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Preparation of the Isomeric Azaindoline Family by Intramolecular Carbolithiation

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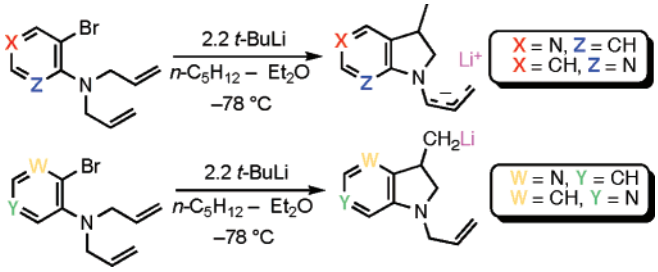
ABSTRACT



An operationally convenient, one-pot, three-step sequence has been developed that provides access to 3-substituted 4-, 5-, 6-, and 7-azaindolines (2,3-dihydro-1*H*-pyrollopyridines) via intramolecular carbolithiation of the aryllithium derived from an appropriate (*N*,*N*-diallylamino)bromopyridine. Whereas cyclization proceeds as expected to give 1-allyl-3-methyl-4-azaindoline and 1-allyl-3-methyl-6-azaindoline following protonation of the 3-CH_2Li group of the azaindoline, the isomeric 3-methyl-5-azaindoline and 3-methyl-7-azaindoline are generated as 3-methyl-*N*-allyl anions prior to quench with MeOH.

The 5-exo cyclization of unsaturated organolithiums has been rather widely used for the preparation of carbocyclic products,[1] but the synthesis of heterocyclic compounds using this methodology is less well developed.[2] In light of the fact that indolines are readily prepared by cyclization of the aryllithium derived from a 2-bromo-*N*-allylaniline,[3] it occurred to us that it might be possible to access all four isomeric azaindolines[4] from aminobromopyridines by analogous routes provided that the cyclization is more rapid than are potential anion-consuming reactions, such as the well-precedented intermolecular addition of organolithiums to the azomethine moiety of the pyridine.[5]

The azaindolines are attractive targets: there is no general synthetic route to these simple heterocycles. Indeed, whereas a variety of 7-azaindolines have been prepared and characterized,[6] synthetic routes to 5-azaindolines[7] and 6-azaindolines[8] are limited, and to the best of our knowledge, only

(1) For reviews, see: (a) Bailey, W. F.; Ovaska, T. V. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; Vol. 3, Mechanisms of Importance in Synthesis; JAI Press: Greenwich, CT, 1994; pp 251−273. (b) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon Press: New York, 2002; pp 293−335.

(2) For, a review, see: Bailey, W. F.; Mealy, M. J. *J. Organomet. Chem.* **2002**, *646*, 59.

(3) (a) Bailey, W. F.; Jiang, X.-L. *J. Org. Chem.* **1996**, *61*, 2596. (b) Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1996**, *61*, 2594.

(4) Azaindoline is used here to describe the pyrrolopyridine system; thus, 4-azaindoline is 2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine, 5-azaindoline is 2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine, 6-azaindoline is 2,3-dihydro-1*H*-pyrrolo-[2,3-*c*]pyridine, and 7-azaindoline is 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine.

(5) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon Press: New York, 1974.

(6) (a) Kruber, O. Chem. Ber. **1943**, *76*, 128. (b) Clemo, G. R.; Swan, G. A. *J. Chem. Soc.* **1945**, 603. (c) Robison, M. M.; Robison, B. L. *J. Am. Chem. Soc.* **1955**, *77*, 457. (d) Willette, R. E. Monoazaindolines: The Pyrrolopyridines. In *Adv. In Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York 1968; Vol. 9, pp 27−105. (e) Taylor, E. C.; Pont, J. L. *Tetrahedron Lett.* **1987**, *28*, 379. (f) Taylor, E. C.; Macor, J. E.; Pont, J. L. *Tetrahedron* **1987**, *43*, 5145. (g) Frissen, A. E.; Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron Lett.* **1987**, *28*, 1589. (h) Taylor, E. C; Warner, J. C.; Pont, J. L. *J. Org. Chem.* **1988**, *53*, 800. (i) Frissen, A. E.; Marcelis, A. T. M.; van der Plas, H. C *Tetrahedron* **1989**, *45*, 803. (j) Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 2693. (k) Ciganek, E. *J. Org. Chem.* **1992**, *57*, 4521. (l) Ly, T.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533. (m) Johnston, J. N.; Plotkin, M A.; Viswanathan, R.; Prabhakaran, E. N. *Org. Lett.* **2001**, *3*, 1009. (n) Viswanathan, R.; Mutnick, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 7266. (o) Bacqué, E.; Qacemi, M. E.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671. (p) Davies, A. J.; Brands, K. M.; Cowden, C. J.; Dolling, U. H.; Liebermann, D. R. *Tetrahedron Lett.* **2004**, *45*, 1721. (q) Sanders, W. J.; Zhang, X.; Wanger, R. *Org. Lett.* **2004**, *6*, 4527−4530.

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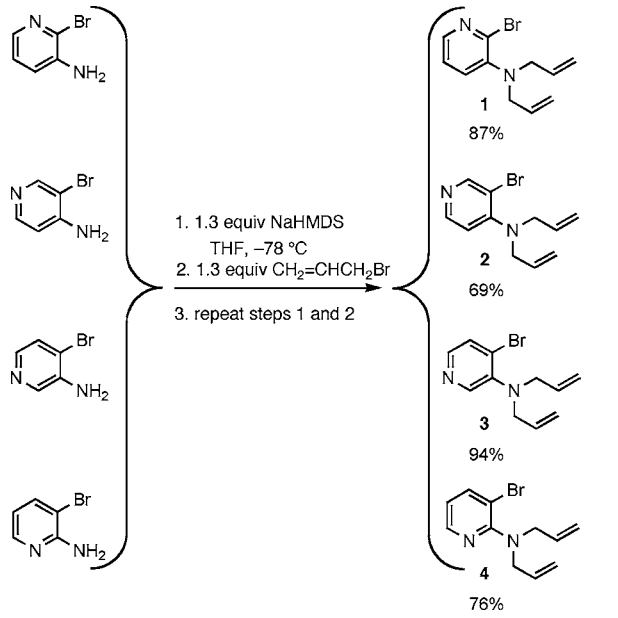
two 4-azaindolines have been reported in the literature.[9] Herein we report that cyclization of the aryllithium derived from the appropriate (*N*,*N*-diallylamino)bromopyridine provides a general and expedient route to all four isomeric azaindolines.

The aminobromopyridines used in this exploratory study were readily prepared following literature procedures.[10,11] However, the seemingly simple conversion of these materials to their *N*,*N*-diallyl derivatives proved problematic; in short, the pyridine nitrogen is more nucleophilic than is the NH_2 group and activation of the amino nitrogen via deprotonation may lead to a Chichibabin reaction (viz., intermolecular, nucleophilic addition of aryl-NH^- to the pyridine). After considerable experimentation, a somewhat unorthodox, one-pot route to *N*,*N*-diallyl derivatives, illustrated in Scheme 1,

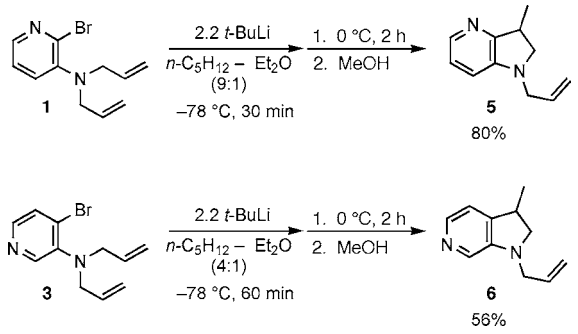
Scheme 1



was developed that delivers substrates **1**−**4** in reproducible yields of 70−90%.

Treatment of an approximately 0.1 M solution of 2-bromo-3-(*N*,*N*-diallylamino)pyridine (**1**) in dry *n*-pentane−diethyl ether (9:1 by vol) at −78 °C with 2.2 molar equiv of *t*-BuLi in heptane following our general protocol for lithium−halogen exchange[12] cleanly generates the corresponding aryllithium as demonstrated by the fact that quench of such a reaction mixture with MeOH at −78 °C affords 3-(*N*,*N*-diallylamino)pyridine in essentially quantitative yield. Allowing a solution of the aryllithium derived from **1** to stand under an atmosphere of argon at 0 °C for 2 h before quench with MeOH delivered the novel 1-allyl-3-methyl-4-azaindoline (**5**) in 80% isolated yield (Scheme 2); quench with

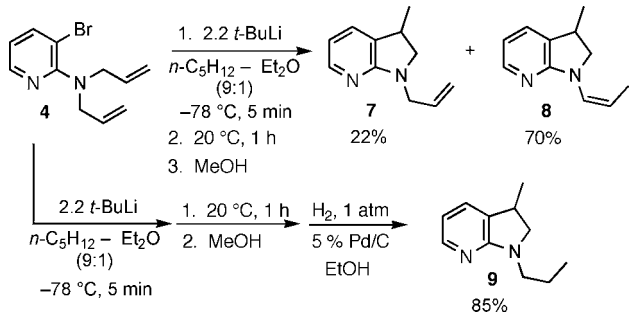
Scheme 2



MeOD gave a comparable yield of the 3-CH_2D product having a deuterium content of 95%. As illustrated in Scheme 2, the aryllithium derived from 4-bromo-3-(*N*,*N*-diallylamino)pyridine (**3**), which was generated by lithium−bromine exchange in *n*-pentane−diethyl ether (4:1 by vol) due to the limited solubility of **3** in a more pentane-rich solvent system, behaves similarly: 1-allyl-3-methyl-6-azaindoline (**6**) was isolated in 56% yield.

The cyclization of the aryllithium derived from 3-bromo-2-(*N*,*N*-diallylamino)pyridine (**4**) followed an unanticipated course. As illustrated in Scheme 3, two isomeric 7-azain-

Scheme 3



dolines were isolated: the expected 1-allyl-3-methyl-7-azaindoline (**7**) was the minor product and enamine **8**, largely the Z-isomer (Z/E ~30/1 by ^{1}H NMR; the product rapidly isomerizes to the apparently more stable E isomer upon

(7) (a) Yakhontov, L. N.; Azimov, V. A.; Lapan, E. I. *Tetrahedron Lett.* **1969**, *24*, 1909. (b) Kauffmann, T.; Fischer, H. *Chem. Ber.* **1973**, *106*, 220. (c) Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Cottrell, I. F.; Wright, S. H. *Synthesis* **1996**, 877. (d) Spivey, A. C.; Fekner, T.; Spey, S. E.; Adams, H. *J. Org. Chem.* **1999**, *64*, 9430.

(8) (a) Dekhane, M.; Potier, P.; Dodd. R. H. *Tetrahedron* **1993**, *49*, 8139. (b) Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Cottrell, I. F.; Wright, S. H. *Synthesis* **1996**, 877. (c) De Bie, D. A.; Ostrowicz. A.; Geurtsen, G.; Van Der Plas, H. C. *Tetrahedron* **1998**, *44*, 2977. (d) Fayol, A.; Zhu, J. *Org. Lett.* **2005**, *7*, 239.

(9) (a) Donati, D.; Fusi, S.; Ponticelli, F. *Eur. J. Org. Chem.* **2002**, 4211. (b) 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.

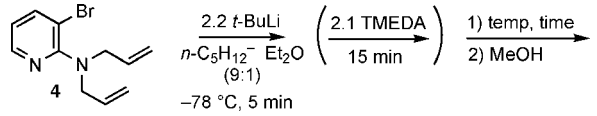
(10) 2-Amino-3-bromopyridine, 3-amino-4-bromopyridine and 4-amino-3-bromopyridine, see: Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 1505.

(11) 3-Amino-2-bromopyridine, see: Cañibano, V.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A.; Carreño, M. C.; González, G.; García-Ruano, J. L. *Synthesis* **2001**, *14*, 2175.

(12) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404.

standing in $CDCl_3$ solution), was produced in 70% yield. The enamine was not stable on silica gel, but the compound could be purified by careful chromatography over neutral alumina and isolated in 54% yield. Repetition of the cyclization, followed by reduction of the crude product as shown in Scheme 3, delivered 3-methyl-1-propyl-7-azaindoline (**9**) in 85% yield. In light of the unexpected generation of the enamine product (**8**), a series of exploratory cyclizations were conducted under a variety of conditions. The results of these experiments, summarized in Table 1, demonstrate that, although the ring closure of the aryllithium derived from **4** is accelerated in the presence of TMEDA, the enamine (**8**) was invariably the major product under all conditions.

Table 1. Exploratory Cyclizations of Aryllithium Derived from **4**

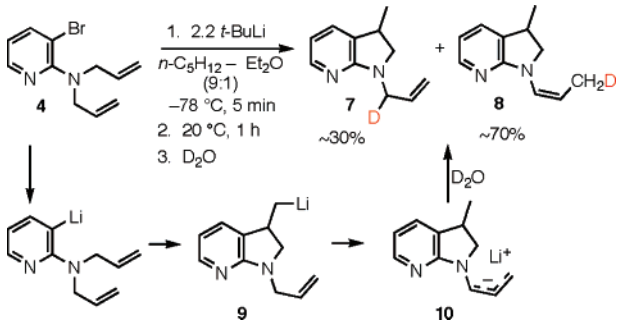


				products, % yield[a]	
entry	temp (°C)	time (h)	ligand	**7**	**8**
1	−40	1.0	none	6	9
2	−20			23	33
3	0			25	55
4	20			22	70
5	−20	1.5	TMEDA	22	68
5	0			19	76
7	20			19	74

[a] Product yield determined by capillary GC analysis; in each case, 2-(*N*,*N*-diallylamino)pyridine accounted for the remainder of the product mixture.

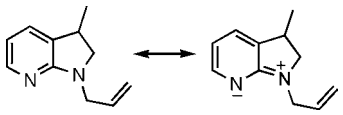
The origin of the enamine product (**8**) became apparent from analysis of a product mixture that had been quenched with D_2O; both isomeric azaindoline products, **7** and **8**, were found by GC/MS analysis to have a high a deuterium content (>90%) but neither product contained appreciable deuterium at the 3-methyl position. Indeed, ^2H NMR analysis of the crude product mixture revealed, as illustrated in Scheme 4, that deuterium had been incorporated in the *N*-allyl and *N*-propenyl groups of **7** and **8**, respectively. The methylene hydrogens of the allyl group in **7** are diastereotopic, and the ^2H NMR of the deuterated material displays two multiplets (δ = 4.12 and 3.89) corresponding to deuteration at these positions; the ^2H NMR of **8** is a clean doublet of triplets (δ = 1.82, J = 2.3 Hz, J = 1.8 Hz) as appropriate for the CH═CH−CH_2D group in this compound.

Scheme 4



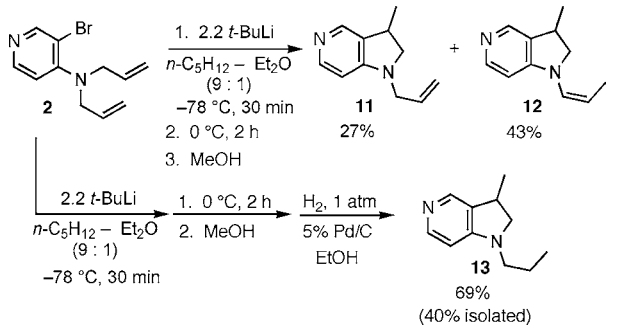
Apparently, both **7** and **8** derive from a common precursor, and the most reasonable candidate is a Z-configured allylic anion (**10**), shown in Scheme 4, generated from the initial cyclization product, **9**, via proton transfer.[13]

In retrospect, it may appear somewhat surprising that analogous deprotonation of the *N*-allyl group was not observed in cyclizations leading to 4-azaindoline or 6-azaindoline (Scheme 2). Evidently, the etiology of the enhanced acidity resides in the 7-azaindoline framework. As a working hypothesis, the partial positive character of the N(1) position in a 7-azaindoline, rationalized by the resonance structures displayed below, may be invoked to account for the effect.



Clearly, comparable structures may be drawn for 5-azaindoline in which the nitrogens bear a 1,4 relationship. Indeed, cyclization of the aryllithium derived from 3-bromo-4-(*N*,*N*-diallylamino)pyridine (**2**) proceeds, as shown in Scheme 5, to give a mixture consisting of 27% 1-allyl-3-methyl-5-azaindoline (**11**) and 43% of enamine **12** following quench of the reaction mixture; 4-(*N*,*N*-diallylamino)pyridine constituted the balance of the product mixture. An analytical sample of **11** was isolated in low yield by column chromatography, but it was not possible to purify the labile enamine. Reduction of a crude product mixture subsequent to cyclization and quench with MeOH delivered pure 3-methyl-1-propyl-5-azaindoline (**13**) in 40% yield over four steps.

Scheme 5



(13) It is likely that the proton transfer is an intermolecular process catalyzed by a small quanity of 1-allyl-3-methyl-7-azaindoline peresent in the reaction mixture as a consequence of inadvertent quench of **9** by solvent or adventitious acid. Thus: **9** + 1-allyl-3-methyl-7-azaindoline → 1-allyl-3-methyl-7-azaindoline + **10**.

In summary, intramolecular carbolithiation of the aryllithium derived from an appropriate (*N*,*N*-diallylamino)-bromopyridine provides the first general route to all four isomeric azaindolines. Ring-closure to give 1-allyl-3-methyl-4-azaindoline (**5**) and 1-allyl-3-methyl-6-azaindoline (**6**) proceeds in the normal way,[3] but 3-methyl-5-azaindolines and 3-methyl-7-azaindolines are generated as 3-methyl-*N*-allyl anions prior to quench with MeOH.

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Supporting Information Available: Detailed experimental procedures and NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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