Preparation of Substituted Indolines via Anionic Cyclization

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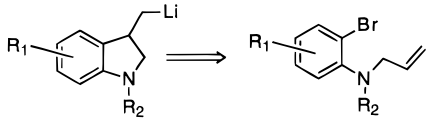
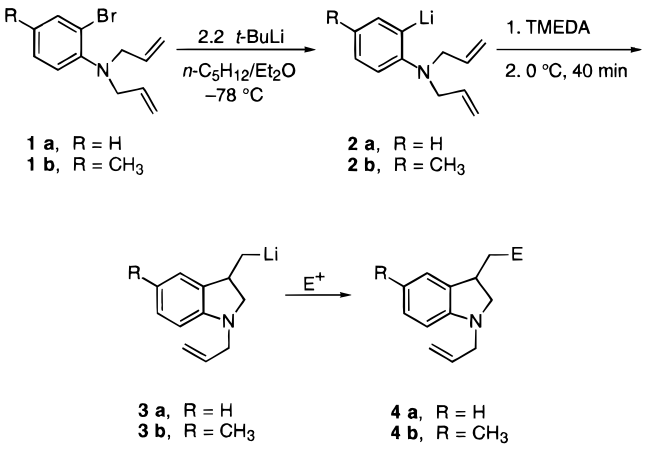
The 5-exo cyclization of substituted 5-hexenyllithiums provides a convenient route five-membered-ring-containing carbocycles.[1] Much less information is available on the potential utility of such "anionic" cyclizations[2] for the preparation of heterocycles.[3] Herein we report that cycloisomerization of the organolithium derived from a 2-bromo-*N*-allylaniline by lithium−bromine exchange provides a novel and experimentally simple route to substituted indolines (2,3-dihydro-1*H*-indoles) bearing a variety of functionalities at the C(3) position. Classical approaches to such materials, which typically involve reduction of the corresponding indole, have been extensively reviewed.[4]



In the interest of synthetic simplicity, 2-bromo-*N*,*N*-diallylanilines **1**, which are readily prepared by diallylation of a 2-bromoaniline (allyl bromide/Na_2CO_3 in DMF), were used in this exploratory study. Treatment of an approximately 0.1 M solution of **1** in dry *n*-pentane−diethyl ether (9:1 by vol) at −78 °C with 2.2 molar equiv of *tert*-butyllithium (*t*-BuLi) following our general protocol for lithium−halogen exchange[5] cleanly generates the corresponding aryllithium **2** as demonstrated by the fact that quench of such a reaction mixture with MeOH at −78 °C affords the *N*,*N*-diallylaniline in essentially quantitative yield. Cyclization of **2** to give a (1-allyl-3-indolinyl)methyllithium (**3**) was easily effected, as illustrated in Scheme 1, by addition of 2.2 equiv of dry, oxygen-free *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) to the −78 °C solution and allowing the resulting mixture to stand under an atmosphere of argon at 0 °C for 40 min. As demonstrated by the results presented in Table 1, the [(1-allyl-3-indolinyl)methyl]lithium (**3**) may be trapped by addition of any of a variety of electrophiles (Scheme 1, **3** → **4**) to give 70−90% isolated yields of 3-substituted indolines[6] (**4**). As a practical matter, isolation of pure product (Table 1) is a fairly simple matter since the only byproduct is a small quantity of the *unfunctionalized N*,*N*-diallylaniline derived, as detailed elsewhere,[5] from formal reduction of **1** during the exchange reaction.

Scheme 1



It should be noted that the 5-exo cyclization of **2** is a facile process that does not require the presence of TMEDA. Indeed, substituted indolines may be prepared in the absence of the additive, albeit with some loss of yield, by allowing solutions of **2** in *n*-pentane−diethyl ether to warm and stand at room temperature for 1 h prior to the addition of the electrophile. The use of TMEDA to facilitate the isomerization of **2** to **3** is, however, the recommended procedure: exploratory experiments revealed that a portion of the organolithium product **3** is inadvertently quenched by proton abstraction from the solvent at the elevated temperatures needed to effect cyclization of **2** in the absence of the additive.

As a consequence of employing 2-bromo-*N*,*N*-diallylanilines to generate **2**, the 3-substituted indoline products **4** depicted in Table 1 bear an *N*-allyl substituent. The allyl protecting group may be conveniently removed, as shown below, using catalytic $Pd_2(dba)_3$ and 1,4-bis-

(1) (a) Bailey, W. F.; Ovaska, T. V. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 3, Mechanisms of Importance in Synthesis, pp 251−273. (b) Bailey, W. F.; Patricia, J. J.; DelGobbo, V. C.; Jarret, R. M.; Okarma, P. J. *J. Org. Chem.* **1985**, *50*, 1999. (c) Ross, G. A.; Koppang, M. D.; Bartak, D. E.; Woolsey, N. F. *J. Am. Chem. Soc.* **1985**, *107*, 6742. (d) Chamberlin, A. R.; Bloom, S. H *Tetrahedron Lett.* **1986**, *27*, 551. (e) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442. (f) Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 4788. (g) Bailey, W. F.; Rossi, K. *J. Am. Chem. Soc.* **1989**, *111*, 765. (h) Bailey, W. F.; Khanolkar, A. D. *J. Org. Chem.* **1990**, *55*, 6058. (i) Krief, A.; Barbeaux, P. *Synlett* **1990**, 511. (j) Krief, A.; Barbeaux, P. *Tetrahedron Lett.* **1991**, 32, 417. (k) Bailey, W. F.; Khanolkar, A. D. *Tetrahedron Lett.* **1990**, *31*, 5993. (l) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720. (m) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K. V. *J. Am. Chem. Soc.* **1992**, *114*, 8053. (n) Cooke, M. P., Jr. *J. Org. Chem.* **1992**, *57*, 1495. (o) Bailey, W. F.; Khanolkar, A. D. *Organometallics* **1993**, *12*, 239. (p) Bailey, W. F.; Gavaskar, K. V. *Tetrahedron* **1994**, *50*, 5957.

(2) While the cyclization of 5-hexenyllithium and related species may be viewed as a formally anionic process, it should be noted that the lithium atom is intimately involved in the rearrangement. Indeed, 5-hexenyllithium is unique among the 5-hexenylalkalis in it ability to undergo facile cyclization. See: Bailey, W. F.; Punzalan, E. R. *J. Am. Chem. Soc.* **1994**, *116*, 6577.

(3) To date, the only published investigations of heteroatom-containing 5-hexenyllithiums involve (2-oxa-5-hexenyl)-, (3-oxa-5-hexenyl)-, and (4-oxa-5-hexenyl)lithiums. For the 2-oxa system, which undergoes 5-exo closure on warming to give [(3-tetrahydrofuranyl)methyl]lithiums in good yield, see: (a) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336. (b) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981. (3-Oxa-5-hexenyl)lithium is inherently unstable and fragments at low temperature via *β*-elimination: Bailey, W. F.; Punzalan, E. R.; Zarcone, L. M. J. *Heteroat. Chem.* **1992**, *3*, 55. The 4-oxa system isomerizes on warming to give the lithium salt of a 4-alken-1-ol in the formal equivalent of a [1,4]-Wittig rearrangement: Bailey, W. F.; Zarcone, L. M. J. *Tetrahedron Lett.* **1991**, *32*, 4425.

(4) (a) Preobrazhenskaya, M. N. *Russ. Chem. Rev.* **1967**, *36*, 753. (b) Sundberg, R. J. *Chemistry of Indoles*; Academic Press: New York, 1970. (c) Houlihan, W. J., Ed. *Indoles*; Wiley-Interscience: New York, 1972; Parts 1 and 2; 1979; Part 3. (d) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1988**, *27*, 2225. (e) Pindur, U.; Adam, R. J. *Heterocycl. Chem.* **1988**, *25*, 1. (f) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113. (g) Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry*, 3rd ed.; Chapman and Hall: New York, 1995; pp 305−349.

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

(6) All products were homogeneous by both TLC and capillary GC. Exact mass spectroscopic molecular weights have been determined for all previously unreported compounds, and their IR and ^1H NMR and ^{13}C NMR spectra are fully in accord with the assigned structures.

0022-3263/96/1961-2596$12.00/0

Scheme 2

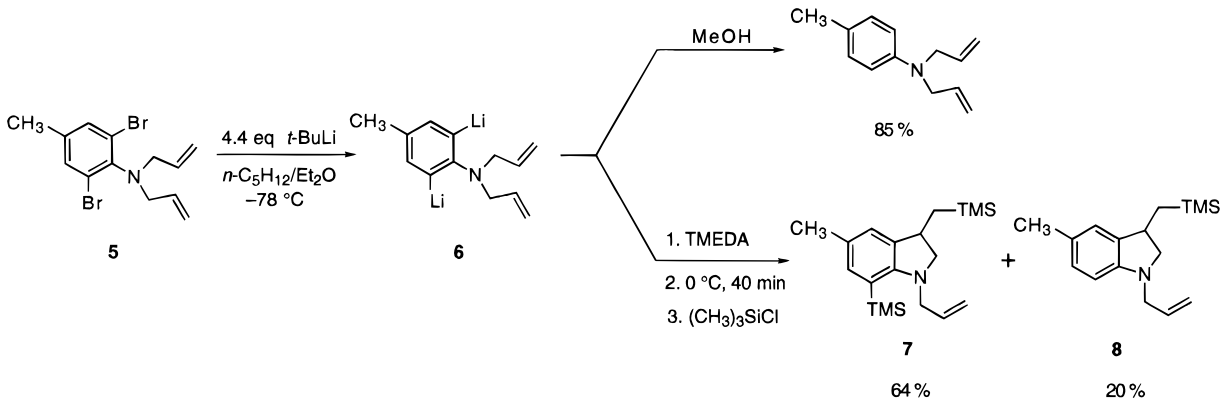
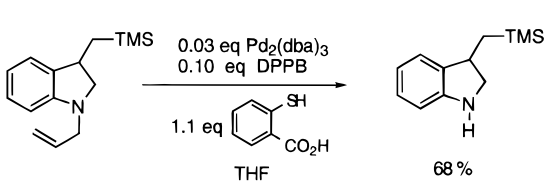


Table 1. Preparation of 3-Substituted Indolines[a]

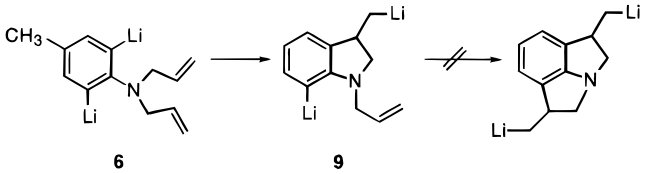
entry	R	E^+	E	yield,[b] %
1	H	CH_3OH	H	90
2		CH_3OD	D	76[c]
3		$(CH_3)_3SiCl$	$Si(CH_3)_3$	82
4		$(n\text{-}Bu)_3SnCl$	$Sn(n\text{-}Bu)_3$	83
5		$(CH_3)_2NCHO$	CHO	78
6		$(CH_3)_3CCHO$	$(CH_3)_3CCH(OH)$	74[d]
7	CH_3	CH_3OH	H	90
8		CH_3OD	D	80[c]
9		$(CH_3)_3SiCl$	$Si(CH_3)_3$	80
10		$Br(CH_2)_2Br$	Br	75
11		$ClCO_2C_2H_5$	$CO_2C_2H_5$	70
12		$(CH_2O)_n$	CH_2OH	76

[a] [2-(*N*,*N*-Diallylamino)phenyl]lithium (**2**) was generated at −78 °C by addition of 2.2 equiv of *t*-BuLi to a solution of **1** in *n*-pentane−diethyl ether (9:1 by vol), 2.2 equiv of TMEDA were then added, the cooling bath was removed, and the mixture was allowed to stand at 0 °C for 40 min before the addition of an excess of the electrophile. [b] Isolated yield of chromatographically pure product. [c] Determined by GC/MS analysis of the product. [d] Product was an approximately 1:1 mixture of diastereoisomers.

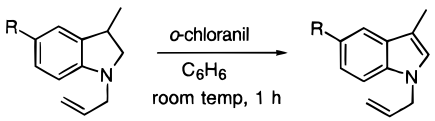
(diphenylphosphino)butane (DPPB) in the presence of 2-mercaptobenzoic acid following the procedure of Genêt.[7]



The methodology described above may also be used for the preparation of indolines functionalized at both the C(3) and C(7) positions. Treatment of 2,6-dibromo-4-methyl-*N*,*N*-diallylaniline (**5**) in *n*-pentane−diethyl ether (9:1 by vol) at −78 °C with 4.4 equiv of *t*-BuLi effects exchange of both bromines and generates the dilithioaryllithium **6**: as illustrated in Scheme 2, quenching a solution of **6** at −78 °C delivers 4-methyl-*N*,*N*-diallylaniline in 85% isolated yield. It might be anticipated that **6** would undergo a dual 5-exo cyclization when warmed. However, as summarized in Scheme 2, allowing a solution of **6** to stand at 0 °C for 40 min in the presence of 4.4 equiv of TMEDA followed by addition of an excess of TMS-Cl afforded only monocyclized adducts **7** and **8** (the remainder of the product mixture was unfunctionalized 4-methyl-*N*,*N*-diallylaniline). Significantly, the major product of the reaction sequence, **7** (64% isolated yield), was functionalized at both the C(3) methylene as well as at the aromatic C(7) position. These results, which demonstrate that cyclization of **9** is much less facile than is ring closure of **6**, suggest that easily prepared 2,6-dibromo-*N*,*N*-diallylanilines may serve as precursors for the one-pot synthesis of indolines bearing functionality at both C(3) and C(7).



The chemistry described above, and summarized in Schemes 1 and 2, constitutes a novel route to substituted indolines from readily available starting materials. It should be noted that the indoline products generated by this methodology (Table 1) may be easily oxidized to the corresponding indoles. While a variety of oxidants have been employed for this purpose,[4] the use of 1 molar equiv of *o*-chloranil at room temperature is a particularly attractive, mild technique;[8] representative examples are presented below. A variety of protocols are available for N-deallylation of the resulting N-allylindoles.[7,9]



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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds are available (43 pages).

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(7) Lemaire-Audoire, S.; Savignac, M.; Genêt, J. P.; Bernard, J.-M. *Tetrahedron Lett.* **1995**, *36*, 1267.

(8) Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1996**, *61*, xxxx.

(9) Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797 and references therein.