THE SYNTHESIS OF 1-AMINO-3,8-DIPYRIDYLMETHYL-7-METHYLISOQUINOLINE INVOLVING A TANDEM ADDITION REARRANGEMENT ARYNE REACTION

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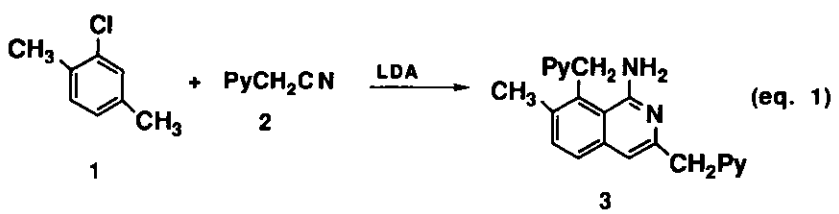
Abstract - The synthesis of 1-amino-3,8-dipyridylmethyl-7-methylisoquinoline (**3**) accomplished by the reaction of 2-chloro-1,4-dimethylbenzene with pyridylacetonitrile under aryne forming conditions is reported. A mechanism is suggested in which a cyano group is introduced ortho to one of the ring methyl groups via a tandem-addition rearrangement aryne process. Such positioning of the cyano group facilitates lithiation of the adjacent methyl group by stabilizing the resulting CH_2Li group by resonance delocalization. The CH_2Li group then reacts with another molecule of pyridylacetonitrile affording a cyano-imine intermediate which condenses intramolecularly to afford **3** after a successive tautomeric shift and proton quench.

INTRODUCTION

During the course of our studies on the effect of substituents on the competition between the usual aryne arylation and tandem-addition rearrangement aryne pathways,[1] we treated 2-chloro-1,4-dimethylbenzene (**1**) with pyridylacetonitrile (**2**) in the presence of lithium diisopropylamide (LDA). After the usual workup of the reaction mixture, a solid was obtained which was



(eq. 1)

identified as 1-amino-3,8-dipyridylmethyl-7-methylisoquinoline (**3**) on the basis of the usual spectrophotometric analysis (see experimental section). For example, the amino group in **3** was indicated by a characteristic ir NH stretching band at 3314 cm^{-1} and

a broad singlet at δ 6.49 in its ^{1}H nmr spectrum which disappeared upon the addition of D_2O. The ^{1}H and ^{13}C nmr spectra revealed that **3** exists in two distinct forms (perhaps amine-imine tautomers) in solution. Additionally, single-crystal analysis confirmed the structure of **3** whose ORTEP drawing is shown in Figure 1.[2] Particularly revealing in that figure is the intramolecular hydrogen-bonding bridging between one of the pyridyl ring nitrogen atoms and the 1-amino group.

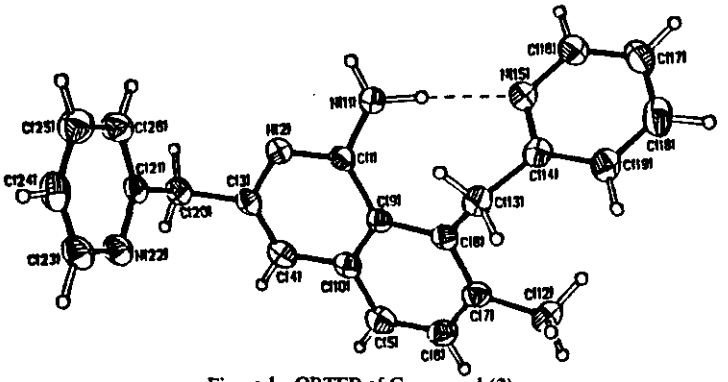


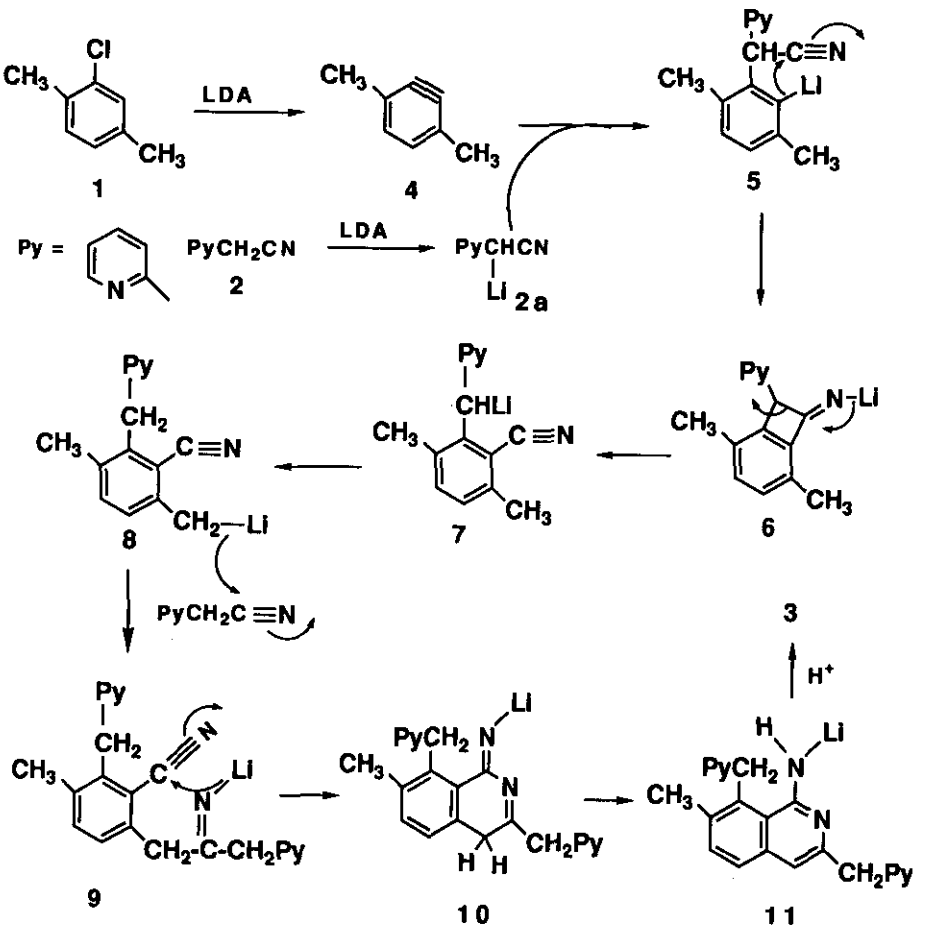
Figure 1. ORTEP of Compound (**3**)

Scheme 1 outlines a possible mechanism to account for the synthesis of **3**. As shown, 2-chloro-1,4-dimethylbenzene (**1**) reacts with LDA to yield 3,6-dimethylbenzyne (**4**), which undergoes nucleophilic addition by α–lithio-2-pyridylacetonitrile (**2a**) to yield adduct (**5**). Cyclization of **5** supplies the benzocyclobutanimine (**6**), which opens to the rearranged 2,4-dimethylbenzonitrile (**7**). The introduction of a cyano group enhances, by resonance, the acidity of the ortho methyl group to such an extent that the latter readily undergoes lithiation affording the lithiomethyl derivative (**8**), which reacts with pyridylacetonitrile yielding the cyano-imine derivative (**9**). Compound (**9**) then undergoes a imine-cyano intramolecular condensation to the iminium 1,4-dehydroisoquinoline compound (**10**), which upon aromatization to **11** followed by proton quench provides title compound (**3**). The tandem-addition rearrangement aryne (TARA) mechanism, which accounts for the conversion of **1** and **2** to the rearranged α–lithio rearranged species (**7**), was originally proposed by Meyers et al.[3] We subsequently proposed a similar TARA mechanism to account for the obtention of 2- arylmethyl -3,6-dimethylbenzonitriles from the reaction of **1** with arylacetonitriles.[4] The proposed cyano-imine condensation of **7** has literature precedent.[5]

The synthesis of the 1-aminoisoquinoline (**3**) involving an aryne intermediate is novel, and it may develop into a convenient synthesis of these potentially valuable heterocycles.

EXPERIMENTAL

General Aspects: ^{1}H and ^{13}C nmr spectra were measured in $CDCl_3$ solution on a WP 200-SY Bruker spectrometer. All chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Ir spectra were recovered on



Scheme 1

a Perkin-Elmer 283 grating spectrophotometer. Mass spectra (70eV) were obtained on a Hewlett-Packard Model 5988A chromatograph/mass spectrometer. E. Merck silica gel 9385 (230-400 mesh) was used for flash chromatography. Reported boiling points are uncorrected; melting points were determined on an electrothermal apparatus and are uncorrected. All reactions were carried out in flame-dried flasks under nitrogen atmosphere.

General Procedure for the Reaction of 2-Chloro-1,4-dimethylbenzene (1) with 2-Pyridylacetonitrile (2) and LDA. LDA was prepared in a flamed-dried flask flushed with nitrogen by adding diisopropylamine (0.181 g, 18 mmol) into a -78 °C solution of n-BuLi (15 mmol, 2.5M in hexane) in THF (25 ml) under nitrogen atmosphere (using septum cap technique). After stirring the solution for 10 min at -78 °C, 2-pyridylacetonitrile (2) (0.59 g, 5 mmol) in THF (25 ml) was added over a period of 10 min, and the resulting solution was warmed to -40 °C. Then 2-chloro-1,4-dimethylbenzene (1)

(0.71 g, 5 mmol) was added dropwise over 20 min at -40 °C. The reaction mixture was stirred for 10 more additional min, then the dark reddish brown solution was quenched with saturated aqueous ammonium chloride solution and allowed to warm to room temperature. The solvent was then removed (rotatory evaporator), and the residue was extracted with CH_2Cl_2. The solvent was removed, and the residue was washed with acetone to yield a crystalline solid (3) (440 mg, 52%), which was purified by recrystalli-zation from ethyl alcohol; mp 178-179 °C; ^{1}H nmr ($CDCl_3$) δ 2.31 (s, 3 H), 4.21 (s, 2 H), 4.73 (s, 2 H), 6.49 (br s, 2 H), 6.83 (s, 1 H), 7.02-7.63 (m, 8 H), 8.42-8.45 (m, 1 H), 8.51-8.54 (m, 1 H), 8.52 (m, 1 H); *ir* ν_{max} ($CHCl_3$) cm^{-1} 3314, 3144, 1466, 1376; ^{13}C nmr ($CDCl_3$) δ 20.70, 39.00, 46.41, 111.56, 118.61, 121.03, 121.30, 123.47, 123.95, 125.41, 132.68, 136.65, 135.08, 126.16, 136.89, 138.92, 149.13, 149.28, 157.43, 160.07, 160.33; Anal. Calcd for $C_{22}H_{20}N_4$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.82; H, 5.86; N, 16.64.

ACKNOWLEDGEMENTS

This work was sponsored in part by grants from the Welch Foundation, Houston, TX and the Donors of the Petroleum Research Foundation, administered by the American Chemical Society.

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2. X-ray data for 3: $C_{22}H_{20}N_4$, formula weight 340.43. Triclinic, space group $P\bar{1}$, $\alpha = 8.356$ (2), $\beta = 10.929$ (3), $\gamma = 10.995$ (3) Å, $\alpha = 65.91$ (2), $B = 72.38$ (2), $\gamma = 76.87$ (2)°, V = 867.5 (4) Å^3, $z = 2$, $D_c = 1.303$ g-cm^{-3}, $R = 0.030$, $Rw = 0.037$ for 1567 observed reflections [$I \geq 2\sigma(I)$]. Intensity data were collected on a *Nicolet R3m/v* diffractometer with graphite-monochromated Mo-$K\alpha$ radiation, $3.5 \geq 2\theta \geq 42.0$, $\theta/2\theta$ scan. The structure was solved by direct methods using *SHELXTL-Plus* program package (G. M. Sheldrick, *Structure Determination Software Packages*, Siemens Analytical X-Ray Instruments, Inc., USA, 1990) and anisotropically refined for all non H-atoms by full-matrix least-squares analysis. All H-atoms located from DF maps and refined isotropically. The isoquinolyl group, [C(1), N(2), and C(10), is basically planar with the mean deviation from the best plane of the 10 atoms 0.087 Å. Intramolecular hydrogen-bonding N(11) - H(11a) ···N(15) was found in the structure with the values of N(11) -0.985 Å, H(11a)···N(15) 1.989 Å, N(11) - H(11a)···N(15) 168.6°. Atomic coordinates, bond lengths and angles, thermal parameters and H-atom coordinates available upon request.
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Received, 2nd October, 1991