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Pd-catalyzed regiocontrolled Sonogashira and Suzuki cross-coupling reaction of 3,6-dihalogenoimidazo[1,2-*a*]pyridines: one-pot double-coupling approach

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ABSTRACT

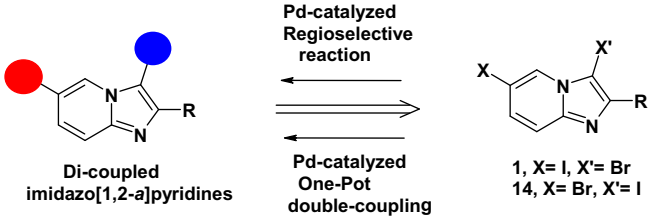
New and efficient regioselective Sonogashira and Suzuki–Miyaura palladium-catalyzed coupling reactions of 3,6-dihalogenoimidazo[1,2-*a*]pyridines followed by another cross-coupling has been successfully developed. Various solvents, palladium species and bases were tested. Scope and limitations of this regiocontrolled palladium-catalyzed reaction were investigated. The synthesis of 3,6-disubstituted imidazo[1,2-*a*]pyridine derivatives using one-pot regioselective double-coupling approach was developed. This procedure affords convergent syntheses of polysubstituted compounds in high yields in a very few steps.

1. Introduction

Palladium(0)-catalyzed carbon–carbon (Csp^2–Csp^2) bond-forming processes are widely used in synthetic chemistry.[1] Sonogashira[2] and Suzuki–Miyaura[3] cross-coupling reactions have found extensive use in natural products synthesis and for the construction of complex molecules.[4] Recently, many examples of regioselective Sonogashira and Suzuki–Miyaura[5] palladium-catalyzed reactions were described, but never in the context of imidazo[1,2-*a*]pyridines. Conducting more than one coupling in the same reaction vessel is quite rare.[6] Within the area of heteroaromatic systems, palladium is often used to catalyze single reactions. The use of alkynes as reactants in one-pot Sonogashira–Sonogashira couplings was not investigated with (hetero)aromatic systems excepted for multiple Sonogashira reactions of hexa- and pentachlorobenzene.[7]

In a previous paper, we described the regioselective palladium insertion at the position 3 of imidazo[1,2-*b*]pyridazines.[8] Our aim was to improve the efficiency of cross-coupling chemistry for the preparation of polysubstituted bicyclic heterocycles with a bridgehead nitrogen atom.[9] This initial approach was further investigated and applied to the regioselective Sonogashira and Suzuki–Miyaura palladium-catalyzed reactions of 3,6-dihalogenoimidazo[1,2-*a*]pyridines. We achieved selective functionalization of imidazo[1,2-*a*]pyridine derivatives into dissimilarly trisubstituted aromatic compounds, which is still a significant challenge in organic synthesis (Scheme 1). A synthesis of polysubstituted imidazo[1,2-*a*]pyridines via microwave-assisted one-pot Suzuki coupling/palladium-catalyzed heteroarylation and cyclization/Suzuki coupling/palladium-catalyzed heteroarylation was already developed by our team in order to reduce the number of steps requiring separation.[10]

Based on our recent study, the one-pot Suzuki–Suzuki and one-pot Sonogashira–Sonogashira cross-coupling using 3,6-dihalogenoimidazo[1,2-*a*]pyridines as starting material would be a useful method to access to desired polyfunctionalized heterocyclic precursors (Scheme 1).



Scheme 1. Convergent approach to dissimilarly 3,6-disubstituted imidazo [1,2-*a*] pyridines.

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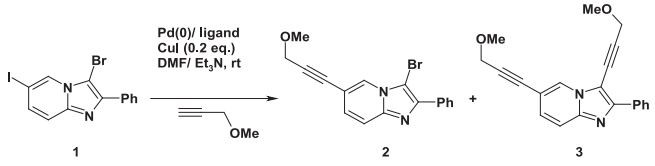
2. Results and discussion

For initial exploration, we chose 6-iodo-3-bromoimidazo[1,2-*a*]pyridine **1** then 6-bromo-3-iodoimidazo[1,2-*a*]pyridine **14** as model system (Scheme 1).

2.1. Sonogashira cross-coupling on compound 1

Initial work focused on the optimization of the first Sonogashira coupling reaction conditions to improve the reaction yield of desired monosubstituted compound without generation of symmetrical bis-alkynyl product. A model reaction was carried out with 6-iodo-3-bromoimidazo[1,2-*a*]pyridine **1** and methyl propargyl ether (1.1 equiv) under standard conditions using $PdCl_2(PPh_3)_2$ (0.05 equiv) and CuI (0.2 equiv) in a mixture of DMF/Et_3N at room temperature for 24 h.[9] In this case, compound **2** was obtained in only 74% yield (8% of starting material was recovered). Total conversion was observed with 1.3 equiv of methyl propargyl ether under the same reaction conditions and desired product **2** was generated in 92% yield (Table 3, entry 2). Influence of the Pd-catalysts on the regioselective Sonogashira cross-coupling reaction was studied. Replacement of $PdCl_2(PPh_3)_2$ by $Pd(PPh_3)_4$ afforded compound **2** and by-product **3** in 90% and 3% yield, respectively (Table 3, entry 3). [$Pd(OAc)_2$ (0.05 equiv)/PPh_3(0.1 equiv)] catalytic system used under the same reaction conditions provided compound **2** and **3** in 88% and 8% yields, respectively (Table 3, entry 4).

Table 1
Optimization of regioselective Sonogashira cross-coupling on 2-phenylimidazo[1,2-*a*]pyridine **1**



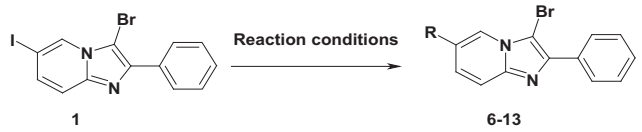
Entry	Pd(0)/ligand	Alkyne (equiv)	Time (h)	Yield[a] (%) **1**/**2**/**3**
1	$PdCl_2(PPh_3)_2$ (0.05 equiv)	1.1	24	8/74/0
2	$PdCl_2(PPh_3)_2$ (0.05 equiv)	1.3	4	0/92/0
3	$Pd(PPh_3)_4$ (0.05 equiv)	1.3	3	0/90/3
4	$Pd(OAc)_2$(0.05 equiv)/PPh_3 (0.1 equiv)	1.3	4	0/88/8

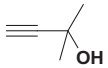
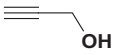
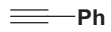
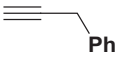
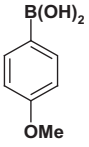
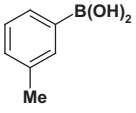
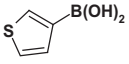
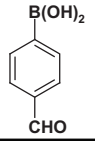
[a] Yields are given as isolated products.

2.2. Suzuki cross-coupling on compound 1 (exploration of the potential of regioselective Suzuki reaction)

6-Iodo-3-bromo-2-phenylimidazo[1,2-*a*]pyridine **1** was treated with 3-methoxyphenylboronic acid (1.2 equiv) in the presence of $Pd(PPh_3)_4$ (0.1 equiv) and NaOH (2 equiv) in a mixture of DME/H_2O[9d] at 80 °C for 2 h. Desired monocoupled compound **4** and the dicoupled **5** were isolated in 70% and 19% yield, respectively (Table 2, entry 1). Interestingly, desired compound **4** was obtained in 90% yield when using $Pd(OAc)_2$(0.1 equiv)/PPh_3(0.2 equiv) and K_2CO_3 (2 equiv) in DMF at 100 °C with no trace of compound **5** (Table 2, entry 2).

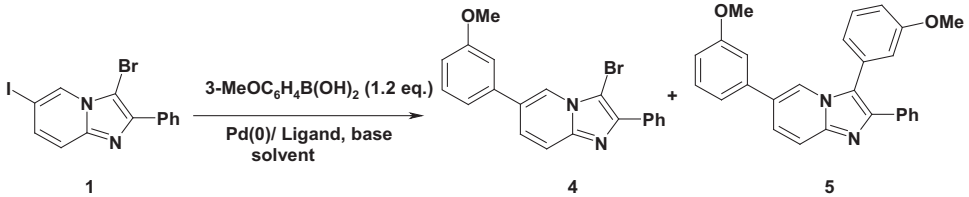
Table 3
Regioselective Sonogashira and Suzuki cross-coupling on imidazo[1,2-*a*]pyridine **1**



Entry	R	Product N°	Yield[a] (%)
1		**6**	95[b]
2		**7**	93[b]
3		**8**	91[b]
4		**9**	94[b]
5		**10**	88[c]
6		**11**	87[c]
7		**12**	90[c]
8		**13**	85[c]

[a] Yields are given as isolated products.
[b] Alkyne (1.3 equiv), $PdCl_2(PPh_3)_2$ (0.05 equiv), CuI (0.2 equiv), DMF/Et_3N, rt, 2–3 h.
[c] $RB(OH)_2$ (1.2 equiv), K_2CO_3 (2 equiv), $Pd(OAc)_2$ (0.1 equiv)/PPh_3 (0.2 equiv) in DMF at 100 °C, 2 h.

Table 2
Optimization of regioselective Suzuki cross-coupling on 2-phenylimidazo[1,2-*a*]pyridine **1**



Entry	Pd(0)/ligand	Base (2 equiv)	Solvent	*T*°C/time (h)	Yield[a] (%) **1**/**4**/**5**
1	$Pd(PPh_3)_4$(0.1 equiv)	NaOH	H_2O/DME	Reflux/2	0/70/19
2	$Pd(OAc)_2$ (0.1 equiv)/PPh_3(0.2 equiv)	K_2CO_3	DMF	100/2	0/90/0

[a] Yields are given as isolated products.