Organic LETTERS

Letter

pubs.acs.org/OrgLett

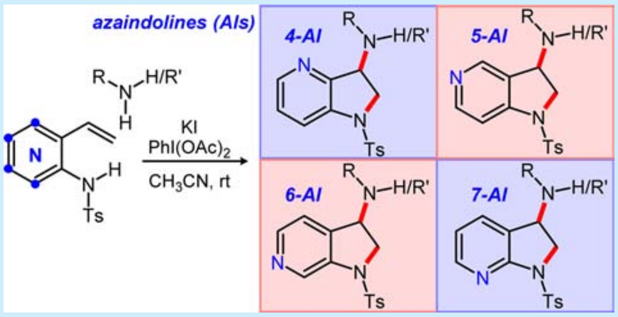
A Unified Approach to the Four Azaindoline Families by Inter-/Intramolecular Annulative Diamination of Vinylpyridines

Michael W. Danneman, Ki Bum Hong,* and Jeffrey N. Johnston*

Department of Chemistry and Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, Tennessee 37235, United States

Ⓢ *Supporting Information*

ABSTRACT: An operationally straightforward and metal-free inter-/intramolecular oxidative diamination of vinyl aminopyridines is a common gateway to access all four azaindoline heterocycle families. 3-Amino azaindolines are formed by the reaction of *ortho*-vinyl *N*-tosyl anilines with electron-rich amines using phenyliododiacetate (PIDA) and an iodide additive.

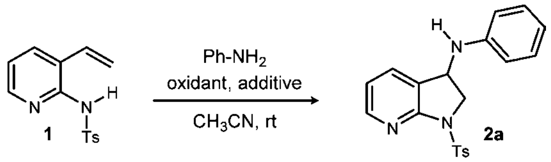


The indole and azaindole ring systems are among the most ubiquitous and privileged heterocyclic structures found in both natural products and biologically active medicinal agents.[1] Consequently, preparation of these fused [5,6] ring systems is a highly explored area in organic synthesis.[2] In contrast, methods to construct azaindoline backbones are relatively scarce. The most accessible azaindoline backbone to date is the 7-azaindoline core.[3] Methods to prepare the 7-azaindoline motif include radical cyclizations,[4] as well as base- and metal-mediated annulations.[5−7] However, only a limited number of synthetic methods en route to 6-azaindolines,[8] 5-azaindolines,[9] and 4-azaindolines[10] have been reported thus far. To the best of our knowledge, the carbolithiation of *N*,*N*-diallyl amino pyridine derivatives[11] remains the only general synthetic approach reported that readily accesses all four isomeric azaindolines, doing so by (aryl) carbon−carbon bond formation.[12]

We recently described a new method for the annulative diamination of alkenes leading to 3-aminoindolines via a hypervalent iodine-/iodide-mediated double carbon−nitrogen bond formation with electron-rich, Brønsted basic amines.[13] This approach provides direct entry to diverse 3-aminoindoline derivatives with both mono- and disubstituted amines,[14] without amine preactivation and protection. Its extension to azaindoline synthesis provided an opportunity to evaluate the effect of nitrogen substitution, introducing concerns about the compatibility of a Lewis basic pyridine nitrogen with the oxidative, electrophilic ("I$^+$") conditions. Indeed, this modification caused unusual behavior in Bailey's work with 5- and 7-azaindolines.[10] In this report, a unified approach to the four isomeric 3-aminoazaindoline ring systems is described.

Our initial optimization scheme paralleled previous studies in which *N*-iodosuccinimide (NIS) or a PIDA/halide additive combination was used in the presence of a primary amine.[15] Our mechanistic constructs invoke the formation of an electrophilic nitrogen source that coexists with a nucleophilic amine. Although NIS alone can be effective in this capacity,[16] only a minimal amount of desired product was isolated when combining it with vinyl aminopyridine **1** (Table 1, entry 1). Yet when an oxidant/halide additive combination (PIDA/KI) was used, the desired 3-amino-7-azaindoline **2a** was furnished in

Table 1. Annulative Alkene Diamination Using 3-Vinyl 2-Tosylaminopyridine



1 **2a**

entry^a	oxidant (equiv)	additive (equiv)	conversion (%)^b	yield (%)^c
1	NIS (1.2)	–	100	11
2	**PhI(OAc)$_2$ (1.5)**	**KI (1.0)**	**100**	**96**
3	PhI(OAc)$_2$ (1.5)	^{n}Bu$_4$NI (1.0)	100	80
4	PhI(OAc)$_2$ (1.5)	NH$_4$I (1.0)	77	29
5	PhI(OAc)$_2$ (1.5)	–	0	–
6	–	^{n}Bu$_4$NI (1.0)	0	–
7	–	KI (1.0)	0	–
8	PhI(OAc)$_2$ (1.5)	KI (0.3)	75	63
9	PhI(OAc)$_2$ (1.5)	KI (0.5)	88	65

[a] All reactions were performed on a 0.2 mmol scale (0.1 M) with a standard 18 h reaction time. [b] Conversion was determined by ^{1}H NMR using CH$_2$Br$_2$ as an internal standard. [c] Isolated yield.

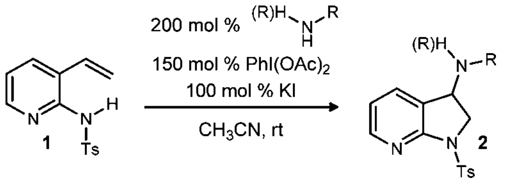
Received: June 19, 2015
Published: July 17, 2015

DOI: 10.1021/acs.orglett.5b01783
Org. Lett. 2015, 17, 3806−3809

96% isolated yield (Table 1, entry 2). Use of tetrabutylammonium iodide as the additive proved slightly inferior as azaindoline **2a** was afforded in 80% isolated yield, while ammonium iodide showed a significant drop in both reactivity and yield (Table 1, entries 3–4). Use of both components of the oxidant/additive combination proved vital, as no conversion to product was observed when starving the reaction of either the oxidant or the halide additive (Table 1, entries 5–7). The halide additive could be used catalytically, as 30 mol % and 50 mol % loadings of KI provided nearly full conversion and moderate yields, respectively (Table 1, entries 8–9). However, use of stoichiometric quantities of the additive provided the most generally effective conditions.

With optimal conditions in hand, we then sought to expand the 3-amino-7-azaindoline library and subsequently give rise to a 3-amino-6-azaindoline library. After seeing how well aniline performed under ideal reaction conditions en route to its corresponding 7-azaindoline **2a** (Table 2, entry 1), we turned our attention to other aliphatic amines. Benzylamine and allylamine engaged in diamination, as 3-amino-7-azaindoline products **2b** and **2c** were afforded in 73% and 62% yields, respectively (Table 2, entries 2–3). Heterocyclic secondary amines were also tolerated in this reaction system, as thiomorpholine and morpholine were converted to their desired 3-amino-7-azaindolines **2d** and **2e**, albeit in depressed yields (Table 2, entries 4–5). Efforts then shifted toward generating a 6-aza-3-aminoindoline library using aromatic, primary, and secondary amines. Aniline and benzylamine proved tolerant in the 6-azaindoline system, as diamines **4a** and **4b** were furnished in 11% and 48% yields, respectively (Table 3, entries 1–2). *N*-Protected piperazines led to 3-amino-6-azaindoline products **4c**–**4e** with good yields (Table 3, entries 3–5), allowing for subsequent unmasking of the piperazine under neutral, acidic, or basic conditions.

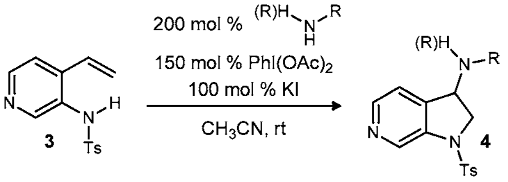
Table 2. Inter-/Intramolecular Diamination Route to 3-Amino-7-azaindolines

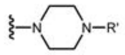


entry[a]	2	R	yield (%)[b]
1	a	Ph	96
2	b	CH_2Ph (benzylamine)	73
3	c	CH_2CHCH_2 (allylamine)	62
4[c]	d	C_4H_8S (thiomorpholine)	39
5	e	C_4H_8O (morpholine)	57

[a] All reactions were performed on a 0.150 mmol scale (0.1 M) with a standard 18 h reaction time. [b] Isolated yield. [c] 2.0 equiv of PIDA, 1.2 equiv of KI, 3.0 equiv of amine used.

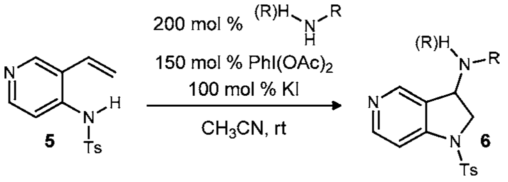
Table 3. Inter-/Intramolecular Diamination Route to 3-Amino-6-azaindolines



entry	4	R	yield (%)[e]
1[a]	a	Ph	11[f]
2[b]	b	CH_2Ph (benzylamine)	48
3[c]	c	 R′ = Cbz	63
4[d]	d	R′ = CO_2Et	66
5[c]	e	R′ = Boc	74

[a] Reaction performed on a 0.040 mmol scale (0.1 M) with a standard 18 h reaction time. [b] Reactions performed on a 0.047 mmol scale. [c] Reactions performed on a 0.050 mmol scale. [d] Reactions performed on a 0.084 mmol scale. [e] Isolated yield. [f] 83% Conversion estimated by ^1H NMR (CH_2Br_2 internal standard).

Table 4. Inter-/Intramolecular Diamination Route to 3-Amino-5-azaindolines



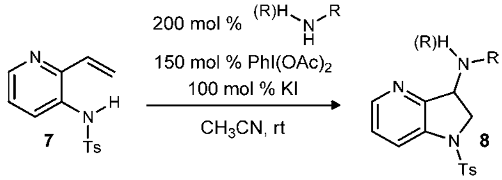
entry[a]	6	R	yield (%)[b]
1	a	Ph	81
2	b	CH_2Ph (benzylamine)	43
3	c	$CH_3C_6H_4CH_2$ (4-methylbenzylamine)	45
4	d	$FC_6H_4CH_2$ (4-fluorobenzylamine)	51
5	e	$(CH_2)_3OMe$ (3-methoxypropylamine)	48
6	f	$CH_2CH_2C_6H_5$ (phenethylamine)	48
7	g	C_5H_9O (4-aminotetrahydropyran)	33
8[c]	h	$^{3}CH_2C_5H_4N$ (3-picolylamine)	64
9	i	C_4H_8S (thiomorpholine)	34

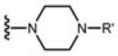
[a] All reactions were performed on a 0.075 mmol scale (0.1 M) with a standard 18 h reaction time. [b] Isolated yield. [c] Reaction performed on a 0.2 mmol scale.

Our focus then centered upon successfully generating 5-azaindoline and 4-azaindoline congeners in order to demonstrate that all four isomeric azaindoline families could be readily accessed. Vinyl aminopyridine **5**, the precursor to 5-azaindoline diamines, proved to be an effective substrate as it was compatible with a wide array of amines. Aniline performed well under optimal conditions, as its 3-amino-5-azaindoline **6a** was furnished in 81% yield (Table 4, entry 1). Benzylamine and derivatives were converted to 3-amino-5-azaindolines **6b**–**6d** in 43–51% yield (Table 4, entries 2–4). Alkyl amines including 3-methoxypropylamine and phenethylamine performed similarly (Table 4, entries 5–6). Other primary amines such as 4-aminotetrahydropyran and 3-picolylamine gave rise to their corresponding 3-amino-5-azaindolines **6g** and **6h** in 33% and 64% yields respectively, when subjected to standard conditions (Table 4, entries 7–8). Additionally, a secondary amine in thiomorpholine proved tolerant as 5-azaindoline **6i** was afforded, but in lower yield (Table 4, entry 9).

Development of the 4-azaindoline library was straightforward and suitable with aromatic, primary, and secondary amines. Aniline and 4-*tert*-butylaniline were successfully converted to their corresponding 3-amino-4-azaindoline **8a** and **8b** in 70% and 41% yields, respectively (Table 5, entries 1–2). Benzyl-

Table 5. Inter-/Intramolecular Diamination Route to 3-Amino-4-azaindolines



entry[a]	8	R	yield (%)[b]
1	a	Ph	70
2	b	4-^{t}Bu-C_6H_4	41[d]
3	c	CH_2Ph (benzylamine)	88
4	d	C_5H_9 (cyclopentylamine)	59
5	e	$CH_2CH_2C_6H_5$ (phenethylamine)	68
6	f	C_5H_{10} (piperidine)	63
7	g	$C_8H_{14}O_2$ (ethyl isonipecotate)	71
8	h	 R' = CO_2Et	86
9	i	R' = Boc	74
10	j	R' = $CH_2CHCHC_6H_5$	66
11[c]	k	CH_2COOCH_3•HCl (glycine methyl ester•HCl)	63

[a] All reactions were performed on a 0.150 mmol scale (0.1 M) with a standard 18 h reaction time. [b] Isolated yield. [c] 2.0 equiv of K_2CO_3 used. [d] 51% Conversion estimated by ^{1}H NMR (CH_2Br_2 internal standard).

amine performed well, as its 4-azaindoline (**8c**) was furnished in good yield (Table 5, entry 3). Other primary amines in the form of cyclopentylamine and phenethylamine also proved compatible under optimal conditions, as diamines **8d** and **8e** were afforded in 59% and 68% yields, respectively (Table 5, entries 4–5). Secondary amines in piperidine and ethyl isonipecotate were also tolerated in this reaction system, as 4-azaindoline diamines **8f** and **8g** were isolated in modest to good yields (Table 5, entries 6–7). *N*-Protected piperazines led to 3-amino-4-azaindolines **8h** and **8i** in good yields (Table 5, entries 8–9), allowing for subsequent unmasking of the piperazine under both acidic and basic conditions. Further success with piperazines was demonstrated when *N*-cinnamyl piperazine provided a 66% yield of 4-azaindoline **8j** (Table 5, entry 10). Lastly, the HCl salt of glycine methyl ester delivered 3-amino-4-azaindoline **8k** (Table 5, entry 11). For this particular case, K_2CO_3 was incorporated in the reaction system with the sole purpose of liberating the free base of the glycine methyl ester. This modification had little or no effect on reaction progression, as azaindoline **8k** was cleanly isolated in 63% yield. This entry demonstrates that amino acid derivatives can be readily incorporated into azaindoline motifs.

In summary, we have developed a hypervalent iodine(III)-assisted direct diamination reaction to access all four of the 3-amino azaindoline families. This unique approach provides rapid, convergent access to a diverse range of *vic*-diamines using commercially available amines.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete preparatory and analytical data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01783.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ki.b.hong@vanderbilt.edu.
*E-mail: jeffrey.n.johnston@vanderbilt.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Science Foundation (CHE 1153003) for support of this work.

■ REFERENCES

(1) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278. Kuethe, J. T.; Wong, A.; Qu, C.; Smitrovich, J.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2005**, *70*, 2555. Van Zandt, M. C.; Jones, M. L.; Gunn, D. E.; Geraci, L. S.; Jones, J. H.; Sawicki, D. R.; Sredy, J.; Jacot, J. L.; DiCioccio, A. T.; Petrova, T.; Mitschler, A.; Podjarny, A. D. *J. Med. Chem.* **2005**, *48*, 3141. Badland, M.; Devillers, I.; Durand, C.; Fasquelle, V. r.; Gaudillière, B.; Jacobelli, H.; Manage, A. C.; Pevet, I.; Puaud, J.; Shorter, A. J.; Wrigglesworth, R. *Tetrahedron Lett.* **2011**, *52*, 5292.

(2) Cacchi, S.; Fabrizi, G. *Chem. Rev. (Washington, DC, U. S.)* **2005**, *105*, 2873. Humphrey, G. R.; Kuethe, J. T. *Chem. Rev. (Washington, DC, U. S.)* **2006**, *106*, 2875. Popowycz, F.; Merour, J.-Y.; Joseph, B. *Tetrahedron* **2007**, *63*, 8689. Popowycz, F.; Routier, S.; Joseph, B.; Merour, J.-Y. *Tetrahedron* **2007**, *63*, 1031. Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120. Merour, J.-Y.; Routier, S.; Suzenet, F.; Joseph, B. *Tetrahedron* **2013**, *69*, 4767.

(3) Jakhontov, L. N.; Krasnokutsaya, D. M.; Peresleni, E. M.; Sheinker, J. N.; Rubtsov, M. V. *Tetrahedron* **1966**, *22*, 3233. Frissen, A. E.; Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron Lett.* **1987**, *28*, 1589. Taylor, E. C.; Macor, J. E.; Pont, J. L. *Tetrahedron* **1987**, *43*, 5145. Taylor, E. C.; Pont, J. L. *Tetrahedron Lett.* **1987**, *28*, 379. Frissen, A. E.; Marcelis, A. T. M.; Van Der Plas, H. C. *Tetrahedron* **1989**, *45*, 803. Adam, W.; Saha-Möller, C. R.; Zhao, C. G. *J. Org. Chem.* **1999**, *64*, 7492. Sanders, W. J.; Zhang, X.; Wagner, R. *Org. Lett.* **2004**, *6*, 4527. Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2005**, *61*, 10603. Sánchez, A.; Núñez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron Lett.* **2006**, *47*, 8343. Suwa, A.; Konishi, Y.; Uruno, Y.; Takai, K.; Nakako, T.; Sakai, M.; Enomoto, T.; Ochi, Y.; Matsuda, H.; Kitamura, A.; Uematsu, Y.; Kiyoshi, A.; Sumiyoshi, T. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2909. Takai, K.; Inoue, Y.; Konishi, Y.; Suwa, A.; Uruno, Y.; Matsuda, H.; Nakako, T.; Sakai, M.; Nishikawa, H.; Hashimoto, G.; Enomoto, T.; Kitamura, A.; Uematsu, Y.; Kiyoshi, A.; Sumiyoshi, T. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3189.

(4) Radical cyclization using xanthate: Ly, T.-M.; Quiclet-Sire, B. a.; Sortais, B. t.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533. Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671. Liu, Z.; Qin, L.; Zard, S. Z. *Org. Lett.* **2014**, *16*, 2704. Radical cyclization using azomethine: Johnston, J. N.; Plotkin, M. A.; Viswanathan, R.; Prabhakaran, E. N. *Org. Lett.* **2001**, *3*, 1009. Viswanathan, R.; Mutnick, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 7266. Srinivasan, J. M.; Burks, H. E.; Smith, C. R.; Viswanathan, R.; Johnston, J. N. *Synthesis* **2005**, *2005*, 330.

(5) Davies, A. J.; Brands, K. M. J.; Cowden, C. J.; Dolling, U.-H.; Lieberman, D. R. *Tetrahedron Lett.* **2004**, *45*, 1721. Nguyen, H. N.; Wang, Z. J. *Tetrahedron Lett.* **2007**, *48*, 7460.

(6) Desarbre, E.; Mérour, J.-Y. *Tetrahedron Lett.* **1996**, *37*, 43.

(7) Moss, T. A.; Hayter, B. R.; Hollingsworth, I. A.; Nowak, T. *Synlett* **2012**, *23*, 2408.

(8) De Bie, D. A.; Ostrowica, A.; Geurtsen, G.; Van Der Plas, H. C. *Tetrahedron* **1988**, *44*, 2977. Dekhane, M.; Potier, P.; Dodd, R. H. *Tetrahedron* **1993**, *49*, 8139. Fayol, A.; Zhu, J. *Org. Lett.* **2005**, *7*, 239. Fayol, A.; Zhu, J. *Org. Lett.* **2005**, *7*, 239.

(9) Yakhontov, L. N.; Azimov, V. A.; Lapan, E. I. *Tetrahedron Lett.* **1969**, *10*, 1909. Kauffmann, T.; Fischer, H. *Chem. Ber.* **1973**, *106*, 220. Spivey, A. C.; Fekner, T.; Adams, H. *Tetrahedron Lett.* **1998**, *39*, 8919. Spivey, A. C.; Fekner, T.; Spey, S. E.; Adams, H. *J. Org. Chem.* **1999**, *64*, 9430. Wipf, P.; Maciejewski, J. P. *Org. Lett.* **2008**, *10*, 4383. Laot, Y.; Petit, L.; Zard, S. Z. *Org. Lett.* **2010**, *12*, 3426.

(10) Donati, D.; Fusi, S.; Ponticelli, F. *Eur. J. Org. Chem.* **2002**, *2002*, 4211. Leroi, C.; Bertin, D.; Dufils, P.-E.; Gigmes, D.; Marque, S.; Tordo, P.; Couturier, J.-L.; Guerret, O.; Ciufolini, M. A. *Org. Lett.* **2003**, *5*, 4943. Bailey, W. F.; Salgaonkar, P. D.; Brubaker, J. D.; Sharma, V. *Org. Lett.* **2008**, *10*, 1071.

(11) Bailey, W. F.; Salgaonkar, P. D.; Brubaker, J. D.; Sharma, V. *Org. Lett.* **2008**, *10*, 1071.

(12) See also: Zard, S.; Bacqué, E.; El Qacémi, M. *Heterocycles* **2012**, *84*, 291.

(13) Hong, K. B.; Johnston, J. N. *Org. Lett.* **2014**, *16*, 3804.

(14) Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 7119.

(15) A standard amount of excess amine (1 equiv) was used in these studies as a protocol to apply broadly. Similar outcomes can be achieved with a stoichiometric amount of amine.

(16) Danneman, M. W.; Hong, K. B.; Johnston, J. N. *Org. Lett.* **2015**, *17*, 2558.