 17% yield, respectively (Table 1, entry 3). To reduce the formation of the dicoupled compound **4**, other catalyst systems were tested. The replacement of PdCl₂(PPh₃)₂ with Pd(OAc)₂/PPh₃ afforded compound **3** and byproduct **4** in 72% and 15% yield, respectively (Table 1, entry 5). Finally, the best results were obtained when Pd₂(dba)₃ and Ph₃As were used as catalytic system (Table 1, entry 6).

Under these conditions, compound **3**²³ was obtained in 84% yield, whereas only 6% of **4** was isolated. All reactions were conducted in DMF at 50 °C.

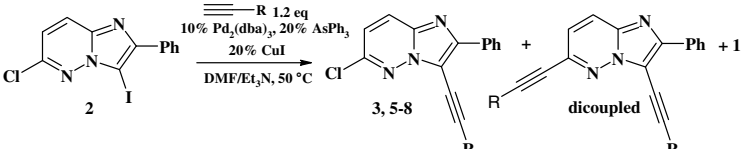
To study the scope and limitation of the reaction, we decided to apply the optimized reaction conditions to

Table 1
Optimization of Sonogashira cross-coupling on 6-chloro-3-iodoimidazo[1,2-*b*]pyridazine



Entry	Pd(0)	CuI (equiv)	Alkyne (equiv)	Time (h)	Conversion (%)	Yield (%)		
						3	4	1
1	PdCl ₂ (PPh ₃) ₂ (0.1 equiv)	0.05	1.5	48	60	33	—	20
2	PdCl ₂ (PPh ₃) ₂ (0.1 equiv)	0.05	2	48	75	36	—	15
3	PdCl ₂ (PPh ₃) ₂ (0.1 equiv)	0.1	2	24	85	64	—	10
4	PdCl ₂ (PPh ₃) ₂ (0.1 equiv)	0.2	2.2	12	100	74	17	—
5	Pd(OAc) ₂ (0.1 equiv)/PPh ₃ (0.2 equiv)	0.2	2.2	12	100	72	15	—
6	Pd ₂ (dba) ₃ (0.1 equiv)/Ph ₃ As (0.2 equiv)	0.2	2.2	12	100	84	6	—

Table 2
Sonogashira cross-coupling reaction



Entry	R	Time (h)	Product	% Yield		
				3, 5-8	Dicoupled	1
1	–CH ₂ OMe	12	3 ²³	84	6	0
2	–(CH ₃) ₂ OH	12	5	89	0	9
3	–C ₆ H ₅	12	6	90	0	0
4	–CH ₂ OH	24	7	60	0	20
5	–2-pyridyl	24	8	50	0	25

6-chloro-3-iodo-2-phenylimidazo[1,2-*b*]pyridazine **2** and various alkynes (Table 2). In most cases, the expected products were obtained in good yields (Table 2). We noticed that the coupling between **2** and propargyl alcohol or pyridine acetylene (Table 2, entries 4 and 5) afforded the desired compounds in moderate yields only and significant amounts of starting material were recovered.

3. Stille cross-coupling

We then decided to test the regioselectivity of the Stille cross-coupling. Thus, under the reaction conditions previously reported,^{14a,b} 6-chloro-3-iodo-2-phenylimidazo[1,2-*b*]pyridazine **2** was treated with various stannanes in the presence of triphenylarsine and tris(dibenzylidenacetone) dipalladium(0) in dioxane at 50 °C (Table 3, method A),¹⁸ to give the expected products **9–11** in 85–95% yield (Table 3, entries 1–3). Compound **12** was obtained in 85% using method B. Finally, we noticed that conditions A gave compound **13** in only 45%, this yield was increased to 85% using an excess of reagent (Table 3, entry 5, method C).

It is important to note that, the Sonogashira cross-coupling reaction seemed to be less regioselective than the Stille reaction on 6-chloro-3-iodoimidazo[1,2-*b*]pyridazine. Moreover, the identification of palladium-catalyzed cross-coupling reactions that tolerate a chloro substituent at the 6-position is important for biological activity^{19,20} or the possibility to carry out supplementary transformations.

Table 3
Stille cross-coupling reaction

Entry	R	Conditions	Product	% Yield	
				9-13	1
1		A	9	95	0
2		A	10	89	0
3		A	11	90	0
4		B	12	85	0
5		A	13	45	30
		C		85	8

Reaction conditions:

A: RSnBu₃ (1.2 equiv), Pd₂(dba)₃ (0.1 equiv)/Ph₃As (0.2 equiv) in dioxane at 50 °C 12 h.

B: RSnBu₃ (1.2 equiv), Pd₂(dba)₃ (0.1 equiv)/Ph₃As (0.2 equiv) in dioxane at 50 °C, then acid hydrolysis, HCl 10%.

C: RSnBu₃ (2.4 equiv), Pd₂(dba)₃ (0.1 equiv)/Ph₃As (0.2 equiv) in dioxane at 50 °C.

Table 4

Nucleophilic aromatic substitution with primary alcohols

	R	R ₁	Product	Yield (%)
1	H	Me	14	98
2	$\equiv\text{CH}_2\text{OCH}_3$	Me	15	96
3	$\equiv\text{CH}_2\text{OCH}_3$	Et	16	95
4	$\equiv\text{CH}_2\text{OCH}_3$	Isopropyl	17	90
5		Me	18	92

4. Functionalization of imidazo[1,2-*b*] pyridazines at the 6-position with S_NAr and palladium-catalyzed N-arylation

For additional decoration around the imidazo[1,2-*b*]pyridazines, we next focused our effort on S_NAr and N-arylation methods. Thus, 6-alkoxy-2-phenylimidazo[1,2-*b*]pyridazines **14–18** were successfully synthesized by the displacement of the chloro group at the 6-position with various primary alcoholates. This method afforded the desired compounds in excellent yields (90–98%). The results are summarized in Table 4.

Then, we became interested in the preparation of other derivatives by generating the C–N bond by nucleophilic displacement of the 6-chloro leaving group of different imidazo[1,2-*b*]pyridazines. For this reason, compound **9**

Table 5
Results of the amination reaction at the 6-position

Entry	R	R ₁	Time (h)	Product	Yield (%)
1			24 4	19	0 (A) 86 (B)
2	H		3	20	87 (B)
3	$\equiv\text{CH}_2\text{OCH}_3$		3	21 ²⁴	88 (B)
4	$\equiv\text{CH}_2\text{OCH}_3$		12	22	70 (B)

Conditions A: R₁NH₂ reflux in THF.

Conditions B: R₁NH₂, XANTPHOS (0.2 equiv), Pd(OAc)₂ (0.1 equiv), K₂CO₃ (20 equiv), reflux in dioxane.

was treated with an excess of amine in refluxing THF (Table 5, entry 1). Unfortunately, no reaction was observed. We then turned our attention to palladium-catalyzed amination recently developed in our laboratory²¹ using XANTPHOS²² (0.2 equiv), Pd(OAc)₂ (0.1 equiv), and K₂CO₃ (20 equiv) in the presence of 1.2 equiv of various amines in refluxing dioxane. This method gave the desired product in good yields (70–86%, Table 5).

In conclusion, we have applied short, efficient, and versatile palladium-assisted synthetic approaches (Stille and Sonogashira cross-coupling) to achieve structural diversification at the 3-position of the imidazo[1,2-*b*]pyridazine system. Then, 6-substituted analogs were prepared in good yield using either nucleophilic aromatic substitution with primary alcohols or palladium-mediated N-arylation.

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- XANTPHOS = 9,9-dimethyl-4,5-bis(diphenylphosphino)-xanthene.
- 6-Chloro-3-(3-methoxy-prop-1-ynyl)-2-phenyl-imidazo [1,2-*b*]pyridazine (**3**). Under argon, a mixture of 6-chloro-3-iodoimidazo[1,2-*b*]pyridazine (0.2 g, 0.56 mmol), methyl propargyl ether (0.086 mL, 1.2 mmol), Pd₂(dba)₃ (0.051 g, 0.056 mmol), and AsPh₃ (0.034 g, 0.0113 mmol) dissolved in a mixture of Et₃N/DMF (1:1, v/v) was heated to 50 °C and stirred for 12 h. The mixture was then cooled to room temperature and extracted with CH₂Cl₂ (3×). The combined organic layer was dried over MgSO₄ and concentrated under vacuum. The residue was purified by column chromatography on a silica gel (EtOAc/PE) to give 6-chloro-3-(3-methoxy-prop-1-ynyl)-2-phenyl-imidazo[1,2-*b*]pyridazine **3** (0.140 g, 84%) as a yellow solid. NMR ¹H (CDCl₃): δ 3.50 (s, 3H), 4.52 (s, 2H), 7.07 (d, 1H, *J* = 9.3 Hz), 7.40–7.45 (m, 3H), 7.84 (d, 1H, *J* = 9.3 Hz), 8.25 (d, 2H). NMR ¹³C (CDCl₃): δ 58.0, 60.8, 74.3, 98.3, 109.5, 120.3, 126.4, 127.3, 128.7, 129.3, 132.6, 137.8, 147.4, 148.5.
- (4-Methoxy-phenyl)-[3-(3-methoxy-prop-1-ynyl)-2-phenyl-imidazo[1,2-*b*]pyridazin-6-yl]-amine (**21**). A three-necked flask was flushed with argon and charged with XANTPHOS (0.065 g, 0.113 mmol) and dry dioxane (1 mL). After degassing, Pd(OAc)₂ (0.013 g, 0.28 mmol) was added, and the mixture was stirred under argon for 10 min. In another three-necked round-bottom flask, 6-chloro-3-(3-methoxy-prop-1-ynyl)-2-phenyl-imidazo[1,2-*b*]pyridazine **3** (0.2 g, 0.56 mmol), 4-methoxyphenylamine (0.083 g, 0.68 mmol), and K₂CO₃ (1.55 g, 11.3 mmol) were poured into dry dioxane (2 mL). Then, the Pd(OAc)₂/XANTPHOS solution was added with double syringe. The resulting mixture was subsequently heated to reflux. After cooling, the reaction mixture was extracted with CH₂Cl₂ (3×). The combined organic layer was dried over MgSO₄ and concentrated under vacuum. The residue was purified by column chromatography on a silica gel (MeOH/CH₂Cl₂) to give (4-methoxy-phenyl)-[3-(3-methoxy-prop-1-ynyl)-2-phenyl-imidazo[1,2-*b*]pyridazin-6-yl]-amine **21** (0.227 g, 88%) as a yellow solid. NMR ¹H (CDCl₃, 250, 131 Hz): δ = 3.54 (s, 3H), 3.80 (s, 3H), 4.56 (s, 2H), 6.65 (d, 1H, *J* = 9.3 Hz), 6.83 (s, 1H), 6.88 (d, 2H, *J* = 9.3 Hz), 7.32–7.48 (m, 6H), 7.64 (d, 1H, *J* = 9.3 Hz), 8.25 (d, 2H). NMR ¹³C (CDCl₃): δ 56.1, 58.3, 61.4, 97.2, 109.3, 113.5, 115.1, 123.3, 126.2, 126.5, 127.3, 128.9, 129.1, 133.0, 134.0, 137.3, 146.6, 152.5, 156.8.