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Synthesis of Trisubstituted 6-Azaindoles *via* Palladium-catalyzed Heteroannulation

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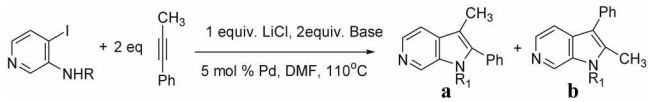
There has arisen considerable synthetic interest in azaindoles as a bioisosteres for indoles. The additional nitrogen atom in the 6-membered ring confers its own unique properties to the systems.[1] Although naturally occurring azaindoles are relatively scare,[2] they have been used for potential pharmaceutical agents.[3] The azaindoles have been prepared by classical methods such as Fisher, Madelung, and Reissert procedures.[4] In spite of those successes, the procedures generally showed harsh reaction conditions or limited introduction of functional group to azaindole core. Recently, palladium mediated cyclization reactions of alkynes[5] are convenient synthetic method for the preparation of condensed heteroaromatic compounds such as indoles,[6] azaindoles,[7] and pyrroloquinolines.[8] The heteroannulation of unsymmetrical alkynes has proven to be highly regioselective. However, Ujjainwalla *et al.*[9] reported the reactions using aromatic substituted internal alkynes provided very low yield of azaindoles with long reaction time. In this paper, we discuss heteroannulation of 3-amino-4-iodopyridines with aromatic internal alkynes to synthesize 6-azaindole derivatives, which have shown various biological activities such as HIV-1 inhibitory activity,[10a] 5-HT_6 antagonist,[10b] and antagonist of gonadotropin releasing hormone.[10c]

The 3-amino-4-iodopyridine derivatives were prepared as shown in Scheme 1 for the palladium-catalyzed heteroannulation.[11]

Initial studies were aimed at finding a set of general reaction conditions for palladium-catalyzed heteroannulation procedure. The reactions of 3-amino-4-iodopyridine derivatives with 1-phenyl-1-propyne were chosen as the model study. The results are summarized in Table 1. The reactions of 3-amino-4-iodopyridine using several different palladium sources provided below 20% of azaindole products with recovery of 30-40% starting aryl halide under long reaction time (Entries 1-3).

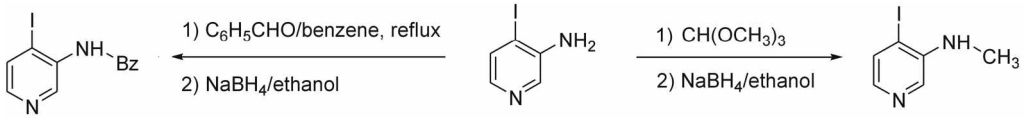
Table 1. Optimization of palladdium-catalyzed heteroannulation with 1-phenyl propyne



Entry[a]	R	Pd source	Base	Reaction time (h)	Isolated yield (%) Isomer ratio (**a** : **b**)[b]
1	H	$Pd(OAc)_2$	KOAc	24	13 (2:1)
2		$Pd(dba)_2$		24	14 (2:1)
3		$Pd(PPh_3)_2Cl_2$		24	17 (2:1)
4	Bz	$Pd(OAc)_2$		10	78 (2.3:1)
5			K_2CO_3	10	71 (2.1:1)
6			Na_2CO_3	10	62 (1.8:1)
7			Cs_2CO_3	10	64 (2.1:1)
8	CH_3		KOAc	10	54 (3.5:1)

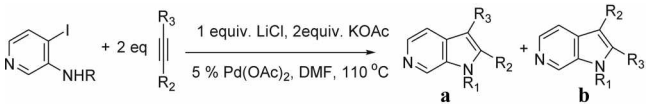
[a]All reaction were run on a 0.5 mmol scale. [b]The isomeric ratio was determined by ^1H NMR spectrum and GC.

We examined the reaction of *N*-benzyl-3-amino-4-iodopyridine with 1-phenyl-1-propyne under our previous reaction conditions.[7-8] the reaction provided high yield of desired products with an isomeric ratio 2.3 : 1. (Entry 4). The major isomer was identified by methyl peak of 6-azaindole in the ^1H NMR spectrum. The reactions of *N*-benzyl-3-amino-4-



Scheme 1

Table 2. Synthesis of 1,2,3-trisubstituted 6-azainoles by heteroannulation



Entry[a]	R_1	R_2	R_3	Reaction time (h)	% Isolated yield (**a** : **b**)[b]
1	CH_3	Ph	CO_2Et	10	53 (1:1)
2		*n*-Pr	CO_2Et	10	63 (1:1)
3	Bz	Ph	CO_2Et	10	68 (1:1)
4		Ph	*n*-Bu	10	60 (1.7:1)
5	"	3-CH_3Ph	"	10	60 (1:1)
6		3-CF_3Ph	"	12	64 (1.4:1)
7		3-Pyridinyl	"	10	71 (2.5:1)
8		2-Thiophenyl		24	63 (3:1)
9		5-Pyrimidinyl		24	65 (4:1)
10		Ph	Ph	10	69
11	"	$(CH_3)_3C$	CH_3	10	62
12	"	$(CH_3)_3Si$		10	67
13	"	$(CH_3)_3Si$	CH_2OH	10	61

[a]All reaction were run on a 0.5 mmol scale. [b]The isomeric ratio was determined by ^1H NMR spectrum.

iodopyridine under various carbonate bases were attempted to examine the effect in the reaction. However, the isomeric ratio was not significantly improved (Entry 5-7). Finally, the reaction using *N*-methyl-3-amino-4-iodopyridine as a arylhalide was examined, the reaction slightly increased isomeric ratio of 3.5 : 1. From the above results, the regioselectivity of heteroannulation was not much influenced by palladium source, base, and substituent of 3-amino group. In order to further explore alkyne's effect, the reactions of 3-amino-4-iodopyridines with several different unsymmetrical internal alkyne were examined under our standard reaction conditions (5 mol % $Pd(OAc)_2$, 2 equiv. alkyne, 1 equiv. LiCl, 2 equiv. KOAc, and DMF). The results are summarized in Table 2. The reactions of *N*-substituted 3-amino-4-iodopyridine with internal alkynes containing ester group were examined, the reactions afforded moderate yields of 6-azaindole products in an isomeric ratio 1 : 1 (Entry 1-3). The reactions of *N*-benzyl-3-amino-4-iodopyridine with substituted phenyl or heteroaromatic internal alkyne were also examined. Specially, the reactions with heteroaromatic internal alkyne provided good yield of desired products with higher regioselectivity compared with substituted phenyl internal alkynes (Entry 4-9). Finally, the reactions of *N*-benzyl-3-amino-4-iodopyridine with unsymmetrically alkyl-substituted internal alkynes were examined to explore generalization of the reaction procedure. The reactions afforded quite regioselective products without formation of any isomeric products. The annulated products showed sterically bulkier groups end up near the nitrogen atom in the 6-azaindoles (Entry 11-13).

In conclusion, the palladium-catalyzed heteroannulation of aromatic internal alkynes with 3-amino-4-iodopyridine derivatives provides a convenient route to synthesize various 1,2,3-trisubstituted 6-azainoles with moderate regioselectivity. The regioselectivity was quiet dependent on aromatic substituent and functional group in alkynes. We will further examine functional group transformation of 6-azaindoles and their application to biologically active compounds.

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12. Typical procedure: Palladium acetate (6 mg, 0.0125 mmol), LiCl (22 mg, 0.5 mmol), KOAc (98 mg, 1.0 mmol), *N*-benzyl-3-amino-4-iodopyridine (155 mg, 0.5 mmol), alkyne (1.0 mmol) and 10 mL of DMF were added to a pressure tube with a stirring bar. After heating appropriate time at 110 °C, the reaction mixture was diluted with ethyl ether and washed with saturated aqueous ammonium chloride solution. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography using hexane-ethyl acetate as an eluent.