# SYNTHESIS AND BASICITY OF 4-(*N,N*-DIMETHYLAMINO)-2-ARYLQUINAZOLINES

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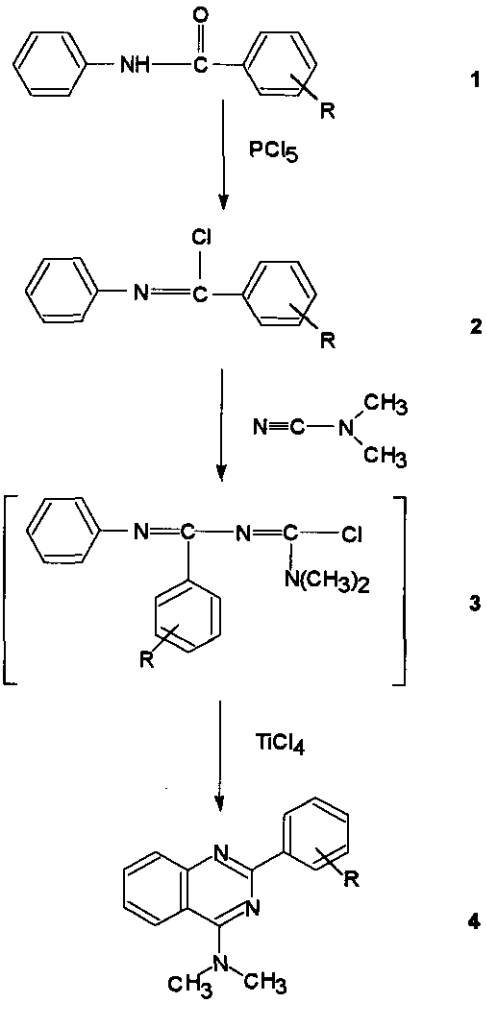
**Abstract**- The reaction of substituted *N*-phenylbenzimidoyl chlorides with *N,N*-dimethylcyanamide in the presence of titanium tetrachloride has yielded seven 4-(*N,N*-dimethylamino)-2-arylquinazolines substituted on the phenyl ring with electron donating or withdrawing groups. pKa values have been determined for these compounds and analyzed in conjunction with the Hammett σ constants to observe the influence of these phenyl substituents upon the basicity of 4-(*N,N*-dimethylamino)-2-arylquinazolines. The ρ value, single crystal X-ray analysis and $^{15}$N-nmr spectra give evidence about the preferential site of protonation in such systems.

Quinazolines play an important role in metabolism of living organisms.[1] Synthetic quinazoline derivatives may also exhibit a biological activity due to acid-base interactions which is in addition to behaviour associated with their permeability through cell membranes or their spatial structures.[1] Theoretically, 4-aminoquinazolines have three potential sites of protonation, but the relative basicities of these sites have not been established. In order to identify which site is more susceptible to protonation, we have proceeded in two ways. Analysis of basicity influenced by substituents on the phenyl ring attached to the 2 position of the quinazoline ring constitutes an indirect approach whereas single crystal X-ray analysis of a protonated 4-(*N,N*-dimethylamino)-2-arylquinazoline and $^{15}$N-nmr analysis represent direct solid state and solution approaches.

The indirect approach required 4-(*N,N*-dimethylamino)-2-arylquinazoline derivatives (**4**) substituted at the meta and para positions of the phenyl ring with a range of electron donating and withdrawing substituents (Scheme 1). Literature preparations of 4-aminoquinazoline normally proceed *via* exchange reactions at the 4 position.[1-3] However the reaction of *N*-phenylbenzimidoyl chlorides (**2**) with *N,N*-dimethylcyanamide in the presence of titanium tetrachloride as a catalyst leads to 4-(*N,N*-dimethylamino)-2-arylquinazolines (**4**). This method is based on the Meerwein method for preparation of 2,4-diphenylquinazoline from *N*-phenylbenzimidoyl chloride and benzonitrile[4] which has also been modified for use in the synthesis of 4-aminoquinazolines substituted at the 6 and 7 positions.[5]

Scheme 1




1

2

3

4

R = H, $OCH_3$, $CH_3$, Cl, $NO_2$.

*N*-Phenylbenzimidoyl chlorides (**2**) were obtained in near quantitative yields from the corresponding benzanilides (**1**) upon reaction with $PCl_5$. These were reacted with *N,N*-dimethylcyanamide to yield a linear intermediate product[5] (**3**) which undergoes cyclization to a quinazoline derivative with the use of the Lewis acid catalyst, $TiCl_4$. After several hours of heating in benzene a highly stable quinazoline-$TiCl_4$ complex was isolated. This comlex may be broken with the use of concentrated acid solution, however difficulties with the separation of the quinazoline derivative from post-reaction mixture aversely affect product yield. Products were identified using elementary analysis, mass spectrometry, nuclear magnetic resonance and electronic spectroscopy uv.

Table 1. Characteristics of 4-(*N,N*-dimethylamino)-2-arylquinazolines

| Product | R | Yield [a] | mp [°C] | $R_f$ [b] | pKa |
|---|---|---|---|---|---|
| 4a | H | 78.0 [c] | 67-69 | 0.53 | 6.31 ∓ 0.07 |
| 4b | *p*-$OCH_3$ | 55.0 | 101-102 | 0.66 | 6.62 ∓ 0.05 |
| 4c | *p*-$CH_3$ | 51.0 | 149-150 | 0.73 | 6.40 ∓ 0.08 |
| 4d | *p*-Cl | 65.0 | 141-142 | 0.77 | 5.88 ∓ 0.09 |
| 4e | *p*-$NO_2$ | 12.0 | 154-155 | 0.74 | 4.52 ∓ 0.01 |
| 4f | *m*-$CH_3$ | 50.0 | 75-77 | 0.50 | 6.28 ∓ 0.06 |
| 4g | *m*-Cl | 48.0 | 59-60 | 0.70 | 5.54 ∓ 0.05 |
| 4h | *m*-$NO_2$ | 17.0 | 112-115 | 0.71 | 4.94 ∓ 0.02 |

a) Yield in respect to original anilide

b) Tlc; silica gel; 3:1 [v/v] benzene/ethyl acetate

c) ref. [11] mp 66-68°C.

Table 2. Spectroscopic analysis of 4-(*N,N*-dimethylamino)-2-arylquinazolines

| Product | Uv ( methanol- water ) | | | $^1$H-Nmr ($CDCl_3$-TMS) |
|---|---|---|---|---|
| | med. | λmax [nm] ($\varepsilon\times10^{-3}$) | | δ [ppm] |
| 4a | acidic | 270 (41.35) | 334 (18.42) | 3.40 [s, 6H, $N(CH_3)_2$]; |
| | basic | 254 (37.59) | 336 (19.54) | 7.31-8.57 [m, $9H_{ar}$] |
| 4b | acidic | 300 (35.88) | 313 (33.59) | 3.40 [s, 6H, $N(CH_3)_2$]; 3.85 [s, 3H, $OCH_3$] |
| | basic | 285 (34.35) | 325 (19.08) | 6.90-8.55 [m, $8H_{ar}$] |
| 4c | acidic | 282 (37.08) | 326 (20.42) | 2.45 [s, 3H, $CH_3$]; 3.45 [s, 6H, $N(CH_3)_2$]; |
| | basic | 265 (35.41) | 332 (18.33) | 7.25-8.55 [m, $8H_{ar}$] |
| 4d | acidic | 279 (44.22) | 330 (20.32) | 3.40 [s, 6H, $N(CH_3)_2$]; |
| | basic | 275 (38.64) | 331 (17.93) | 7.35-8.65 [m, $8H_{ar}$] |
| 4e | acidic | 283 (32.92) | 342 (20.83) | 3.45 [s, 6H, $N(CH_3)_2$]; |
| | basic | 279 (27.92) | 350 (18.33) | 7.30-8.80 [m, $8H_{ar}$] |
| 4f | acidic | 275 (27.30) | 330 (11.62) | 2.45 [s,3H, $CH_3$]; 3.45 [s, 6H, $N(CH_3)_2$]; |
| | basic | 258 (27.86) | 332 (10.73) | 7.30-8.60 [m, $8H_{ar}$] |
| 4g | acidic | 270 (38.62) | 332 (18.27) | 3.40 [s, 6H, $N(CH_3)_2$]; |
| | basic | 256 (36.55) | 330 (17.93) | 7.30-8.55 [m, $8H_{ar}$] |
| 4h | acidic | 260 (24.05) | 328 ( 6.84) | 3.40 [s, 6H, $N(CH_3)_2$]; |
| | basic | 255 (29.37) | 331 ( 6.12) | 7.30-8.55 [m, $8H_{ar}$] |

Due to the low solubilites of 4-(*N,N*-dimethylamino)-2-arylquinazolines in water, $pKa_1$ values were determined in a 50% solution of aqueous methanol at 20.0 ± 0.1°C. Uv measurements were made on $10^{-5}$ M solutions using the spectrophotometric methods of Albert and Serjeant.[6] Absorption maxima of the quinazoline ions ($E_2$ and B bands) were selected as analytical wavelengths, bearing in mind their considerable shifts relative to the maxima of the non-protonated forms[7] (Table 2).

Table 3. Results of elementary analysis and mass spectrometry

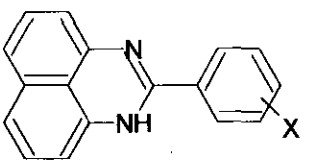
| Product | Molecular formula | Calculated | | | Found | | | MS ( 70 ev ) |
|---|---|---|---|---|---|---|---|---|
| | | %C | %H | %N | %C | %H | %N | m/z ( intensity % ) |
| 4a | $C_{16}H_{15}N_3$ | 77.07 | 6.07 | 16.84 | 77.11 | 6.02 | 16.87 | 249 (80.1) |
| 4b | $C_{17}H_{17}N_3O$ | 73.09 | 6.15 | 15.03 | 72.58 | 6.28 | 14.84 | 279 (56.4) |
| 4c | $C_{17}H_{17}N_3$ | 77.53 | 6.52 | 15.95 | 76.95 | 6.58 | 15.63 | 263 (54.0) |
| 4d | $C_{16}H_{14}N_3Cl$ | 67.66 | 4.98 | 14.80 | 67.67 | 5.02 | 14.71 | 283 (52.0) |
| 4e | $C_{16}H_{14}N_4O_2$ | 65.23 | 4.80 | 19.02 | 64.33 | 4.94 | 18.52 | 293 (16.4) |
| 4f | $C_{17}H_{17}N_3$ | 77.53 | 6.52 | 15.95 | 77.35 | 6.55 | 15.77 | 263 (22.4) |
| 4g | $C_{16}H_{14}N_3Cl$ | 67.66 | 4.98 | 14.80 | 67.51 | 5.10 | 14.68 | 283 (45.8) |
| 4h | $C_{16}H_{14}N_4O_2$ | 65.23 | 4.80 | 19.02 | 64.56 | 4.70 | 18.93 | 294 (24.6) |

Our studies show that the donosicity of the substituent in the meta or para position of the phenyl ring in 4-(*N,N*-dimethylamino)-2-arylquinazoline greatly affects pKa values. Donor substituents cause an increase in basicity (higher pKa values) compared with pKa of the original arrangement (R=H) and withdrawing substituents cause a decrease (lower pKa values).

The dissociation constants determined, $pKa_1$, correlated well with appropriate Hammett $\sigma_m$ and $\sigma_p$ constants[8] ( *Equation*: $pKa_1 = -1.8794*\sigma + 6.1824$; *Number of data points used:* N = 8; *Residual sum of squares*: S=0.0994; *Coefficient of determination:* r = 0.9745 ).

*Aminoquinazolines* have three sites, hence, three pKa values ought to be observable: $pKa_1$ and $pKa_2$ for the two endocyclic nitrogen atoms and $pKa_3$ for the exocyclic amine nitrogen atom substituted at the 4 position. The similarity of ρ reaction parameters for the 4-(*N,N*-dimethylamino)-2-arylquinazoline derivatives (ρ=1.88) and amidine structure (**5**)[9] (ρ=1.92) indicate that one of the endocyclic nitrogen atoms is the protonation centre.

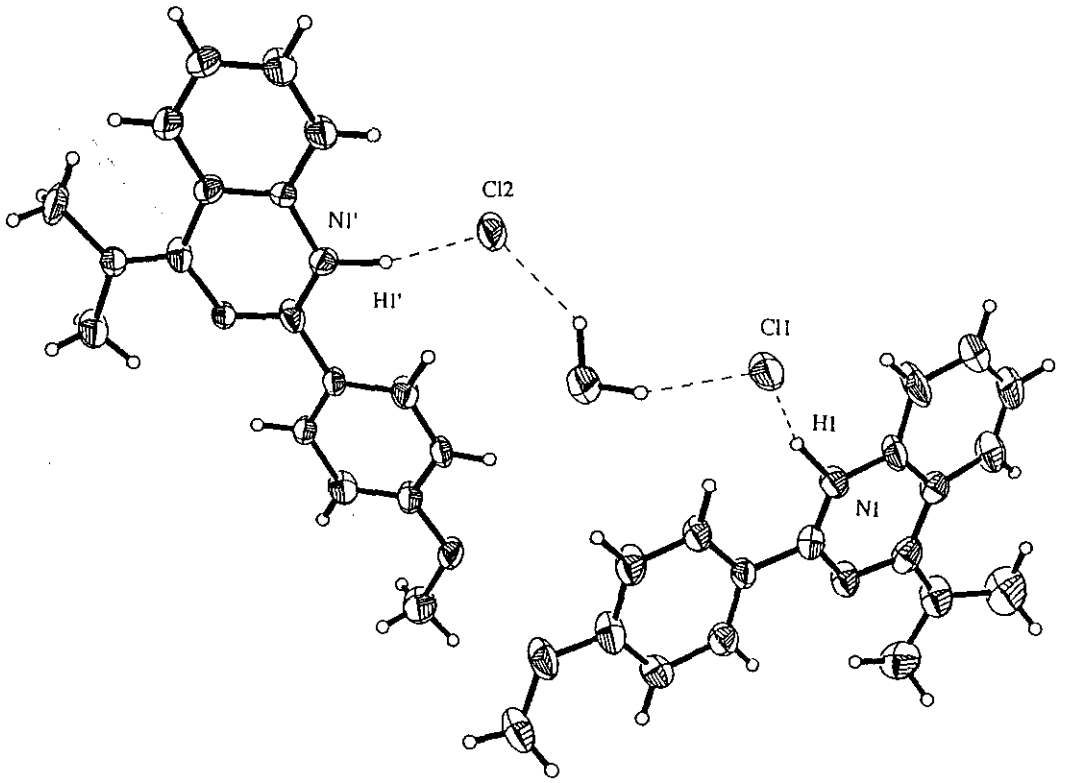
Scheme 2.




**5**

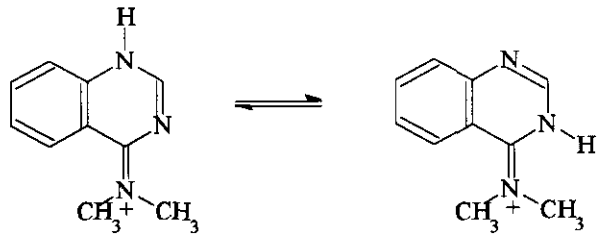
To decide which ring nitrogen atom is protonated, we have carried out single crystal X-ray diffraction analysis[10] of 4-(*N,N*-dimethylamino)-2-(4-methoxyphenyl)quinazoline hydrochloride and observed that the protonation occurs on the nitrogen atom at the 1 position. The material crystallizes with two organic molecules, two ionic HCl units and one water molecule per asymmetric unit in a cell of monoclinic symmetry. Detailes of bonding are substantially the same for the two independent molecules. Hydrogens associated with the water molecule and with the HCl unit were located from a difference Fourrier synthesis. The N1 and N1′ nitrogen atoms are clearly protonated. The water molecule included in the crystalline lattice participates in a network of hydrogen bonding linking two organic molecules and two HCl molecules ( N1--H--Cl--H-O-H--Cl--H--N1′ ) [ N1--H1 1.210(3)Å; H1--Cl1 2.000(3)Å; Cl1--$H_{HOH}$ 2.367(3)Å; $H_{HOH}$--O 1.133(3)Å; O--$H_{HOH}$ 1.127(3)Å; $H_{HOH}$--Cl2 2.232(3)Å; Cl2--H1′ 1.999(3)Å; H1′--N1′ 1.210(3)Å ](Scheme 3). There is no hydrogen bonding interaction involving the second endocyclic nitrogen atom, N3 or N3′ or the exocyclic nitrogen atom, N11 or N11′.

Scheme 3.



However, $^{15}$N-nmr measurements of 4-(*N,N*-dimethylamino)-2-phenylquinazoline trifluorineacetate indicate that the protonation process is more dynamic. Spectral analysis indicates that there is a fast hydrogen exchange between the two endocyclic nitrogen atoms and that possitive charge is concentrated on the exocyclic nitrogen atom of the dimethylamino group. In the $^{1}$H-nmr spectrum, an N-H signal is observed at 11.3 ppm. The coupling constant ($J_{^{15}N-^{1}H}$=5Hz) between the exocyclic nitrogen atom and a hydrogen atom in the $^{15}$N-nmr also testifies to the occurance of only a weak hydrogen bond involving this nitrogen atom.[11] Thus structures (**6a**) and (**6b**) (Scheme 4) dominate.

Scheme 4.



**6a** **6b**

This observation is in contrast to the protonation preference observed in 4-aminopyrimidine salts.[12]

## EXPERIMENTAL

### Synthesis of 4-(*N,N*-dimethylamino)-2-arylquinazoline (4)

The appropriate benzanilide (**1**) (0.05 mol), 150 ml of anhydrous benzene and $PCl_5$ (11.5 g, 0.055 mol) were placed in a 250 ml three necked flask equipped with a stirrer and an air condenser to which calcium chloride-containing drying tube was afixed. The mixture was gently heated at about 50°C until the disappearance of benzanilide (tlc) was completed. Benzene and $POCl_3$ were removed using a rotary evaporator. Anhydrous benzene (100 ml) and *N,N*-dimethylcyanamide (3.5 g, 4 ml, 0.05 mol) were added to the crude *N*-phenylbenzimidoyl chloride (**2**). The mixture was left for 24 h and then, $TiCl_4$ (5 ml, 0.05 mol) in 20 ml of anhydrous benzene was added dropwise followed by agitation at 50°C for 3 h. Benzene was decanted from the resulting gluey solid and 200 ml of 20% aqueous HCl added. The mixture was left to hydrolyze and then filtered under vacuum. The obtained solids were rinsed twice with 20% aqueous HCl solution. The solution was extracted three times with ether (3×25 ml) and neutralized with 20% aqueous NaOH, yielding a precipitate which was extracted twice with chloroform. The combined extracts were dried over $MgSO_4$ and concentrated yielding an oily residue to which 50 ml of methanol and 2 g of

decolorizing charcoal were added followed by boiling under reflux (15 min). After filtration, the methanol was removed using a rotary evaporator and the dry residue was crystallized from hexane or methanol.

**Synthesis of 4-(*N,N*-dimethylamino)-2-(4-methoxyphenyl)quinazoline hydrochloride (4b')** 4-(*N,N*-Dimethylamino)-2-(4-methoxyphenyl)quinazoline (**4b**) (0.5 g, 1.78 mmol) dissolved in 100 ml of ether was saturated with gassy HCl. Resulting white solid was dried and crystallized from benzene giving (**4b'**) (0.52 g, 89.65 %); mp 214-216°C; $C_{17}H_{17}N_3O{\times}HCl{\times}1/2H_2O$; MW 324.80, monoclinic space group, $P2_1/c$, a=22.346(3), b=7.562(1), c=19.090(3)Å, β=92.75(1)°, Vol=3222.1(8)Å$^3$, $D_{calc}$=1.339 mg/m$^3$, $\mu(MoK_\alpha)$=0.247 mm$^{-1}$, R=0.052 for 5884 reflections ($I>\sigma I$, Θmax=51.0°, $MoK_\alpha$, λ=0.71073Å), solution by direct methods, refinement on $F^2$,GOF=0.858 using SHELXL-93,[10] hydrogen atoms associated with N and water located from difference Fourier synthesis, other hydrogen atoms positioned by idealized geometry; $^1$H-Nmr: 3.65 (s, 6H, $N(CH_3)_2$); 3.85 (s, 3H, $OCH_3$); 6.80-9.00 (m, 8$H_{ar}$, $H^{\oplus}$); Anal. Calcd for $C_{17}H_{17}N_3O{\times}HCl{\times}1/2H_2O$: C, 62.84; H, 5.90; N, 12.94; Cl, 10.92. Found: C, 62.80; H, 5.88; N, 12.95; Cl, 10.87.

**Data of 4-(*N,N*-dimethylamino)-2-phenylquinazoline (4a):** $^1$H-Nmr: 7.23 (dd, J=8.3, 8.3 Hz, 1H, H-6), 7.43 (m, 3H, H-3', H-4', H-5'), 7.59 (dd, J=8.3, 8.3 Hz, 1H, H-7), 7.86 (d, J=8.3 Hz, 1H, H-5), 7.89 (d, J=8.3 Hz, 1H, H-8), 8.56 (d, J=6.9 Hz, 2H, H-2', H-6'), 11.30 (1H, NH); $^{15}$N-Nmr: -137.675 (N-1), -144.551 (N-3), -306.062 (N-C4).

**Synthesis of 4-(*N,N*-dimethylamino)-2-phenylquinazoline trifluoroacetate (4a')** 4-(*N,N*-Dimethylamino)-2-phenylquinazoline (**4a**) (0.35 g, 1.4 mmol) was dissolved in 75 ml of absolute ether and a solution of trifluorineacetic acid (0.16 g, 1.4 mmol) in 25 ml of ether was added dropwise into the reaction mixture with its simultaneous agitation. The white solid (**4a'**) was dried and crystallized from benzene: **4a'** (0.47 g, 92.15 %); mp 148-150°C; Anal. Calcd for $C_{18}H_{16}N_3O_2F_3$: C, 59.50; H, 4.44; N, 11.56. Found: C, 59.57; H, 4.39; N, 11.60. $^1$H-Nmr: 7.34 (m, 4H, H-6, H-3',H-5', $H^{\oplus}$), 7.42 (dd, J=7.3, 7.3 Hz, 1H, H-4'), 7.56 (dd, J=7.2, 8.2 Hz, 1H, H-7), 7.94 (d, J=8.2 Hz, 1H, H-5), 8.14 (d, J=8.2 Hz, 1H, H-8), 8.27 (d, J=7.3 Hz, 2H, H-2', H-6'); $^{15}$N-Nmr: -154.374 (N-1, N-3), -271.126 ($J_{^{15}N-^1H}$=5 Hz,(N-C4)).

**Analysis of products**

$^{1}$H-Nmr spectra were recorded at 25°C by TESLA BS 587 (80 MHz) spectrometer. $^{15}$N-Nmr spectra were recorded at 25°C by BRUKER AM 500 spectrometer. Uv spectra were recorded by SPECORD M-40 spectrophotometer. Ms spectra were made by SHIMADZU QP-200 mass spectrometer. Single crystal X-ray analysis was made by SIEMENS R3m/V apparatus. Elementary analysis was carried out by means of PERKIN-ELMER 240 c analyzer.

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