PREPARATION OF 1-AMINOISOQUINOLINES FROM THE REACTION OF 2-ARYLMETHYLBENZONITRILES AND LITHIUM DIISOPROPYL AMIDE

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Abstract 2-Arylmethyl-3,6-dimethylbenzonitriles, prepared by the arynic reaction of 2-bromo-1,4-dimethylbenzene and arylacetonitriles, undergo self-condensation when treated with LDA to supply 3,7,8-trisubstituted 1-aminoisoquinolines in good yields. The structure of one of these isoquinolines, i.e. 1-amino-8-(4'-methoxyphenylmethyl)-3-(2'-[4-methoxyphenylmethyl])-3',6'-dimethylphenyl)-7-methylisoquinoline was confirmed by x-ray diffractometry.

Introduction

We (2) reported recently that the reaction of 2-bromo-1,4-dimethylbenzene 1 with arylacetonitriles 2 and and lithium diisoproylamide (LDA) gave the corresponding 1,4,5,8-tetramethyl-10-arylanthrones imine 3 in fair to good yields (42-81%). The mechanism of this reaction most likely involves: (a) *in situ* preparation of α-lithiated arylacetonitriles 2' and 3,6-dimethylbenzyne 4 from the reaction of LDA with 2 and 1 respectively; (b) the subsequent reaction of the intermediates 2' and 4 to afford α-lithiated 2-arylmethylbenzonitriles 5' by a tandem addition-rearrangement pathway (3); and (c) the 4+2 cycloaddition of 5' with another molecule of 4 yielding the imines 3. We report herein the results of our attempts to determine if rearranged ions 5' are intermediates in the arynic imine synthesis as well as a new synthesis of novel 3,7,8-trisubstituted derivatives 1-aminoisoquinlolines, uncovered during the study.

Experimental

Melting points were determined on an electrothermal apparatus and are uncorrected. All glassware was dried prior to use and the reactions were carried out under a N_2 atmosphere. Nuclear magnetic resonance (NMR) spectra were determined on an IBM-Bruker WP 200-SY spectrometer; chemical shifts were related to tetramethyl-silane as an internal standard. All chemicals were purchased from Aldrich Chemical Company, except 5 , which were present from previous studies (4). The nitriles were distilled prior to use, butyllithium was used as received, and tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl.

General Procedure for the Reaction of 5 with LDA. In a flame-dried flask flushed with nitrogen, lithium diisopropylamide (LDA) was prepared by adding n-butyllithium (30 mmol, 2.5 M in hexane) to a solution of diisopropylamine (30 mmol) in 40 mL of tetrahydrofuran (THF) at -78 °C under a nitrogen atmosphere (septum cap technique). After 10 min at -78 °C, a solution of the appropriate 2-arylmethylbenzonitrile 5 (10 mmol) in THF (40 mL) was added dropwise over 20 min and the reaction mixture was then warmed to room temperature. At that time, the solution was quenched with methanol (2 mL), the THF was evaporated (rotatory evaporator), and the residue was extracted with CH_2Cl_2 (2 X 50 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated (rotatory evaporator) to provide solid, which was purified by flash column chromatography using a mixture of hexane/ethyl acetate (19:1 of 9:1, depending upon the polarity of the product) as eluent. The physical and spectral properties of the compounds isolated in pure form are shown below.

1-Amino-8-(4'-methoxyphenylmethyl)-3-(2'-[4-'methoxyphenylmethyl])-3',6'-dimethylphenyl)-7-methylisoquinoline 6a. mp 162-163 °C; NMR ($CDCl_3$) δ 2.18 (s, 3 H), 2.25 (s, 3 H), 2.44 (s, 3 H), 3.71 (s, 3 H), 3.82 (s, 3 H), 4.73 (s, 2 H), 5.09 (s, 2 H), 6.63-7.45 (m, 13 H). HRMS. Calcd for $C_{34}H_{34}N_2O_2$: 502.2620. Found ,502.2629.

1-Amino-8-(phenylmethyl)-3-(2'-[phenylmethyl])-3',6'-dimethylphenyl)-7-methylisoquinoline 6 b . mp 125-126°C; NMR ($CDCl_3$) δ 2.28 (s, 3 H), 2.33 (s, 3 H), 2.53 (s, 3 H), 4.85 (s, 2 H), 5.10 (s, 2 H), 6.63-7.45 (m, 15 H). HRMS: Calcd for $C_{33}H_{32}N_2$: 472.2620. Found ,472.2629.

1-Amino-8-(3'-methoxyphenylmethyl)-3-(2'-[3-methoxyphenylmethyl])-3',6'-dimethylphenyl)-7-methylisoquinoline 6c. mp 158-159. ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3 H), 2.25 (s, 3 H), 2.44 (s, 3 H), 3.71 (s, 3 H), 3.82 (s, 3 H), 4.73 (s, 2 H), 5.09 (s, 2 H), 6.63-7.45 (m, 13 H).HRMS. Calcd for $C_{34}H_{34}N_2O_2$: 502.2620,. Found , 502.2635.

1-Amino-8-(2'-methoxyphenylmethyl)-3-(2'-[2'--methoxyphenylmethyl])-3',6'-dimethylphenyl)-7-methylisoquinoline 6a. mp thick liquid; NMR ($CDCl_3$) δ 2.13(s, 3 H), 2.18 (s, 3 H), 2.30 (s, 3 H), 3.60 (s, 3 H), 3.96 (s, 3 H), 4.52 (s, 2 H), 5.09 (s, 2 H), 6.60-7.38 (m, 13 H). HRMS. Calcd for $C_{34}H_{34}N_2O_2$: 532.2620. Found , 532.2629.

Results

We attempted to determine if α-lithiated 2-arylmethylbenzonitriles 5' are intermediates in the arynic imine sytheses by generating aryne 4, by the reaction of 2-bromo-1,4-dimethylbenzene 1 in the presence of 5a', freshly prepared by the reaction of LDA and 2-(4'-methoxyphenylmethyl)-3,6-dimethylbenzonitrile 5a. However, the reaction did not afford the desired imine, but rather gave 1-amino-8-(4'-methoxyphenylmethyl)-3-(2'-[4-methoxy-phenylmethyl])-3',6'-dimethylphenyl)-7-methylisoquinoline 6a in 52 % yield. The structure of 6a was confirmed by X-ray crystallographic analysis (5); its ORTEP drawing is shown in Fig. 1.

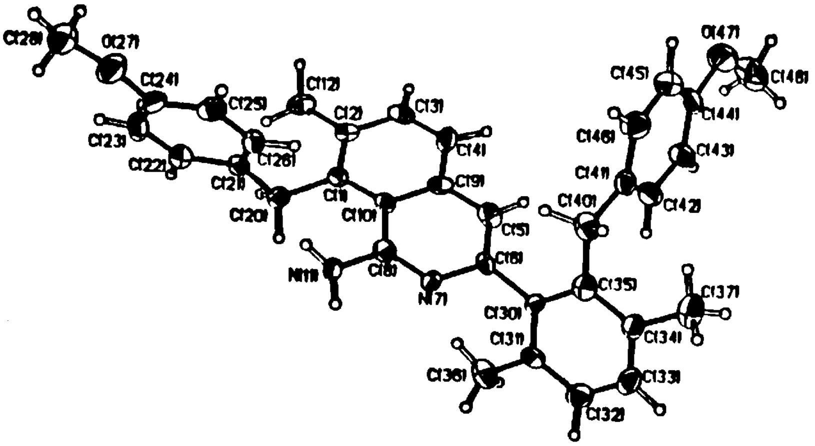
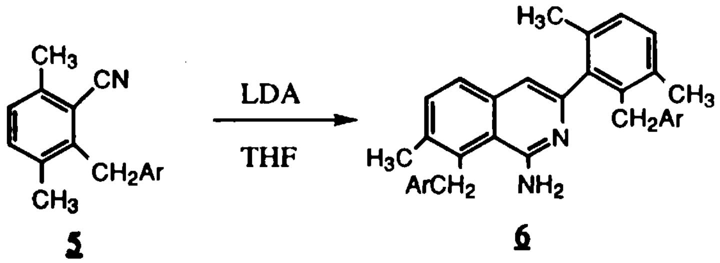


Figure 1. ORTEP Drawing of Compound 6a

Clearly, isoquinoline 6a, which is essentially a dimer of the benzonitrile 5a, was formed prior to the generation of aryne 4. Thus, we treated 5a and other 2-arylmethylbenzonitriles 5b-d with 2 equiv of LDA in the absence of the aryne precursor 1 and, as shown in eq. 1, obtained the corresponding 1-aminoisoquinolines 6a-d in 52-84% yields.



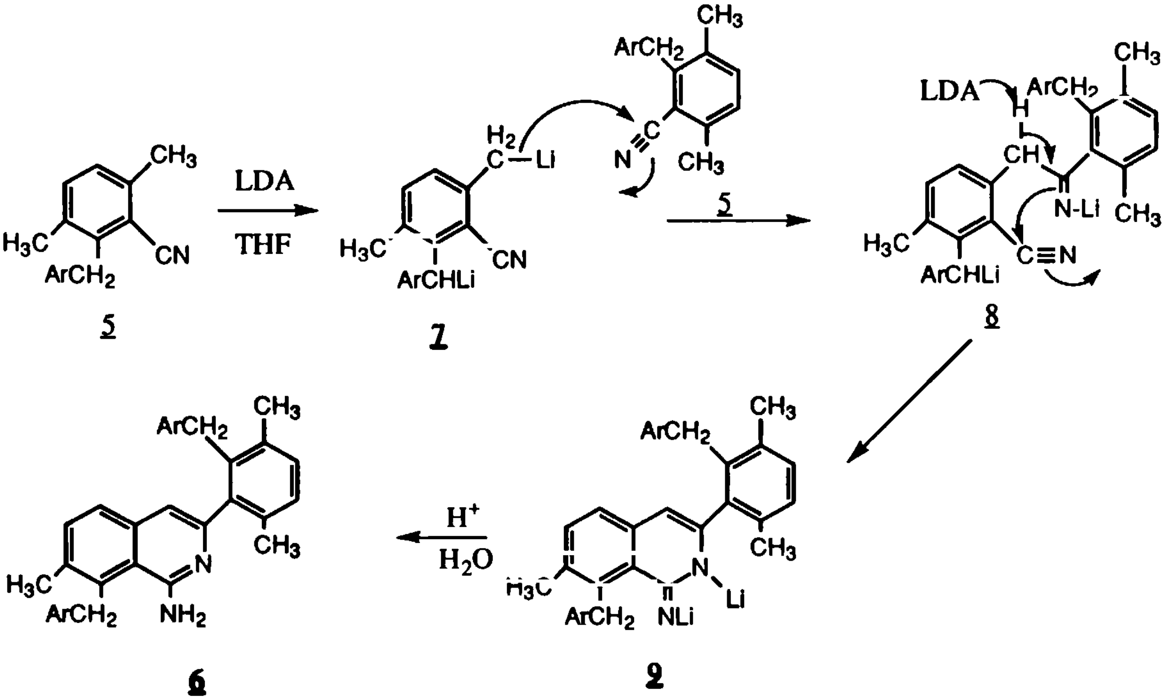
eq. 1

a.	$Ar = 4\text{-}CH_3O\text{-}C_6H_4\text{-}$	84%	c.	$Ar = 3\text{-}CH_3O\text{-}C_6H_4\text{-}$	63%
b.	$Ar = C_6H_5\text{-}$	77%	d.	$Ar = 2\text{-}CH_3O\text{-}C_6H_4\text{-}$	52%

Discussion

A possible pathway for the formation of 6 is shown in Scheme 1 . Thus, treatment of 5 with excess LDA gives the α-6-dilithiomethyl dianion 7 whose more nucleophilic 6-lithiomethyl group adds intermolecularly to the nitrile group in 5 (or its α-lithiated derivated 5a) affording the N-lithioimino derivative 8. For simplicity, only the addition to 5

Scheme 1



in Scheme 1. Tautomerization of the imino group of 8 yields the amino form 9 which upon acidic hydrolysis is is converted to 6. We assume that the CHArLi group is protonated by liberated diisopropylamine during the cyclization process since its basicity is substantially increased due to the loss of resonance stabilization previously provided by the reacted nitrile group.

Conclusions

We have reported herein a quick, convenient synthesis of novel trisubstituted 1-aminoisoquinolines from 3,6-dimethyl-2-arylmethylbenzonitriles 5, which can be easily prepared by the arynic tandem addition-rearrangement of commercially available 2-bromo-1,4-dimethylbenzene and arylacetonitriles (4). One of the most significant aspect of this synthetic methodology is that a cyano group is introduced ortho to a methyl group. This allows deprotonation of that methyl group, the crucial step in the synthetic pathway to 1-aminoisoquinolines. Interestingly, the parent dinitrile, α–cyano-o-tolunitrile, dimerizes to 1-amino-3-o-cyanobenzyl-4-cyanoisoquinoline in only 44% yield when treated with sodium methoxide in reluxing dimethyl sulfoxide for 2 h (6). We are presently investigating the scope of this reaction and the chemistry of the 1-aminoisoquinolines and will report the results in due course.

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5. A single crystal of 6a was found to be monoclinic with a $P2_1n$ space group. One molecule is found in the unit cellwith dimensions as follows: a = 12.754 (5), b = 7.436 (2), c = 28.839 (9) Å, β = 100.50 (3)°, and the volume = 2689 (4) $Å^3$. The calculated density is 1.24 $g\text{-}cm^3$. Of the 2657 data collected, 1253 observed reflections [2Θ 3.50-40.00°, $F_o > 3\sigma(F_o)$] were used in the solution and refinement of the structure. All non-hydrogen atoms were anisotropically refined. All the aromatic hydrogen atoms were refined with fixed U = 0.08 $Å^2$, while methyl and methylene H's were at calculated positions. The final values are: R = 0.048, wR = 0.058, GOF = 1.33 $\Delta\rho_{(max, min)}$ = 0.23, -0.23 $e.Å^{-3}$.

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