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A Facile Synthesis of 2,3-Disubstituted Pyrrolo[2,3-*b*]pyridines *via* Palladium-Catalyzed Heteroannulation with Internal Alkynes

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Abstract: 2,3-Disubstituted pyrrolo[2,3-*b*]pyridines were synthesized by palladium-catalyzed heteroannulation of 2-amino-3-iodopyridine derivatives and internal alkynes with $Pd(OAc)_2$, LiCl, and KOAc in DMF. The 2-trimethylsilyl-3-methylpyrrolo[2,3-*b*]-pyridine was transformed to 2-substituted-3-methylpyrrolo[2,3-*b*]pyridines.

Pyrrolopyridines have attracted considerable attention as an analog of indole nucleus because of their interesting biological activities.[1] There are only a few pyrrolopyridine derivatives in nature,[2] so many pyrrolopyridine derivatives are synthetically prepared for the development of pharmaceutical agents. The general synthetic methods for pyrrolopyridines include Mandelung, Fischer, and Reissert type syntheses.[3] In spite of those successes, they provided desired products in low yields under drastic reaction conditions. The directed *ortho* lithiation of aminopyridines and its derivatives has been shown to be a useful synthetic method for the preparation of substituted pyrrolopyridines through sequence of several reactions.[4] With continuing refinement of transition metal-mediated organic synthetic methodology, a number of new and potentially versatile method for both the synthesis and functionalization of indoles have been developed to overcome the classical synthetic disadvantages.[5] However, there are only several transition metal-mediated pyrrolopyridine synthesis in literature.[6] Recently, two papers[7] reported the palladium-catalyzed azaindole synthesis with discouraging results under the same heteroannulation procedure for indoles.[8]

We now report a convenient and simple approach to pyrrolo[2,3-*b*]pyridines (7-azaindole) involving palladium-catalyzed heteroannulation of internal alkynes with 2-amino-3-iodo-pyridine and its derivatives. To overcome previous discouraging reports, initial studies were aimed at finding a set of general reaction conditions for palladium-catalyzed heteroannulation procedure. The reaction between 2-amino-3-iodopyridine derivatives which was prepared by literature procedures[9] and 1-trimethylsilylpropyne was chosen as the model study. The results are summarized in Table 1.

The reactions employing quarternary ammonium chlorides provided around 40 % of cyclized product **A** and 20 % of coupling product **B** (Entries 1-3). On the other hand, the reactions using LiCl afforded predominantly cyclized pyrrolopyridines **A** (Entry 4) with improved yields and better reproducibility (Entries 1-4).[10] We also examined effect of various substituents on 2-amino-3-iodopyridines (Entries 5-13). The reactions using acyl or pivaloyl substituted 2-amino-3-iodopyridine derivatives provided only coupling products **B** (Entries 5-6). Although Boc group has similar steric effect to pivaloyl group, the reaction using 2-Boc-amino-3-iodopyridine provided pyrrolopyridine **A** and coupling product **B** in

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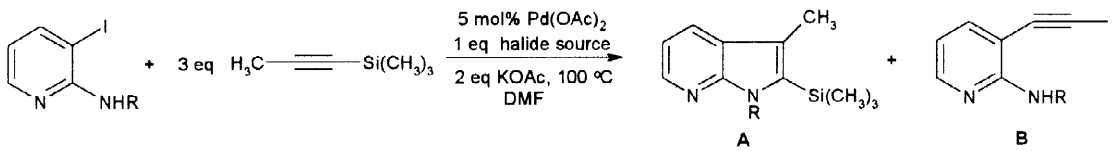
similar amounts (Entry 7). The reactions using *p*-methoxyphenyl or *p*-methoxybenzyl substituted 2-amino-3-iodopyridine showed improved yield of desired products (Entries 9-13).

Table 1. Synthesis of 3-Methyl-2-trimethylsilyl-1*H*-pyrrolo[2,3-*b*]pyridine Derivatives



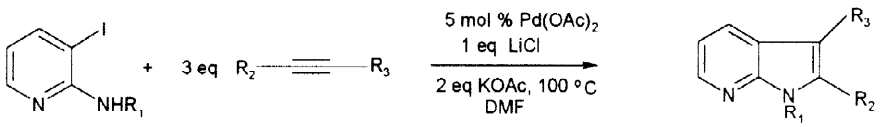
Entry[a]	R	Halide source	Isolated yield (%) **A** : **B**	Entry[a]	R	Halide source	Isolated yield (%) **A** : **B**
1	H	n-Bu_4NCl	37 : 18	8	CH_3	LiCl	82 : -
2	H	Me_4NCl	42 : 20	9	$C_6H_5CH_2$	"	84 : -
3	H	Et_4NCl	40 : 12	10	p-$MeOC_6H_4CH_2$	"	91 : -
4	H	LiCl	72 : -	11	C_6H_5	"	66 : -
5[b]	COMe	"	- : 30	12	p-$MeOC_6H_4$	"	72 : -
6[b]	$COCMe_3$	"	- : 47	13[c]	p-$NO_2C_6H_4$	"	no reaction
7	Boc	"	27 : 34				

[a]All reactions were run on a 0.5-mmol scale. [b]Some of starting pyridyl halides were recovered. [c]All of starting pyridyl halide was recovered.

In order to further examine the regioselectivity of heteroannulation process, the reactions using variety of internal alkynes and substituted 2-amino-3-iodopyridine derivatives were examined. The results were summarized in Table 2. The heteroannulation of unsymmetrical alkynes has proven to be highly regioselective. The sterically bulkier groups end up nearer the nitrogen atom in the pyrrolopyridines. Specially, the reactions using non-substituted aminopyridines provided low yield of desired product compared to the reactions using substituted aminopyridines. The reaction usings 1-phenylpropyne provided different regio-selectivity depending on the substituent on amino group. All of regioselectivity were examined by desilylation or debenzylation of products with comparison of spectral data in literature, or NOE spectral experiments.

The facile annulation of silylalkynes broadens tremendously the scope of this synthetic process. The 2-trimethylsilylpyrrolo[2,3-*b*]pyridine derivatives could be transformed to various 2-substituted pyrrolopyridines by protonolysis, halogenation, debenzylation, or coupling reaction (**Scheme 1**).

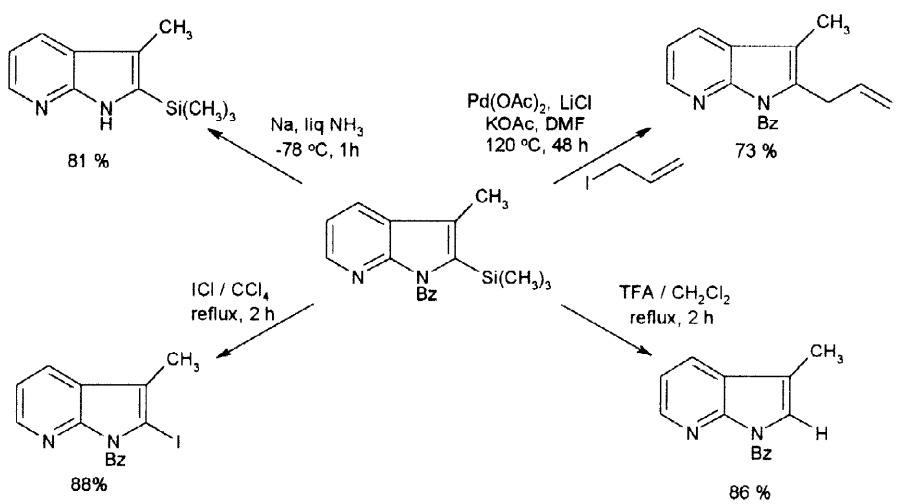
Table 2. Synthesis of 2,3-Disubstituted Pyrrolo[2,3-*b*]pyridine Derivatives



Entry[a]	R_1	R_2	R_3	Reaction time (h)	Isolated yield (%)
1	CH_3	$Si(CH_3)_3$	CH_2OH	12	74
2	$C_6H_5CH_2$	"	"	8	71
3	*p*-$MeOC_6H_4CH_2$	"	"	6	78
4	$C_6H_5CH_2$	$Si(CH_3)_3$	CH_2CH_2OH	8	80
5	H	"	Ph	18	27
6	CH_3	"	"	15	58
7	CH_3	*n*-Pr	*n*-Pr	12	84
8	$C_6H_5CH_2$	"	"	8	82
9	*p*-$MeOC_6H_4CH_2$	"	"	8	88
10	H	$C(CH_3)_3$	CH_3	48	37
11	CH_3	"	"	15	80
12	$C_6H_5CH_2$	"	"	24	62
13	*p*-$MeOC_6H_4CH_2$	"	"	8	81
14	H	Ph	CH_3	48	45
15[b]	CH_3	"	"	18	79 (52:27)
16[b]	$C_6H_5CH_2$	"	"	24	73 (50:23)

[a]All reaction products were identified by ^1H NMR, ^{13}C NMR, and mass spectra.
[b]The minor regioisomer was 1-substituted 2-methyl-3-phenylpyrrolo[2,3-*b*]pyridine.

Scheme 1



In conclusion, the palladium-catalyzed heteroannulation of alkynes with 2-amino-3-iodopyridine derivatives provides a convenient new route to synthesize various 2,3-disubstituted pyrrolo[2,3-*b*]pyridines with high regioselectivity. The facile elaboration of silyl group can provide variety of 2-substituted-3-methylpyrrolo[2,3-*b*]pyridines. We will further examine possible application to biologically active pyrrolopyridine derivatives.

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10. Typical procedure: 3-Methyl-2-trimethylsilyl-1*H*-pyrrolo[2.3-*b*]pyridine (A). Palladium acetate (6 mg, 0.0125 mmol), LiCl (22 mg, 0.5 mmol), KOAc (98 mg, 1.0 mmol), 2-amino-3-iodopyridine (110 mg, 0.5 mmol), and 3-trimethylsilylpropyne (170 mg, 1.5 mmol) in DMF (10 ml) were added to a pressure tube with a stirring bar. After heating for 12 h at 100 ℃, the reaction mixture was diluted with ether and washed with saturated aqueous ammonium chloride solution. The organic layer was dried over anhydrous magnesium sulfate, filtered, concentrated, and the residue was purified by silica gel column chromatograpy using hexane - ethyl acetate (3:1) as an eluent. The 3-methyl-2-trimethylsilyl-1*H*-pyrrolo[2.3-*b*]pyridine (73 mg, 0.36 mmol, 72 %) was obtained as a yellow solid: mp 88-90 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.39 (s, 9H, $Si(CH_3)_3$), 2.38 (s, 3H, CH_3), 7.00 (dd, 1H, J=4.8, 7.9 Hz, ArH), 7.81 (dd, 1H, J=1.5, 7.0 Hz, ArH), 8.27 (dd, 1H, J=1.6, 4.8 Hz, ArH), 9.31-9.52 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 52 MHz) δ 150.8, 143.0, 134.3, 126.7, 121.9, 118.3, 114.7, 10.5, -0.6; High-resolution mass spectrum calcd for $C_{11}H_{16}N_2Si$ 204.1083, found 204.1062.