Pergamon

Tetrahedron Letters, Vol. 38, No. 8, pp. 1329-1332, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00032-4

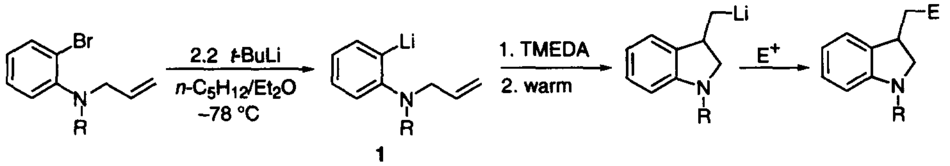
Reaction of Organolithiums with Fluoro-N,N-diallylanilines: A Benzyne–Mediated Anionic Cascade Leading to 3,4-Disubstituted Indolines

William F. Bailey* and Matthew W. Carson

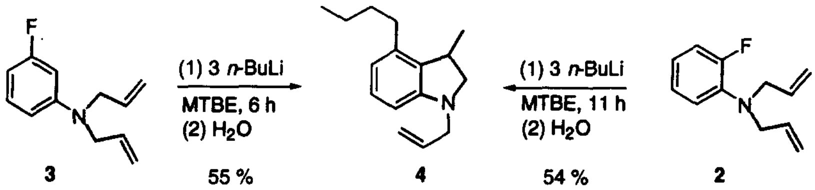
Department of Chemistry, University of Connecticut, Storrs, CT 06269-4060

Abstract: Regioselective ortho-lithiation of either 2-fluoro- (2) or 3-fluoro-N,N-diallylaniline (3) initiates an anionic cascade leading to an N-allyl-3,4-disubstituted indoline. The transformation involves loss of LiF from the ortho-lithiated species, regioselective intermolecular addition of the organolithium to the benzyne intermediate, and cyclization of the resulting [6-substituted-2-(N,N-diallylamino)phenyl]lithium.

We and the Liebeskind group recently reported that 3-substituted indolines (2,3-dihydro-1H-indoles) may be prepared by cyclization of a [2-(N-allylamino)phenyl]lithium (1) derived from a 2-bromo-N-allylaniline by lithium–bromine exchange.[1] It occurred to us that an aryllithium analogous to 1 would be generated by ortho-lithiation[2] of a 3-fluoro-N-allylaniline and it was of interest to determine if such a species would cyclize prior to expulsion of LiF to generate a benzyne intermediate.[3] As detailed below, regioselective ortho-lithiation of either 2-fluoro- (2) or 3-fluoro-N,N-diallylaniline (3) with an organolithium initiates an anionic cascade leading to an N-allyl-3,4-disubstituted indoline via loss of LiF, regioselective intermolecular addition of the organolithium to the benzyne intermediate, and cyclization of the resulting [6-substituted-2-(N,N-diallylamino)phenyl]lithium.

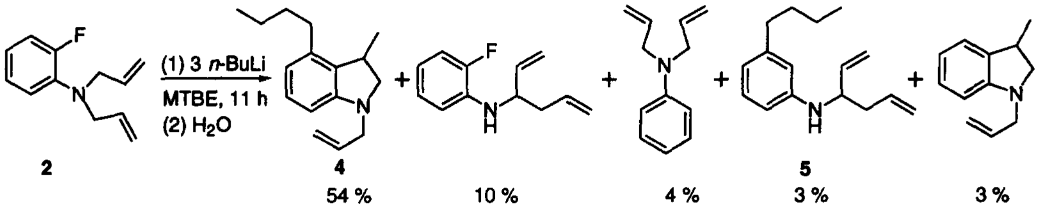


Initial experiments, involving treatment of approximately 0.1 M solutions of 3-fluoro-N,N-diallylaniline (3) in dry methyl *t*-butyl ether (MTBE) with one molar equivalent of *n*-butyllithium (*n*-BuLi) and warming to room temperature, revealed that, not unexpectedly,[3] loss of LiF from the ortho-lithiated intermediate is a much more facile process than is cycloisomerization. However, an intriguing observation made in the course of this exploratory study prompted further investigation: the major tractable product obtained from the reaction of 3 with *n*-BuLi was N-allyl-4-butyl-3-methylindoline[4] (4). Indeed, as illustrated below, when 3 molar equivalents of *n*-BuLi were employed, and the reaction mixture was allowed to warm and stand at room temperature for 6 h prior to quench with water, 4 was produced in 55 % yield. Moreover, 4 may be prepared in essentially the same yield, albeit more slowly, by treatment of 2-fluoro-N,N-diallylaniline (2) with *n*-BuLi in MTBE.



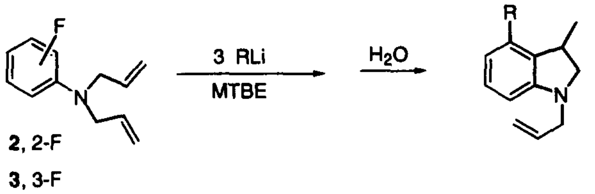
As demonstrated by the results summarized in Table 1, various 4-substituted-N-allyl-3-methylindolines may be prepared in analogous fashion by simply stirring a solution of either 2-fluoro- (**2**) or 3-fluoro-N,N-diallylaniline (**3**) and the appropriate organolithium in dry MTBE. It might be noted that the N-allyl substituent may be conviently removed to give a 3,4-disubstituted indoline using catalytic $Pd_2(dba)_3$ and 1,4-bis(diphenylphosphino)butane in the presence of 2-mercaptobenzoic acid.[1,5]

The modest yield of isolated products (Table 1) belies the potential synthetic utility of this route to 3,4-disubstituted indolines: the bulk of the tractable material produced in the reaction is the indoline which is easily separated from residual tar by flash chromatography or distillation. Thus, for example, careful GC-analysis of the crude reaction mixture produced upon treatment of **2** with *n*-BuLi (Table 1, entry 1) revealed that five products, illustrated below, accounted for 74 % of the material balance; unidentified oligomeric material constitutes the remainder. Given this product composition, the yield of **4** (i.e., 54 %) represents ~73 % of the tractable material produced in the reaction. In this connection, it is worth noting that the product composition is dramatically altered when reactions are conducted in THF solution: treatment of a solution of **2** in dry THF with 3 molar equiv of *n*-BuLi for 0.5 h at room temperature afforded a complex mixture containing **5** as the major tractable product (32 % yield)[6] along with 18 % of **4**.



The conversion of 2-fluoro- (**2**) or 3-fluoro-N,N-diallylaniline (**3**) to a 4-substituted-N-allyl-3-methylindoline upon treatment with an organolithium most likely involves four discrete steps (Scheme 1), each of which finds ample literature precedent. The remarkable feature of the overall transformation is the cooperative selectivity of the steps. The reactions of **2** or **3** with an organolithium are initiated by regioselective lithiation ortho to the fluorine substituent[2,7] (viz., C(3) of **2** or C(2) of **3**) followed by loss[3] of LiF to give 3-(N,N-diallylamino)-1,2-dehydrobenzene as a common intermediate. While intermolecular addition of an organolithium to this intermediate could occur at either terminus of the benzyne triple bond,[3] a regioselective meta-addition[8] is required to produce the [6-substituted-2-(N,N-diallylamino)-6-substitutedphenyl]lithium that subsequently cyclizes,[1] as illustrated in Scheme 1, to give the observed indoline framework. In light of the probable intermediacy of a 1,2-dehydrobenzene, it is not surprising that the reaction of **2** or **3** with an organolithium also produces sizable quantities of intractable material; intermolecular anionic additions to benzynes are often accompanied by oligomerization to give tars.[3]

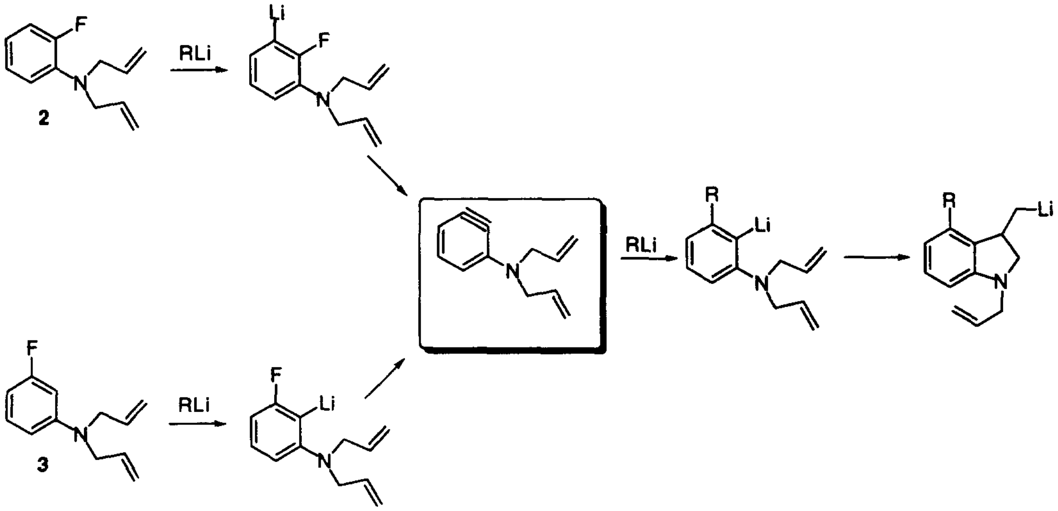
Table 1. Reaction of 2-Fluoro- (**2**) and 3-Fluoro-N,N-diallylaniline (**3**) with Organolithiums.[a]



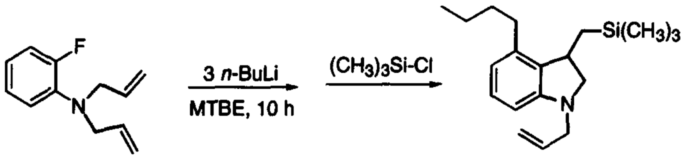
entry	substrate	R	time,[b] h	yield,[c] %
1	2-F (**2**)	*n*-Bu	11	54 (41)
2		*t*-Bu	1.5	19
3		Ph	78	41
4	3-F (**3**)	*n*-Bu	6	55
5		*t*-Bu	1.5	33 (15)
6		Ph	52	53 (35)[d]

[a] Reactions were conducted at either room temperature (*n*-BuLi or PhLi) or 0 °C (*t*-BuLi) under an atmosphere of argon by addition of 3.0 molar equivalents of the appropriate organolithium to an approximately 0.1 M solution of **2** or **3** in dry MTBE. [b] Reaction mixtures were stirred at room temperature for the indicated time prior to quench with water. [c] Yields were determined by GC analysis using an internal standard and correction for detector response; isolated yield of analytically pure product[4] in parentheses. [d] Preparative reaction conducted in MTBE–THF (19:1 by vol).

Scheme 1.



While 4-substituted-N-allyl-3-methylindolines were generated in this exploratory investigation by quench of reaction mixtures with water (Table 1), it should be noted that the [(3-indolinyl)methyl]lithium produced by the anionic cascade depicted in Scheme 1 may be trapped by addition of electrophiles to give products functionalized at the C(3) position.[1] Thus, for example, treatment of **2** with *n*-BuLi followed by addition of trimethylsilyl chloride affords the TMS derivative, depicted below, in 51 % isolated yield.



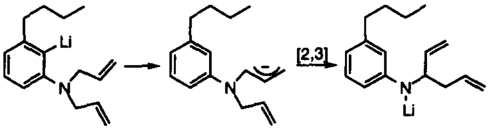
2

51 %

Acknowledgment. This work was supported by the Connecticut Department of Economic Development.

References and Notes

1. (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.
2. (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, 1. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Wittig, G.; Pieper, G.; Fuhrmann, G. *Chem. Ber.* **1940**, *73*, 1193. (d) Gilman, H.; Soddy, T. S. *J. Org. Chem.* **1957**, *22*, 1715.
3. Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967.
4. Satisfactory C and H analyses and/or exact mass spectroscopic molecular weights have been determined for all previously unreported compounds and their IR, ^{1}H NMR, and ^{13}C NMR spectra are fully in accord with the assigned structures.
5. Lemaire-Audoire, S.; Savignac, M.; Genêt, J. P.; Bernard, J.-M. *Tetrahedron Lett.* **1995**, *36*, 1267.
6. The fact that **5** is the major product of the reaction of **2** with *n*-BuLi when conducted in THF solution suggests that intramolecular 1,5-proton transfer effectively competes with cycloisomerization of the [2-(N,N-diallylamino)phenyl]lithium intermediate in THF solvent. As illustrated below, such proton transfer generates an allyllithium intermediate that would be expected to undergo [2,3]-sigmatropic rearrangement under the conditions of the reaction. Indeed, when reaction mixtures produced upon treatment of **2** with *n*-BuLi in THF were quenched with D_2O, there was no deuterium above the natural abundance level on any aromatic carbon of **5**.



7. (a) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191. (b) Katsoulos, G.; Takagishi, S.; Schlosser, M. *Synlett* **1991**, 731.
8. In this connection, it is should be noted that addition of PhLi to 3-(dimethylamino)-1,2-dehydrobenzene is reported to give 3-(dimethylamino)biphenyl as the major product: Möbius, L. Doctoral Dissertation, Universität München, 1961, as reported in ref. 3, p. 107. For other regioselective additions of organolithiums to 3-substituted benzynes, see: (a) Adejare, A.; Miller, D. D. *Tetrahedron Lett.* **1984**, *25*, 5597. (b) Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178. (c) Mulhern, T. A.; Davis, M.; Krikke, J. J.; Thomas, J. A. *J. Org. Chem.* **1993**, *58*, 5537.

(*Received in USA* 9 *December* 1996; *accepted* 6 *January* 1997)