A FACILE SYNTHESIS OF 2-ARYL- AND 2-HETEROARYL-SUBSTITUTED 4-AMINOQUINOLINES

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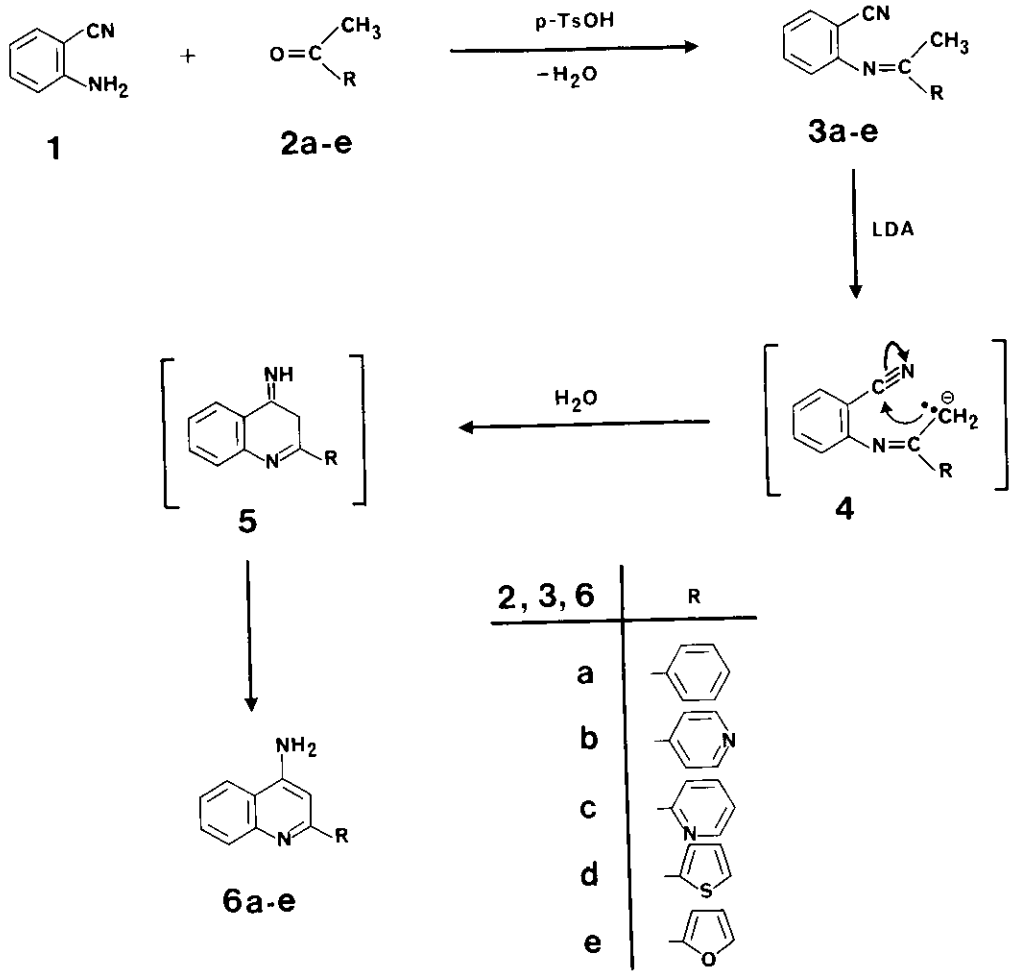
Abstract - Schiff's bases, obtained from 2-aminobenzonitrile and aryl or heteroaryl methyl ketones, are lithiated with lithium diisopropylamide at the methyl group. The intermediate carbanions undergo cyclization to a quinoline system in a high yield. The corresponding Schiff's base obtained from propiophenone undergoes an unusual addition reaction with the lithium reagent instead.

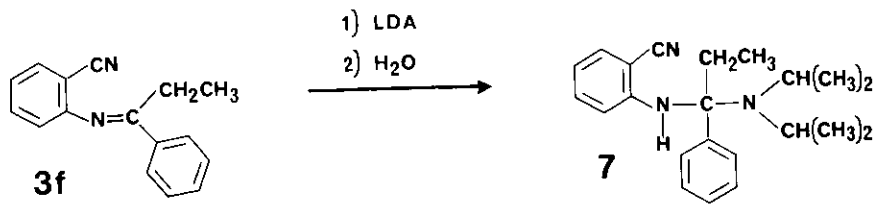
2-Aminobenzonitrile (**1**) is a versatile synthon for the construction of nitrogen heterocycles. The amino group of **1** is readily substituted with a number of electrophiles to form intermediate products that are cyclized in the reaction with organometallic and other nucleophilic reagents or under the conditions of general acid/base catalysis.[1] This approach has been used in the preparation of several quinazolines,[1-4] dihydroquinazolines,[2,3] benzodiazepinones,[5] quinolinones,[5,6] 2,4-diaminoquinolines,[7] 4-amino-2-methylquinolines,[6,8] and other closely related systems.[1,6,9-11]

In this paper we wish to report an additional, apparently overlooked application of the general synthetic strategy discussed above for the preparation of 2-aryl- and 2-heteroaryl-substituted 4-aminoquinolines **6** (Scheme 1). Our synthetic route to **6** involves condensation of **1** with methyl ketones **2** to form Schiff's bases **3** as single E-diastereomers,[12] followed by lithium diisopropylamide-induced cyclization of **3**. The two-step method is experimentally simple and efficient. Moreover, this synthetic route is superior to a non-related approach[13] used previously for synthesis of the first two members of the series, **6a** and **6b**.

Mechanistic studies of the cyclization reaction have been conducted with the Schiff's base **3a** obtained from **1** and acetophenone. Treatment of **3a** with LDA at -78°C followed by quenching of the mixture with D_2O produced traces of quinoline **6a** and a high yield of **3a** mono-deuterated at the methyl group. When the mixture was allowed to stand at 20°C before quenching, the quinoline **6a** was obtained in a high yield as a sole low-molecular weight product. These results demonstrate that the lithiation reaction of **3a** with LDA to produce anion **4** is relatively fast in comparison to the subsequent cyclization of the anion **4**. The slow cyclization must be attributed to steric effects in **4** which do not favor the conformation with the



Scheme 1



Scheme 2

anionic methylene and the cyano group in close proximity. Aminoquinolines **6** are apparently produced through isomerization of the intermediate imino-tautomers **5**. Thus, two major products were observed by TLC for all reaction mixtures immediately after quenching. If the quenched mixture was allowed to stand before the TLC analysis, an increasing intensity of the spot corresponding to **6** was observed at the expense of the other one. Preparative chromatography gave only **6**.

In an attempt to synthesize a 3-methyl-substituted analogue of **6a**, compound **1** was condensed with propiophenone, and the resultant Schiff's base **3f** (obtained as a mixture of E- and Z-diastereomers in the ratio of 9:1) was treated with LDA (Scheme 2). To our astonishment the only product isolated in a high yield was the adduct **7**. Moreover, quenching of the reaction between **3f** and LDA with D_2O did not produce deuterated **3f** regardless of the conversion level of **3f** into **7**, as shown by analysis of ^{1}H-nmr and mass spectra of the recovered starting material. We have thus shown that Schiff's bases obtained from **1** and methyl ketones are lithiated at the methyl group upon treatment with LDA, while the more sterically hindered ethyl derivative **3f** undergoes an addition reaction with the same reagent.[14] Both the kinetic and thermodynamic factors may be responsible for the apparent lack of lithiation of **3f**. First, the methylene portion of **3f** is less accessible to the base than the methyl group of **3a**. Second, the corresponding anion that would be derived from **3f** in an apparently reversible reaction is expected to be thermodynamically less stable than the anion **4**. We also suggest that the relief of steric strain[12] within the carbon-nitrogen double bond of **3f** is a partial driving force for the observed addition reaction.

EXPERIMENTAL SECTION

All experiments with lithium diisopropylamide were conducted under a nitrogen atmosphere and with ethyl ether distilled from sodium benzophenone ketyl immediately before use. Melting points (Pyrex capillary) are uncorrected. Mass spectra (70 eV) and ir spectra were recorded on a Varian MAT spectrometer and a Bomem Michelson-100 instrument, respectively. Proton nmr spectra including NOE spectra were obtained on a Varian VXR-400 (400 MHz) spectrometer. The spectra were taken at 25°C in $CDCl_3$ solutions (0.05 M) with Me_4Si as an internal standard. The chemical shift assignments were obtained using 1D NOE, 1D decoupling, and 2D COSY experiments. In the description of the nmr spectra the abbreviations Quin, Py, Th, Fur, and Ph stand for quinolyl, pyridyl, thienyl, furyl, and phenyl, respectively. Estimated errors for the reported chemical shifts and coupling constants are ±0.005 ppm and ±0.4 Hz, respectively. The coupling constants smaller than 1.2 Hz are not reported. The NOE experiments were also conducted to determine E/Z

stereochemistry of Schiff's bases **3a-f**. Thus, irradiation of the methyl group in **(E)-3a-e** gave strong NOE to the adjacent ortho protons of the aromatic (heteroaromatic) substituent and to H-3 of the benzonitrile. A similar result was obtained upon irradiation of the methylene of **(E)-3f**. In contrast, the same experiment with the Z diastereomer of **3f** gave NOE to the adjacent ortho protons only.

Synthesis of Schiff's bases 3a-f: General procedure

A mixture of 2-aminobenzonitrile (**1**, 5g, 42.3 mmol), a methyl ketone **2** (85 mmol), a catalytic amount of p-toluenesulfonic acid, and toluene (150 ml) was heated under reflux for 10 h with azeotropic removal of water. The mixture was then cooled to 20°C, washed with a solution of $NaHCO_3$, and dried over Na_2SO_4. Removal of the toluene and ketone **2** under reduced pressure was followed by crystallization of the resultant Schiff's base **3** from ethyl ether/hexanes.

(E)-2-[(1-Phenylethylidene)amino]benzonitrile (**3a**, from **1** and acetophenone): yield 87%; mp 68-69°C. Ms, m/z 77(25), 102(28), 143(18), 205(100), 220(54, M+). FT-ir (film) 1637, 2224 cm^{-1}. Nmr δ 2.30 (s, CH_3), 6.91 (d, J=8 Hz, H3 of PhCN), 7.16 (t, J=8Hz, H5 of PhCN), 7.45-7.50 (m, H3, H4, and H5 of Ph), 7.56 (t, J=8 Hz, H4 of PhCN), 7.65 (d, J=8 Hz, H6 of PhCN), 8.02 (d, J=7 Hz, H2 and H6 of Ph). Anal. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49. Found: C, 81.70; H, 5.55.

(E)-2-[[(1-(4-Pyridyl)ethylidene]amino]benzonitrile (**3b**, from **1** and 4-acetylpyridine): yield 83%; mp 78-80°C. Ms, m/z 206(100), 221(50, M+). FT-ir (nujol) 1625, 2205 cm^{-1}. Nmr δ 2.30 (s, CH_3), 6.91 (d, J=8 Hz, H3 of PhCN), 7.21 (t, J=8 Hz, H5 of PhCN), 7.59 (t, J=8 Hz, H4 of PhCN), 7.68 (d, J=8 Hz, H6 of PhCN), 7.84 (d, J=4.5 Hz, H3 and H5 of Py), 8.77 (d, J=4.5 Hz, H2 and H6 of Py). Anal. Calcd for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01. Found: C, 76.05; H, 5.03.

(E)-2-[[(1-(2-Pyridyl)ethylidene]amino]benzonitrile (**3c**, from **1** and 2-acetylpyridine): yield 79%; mp 79-80°C. Ms, m/z 78(31), 102(39), 143(100), 180(42), 206(24), 221(78, M+). FT-ir (nujol) 1630, 2210 cm^{-1}. Nmr δ 2.40 (s, CH_3), 6.92 (d, J=8 Hz, H3 of PhCN), 7.18 (t, J=8 Hz, H5 of PhCN), 7.41 (d of d, J=8 Hz, J=5 Hz, H5 of Py), 7.57 (t, J=8 Hz, H4 of PhCN), 7.67 (d, J=8 Hz, H6 of PhCN), 7.81 (t, J=8 Hz, H4 of Py). 8.33 (d, J=8 Hz, H3 of Py) 8.68 (d, J=5 Hz, H6 of Py). Anal. Calcd for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01. Found: C, 75.82; H, 5.04.

(E)-2-[[(1-(2-Thienyl)ethylidene]amino]benzonitrile (**3d**, from **1** and 2-acetylthiophene): yield 76%; mp 85-87°C. Ms, m/z 211(100), 226(44, M+). FT-ir (nujol) 1635, 2220 cm^{-1}. Nmr δ 2.29 (s, CH_3), 6.92 (d, J=8 Hz, H3 of PhCN), 7.11 (d of d, J=5 Hz, J=4 Hz, H4 of Th), 7.15 (t, J=8 Hz, H5 of PhCN), 7.52-7.57 (m, H4

of PhCN, H3 of Th, H5 of Th), 7.63 (d, J=8 Hz, H6 of PhCN). Anal. Calcd for $C_{13}H_{10}N_2S$: C, 68.98; H, 4.46. Found: C, 69.08; H, 4.46.

(E)-2-[[(1-(2-Furyl)ethylidene]amino]benzonitrile (**3e**, from **1** and 2-acetylfuran): yield 75%; mp 50-51°C. Ms, m/z 102(22), 195(100), 210(72, M+). FT-ir (film) 1620, 2210 cm^{-1}. Nmr δ 2.19 (s, CH_3), 6.55 (d of d, J=4 Hz, J=2 Hz H4 of Fur), 6.92 (d, J=8 Hz, H3 of PhCN), 7.07 (d, J=4 Hz, H3 of Fur), 7.15 (t, J=8 Hz, H5 of PhCN), 7.54 (t, J=8 Hz, H4 of PhCN), 7.59 (d, J=2 Hz, H5 of Fur), 7.62 (d, J=8 Hz, H6 of PhCn). Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79. Found: C, 74.20; H, 4.81.

2-[(1-Phenylpropylidene)amino]benzonitrile (**3f**, obtained from **1** and propiophenone as a mixture of E- and Z-diastereomers in the ratio of 9:1): yield 67%; mp 74-75°C. Ms m/z 77(23), 102(21), 205(100), 234(32, M+). FT-ir (nujol) 1635, 2220 cm^{-1}. Nmr for the major E-isomer: δ 1.11 (t, J=7 Hz, CH_3), 2.66 (q, J=7 Hz, CH_2), 6.89 (d, J=8 Hz, H3 of PhCN), 7.15 (t, J=8 Hz, H5 of PhCN), 7.45-7.52 (m, H3, H4, and H5 of Ph), 7.55 (t, J=8 Hz, H4 of PhCN), 7.65 (d, J=8 Hz, H6 of PhCN), 7.97 (d, J=8 Hz, H2 and H6 of Ph). Nmr for the minor Z-isomer: δ 1.23 (t, J=7 Hz, CH_3), 3.03 (q, J=7 Hz, CH_2), 6.73 (t, J=8 Hz, H5 of PhCN), 6.74 (d, J=8 Hz, H3 of PhCN), 7.32 (t, J=8 Hz, H4 of PhCN), 7.39 (d, J=8 Hz, H6 of PhCN), 7.45-7.52 (m, H3, H4, and H5 of Ph), 7.99 (d, J=8 Hz, H2 and H6 of Ph). Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.94; H, 6.08; N, 11.90. When a solution of this sample in $CDCl_3$ was allowed to stand at 20°C, an increasing amount of the Z-isomer was observed by nmr. The equilibrium with E:Z=2:1 was reached after several weeks.

Synthesis of quinolines 6a-e: General procedure.

n-Butyllithium (1.6 M in hexanes, 1.8 ml, 2.9 mmol) was added dropwise at -10°C to a solution of diisopropylamine (1 ml, 7.2 mmol) in ethyl ether (30 ml). The mixture was stirred at -10°C for 10 min and then cooled to -60°C and treated dropwise with a solution of Schiff's base **3** (1.5 mmol) in ethyl ether (5 ml). With continuous stirring the temperature was allowed to reach 20°C within 30 min. After 4 h of stirring at 20°C the mixture was quenched with H_2O (10 ml) and extracted with ethyl ether (3x50 ml). The ether was dried (Na_2SO_4) and evaporated. Crude **6** was purified by flash chromatography on silica gel (EtOH/NEt_3/CH_2Cl_2, 1:2:2) followed by crystallization from ethanol/hexanes.

4-Amino-2-phenylquinoline (**6a**): yield 82%; mp 163-165°C (reported[13] mp 162-166°C).

4-Amino-2-(4-pyridyl)quinoline (**6b**): yield 91%; mp 228-234°C (reported[13] mp 223-230°C).

4-Amino-2-(2-pyridyl)quinoline (**6c**): yield 67%; mp 216-219°C. Ms m/z 221 (100, M+). Nmr δ 4.81 (br s, exchangeable with D_2O, NH_2), 7.33 (d of d, J=8 Hz, J=4.5 Hz, H5 of Py), 7.47 (t, J=8 Hz, H6 of Quin),

7.68 (t, J=8 Hz, H7 of Quin), 7.79 (d, J=8 Hz, H5 of Quin), 7.80 (s, H3 of Quin), 7.85 (t, J=8 Hz, H4 of Py), 8.10 (d, J=8 Hz, H8 of Quin), 8.62 (d, J=8 Hz, H3 of Py), 8.70 (d, J=4.5 Hz, H6 of Py). Anal. Calcd for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01. Found: C, 76.04; H, 5.04.

4-Amino-2-(2-thienyl)quinoline (6d): yield 86%; mp 163-165°C. Ms m/z 226 (100, M+). Nmr δ 4.72 (br s, exchangeable with D_2O, NH_2), 7.04 (s, H3 of Quin), 7.13 (d of d, J=5.2 Hz, J=3.6 Hz, H4 of Th), 7.39-7.43 (m, H6 of Quin and H5 of Th), 7.62-7.66 (m, H7 of Quin and H3 of Th), 7.71 (d, J=8 Hz, H5 of Quin), 8.01 (d, J=8 Hz, H8 of Quin). Anal. Calcd for $C_{13}H_{10}N_2S$: C, 68.99; H, 4.45. Found: C, 68.91; H, 4.46.

4-Amino-2-(2-furyl)quinoline (6e): yield 76%; mp 155-157°C. Ms m/z 182(55), 210 (100, M+). Nmr δ 4.74 (br s, exchangeable with D_2O, NH_2), 6.56 (d of d, J=3.5 Hz, J=2 Hz, H4 of Fur), 7.08 (s, H3 of Quin), 7.15 (d, J=3.5 Hz, H3 of Fur), 7.42 (t, J=8 Hz, H6 of Quin), 7.58 (d, J=2 Hz, H5 of Fur), 7.65 (t, J=8 Hz, H7 of Quin), 7.72 (d, J=8 Hz, H5 of Quin), 8.04 (d, J=8 Hz, H8 of Quin). Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79. Found: C, 74.15; H, 4.83.

2-(1-Diisopropylamino-1-phenylpropylamino)benzonitrile (7)

A mixture of LDA (2.9 mmol, prepared as described above) and Schiff's base **3f** (351 mg, 1.5 mmol) in ethyl ether (35 ml) was allowed to react at -78°C for 2 h, and then quenched with a solution of water (0.5 ml) in tetrahydrofuran (2 ml). Chromatography on silica gel (hexanes/NEt_3/EtOH, 7/2/1) gave 463 mg (92%) of **7** as a viscous, colorless oil. Ms m/z 264(26), 306(100), 307(22), 334(2), 335 (1, M+). FT-ir (film) 2212, 3384 cm^{-1}. Nmr δ 0.88 (t, J=7.4 Hz, CH_3 of ethyl), 1.32 (d, J=7 Hz, CH_3 of isopropyl), 1.90 (m, 1H, J=14 Hz, J=7.4 Hz, CH_2), 2.01 (m, 1H, J=14 Hz, J=7.4 Hz, CH_2), 3.74 (septet, J=7 Hz, CH of isopropyl), 4.32 (br s, NH), 6.59 (t, J=8 Hz, H5 of PhCN), 6.62 (d, J=8 Hz, H3 of PhCN), 7.09 (t, J=8 Hz, H4 of PhCN), 7.12 (t, J=7.5 Hz, H4 of Ph), 7.20 (d, J=8 Hz, H6 of PhCN), 7.23 (t, J=7.5 Hz, H3 and H5 of Ph), 7.42 (d, J=7.5 Hz, H2 and H6 of Ph). Anal. Calcd for $C_{22}H_{29}N_3$: C, 78.76; H, 8.71; N, 12.53. Found: C, 78.61; H, 8.79; N, 12.41.

Reactivities of 3a and 3f toward LDA.

Two identical solutions of LDA (2.9 mmol) in ethyl ether (30 ml) were prepared as described above and kept at -78°C. One solution was treated with **3a** (1.5 mmol in 5 ml of ether), and the other one with **3f** (1.5 mmol in 5 ml of ether). The mixtures were allowed to react at -78°C for 30 min, and then quenched with D_2O (0.5 ml) in dry tetrahydrofuran (2 ml). The components were separated by chromatography and analyzed by ms.

The reaction of 3a: **3a**-d_1 (64%) and **3a** (34%), obtained as a mixture. Quinoline **6a** was not found.

The reaction of 3f: **7** (after treatment with H_2O to exchange D for H at the nitrogen, 85%) and **3f** (13%). The treatment of **3a** with LDA for 2 h at -78°C followed by quenching with D_2O produced quinoline **6a** (<5%) and **3a**-d_1 of about 90% isotopic purity: Ms m/z 143(2, **3a** - Ph), 144 (17, **3a**-d_1 - Ph), 205(100, **3a** - CH_3 and **3a**-d_1 - CH_2D), 220(6, M+ for **3a**), 221(53, M+ for **3a**-d_1).

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