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Nucleophilic Addition of β-Amino Carbanions to Arynes: One-Pot Synthesis of 4-Aryl-*N*-methyl-1,2,3,4-tetrahydroisoquinolines

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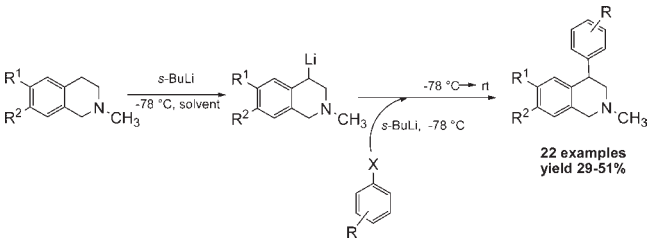
ABSTRACT



A novel approach for the direct C-4 arylation of *N*-methyl-1,2,3,4-tetrahydroisoquinolines by nucleophilic addition of β-aminocarbanions to benzynes is described which provides a one-pot procedure for synthesis of the title compounds.

Tetrahydroisoquinoline is a common structural motif present in a large number of natural products[1] and synthetic compounds of biological importance.[2] The 4-aryl-*N*-methyl-1,2,3,4-tetrahydroisoquinolines have attracted attention because of their wide range of physiological activities.[3] This basic skelton **1a** (Figure 1) is present in many natural products and drugs; cherylline (**1b**) and latifine (**1c**) are isolated from Amaryllidaceae plants,[4] and nomifensine[5] (**1d**) and diclofensine[6] (**1e**) exhibit CNS activity and inhibit the serotonine and dopamine uptake mechanism. Many approaches for the synthesis of 4-aryl-*N*-methyl-1,2,3,4-tetrahydroisoquinolines have been developed,[7] and most of these involve the construction of a nitrogen-containing ring.[8] More recently, a two-step process which involves a palladium-catalyzed α-arylation between dihydroisoquinolinones and aryl halides followed by BH_3 reduction of the carbonyl group has been reported.[9]

Our research group has been actively engaged in the generation and reactions of amino carbanions derived

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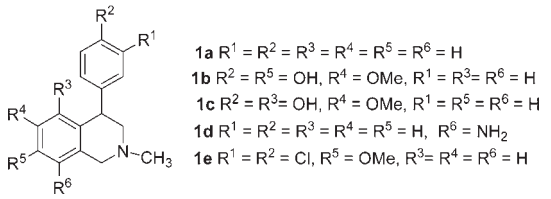
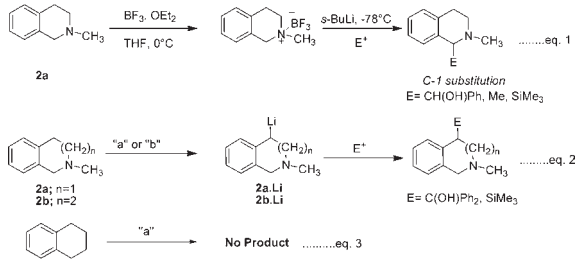


Figure 1. 4-Aryl-*N*-methyl-1,2,3,4-tetrahydroisoquinolines.

from tertiary amines.[10] It was established that addition of 1 equiv of a strong Lewis acid ($BF_3 \cdot OEt_2$) to the tertiary amine followed by treatment with *s*-BuLi in THF at −78 °C results in carbanion formation at a position α to the nitrogen atom. Subsequent reaction with electrophiles furnished the α-substituted products in excellent yields (Scheme 1, eq 1).[11] This procedure was utilized for the synthesis of many *N*-methyltetrahydroisoquinoline

Scheme 1. Lithiation/Substitution of Tertiary Amines



alkaloids.[12] Furthermore, it was observed that in absence of the Lewis acid the carbanion formation and reaction with electrophiles occurred at a distant position (Scheme 1, eq 2).[13] The nitrogen atom had a definitive role in these reactions as in the corresponding carbocyclic compounds; no reaction was observed under these conditions (Scheme 1, eq 3).[13a]

Aryne chemistry has been extensively reviewed.[14] One of the methods of aryne generation involves treating aryl fluorides or chlorides with alkyllithium at low temperatures.[15] Detailed studies with these and their methoxy-substituted analogues have been carried out to delineate the temperature range of formation of *o*-halolithiated species and subsequent benzyne generation.[16] These intermediates undergo efficient intermolecular/intramolecular reactions with many nucleophiles including carbanions derived with the help of suitably placed electron-withdrawing substituents.[17]

To the best of our knowledge, the nucleophilic coupling of amino carbanions derived from tertiary amines with arynes has not been investigated. We reasoned that the nucleophilic addition of the C-4-lithiated *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**2a·Li**) to the in situ generated benzyne could be a valuable strategy for direct access to C-4-arylated products. In this paper, we describe our results on the basis of this novel approach.

In the initial studies, the C-4-lithiated species **2a·Li** was generated by taking tetrahydroisoquinoline **2a** (1.36 mmol) in THF (4 mL) at −78 °C and adding *s*-BuLi (1 equiv). After an interval of 30 min, a second installment of *s*-BuLi (1.2 equiv) was added followed by chlorobenzene (**3a**) (1 equiv). The reaction mixture was stirred at −78 °C for another 45 min and then allowed to warm to ambient temperature (Scheme 2). It was quenched with 10% HCl. Workup and purification by column chromatography afforded the C-4 arylated product **1a** in a low yield of 22%.[18] In an effort to improve the yield, the quantities of the base and chlorobenzene were increased, and the results are summarized in Table 1. A maximum yield of 38% was obtained by using 2.2 equiv of *s*-BuLi in the first installment, 3 equiv in the second installment, and addition of 3 equiv of chlorobenzene (Table 1, entry 4). A further increase in these quantities did not have the desired result (Table 1, entry 6). Changing the benzyne precursor from

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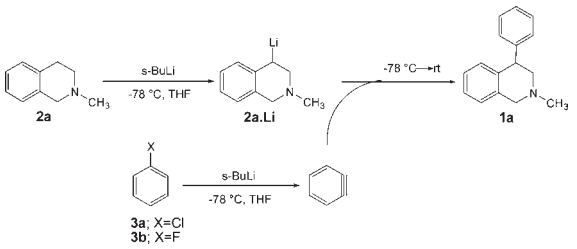
(18) (a) All new products were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy and mass spectrometery (APCI-MS and HRMS). (b) In all of the reactions reported in this paper, some unreacted starting amine was always recovered. This could be (i) due to incomplete formation of the lithiated intermediate of **2a** or (ii) because the lithiated intermediate of **2a** gets partially quenched by another proton source (e.g., C-4 benzylic proton of arylated product **1a** or from the solvent). To get some information on these aspects the following two experiments were carried out: (I) A solution of the amine **2a** (1mmol) in THF (3 mL), at −78 °C, containing *s*-BuLi (2.2 mmol) was quenched with MeOD after 30 min. The ^{1}H NMR spectrum of the material obtained after workup revealed 100% deuterium incorporation at C-4 position, indicating that complete C-4 carbanion formation had occured. (II) The reaction of **2a** and **3a** was carried out in the normal manner, but in the end, it was quenched with MeOD instead of 10% HCl. The ^{1}H NMR spectrum of the isolated C-4 arylated product **1a** did not show any deuterium incorporation, indicating that once **1a** is formed in the reaction mixture it does not transfer the C-4 benzylic proton to **2a·Li**. (We are grateful to a reviewer for suggesting these two experiments.)

Scheme 2. C-4 Arylation of *N*-Methyl-1,2,3,4- tetrahydroisoquinoline



chlorobenzene (**3a**) to fluorobenzene (**3b**) gave similar results (Table 1, entry 5).

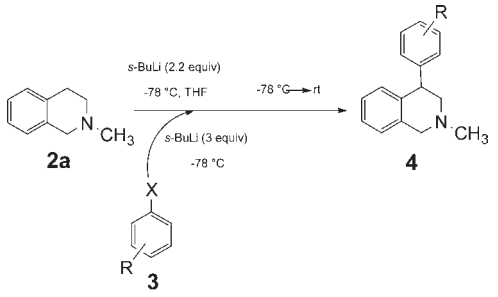
Table 1. Optimization of Reaction Conditions for C-4 Arylation of *N*-Methyl-1,2,3,4-tetrahydroisoquinoline (**2a**)

	base (*s*-BuLi in equiv)			
entry	first installment	second installment	**3** (in equiv)	**1a** (% yield)[a]
1	1	1.2	**3a** (1)	22
2	2	1.2	**3a** (1)	28
3	2	2	**3a** (2)	33
4	**2.2**	**3**	**3a (3)**	**38 (55)**[b]
5	2.2	3	**3b** (3)	38
6	2.2	4	**3a** (4)	35

[a] Isolated yield. [b] Yield calculated on the basis of recovered starting amine.

After establishing the optimized conditions,[18] differently substituted benzyne precursors were used to synthesize a variety of C-4-arylated *N*-methyl-1,2,3,4-tetrahydroisoquinolines (Table 2). It is noteworthy to mention here that whereas *p*-methoxyfluorobenzene (**3d**) reacted to give the product **4d** (Table 2, entry 2), *p*-methoxychlorobenzene (**3c**) failed to react under these conditions (Table 2, entry 1). This failure can be attributed to the preferential lithiation at a position *ortho* to the methoxy group rather than *ortho* to the chloro group in **3c**. In **3d**, the lithiation occurs to an extent of 25% *ortho* to fluoro group besides *ortho* to the methoxy group.[16] However, other methoxy-substituted chlorobenzenes **3e**–**g**, which have a site for preferential lithiation between the methoxy and chloro group, reacted to furnish **4e**–**g** (Table 2, entries 3–5). In fact, a maximum yield of 51% was obtained from **3e**. The formation of products **4h**–**j** in which the substituent "R" appears at a different position from the corresponding reactants **3h**–**j** is along expected lines for benzyne-mediated reactions.[19]

Table 2. Synthesis of **4** Using Different Benzyne Precursors[a]



entry	3	4	yield[b] (%)
1	**3c** (X = Cl; R = 4-OMe)		
2	**3d** (X = F; R = 4-OMe)	**4d** (R = 4-OMe)	42 (57)[c]
3	**3e** (X = Cl; R = 3-OMe)	**4e** (R = 3-OMe)	51 (62)
4	**3f** [X = Cl; R = 3,4-$(OMe)_2$]	**4f** [R = 3,4-$(OMe)_2$]	42 (56)
5	**3g** [X = Cl; R = 3,4,5-$(OMe)_3$]	**4g** [R = 3,4,5-$(OMe)_3$]	30 (47)
6	**3h** (X = Cl; R = 2-OMe 3-Cl)	**4h** (R = 3-OMe 4-Cl)	38 (53)
7	**3i** (X = Cl; R = 2-Cl)	**4i** (R = 3-Cl)	29 (46)
8	**3j** (X = Cl; R = 2-CH_3)	**4j** (R = 2- or 3-CH_3)	31 (55)

[a] *N*-Methyl-1,2,3,4-tetrahydroisoquinoline (1 equiv), *s*-BuLi (2.2 equiv, first installment), *s*-BuLi (3 equiv, second installment), aryl halide (3 equiv) and THF (3 mL/mmol). [b] Isolated yield. [c] Yields shown in parentheses are calculated on the basis of recovered starting amine.

The 6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (**5a**) was next examined for C-4 arylation. When the reaction was performed using identical conditions as for **2a**, the C-4-arylated product **6a** was not obtained.[20] Use of toluene/ether (1:1) as solvent, instead of THF, and modification of temperature for C-4 carbanion generation[20] led to the desired products **6**, and the results are summarized in Table 3. In the process, we were able to synthesize (±)-cherylline dimethyl ether[8a,e] (**6b**) in a modest yield of 33% (Table 3, entry 2). Other benzyne precursors **3a**,**e**–**j** also reacted with **5a** to give **6a**,**c**–**h** (Table 3, entries 1 and 3–8). To further evaluate the substrate scope, differently substituted tetrahydroisoquinolines (**5b**–**d**) were also reacted under similar conditions as for **5a**, and the corresponding products **6i**–**n** were obtained in moderate yields (Table 3, entries 9–14).

In summary, we have developed a novel one-pot procedure for direct C-4 arylation of *N*-methyl-1,2,3,4-tetrahydroisoquinolines involving nucleophilic addition of β-amino carbanions to arynes. Although the yields are modest, its utility in the synthesis of (±)-cherylline dimethyl ether has been demonstrated. Regioselective arylation at C-1 position in *N*-methyl-1,2,3,4-tetrahydroisoquinolines by nucleophilic addition of α-amino carbanions, generated

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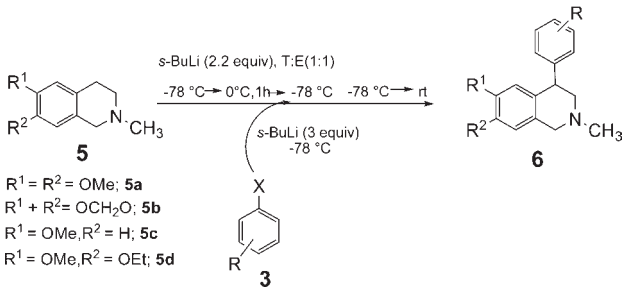
(20) Appearance of deep red color on addition of alkyllithium to solutions of *N*-methyltetrahydroisoquinolines in THF is an indication of formation of C-4 anion. In the case of **2a**, a deep red color appeared at −78 °C and persisted up to 0 °C. However, in the case of **5**, the color disappeared upon warming the solution from −78 → −60 °C. This is probably due to proton abstraction from THF by C-4 anion; see ref 13a and:Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833. When a solution of **5** in toluene/ether (1:1) is treated with *s*-BuLi the color does not appear at −78 °C, but as the solution is warmed to 0 °C the deep red color appears and persists, indicating that in this solvent system, the C-4 anion is stable up to 0 °C. On the other hand, the benzyne generation from **3** occurs at ca. −40 °C as inferred by trapping experiments with furan:Friedman, L; Logullo, F. M. *J. Org. Chem.* **1969**, *34*, 3089.

Table 3. C-4 Arylation of Tetrahydroisoquinolines **5**[a]



entry	5	3	6	yield[b] (%)
1	**5a**	**3a** (X = Cl; R = H)	**6a** ($R^1 = R^2$ = OMe, R = H)	41 (56)[c]
2	**5a**	**3d** (X = F; R = 4-OMe)	**6b** ($R^1 = R^2$ = OMe, R = 4-OMe)	33 (47)
3	**5a**	**3e** (X = Cl; R = 3-OMe)	**6c** ($R^1 = R^2$ = OMe, R = 3-OMe)	38 (56)
4	**5a**	**3f** [X = Cl; R = 3,4-$(OMe)_2$]	**6d** [$R^1 = R^2$ = OMe, R = 3,4-$(OMe)_2$]	32 (51)
5	**5a**	**3g** [X = Cl; R = 3,4,5-$(OMe)_3$]	**6e** [$R^1 = R^2$ = OMe, R = 3,4,5-$(OMe)_3$]	35 (53)
6	**5a**	**3h** (X = Cl; R = 2-OMe-3-Cl)	**6f** ($R^1 = R^2$ = OMe, R = 3-OMe-4-Cl)	35 (55)
7	**5a**	**3i** (X = Cl; R = 2-Cl)	**6g** ($R^1 = R^2$ = OMe, R = 3-Cl)	31 (48)
8	**5a**	**3j** (X = Cl; R = 2-CH_3)	**6h** ($R^1 = R^2$ = OMe, R = 2- or 3-CH_3)	30 (45)
9	**5b**	**3a** (X = Cl; R = H)	**6i** ($R^1 + R^2 = OCH_2O$, R = H)	35 (48)
10	**5b**	**3e** (X = Cl; R = 3-OMe)	**6j** ($R^1 + R^2 = OCH_2O$, R = 3-OMe)	39 (52)
11	**5c**	**3a** (X = Cl; R = H)	**6k** (R^1 = OMe, R^2 = H, R = H)	46 (54)
12	**5c**	**3e** (X = Cl; R = 3-OMe)	**6l** (R^1 = OMe,R^2 = H, R = 3-OMe)	42 (60)
13	**5d**	**3a** (X = Cl; R = H)	**6m** (R^1 = OMe, R^2 = OEt, R = H)	42 (56)
14	**5d**	**3e** (X = Cl; R = 3-OMe)	**6n** (R^1 = OMe,R^2 = OEt, R = 3-OMe)	44 (57)

[a] **5** (1 equiv), *s*-BuLi (2.2 equiv, first installment), *s*-BuLi (3 equiv, second installment), aryl halide **3** (3 equiv) and T:E (1:1) (6 mL/mmol). [b] Isolated yield. [c] Yields shown in parentheses are calculated on the basis of recovered starting amine.

through reaction of Lewis acid complexed amines and *s*-BuLi (Scheme 1, eq 1), to arynes for synthesis of 1-aryl-*N*-methyl-1,2,3,4-tetrahydroisoquinolines[21] is currently being investigated. Furthermore, application of this methodology to obtain 1-aryl-2,3,4,5-tetrahydro-3-benzoazepines[13a,22] will be explored.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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