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FUNCTIONALIZED ARYLLITHIUM INTERMEDIATES. A NEW ROUTE TO 3,4-DIHYDROISOQUINOLINES.

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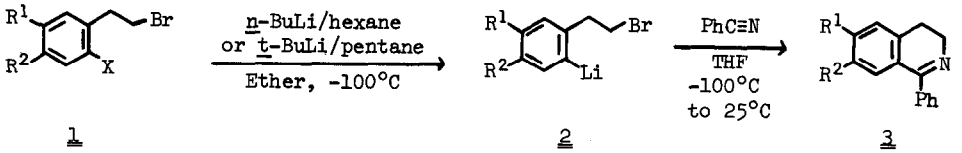
The isoquinoline ring system is a very commonly occurring structural unit in natural products. A large number of isoquinoline alkaloids have been found which possess useful physiological activity, including activity as antibiotics, antitumor agents, drugs for treating mental health disorders, narcotic antagonists, analgesics, and antihypertensive agents.[1] Several methods have been developed for the synthesis of isoquinolines, the most commonly used methods being the Bischler-Napieralski and the Pictet-Spengler reactions.[1,2] A method which is related to our work is the reaction of 2-phenethyl halides with nitriles in the presence of a Lewis acid such as stannic chloride.[3] Because these methods involve electrophilic aromatic substitution in the key ring-forming steps, a limitation of these methods is that they often afford the best results only when the aromatic ring bears electron-donating substituents. We wish to report a new method for the synthesis of the isoquinoline ring system which promises to be of more general utility. Rather than being based upon carbonium ion intermediates, our approach employs nucleophilic carbanionic species.

Recently, Parham reported the selective bromine-lithium exchange reaction of 2-(2'-bromophenyl)ethyl bromide (1a) with n-butyllithium in a mixture of tetrahydrofuran (THF) and hexane to give the aryllithium (2a) which undergoes reactions with various electrophiles including cyclohexanone.[4] We have found that the exchange reaction is not limited to 1a but may readily be performed with a number of additional dihalides of this type (1b-c). The resulting aryllithiums (2a-d) react with benzonitrile to afford 1-phenyl-3,4-dihydroisoquinolines (3a-d) in high yields (equation 1). The results are summarized in the Table.



(1)

1 2 3

a, $R^1=R^2=H$, X=Br
b, $R^1=OCH_3$, $R^2=H$, X=I
c, $R^1=R^2=OCH_3$, X=I
d, $R^1, R^2=OCH_2O$, X=I

Either n-butyl- or t-butyllithium may be used to effect the exchange reaction, although t-butyllithium, as expected, undergoes the reaction more readily. Diethyl ether is the preferred solvent for this step;[5] if THF is employed, substantial amounts of benzocyclobutenes are produced by intramolecular alkylation of 2a-d.[4,6] However, the reaction of the aryllithiums (2) with benzonitrile is facilitated by the addition of a small amount of THF during the second step of the reaction sequence; the addition of THF at this point leads to formation of only small amounts of benzocyclobutenes (0-5%). A typical procedure is given below.

1-Phenyl-3,4-dihydro-6,7-methylenedioxyisoquinoline (3d). To a solution of 1d (0.355 g, 1.00 mmol) in diethyl ether (3 ml) at -100°C under a nitrogen atmosphere was added a 2.62 M solution (0.400 ml, 1.05 mmol) of n-butyllithium in hexane. After 1 h, benzonitrile (0.105 ml, 1.05 mmol) and THF (0.5 ml) were added. The mixture was stirred at -100°C for 1 h, allowed to warm slowly to 25°C, and then diluted with water and additional ether. From the organic layer was isolated 0.241 g (96%) of 3d as a yellow solid: ^{1}H-nmr ($CDCl_3$) δ 7.45 (m, 5H), 6.25 (s, 2H), 5.95 (s, 2H), 3.80 (t, J=8Hz, 2H), and 2.63 (t, J=8Hz, 2H). Recrystallization from ethanol afforded white crystals: mp 139-140°C (lit[7] mp 141°C).

These preliminary studies indicate that the reaction of nitriles with the aryllithiums of structure 2 promises to be a very useful route to the isoquinoline ring system. In contrast to previous methods (vide supra), high yields are obtained whether or not electron-donating substituents are present. Furthermore, the starting materials (1) are readily obtained from commercially available arylacetic acids by straightforward procedures developed by several earlier workers.[4,8,9] A typical preparation involves reduction of an arylacetic acid to the alcohol with borane or lithium aluminum hydride, aromatic halogenation, and conversion of the alcohol to the bromide.

Work is in progress to extend our route to the synthesis of other types of isoquinolines through the use of aliphatic nitriles and of imines. Also, the aryllithiums (2) and their copper derivatives are being employed in the synthesis of other ring systems (e.g. benzocyclobutenes[6] and steroids).

Table. Synthesis of Isoquinoline Derivatives.

Dihalide	Isoquinoline[a]	Yield (%)[b]	Lit. Ref.
1a	3a	85	(10)
1b	3b	80	(11)
1c	3c	82[c]	(12)
1d	3d	96	(7)

[a]The products were identified by comparison of melting points or ^{1}H-nmr spectra to the published data. [b]All yields are for isolated products. [c]See ref. 13.

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FOOTNOTES AND REFERENCES

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13. The yield of 3c varies considerably in different experiments because of the heterogeneous nature of the reaction mixtures resulting from the low solubility of 1c in ether at low temperature. The value of 82% is the highest yield obtained to date.