A Versatile Synthesis of 3-Substituted Indolines and Indoles

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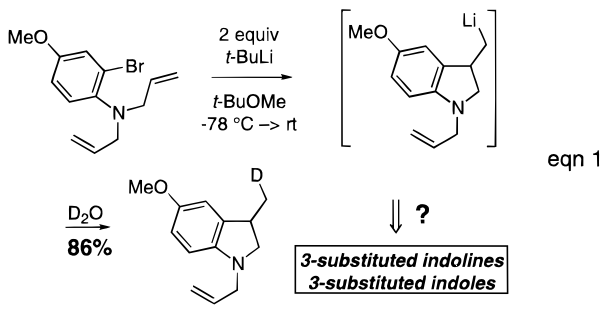
Indolines and their oxidized counterparts, indoles, are very important pharmacophores that appear in numerous biologically active compounds, most notably those affecting the central nervous system.[1,2] In addition to classical methods for the construction of the heteroatom ring of these molecules,[3−5] newer procedures mediated by transition metal species have been documented.[6−18] Herein is reported a new method for the synthesis of 3-substituted indolines and indoles whose operational simplicity and generality should find favor in many applications.

During an attempt to lithiate 2-bromo-4-methoxy-*N*,*N*-diallylaniline with *t*-BuLi for use in another project, a surprisingly facile cyclolithiation to *N*-allyl-3-(lithiomethyl)-5-methoxyindoline occurred, as judged by isolation of *N*-allyl-3-(deuteriomethyl)-5-methoxyindoline in 86% yield after quenching of the reaction with D_2O (eq 1). Recognizing the potential of this transformation as a versatile construction of 3-substituted indolines and indoles, and noting the inherent advantages that accrued from the use of a symmetrically substituted *N*,*N*-diallylaniline group in the chemistry (ease of synthesis, conformational symmetry about the Csp^2−N bond, ease of deprotection of the resulting *N*-allylindoline), we undertook a brief study of this cyclolithiation process. Bailey and others have described a variety of related intramolecular carbolithiations of alkenes and alkynes.[19−26]



Results of the study are depicted in Table 1 and demonstrate that *N*-allylindolines and *N*-allylindoles possessing a variety of substitution patterns can be rapidly constructed. Readily available *o*-bromo-*N*,*N*-diallylanilines **1a**,[17] **1b**,[17] **1c**,[17] and **1d** (see the supporting information) were treated with 2 equiv of *t*-BuLi in *tert*-butyl methyl ether (TBME) at −78 °C, and then the lithiation reaction mixtures were allowed to warm to room temperature. Protonation of the intermediate 3-(lithiomethyl)indolines thus formed provided a variety of 3-methylindolines in good to high yields (**2a** − **2d**, 61%−95%). The indolines **2a** − **2c** were carried forward to their respective 3-methylindoles **6a** − **6c** by treatment with 1 equiv of *o*-chloranil in TBME at room temperature. By quenching the intermediate 3-(lithiomethyl)indolines formed on cyclolithiation of **1a** and **1c** with prochiral carbonyl compounds (3-methoxy-4-(benzyloxy)benzaldehyde[27] and 3,4-diisopropylsquarate[28]), the 3-substituted indolines **3a**, **3c**, **4a**, and **4c** were produced as mixtures of the diastereomers (**3a**, 2:1; **3c**, 1:1; **4a**, 1:1; **4c**, 1:1) in yields between 55% and 78%. Each of the diastereomeric mixtures converged to a single 3-substituted indole (**7a**, **7c**, **8a**, **8c**, respectively) on oxidation with *o*-chloranil in TBME at room temperature.

3-Substituted indoles bearing a basic alkylamino side chain were easily constructed using this cyclolithiation protocol. The indolines **5a** and **5b** were obtained in 57% and 62% yields, respectively, upon reaction of *N*-methylenepiperidinium chloride[29] with the 3-(lithiomethyl)-indolines formed by cyclolithiation of *o*-bromoanilines **1a** and **1b**. Oxidation to the corresponding indoles **9a** and **9b** proceeded uneventfully with 1 equiv of *o*-chloranil in TBME at room temperature (64% and 53%, respectively).

On the basis of analysis of the ratios of indoline to uncyclized products, the cyclolithiation process began slowly at 0 °C and was complete after 2 h at room temperature in *tert*-butyl methyl ether. Both *n*-BuLi and *t*-BuLi were used to effect the cyclolithiation in either diethyl ether or *tert*-butyl methyl ether, the latter organolithium reagent and solvent pair proving the superior combination.

An inherent benefit of the intramolecular carbolithiation of *o*-lithio-*N*,*N*-diallylanilines is the production of *N*-allyl-protected indolines, which should be susceptible to deprotection by a variety of known *N*-deallylation protocols.[17,30,31] To assess the feasibility of *N*-allylindoline deprotection, *N*-allylindolines **2a** and **2b** were treated

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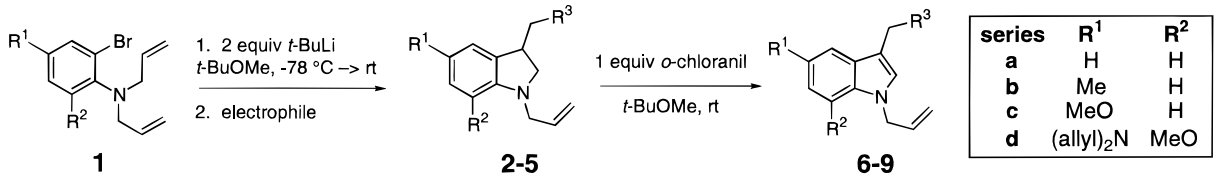
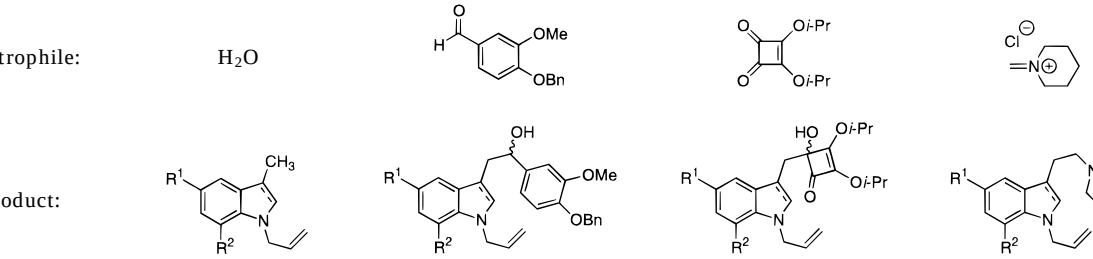
Table 1. Cyclolithiation of *o*-Bromo-*N*,*N*-diallylanilines to Indolines and Their Oxidation to Indoles

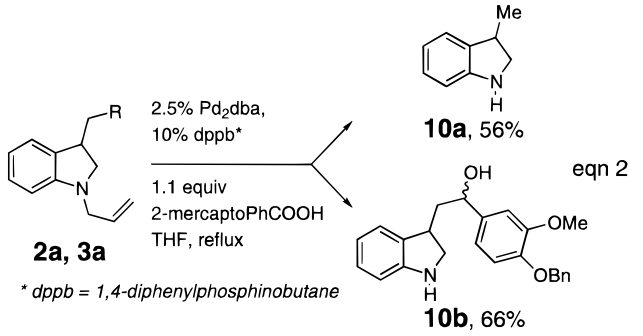




			compd/yield (%)		compd/yield (%)		compd/yield (%)		compd/yield (%)	
aniline	R^1	R^2	indoline	indole[a]	indoline	indole[a]	indoline	indole[a]	indoline	indole[a]
1a	H	H	**2a**/85	**6a**/82	**3a**/67	**7a**/87	**4a**/78	**8a**/65	**5a**/57	**9a**/64
1b	Me	H	**2b**/87	**6b**/82					**5b**/62	**9b**/53
1c	MeO	H	**2c**/95	**6c**/70	**3c**/85	**7c**/74	**4c**/72	**8c**/ 57		
1d	$(allyl)_2N$	MeO	**2d**/61							

[a] The indicated yield is that obtained on oxidation of the indoline to the indole.

with catalytic $Pd_2(dba)_3$/1,4-bis(diphenylphosphino)butane and 2-mercaptobenzoic acid in THF at reflux according to a recently disclosed procedure.[31] This produced moderate isolated yields of the air-sensitive indolines **10a** (56%)[32] and **10b** (66%), the latter as a 1:1 mixture of diastereomers (eq 2).



In conclusion, a concise and technically simple procedure for the construction of 3-substituted indolines and indoles has been uncovered. It bears a resemblance to the nickel- and palladium-catalyzed cyclization of *o*-halo-*N*-allylanilines to indoles, studied by Ban and Hegedus,[6–10] but differs significantly in the range of functionalized indolines and indoles that can be easily obtained from the 3-(lithiomethyl)indoline intermediate. This new procedure should provide the synthetic chemist with the ability to construct a wide variety of substituted indolines and indoles rapidly and with minimal effort.

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Supporting Information Available: A complete description of the synthesis and characterization of all compounds in this paper (16 pages).

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