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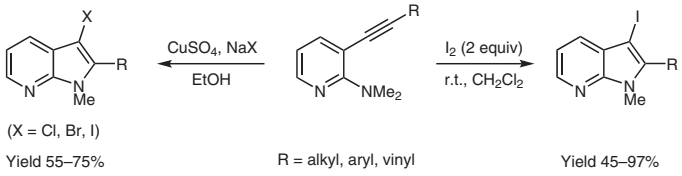
Synthesis of 3-Halo-7-azaindoles through a 5-*endo*-dig Electrophilic Cyclization Reaction

Aimee Philips
Christopher Cunningham
Kajal Naran
Tanay Kesharwani*

Department of Chemistry, University of West Florida, Pensacola, FL 32514, USA
tkesharwani@uwf.edu



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Abstract Biologically useful 7-azaindoles were synthesized by electrophilic cyclization of 3-alkynyl-*N*,*N*-dimethylpyridine-2-amines with molecular iodine. By this simple atom-economical approach under ambient reaction conditions, a library of interesting 3-iodo-7-azaindoles were synthesized in high yields. To synthesize the corresponding 3-bromo- and 3-chloro-7-azaindoles, an environmentally benign copper-mediated cyclization was employed, with inexpensive, nontoxic, and noncorrosive sodium chloride and sodium bromide as the sources of chlorine and bromine, respectively.

Key words electrophilic cyclization, iodocyclization, bromocyclization, chlorocyclization, azaindoles

7-Azaindoles are an important class of naturally occurring nitrogen-containing heterocycles.[1] The 7-azaindole core structure is found in many biologically active molecules[2] and commercially available drugs, such as venetoclax, vemurafenib, and pexidartinib (Figure 1).[3] The antitumor,[4] antimalarial,[5] antiinflammatory,[6] antiproliferative,[7] thrombin-recognition,[8] glycation-inhibitory,[9] antimicrobial,[10] and anti-HIV[11] properties of 7-azaindoles are well documented.

Recently, due to their antiviral[12] and kinase-inhibitory[13] properties, the 3-halo-7-aza indoles have attracted the attention of medicinal chemists; however, there are only a handful of known methods for synthesizing these compounds, which require multistep processes, as shown in Scheme 1. The efficient methods reported in the literature include two-step processes involving cyclization of 3-ethynylpyridin-2-amines **1** by using bases or acids,[10a,14] such as *tert*-BuOK, KH, or triflic acid, or with transition-metal catalysts, such as CuI or $AgNO_3$,[15] followed by electrophilic aromatic substitution (Scheme 1; Previous Methods).[16] Therefore, there is a great need to develop efficient one-step methods for the synthesis of 3-haloazaindoles. One such single-step method was developed by Knight and Amjad, who used electrophilic I_2 to convert a tosylated aminopyridine into a 3-iodo-7-azaindole.[17] Recently, Lessing and Müller developed an efficient one-pot three-step synthesis of 7-azaindoles. They demonstrated that 2-aminopyridyl halides can undergo a copper-free alkynylation–cyclization–alkylation sequence rapidly and efficiently to give highly functionalized 1,2,5-trisubstituted 7-azaindoles.[18]

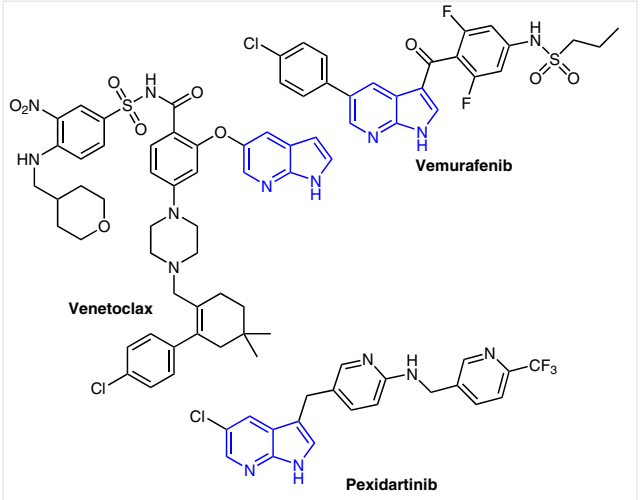
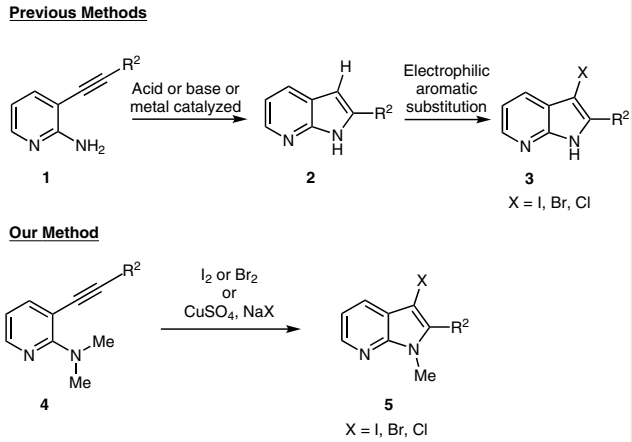
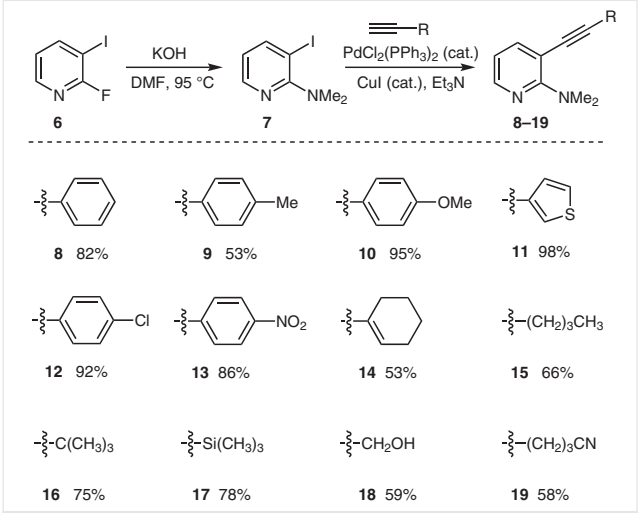


Figure 1 Drug molecules containing 7-azaindole moieties



Scheme 1 Comparison of literature methods with our method for the synthesis of 3-halo-7-azaindoles



Scheme 2 Synthesis of starting 3-alkynyl-*N*,*N*-dimethylpyridine-2-amines

Halogenation of a drug candidate is an established method for optimizing its absorption, distribution, metabolism, excretion, and toxicity profile, thereby increasing its half-life and effectiveness.[19] Consequently, the development of a green, regioselective, and effective method for the synthesis of halogenated heterocycles is crucial in pharmaceutical research. In the past decade, reactions involving an electrophile with an alkyne tethered to a nucleophile for the synthesis of O, N, S, and Se heterocycles have been extensively investigated.[20]

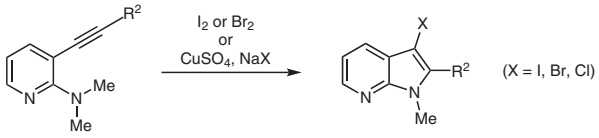
Here we report the synthesis of 3-halo-7-azaindoles **5** in one step by an electrophilic cyclization reaction of 3-alkynyl-*N*,*N*-dimethylpyridine-2-amines **4** (Scheme 1; Our Method). 3-Iodo-7-azaindoles were synthesized from the corresponding alkyne in the presence of molecular iodine as the electrophile, whereas the 3-bromo and 3-chloro derivatives were synthesized by using noncorrosive and nontoxic NaCl and NaBr as sources of electrophilic halogen in the presence of $CuSO_4$.[21]

The desired starting alkynes **8–19** for our method were synthesized by Sonogashira coupling[21,22] of the iodopyridine **7** with various terminal alkynes (Scheme 2). The coupling reaction proceeded in the presence of catalytic CuI and a palladium catalyst at room temperature to give moderate to excellent yields of the desired alkynes **8–19**. The 3-iodo-*N*,*N*-dimethylpyridin-2-amine (**7**) required for the Sonogashira coupling was synthesized in 74% yield by an S_NAr reaction of 2-fluoro-3-iodopyridine (**6**) with potassium dimethylamide, generated in situ by the reaction of DMF with KOH.

To study the scope of electrophilic halocyclization reaction, the functionalized 3-alkynyl-*N*,*N*-dimethylpyridine-2-amines **8–19** were cyclized by using molecular iodine as shown in Scheme 1. The appropriate substituted alkynylpyridine (1 equiv) was treated with I_2 (1.2 equiv) in CH_2Cl_2 at room temperature for twelve hours. The mixture was monitored for completion of the reaction by means of TLC. The crude product mixture was purified by column chromatography. To synthesize the 3-chloro- and 3-bromo-7-azaindoles, alkynylpyridines (1 equiv) were treated with corresponding sodium halide (5 equiv) and $CuSO_4$ (5 equiv) in ethanol.

A diverse library of 3-halo-7-azaindole derivatives was synthesized by using our method (Table 1). We started our study with the iodocyclization of phenyl-substituted alkyne **8** by treatment with I_2. The reaction proceeded with ease to give **20** in 93% yield (Table 1, entry 1). We recently discovered green iodocyclization reaction conditions in which NaI and $CuSO_4$ are used to generate I_2 in situ, thereby avoiding the handling of corrosive and toxic iodine. Employing these green conditions on alkyne **8** resulted in a slightly lower yield of **20** (entry 2). After establishing the iodocyclization reaction of **8**, we turned our attention to bromocyclization with Br_2. Our attempt resulted in a complex reaction mixture; none of the desired bromocyclized product **21** could be isolated (entry 3). Cyclization with NaBr and $CuSO_4$, however, resulted in a 45% yield of **21** at room temperature (entry 4); heating the reaction mixture to 80 °C resulted in an improved yield of 70% (entry 5). After the success of the bromocyclization reaction, we attempted a chlorocyclization of alkynylpyridine **8**, which also resulted in the desired chlorocyclized azaindole **22** in 71% yield (entry 6).

Table 1 5-*endo*-dig Cyclization of 3-Alkynyl-*N*,*N*-dimethylpyridine-2-amines through Electrophilic Halocyclization to the Corresponding 3-Halo-7-azaindoles[a]



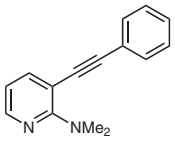
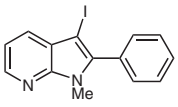
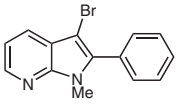
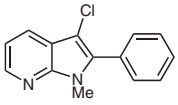
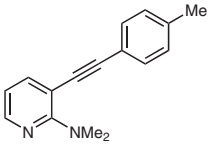
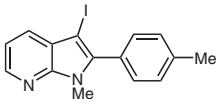
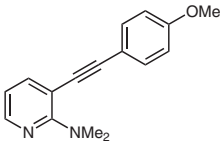
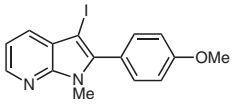
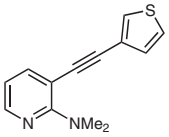
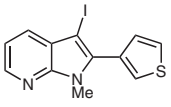
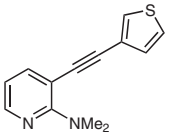
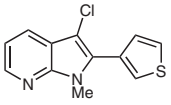
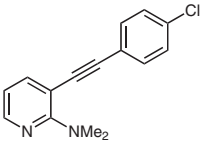
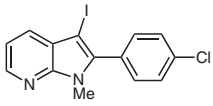
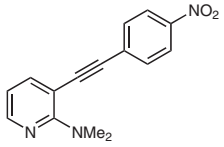
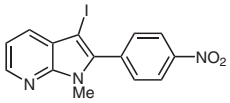
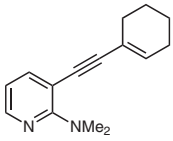
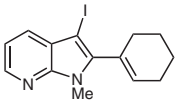
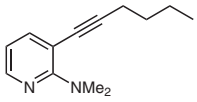
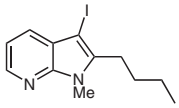
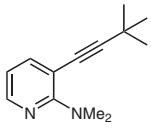
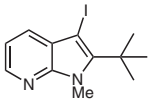
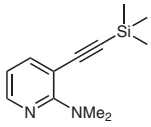
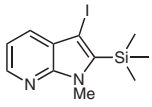
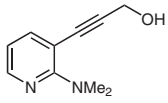
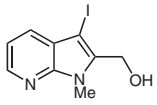
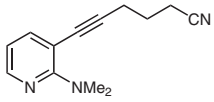
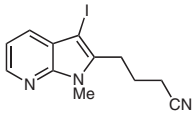
Entry	Alkyne		Method	Product		Yield[b] (%)
1		**8**	A		**20**	93
2		**8**	B		**20**	75
3		**8**	A		**21**	–
4		**8**	B		**21**	45
5		**8**	B		**21**	70[c]
6		**8**	B		**22**	71
7		**9**	A		**23**	97
8		**10**	A		**24**	94
9		**11**	A		**25**	93
10		**11**	B		**26**	55
11		**12**	A		**27**	97

Table (continued)

Entry	Alkyne		Method	Product		Yield[b] (%)
12		**13**	A		**28**	45
13		**14**	A		**29**	52
14		**15**	A		**30**	74
15		**16**	A		**31**	58
16		**17**	A		**32**	–
17		**18**	A		**33**	–
18		**19**	A		**34**	77

[a] Method A: All reactions were performed on a 0.3 mmol scale by using 1.0 equivalent of the alkyne, 2.0 equivalents of halogen (I_2 or Br_2) in CH_2Cl_2 at r.t. for 24 h. Method B: All reactions were performed on a 0.3 mmol scale by using 1.0 equivalent of the alkyne, 5.0 equivalents of $CuSO_4 \cdot 5H_2O$, and 5.0 equivalents of the appropriate sodium halide (NaCl, NaBr, or NaI) in EtOH at r.t. for 48 h.
[b] Isolated yield.
[c] The reaction was conducted at 70 °C.

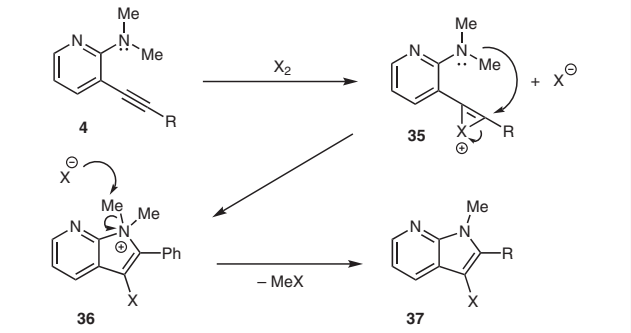
Metal-catalyzed cross-coupling reactions are known to work better with aryl iodides than with other aryl halides. We therefore decided to continue our study with the iodocyclization reaction. After establishing the efficacy of our iodocyclization with I_2, we decided to further explore the functional-group tolerance of the reaction conditions. Alkynylpyridines substituted with electron-rich or electron-deficient aryl groups or with hetaryl, vinyl, TMS, alcohol, ether, or nitrile groups were tested in the synthesis of 2,3-disubstituted 7-azaindoles.

First, we employed the *p*-tolyl-substituted alkyne **9**, which resulted in an improved yield of 97%, higher than that obtained with the unsubstituted phenyl group (compare Table 1, entries 1 and 7). Similarly, the electron-rich *p*-methoxyphenyl-substituted alkyne **10** gave **24** in an excellent yield of 94% (entry 8). These high yields were attributed to the fact that alkynylpyridines substituted with electron-rich aryl groups have a higher electron density on the alkyne carbon bonded to the pyridine ring. This, in turn, facilitates the approach of the electrophile to the alkyne functionality that results in the desired 5-*endo*-dig cyclization. The electron-rich 3-thienyl group was well tolerated, and the resulting iodinated 2-(3-thienyl)-7-azaindole **25** was formed in an excellent 93% yield (entry 9) when alkyne **11** was treated with molecular iodine. Chlorocyclization of **11** was also successful and resulted in the formation of chloro-

azaindole **26** in a modest 55% yield (entry 10). Conversely, electron-deficient aromatic rings reduce the electron density on the alkyne, making it less active toward the desired cyclization reaction. This aligned with our observations, as the cyclization of alkyne **13**, which contained an electron-deficient *p*-nitrophenyl group, resulted in only a 45% yield of the desired azaindole **28** (entry 12).

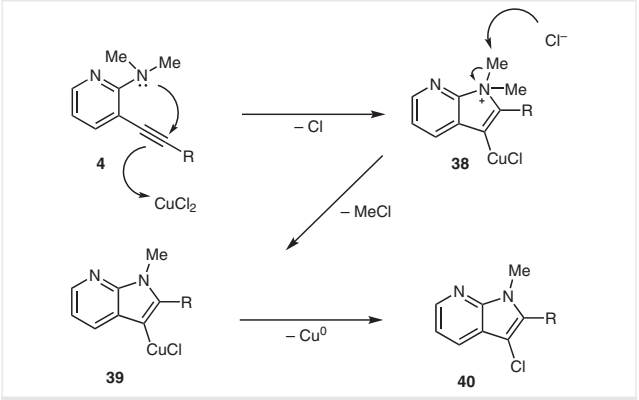
Employing an alkynylpyridine **14** substituted by a vinyl functionality resulted in a moderate 52% yield of azaindole **29** (Table 1, entry 13). Iodocyclization of an unhindered butyl-substituted alkyne **15** resulted in the desired cyclized product **30** in a good yield of 74% (entry 14). The *tert*-butyl-substituted alkynylpyridine gave the azaindole **31** in a lower yield of 58%, suggesting that the bulky group hindered the incoming electrophile during the cyclization reaction (entry 15). Similarly, the alkyne substituted with a sterically demanding TMS group did not work well and, after several attempts, we failed to isolate desired product **32** due to the formation of complex reaction mixtures (entry 16). To our surprise the primary propargylic alcohol **18** also failed to furnish a clean reaction product, and we could not obtain any of the desired azaindole **33** (entry 17). Our reaction conditions tolerated the nitrile functionality, as the 3-iodo-azaindole **34** was obtained from alkyne **19** in a good yield of 77% (entry 18).

It is known that $CuSO_4$ and NaX (X = Cl, Br, I) react to form the corresponding copper(II) salts CuX_2, which, in the case of bromine and iodine, are known to dissociate to CuX and X_2. Therefore, we believe that the mechanism for the bromo- and iodocyclization involving $CuSO_4$ and a sodium halide follows the same mechanism as the reaction involving molecular iodine. A well-established iodocyclization mechanism is outlined in Scheme 3.[23] The iodine or bromine molecule coordinates with the unsaturated C≡C triple bond, resulting in the formation of intermediate **35**. The nearby nucleophilic nitrogen moiety opens the three-membered ring containing the halonium cation, resulting in 5-*endo*-dig ring closure to form the charged azaindole intermediate **36**. Lastly, the halogen anion removes the methyl group from cationic quaternary nitrogen through an S_N2 pathway to give the desired 3-halo-7-azaindole **37**.



Scheme 3 Proposed mechanism for bromo- and iodocyclization with I_2 or Br_2

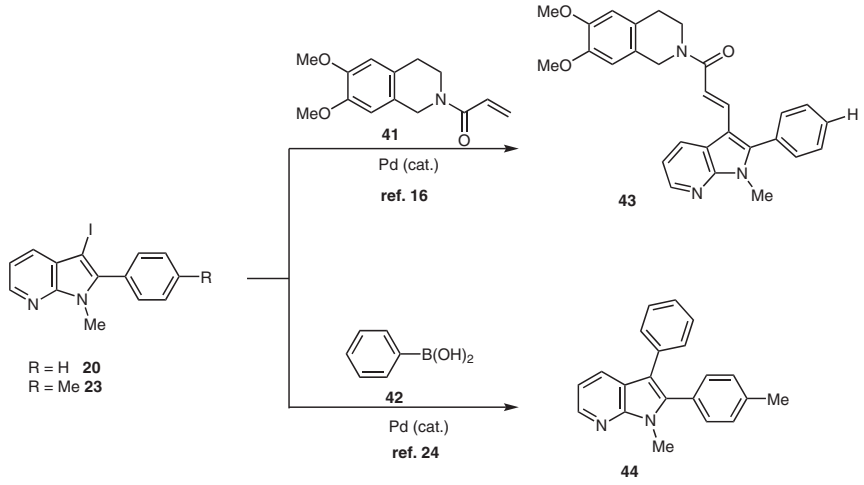
The $CuCl_2$ formed in situ by the reaction of $CuSO_4$ with NaCl is known to be very stable and does not dissociate to generate Cl_2. Therefore, the proposed mechanism for the chlorocyclization outlined in Scheme 4 is different from the aforementioned bromo and iodocyclization mechanism. Alkyne **4**, upon coordination with $CuCl_2$, followed by an *anti*-attack from a nearby nitrogen nucleophile results in the formation of cationic intermediate **38**. The methyl group in **38** is subsequently removed by an S_N2 displacement pathway with the help of the chloride anion to give intermediate **39**. Finally, a reductive elimination leads to the desired azaindole **40**.



Scheme 4 Proposed mechanism for the chlorocyclization reaction

3-Iodo-7-azaindoles might valuable intermediates for the synthesis of natural products or potential drug candidates. There are several reports in the literature on the functionalization of 3-haloindoles through metal-catalyzed cross-coupling reactions such as the Suzuki or Heck coupling reactions (Scheme 5).[16,24] Müller and Lessing have reported a Pd-catalyzed cross-coupling of 3-iodo-2-phenyl-7-azaindole **20** using an acrylamide **41** for the efficient and concise synthesis of azaindole **43**, a transforming growth factor (TGF)-β1 antagonist.[18] 3-Iodo-7-azaindoles have also been coupled with arylboronic acids to give an exciting array of functionalized 3-aryl-7-azaindoles, as demonstrated by Das and co-workers.[24]

In summary, we have developed an efficient and mild synthesis of 7-azaindoles through 5-*endo*-dig electrophilic cyclization of the corresponding 3-alkynyl-*N*,*N*-dimethylpyridine-2-amines.[25] The iodocyclization using molecular iodine proceeded in high yields to form an array of potentially useful 3-chloro-7-azaindole derivatives. In addition, we also developed green reaction conditions for the cyclization reaction by employing a sodium halide as a source of electrophilic halide. Both of our procedures require only moderate temperatures, demonstrate broad functional-group tolerance, and result in excellent yields of the desired product. Our process provides a clean, simple, and mild method for the synthesis of many 3-halo-7-azaindole derivatives.



Scheme 5 Functionalization of 3-iodoazaindole through Pd-catalyzed cross-coupling reactions

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611827.

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(25) **Halocyclization Reaction; General Procedures**
Method A. To a 6-dram vial containing the starting alkyne (0.3 mmol) was added CH_2Cl_2 (4.0 mL). I_2 (2.0 equiv) was then added, and the mixture was stirred at r.t. for 24 h. The reaction mixture was finally purified by column chromatography (silica gel, hexanes–EtOAc).
Method B. To a 6-dram vial containing the starting alkyne (0.3 mmol) was added 95% EtOH (4.0 mL). The appropriate sodium halide (5.0 equiv) and $CuSO_4{\cdot}5\ H_2O$ (5.0 equiv) were added, and the mixture was stirred at r.t. for 48 h. The mixture was finally purified by column chromatography (silica gel, hexanes–EtOAc).
3-Iodo-1-methyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (20a)
Yellow-brown solid; yield: 93 mg (93%); mp 86–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 7.17 (dd, *J* = 7.6, 4.4 Hz, 1 H), 7.48–7.54 (m, 5 H), 7.76 (dd, *J* = 8.0, 1.2 Hz, 1 H), 8.37 (dd, *J* = 4.4, 1.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.56, 56.49, 116.93, 123.69, 128.55, 128.70, 128.97, 129.16, 129.26, 130.69, 131.16, 142.16, 143.98, 148.73.
Other characterization data agreed with the previously reported values (See ref. 26).
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