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

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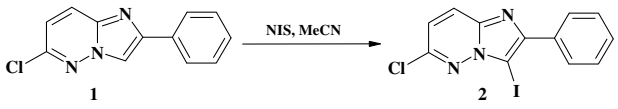
Abstract

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.

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).



1 2

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-3-iodo-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

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

2. Sonogashira cross-coupling

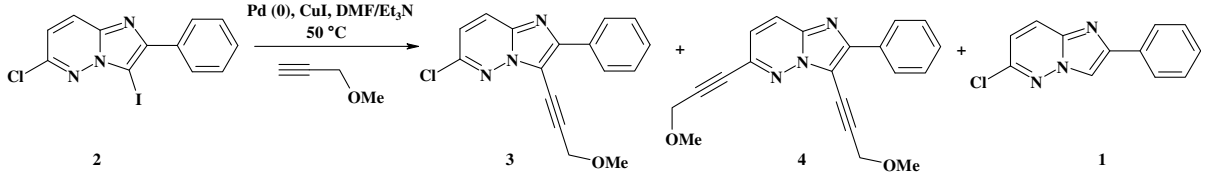
The Sonogashira cross-coupling has been used extensively in organic synthesis.[17] To explore the potential of the regioselective Sonogashira reaction, 6-chloro-3-iodo-2-phenylimidazo[1,2-*b*]pyridazine **2** was first treated under standard conditions with 3-methoxypropyne (1.5 equiv) in the presence of $PdCl_2(PPh_3)_2$ (0.5 equiv) and CuI (0.05 equiv) in a mixture of DMF/Et_3N 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 $PdCl_2(PPh_3)_2$ with $Pd(OAc)_2/PPh_3$ afforded compound **3** and byproduct **4** in 72% and 15% yield, respectively (Table 1, entry 5). Finally, the best results were obtained when $Pd_2(dba)_3$ and Ph_3As were used as catalytic system (Table 1, entry 5).

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.

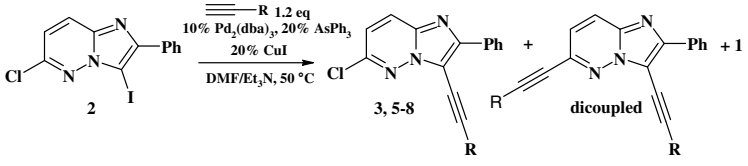
To study the scope and limitation of the reaction, we decided to apply the optimized reaction conditions to

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_3As (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_2OMe	12	**3**[23]	84	6	0
2	–$(CH_3)_2OH$	12	**5**	89	0	9
3		12	**6**	90	0	0
4	–CH_2OH	24	**7**	60	0	20
5		24	**8**	50	0	25

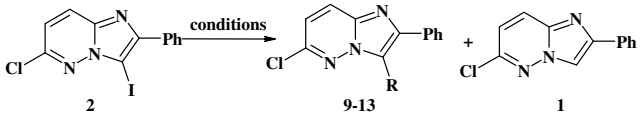
6-chloro-3-iodo-2-phenylimidazo[1,2-*b*]pyridazine **2** and various alkynes (Table 2). In most cases, the expected products were obtained in good yields (Table 2). We noticed that the coupling between **2** and propargyl alcohol or pyridine acetylene (Table 2, entries 4 and 5) afforded the desired compounds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

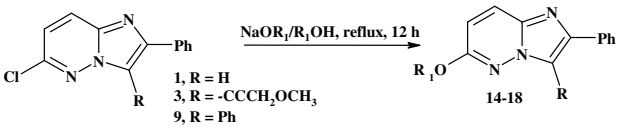
Table 3
Stille cross-coupling reaction



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 C	**13**	45 85	30 8

Reaction conditions:
A: $RSnBu_3$ (1.2 equiv), $Pd_2(dba)_3$ (0.1 equiv)/Ph_3As (0.2 equiv) in dioxane at 50 °C 12 h.
B: $RSnBu_3$ (1.2 equiv), $Pd_2(dba)_3$ (0.1 equiv)/Ph_3As (0.2 equiv) in dioxane at 50 °C, then acid hydrolysis, HCl 10%.
C: $RSnBu_3$ (2.4 equiv), $Pd_2(dba)_3$ (0.1 equiv)/Ph_3As (0.2 equiv) in dioxane at 50 °C.

Table 4
Nucleophilic aromatic substitution with primary alcohols



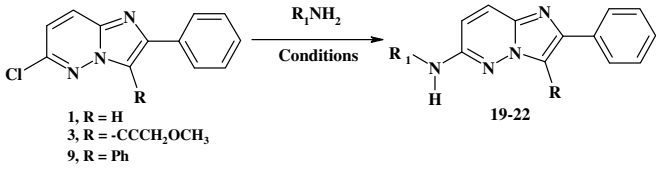
Entry	R	R_1	Product	Yield (%)
1	H	Me	**14**	98
2		Me	**15**	96
3		Et	**16**	95
4		Isopropyl	**17**	90
5		Me	**18**	92

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			3	**21**[24]	88 (B)
4			12	**22**	70 (B)

Conditions A: R_1NH_2 reflux in THF.
Conditions B: R_1NH_2, XANTPHOS (0.2 equiv), $Pd(OAc)_2$ (0.1 equiv), K_2CO_3 (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 laboratory[21] using XANTPHOS[22] (0.2 equiv), $Pd(OAc)_2$ (0.1 equiv), and K_2CO_3 (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.

References and notes

1. (a) Sacchi, A.; Laneri, S.; Arena, F.; Abignente, E.; Gallitelli, M.; D'Amico, M.; Filippelli, W.; Rossi, F. *Eur. J. Med. Chem.* **1999**, *34*, 1003–1008; (b) Hamdouchi, C.; Sanchez-Martinez, C.; Gruber, J.; del Prado, M.; Lopez, J.; Rubio, A.; Heinz, B.-A. *J. Med. Chem.* **2003**, *46*, 4333.
2. Moreau, S.; Coudert, P.; Rubat, C.; Gardette, D.; Valle-Goyet, D.; Couquelet, J.; Bastide, P.; Tronche, P. *J. Med. Chem.* **1994**, *37*, 2153.
3. Moreau, S.; Coudert, P.; Rubat, C.; Valle-Goyet, D.; Gardette, D.; Gramain, J.-C.; Couquelet, J. *J. Bioorg. Med. Chem.* **1998**, *6*, 983.
4. Barlin, G. B.; Davies, L. P.; Glenn, B.; Harrison, P. W.; Ireland, S. J. *Aust. J. Chem.* **1994**, *47*, 609.
5. Almansa, C.; De Arriba, A. F.; Cavalcanti, F. L.; Gòmez, L. A.; Miralles, A.; Merlos, M.; Garcia-Rafanell, J.; Forn, J. *J. Med. Chem.* **2001**, *44*, 350.
6. Ishikawa, T.; Iizawa, Y.; Okonogi, K.; Miyake, A. *J. Antibiot.* **2000**, *53*, 1053.
7. Saturnino, C.; Abarghaz, M.; Schmitt, M.; Wermuth, C.-G.; Bourguignon, J. *J. Heterocycl.* **1995**, *41*, 1491.
8. Roe, A. M. *J. Chem. Soc.* **1963**, 2195.
9. (a) Matyus, P.; Barlin, G. B.; Harrison, P. W.; Wong, M. G.; Davies, L. P. *Aust. J. Chem.* **1996**, *49*, 435; (b) Barlin, G. B.; Davies, L. P.; Harrison, P. W.; Ireland, S. J.; Willis, A. C. *Aust. J. Chem.* **1996**, *49*, 451; (c) Barlin, G. B.; Davies, L. P.; Harrison, P. W.; Ireland, S. J.; Willis, A. C. *Aust. J. Chem.* **1996**, *49*, 451; (d) Barlin, G. B.; Davies, L. P.; Harrison, P. W. *Aust. J. Chem.* **1997**, *50*, 61; (e) Barlin, G. B.; Davies, L. P.; Ireland, S. J.; Ngu-Schwemlein, M. M. L. *Aust. J. Chem.* **1997**, *50*, 91; (f) Schmitt, M.; Bourguignon, J. J.; Barlin, G. B.; Davies, L. P. *Aust. J. Chem.* **1997**, *50*, 779; (g) Barlin, G. B. *J. Heterocycl. Chem.* **1998**, *35*, 1205.
10. Kawano, Y.; Nagaya, H.; Gyoten, M., WO 98/49167, 1998; *Chem. Abstr.*, **1998**, *129*, 343503w.
11. (a) Kuwahara, M.; Kawano, K.; Shimazu, H.; Yamamoto, H.; Ashida, Y.; Miyake, A. *Chem. Pharm. Bull.* **1995**, *43*, 1517; (b) Kuwahara, M.; Kawano, K.; Shimazu, H.; Ashida, Y.; Miyake, A. *Chem. Pharm. Bull.* **1996**, *44*, 122.
12. Fusaka, T.; Ujikawa O.; Kajiwara, T.; Tanaka,Y. PCT, Int. Appl., WO 9711, 075, 1997; *Chem. Abstr.* **1997**, *126*, 293354p.
13. (a) Mavel, S.; Thery, I.; Gueiffier, A. *Arch. Pharm. Pharm. Med. Chem.* **2002**, *335*, 7; (b) Enguehard, C.; Hervet, M.; Allouchi, H.; Debouzy, J.-C.; Leger, J.-M.; Gueiffier, A. *Synthesis* **2001**, *4*, 595–600.
14. (a) El Kazzouli, S.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron Lett.* **2002**, *44*, 6265; (b) El Kazzouli, S.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron Lett.* **2003**, *45*, 3193; (c) El Kazzouli, S.; Berthault, A.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Lett. Org. Chem.* **2005**, *2*, 184; (d) Koubachi, J.; El Kazzouli, S.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Synlett* **2006**, 3237; (e) Koubachi, J.; El Kazzouli, S.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *J. Org. Chem.* **2007**, *72*, 7650.
15. Guillaumet, G.; Berteina-Raboin, S.; El Kazzouli, S.; Delagrange, P.; Caignard, D.-H. PCT, Int. Appl. WO 027474, 2006; *Chem. Abstr.*, **2006**, *144*, 254132.
16. Hamdouchi, C.; de Blas, J.; del Prado, M.; Gruber, J.; Heinz, B. A.; Vance, L. *J. Med. Chem.* **1999**, *42*, 50.
17. (a) Sonogashira, K.; Tohda, Y.; Hagihra, N. *Tetrahedron Lett.* **1975**, *16*, 4467; (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46; (c) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403; (d) Neghishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979; (e) Sakomoto, T.; Shiga, F.; Yasuhara, A.; Yamanaka, H. *Synthesis* **1992**, 746; (f) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.
18. (a) Collot, V.; Varlet, D.; Rault, S. *Tetrahedron lett.* **2000**, *41*, 4363; (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508; (c) Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; Wiley-Interscience: New York, 1998; (d) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359; (e) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176; (f) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704.
19. Gudmundsson, K. S.; Williams, J. D.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2003**, *46*, 1449.
20. Tully, W. R.; Guardner, C. R.; Gillespie, R. J.; Westwood, R. *J. Med. Chem.* **1991**, *34*, 2060.
21. (a) El Kazzouli, S.; Lavecchia, G.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron Lett.* **2006**, *47*, 4437; (b) Garnier, E.; Audoux, J.; Pasquinet, E.; Suzenet, F.; Poullain, D.; Lebret, B.; Guillaumet, G. *J. Org. Chem.* **2004**, *69*, 7809.
22. XANTPHOS = 9,9-dimethyl-4,5-bis(diphenylphosphino)-xanthene.
23. *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), $Pd_2(dba)_3$ (0.051 g, 0.056 mmol), and $AsPh_3$ (0.034 g, 0.0113 mmol) dissolved in a mixture of Et_3N/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 CH_2Cl_2 (3×). The combined organic layer was dried over $MgSO_4$ 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 ($CDCl_3$): 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 ^{13}C ($CDCl_3$): 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.
24. (*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 K_2CO_3 (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 CH_2Cl_2 (3×). The combined organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on a silica gel ($MeOH/CH_2Cl_2$) 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 ($CDCl_3$. 250,131 Hz): $\delta = 3.54$ (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 ^{13}C ($CDCl_3$): 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.