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Synthesis of 5-, 6- and 7-Azaindoles *via* Palladium-Catalyzed Heteroannulation of Internal Alkynes

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Abstract: The palladium-catalyzed heteroannulation of internal alkynes using *ortho*-aminoiodopyridine derivatives is described. This experimentally simple procedure, which employs a Pd(dppf)Cl_2/LiCl/Na_2CO_3 reagent system, allows rapid and reliable access to a structurally diverse range of 5-, 6- and 7-azaindoles. © 1998 Elsevier Science Ltd. All rights reserved.

The indole nucleus is the central building block in a number of natural and unnatural products of differing structure, biological activity and (bio)synthetic origin.[1] The chemical and biological properties of indoles, in general, make them highly attractive synthetic targets. Likewise, azaindoles have fueled considerable synthetic interest, primarily as bioisosteres for indoles, in which adoption of an additional nitrogen atom in the aromatic ring, confers its own unique properties to the system.[2] Although naturally occurring azaindoles are relatively scarce,[3] they have enjoyed widespread application as potential pharmaceutical agents.[4] Azaindoles have been prepared traditionally *via* classical methods such as Fischer, Madelung and Reissert procedures, which inspite of their synthetic value, generally suffer from harsh reaction conditions and modest yields.[5] Consequently, these methods have limited both the degree of substitution and type of functionality that can be incorporated into the azaindole core.

Recently, Larock and Yum published an elegant method for the preparation of indoles involving palladium-catalyzed heteroannulation of internal alkynes using *ortho*-iodoaniline and its derivatives.[6] This reaction proceeded in typically high yields under essentially neutral conditions with excellent regioselectivity. Inspired by their work, we reasoned that this procedure could also be applicable towards the synthesis of azaindoles. This strategy was first attempted by Gronowitz *et al.*[7] with only moderate success and was later optimized by Yum *et al*[8] for 7-azaindole synthesis. Prompted by their recent findings, we would like to disclose our own results and observations in this area which led to the independent conquering of this problem.

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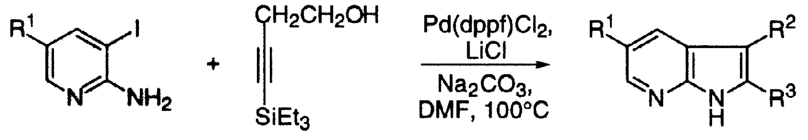
We discovered that Pd(dppf)Cl_2 is a superior catalyst to Pd$(OAc)_2$ for this transformation and LiCl is an essential component with respect to accomplishing good regioselectivity, reproducibility and improved yields.[9] With general conditions in hand,[10] we examined the flexibility of this approach towards 2,3,5-trisubstituted-7-azaindoles (Equation 1). Initially, 4-(triethylsilyl)-3-butyn-1-ol was elected as the alkyne of choice since regioselective control was expected to be very high, and equally important, both the silyl and the hydroxyl groups could serve, in principle, as useful synthetic handles for further elaboration (Table 1).[11] Our preliminary results verified that heteroannulation of the silylalkyne is highly regioselective, providing only the regioisomer shown in Table 1, and that the isolated yields are typically good. Moreover, the reaction is tolerant of functionality adopted at the 5-position of the 2-amino-3-iodopyridine precursor. A limitation of these conditions was identified when a CF_3 group was employed (entry 5); in this case, only a trace amount of a 7-azaindole lacking the C-2 silyl moiety was isolated.



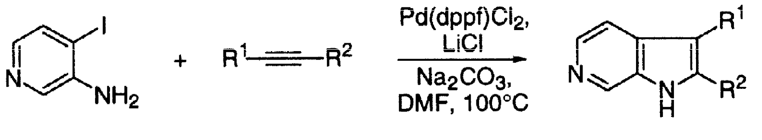
(1)

Table 1. Synthesis of 2,3,5-trisubstituted-7-azaindoles.[12]

Entry	R^1	R^2	R^3	Isolated Yield (%)
1	H	CH_2CH_2OH	$SiEt_3$	77
2	Me	CH_2CH_2OH	$SiEt_3$	67
3	CO_2Me	CH_2CH_2OH	$SiEt_3$	47 (68%)[a]
4	Cl	CH_2CH_2OH	$SiEt_3$	71
5	CF_3	CH_2CH_2OH	H	~5[b]

[a] Yield based on recovered starting material. [b] Yield of desilylated material.

This methodology was subsequently extended to the synthesis of 2,3-disubstituted-6-azaindoles and here alkyne variation was explored (Equation 2, Table 2). Again, the yields were consistently good, except with diphenylacetylene, which was a poor substrate.

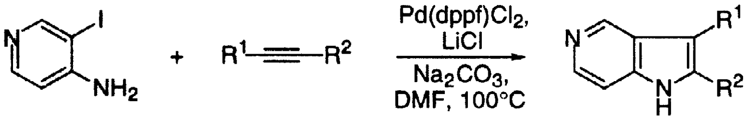


(2)

Table 2. Synthesis of 2,3-disubstituted-6-azaindoles.[12]

Entry	R^1	R^2	Isolated Yield (%)
1	CH_2CH_2OH	$SiEt_3$	69
2	^{n}Pr	^{n}Pr	71
3	H	$SiMe_3$	73
4	Ph	Ph	19

Finally, heteroannulation of internal alkynes using 4-amino-3-iodopyridine was investigated and again, the described conditions proved to be reliable, furnishing good yields of 2,3-disubstituted-5-azaindoles (Equation 3, Table 3). In this study, we have been able to generate a catalyst/reagent system which does not routinely require 'capping' of the amino group for good yields, and ultimately, obviates the necessity for a protection/deprotection protocol.



(3)

Table 3. Synthesis of 2,3-disubstituted-5-azaindoles.[12]

Entry	R^1	R^2	Isolated Yield (%)
1	CH_2CH_2OH	$SiEt_3$	65
2	^{n}Pr	^{n}Pr	78
3	Ph	Ph	22 (76)[a]

[a] Yield based on recovered starting material.

In summary, the foregoing results, when taken in conjunction with the original observation of Larock,[6] would suggest that this strategy has considerable merit and inherent potential for the construction of more complex 5-, 6- and 7-azaindoles. The present methodology is practical in operation and offers considerable versatility with respect to the range of pyridine derivatives and alkynes that can be employed.

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9. For comparative purposes, we have repeated entries 1, 2 and 4 from Table 1 using Pd(OAc)$_2$ as the catalyst, under otherwise identical conditions. The following results were obtained: entry 1, 27% isolated yield; entry 2, 48%; and entry 4, 43% isolated yield of corresponding 7-azaindoles.
10. Typical experimental procedure: **3-(2-Hydroxyethyl)-2-triethylsilyl-1*H*-pyrrolo[2,3-*b*]pyridine**
    A mixture of 2-amino-3-iodopyridine (150 mg, 0.682 mmol), 4-(triethylsilyl)-3-butyn-1-ol (378 mg, 2.05 mmol), Pd(dppf)Cl$_2$ (27.8 mg, 34.1 μmol), LiCl (28.9 mg, 0.682 mmol) and Na$_2$CO$_3$ (145 mg, 1.36 mmol) in DMF (7 mL) was heated at 100 °C for approximately 15h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate/ether (1:1, 20 mL) and poured into water (20 mL). The biphasic suspension was filtered through Celite,® the organic phase separated and the aqueous phase re- extracted with ethyl acetate (2 x 20 mL). The combined organic extract was washed with water (30 mL), brine (30 mL), dried (MgSO$_4$) and the solvent evaporated *in vacuo*. Purification of the residue by flash chromatography on silica gel (gradient elution; 40-45% ethyl acetate in hexanes as eluent) furnished 3-(2-hydroxyethyl)-2-triethylsilyl-1*H*-pyrrolo[2,3-*b*]pyridine (146 mg, 77%) as a colorless solid: ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.52 (bs, 1H), 8.30 (dd, 1H, J = 1.6, 4.8), 7.96 (m, 1H), 7.06 (1H, dd, J = 4.5, 7.9), 3.90 (t, 2H, J = 6.9), 3.10 (t, 2H, J = 6.9), 1.03 (m, 9H), 0.94 (m, 6H); MS (EI) *m/e* 276 ([M$^+$]).
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12. All reactions were conducted on a 0.7 mmol scale. All reactions were performed under an inert atmosphere in DMF at 100 °C using *ortho*-amino iodopyridine (1eq), alkyne (3eq), Pd(dppf)$_2$Cl$_2$ (5 mol%), LiCl (1 eq) and Na$_2$CO$_3$ (2eq). The yields for all reaction products are unoptimized and represent isolated material. All reaction products were identified by ^{1}H NMR (400 or 500 MHz) and mass spectrometry.