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Synthesis of 4-Functionalized Indoles *via* Benzyne Cyclization of *N*-(2-lithioallyl)-2-fluoroanilines

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Abstract

Treatment of *N*-(2-bromoallyl)-*N*-methyl-2-fluoroaniline with *tert*-butyllithium affords 1,3-dimethyl-4-lithioindole, via intramolecular addition to a tethered benzyne intermediate. Further reaction with electrophiles leads to 4-functionalized 3-methylindoles. © 1999 Elsevier Science Ltd. All rights reserved.

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The intramolecular trapping of benzyne intermediates by a side-chain nucleophile to generate a bicyclic system has been shown to be very useful for the synthesis of benzo-fused bicycles [1,2]. This strategy, introduced independently by Huisgen [3,4] and Bunnett [5,6], has been extensively used in natural product synthesis. In this context, a series of benzoxazoles [7] and benzothiazoles, [8] derivatives functionalized at the C(7), have been synthesized. Moreover, 7-substituted indolines have been prepared *via* intramolecular cyclization of (2-phenethyl)formamidines [9]. In these examples, the benzyne intermediates were trapped by heteroatoms (O, S, N). Recently, Bailey et al. have reported the preparation of 4-substituted indans *via* cyclization of a benzyne-tethered propyllithium, where the aryne intermediate has been trapped by a non-stabilized carbon nucleophile [10]. On the other hand, the indole nucleus is a common and important moiety of a variety of natural products and medicinal agents [11,12,13]. However, the introduction of substituents on the carbocyclic ring primarily relies on electrophilic substitution and on organometallic reactions [14]. The former reactions are not under strong regiochemical control and require deactivation of the heterocyclic ring. Reactions *via* organometallic intermediates achieve position selectivity on the basis of prior substitution. Electrophilic thallation directed by 3-substituents (formyl, acetyl, ethoxycarbonyl) has been useful for the synthesis of 4-substituted indoles [15,16]. We have recently reported the intramolecular carbolithiation of *N*-allyl-*N*-(2-lithioallyl)amines [17] and also, we have described the first intramolecular carbometalation of lithiated double

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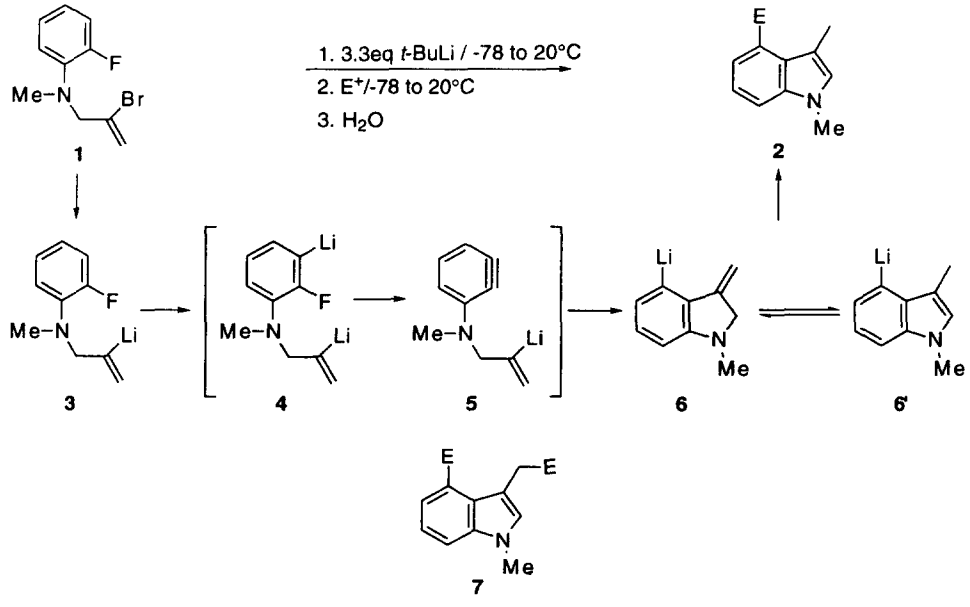
bonds that affords dihydropyrrole and indole derivatives [18]. In the present communication, we extend the use of *N*-(2-lithioallyl)amines to the synthesis of 4-substituted indoles using benzyne-cyclization methodology.

Reaction of *N*-(2-bromoallyl)-*N*-methyl-2-fluoroaniline **1** with 3.3 equiv of *t*-butyllithium from -78 to 20°C in THF and further treatment with different electrophiles gives rise to 4-functionalized indoles **2**, in moderate to good yields, after purification by column chromatography on silica gel (Scheme 1 and Table 1). To clarify this process some tests were done. The reaction of **1** with 2.2 equiv of *t*-butyllithium at -78°C in THF for 30 min affords *N*-(2-lithioallyl)amine **3**, by halogen-metal exchange, that was confirmed by deuteration. If the reaction is carried out with an additional equiv of *t*-butyllithium the abstraction of the proton *ortho* to the fluorine [19] takes place and intermediate **4** would be formed. The subsequent elimination of LiF produces a benzyne [20] intermediate **5**, which is trapped intramolecularly by the 2-lithioallyl moiety, affording a 3-methylenindoline **6** lithiated at the C(4). The isomerization of **6** to the corresponding indole **6'** occurs during the evolution of the process, although the formation of the more stable indole is not completed until electrophilic quench, as it was established by the GC-MS analysis of different aliquots. The addition of deuterium oxide to the mixture of anions **6+6'** gives 4-deuterio-1,3-dimethylindole **2a**, that is partially deuterated at the C(3) methyl substituent. The excess of base, used to ensure complete formation of benzyne, and the directing properties of the preexisting lithium at the C(4) position could account for this additional metalation. In a preliminary experiment, the use of 4 equiv of *t*-butyllithium and further addition of dibenzyl disulfide as electrophile, produces difunctionalized indole **7** (E=SBn), in moderate yield (41%). Nevertheless, stirring of the mixture for 1 h at room temperature removes the primary alkyl lithium. It will probably be due to the THF, that serves as a proton source for the less stable carbanion.



Scheme 1

Table 1

Synthesis of 4-functionalized indoles **2** and difunctionalized indole **7** from *N*-(2-bromoallyl)-*N*-methyl-2-fluoroaniline **1**.

Electrophile	E	Product[a]	Yield[b]
D_2O	D	**2a**	73[c]
Bu_3SnCl	$SnBu_3$	**2b**	65
PhCHO	PhC(H)OH	**2c**	66
$(CH_3)_2CO$	$(CH_3)_2C(OH)$	**2d**	71
$ClCO_2Et$	CO_2Et	**2e**	55
4-ClC_6H_4CN	4-ClC_6H_4CO	**2f**	59
PhCH=NHPh	PhC(H)NHPh	**2g**	57
Bn_2S_2	SBn	**7**	41

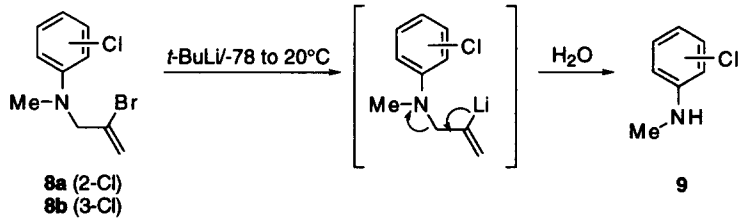
[a]All the products were fully characterized by ^1H- and ^{13}C-NMR and MS.

[b]Based on starting amine **1**.

[c]Partially deuterated at the C(3) methyl group.

Under these reaction conditions, a competitive reaction (involving a β-elimination from the β-amino functionalized organolithium derivative) is operative and *N*-methyl-2-fluoroaniline is also produced in small amounts (15-25%). We attribute this fact to the lower electron density on the nitrogen atom due to the fluorine. In order to minimize this undesired pathway, the reaction was carried out in a mixture of diethyl ether and THF (2:1). Interestingly, the abstraction of the proton *ortho* to the fluorine starts at -78°C but when the temperature increases, some products, not well identified, were detected by GC-MS analysis. If the temperature is maintained at -78°C for 1 h, the subsequent trapping with electrophiles generates with similar chemical yields the corresponding functionalized indole **2**, which in this case was obtained along with a small amount of the corresponding *N*-(2-functionalized allyl)-2-fluoroaniline. Under these conditions the β-elimination products were not observed.

Looking for related substrates capable to generate benzyne intermediates, *N*-(2-bromoallyl)-*N*-methyl-2-chloroaniline **8a**, and *N*-(2-bromoallyl)-*N*-methyl-3-chloroaniline **8b**, were synthesized. However, under the same reaction conditions (treatment with 3.3 equiv of *t*-butyllithium in THF or a mixture of diethyl ether:THF at temperatures ranging between -78 and 20°C), no indole formation takes place and only the products **9** were obtained after hydrolysis (Scheme 2). In these cases the β-elimination process is faster than the proton abstraction.



8a (2-Cl)
8b (3-Cl)

9

Scheme 2

In a typical procedure, amine **1** (2 mmol) was dissolved in THF (15 ml) and then a solution of*tert*-butyllithium in pentane (6.6 mmol) was added at -78°C. The mixture was stirred for 30 min, then the cool bath was removed allowing the solution to reach room temperature and the stirring was continued for 1 h. The reaction mixture was then cooled to -78°C and the electrophile (2.2 mmol) was added. The solution was stirred for 15 min at low temperature and for 1 h at 20°C. The mixture was quenched with water and extracted with ethyl acetate (3 x 20 ml). Solvent was evaporated and the residue was purified by flash chromatography on silica gel to give compounds **2**.

In conclusion, we have described a new route to 3-methylindoles which can be further functionalized at the C(4) position. This method should be of interest due to the availability of the starting materials and the simplicity of the process. Further experiments to explore the synthetic potential of this strategy for the preparation of other heterocycles and to solve the limitations found will be reported in due course.

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