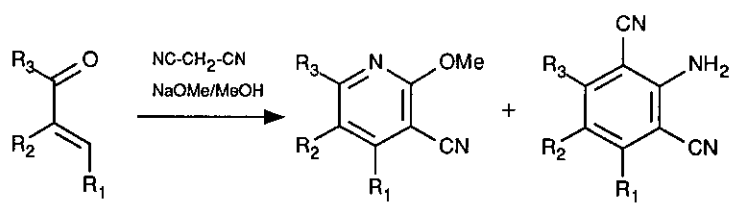
SYNTHESIS OF 4-AMINO-8-CYANOQUINAZOLINES FROM ENONES AND ENALS

Pedro Victory[a]*, José I. Borrell[a], Anton Vidal-Ferran[a], Elvira Montenegro[a], and M. Luisa Jimeno[b]

[a]Departament de Química Orgànica, CETS Institut Químic de Sarrià (Universitat Ramon Llull), E-08017 Barcelona, Spain
[b]Centro Nacional de Química Orgánica C.S.I.C., Juan de la Cierva 3, E-28006 Madrid, Spain

Abstract- The treatment in a sodium methoxide/methanol solution of α,β-unsaturated enones or aldehydes with propanedinitrile in a 1:2 molar ratio led to 2-aminobenzene-1,3-dicarbonitriles. These compounds afforded 4-amino-8-cyanoquinazolines by reaction with formamide or guanidine.

Our group has recently reported the formation of 2-aminobenzene-1,3-dicarbonitriles (**3**) as by-products in the reaction between enones or enals and propanedinitrile in a sodium methoxide/methanol solution (Scheme 1).[1]

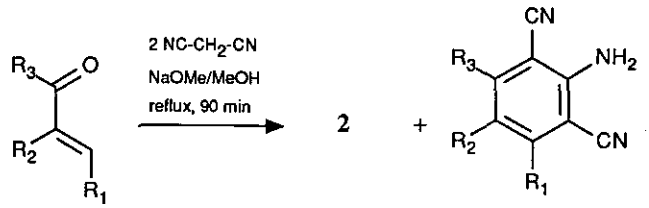


1 **2** **3** (by-product)

Scheme 1

The benzene ring of compounds(**3**)contains an *o,o'*-dicyano substituted amino group and, consequently, they may be used as antecedents[2] of quinazolines using guanidine and formamide as reagents.[3] In connection with this, we wish to report here an improvement in the yields of formation of compounds(**3**)and the synthesis of some quinazolines by reaction with guanidine or formamide.

2-Aminobenzene-1,3-dicarbonitriles (**3**) were initially obtained as by-products in the synthesis of 3-cyano-2-methoxypyridines (**2**) from carbonyl compounds and propanedinitrile in NaOMe/MeOH. However, we observed that the ratio between **2** and **3** varies depending on the experimental conditions employed. Thus, increasing the amount of propanedinitrile in relation to **1**, the formation of **3** with respect to **2** is increased. In particular, **3** was predominantly obtained by using a 2:1 molar ratio between propanedinitrile and **1** (Table 1).[4] These reaction conditions cause both an increase in the amount of **3** and a decrease in the quantity of **2**.



1 3

Table 1

1	R_1	R_2	R_3	Product	Yield of 3 (%)	Yield of 2
a	H	H	Me	**3a**	10	i
b	Ph	H	H	**3b**	10	i
c	H	Me	H	**3c**	5	i
d	H	Ph	H	**3d**	10	i
e	Me	H	Me	**3e**	15	i
f [ii]	Ph	H	Ph	**3f**	20	- - -

[i] Lower than 3% .

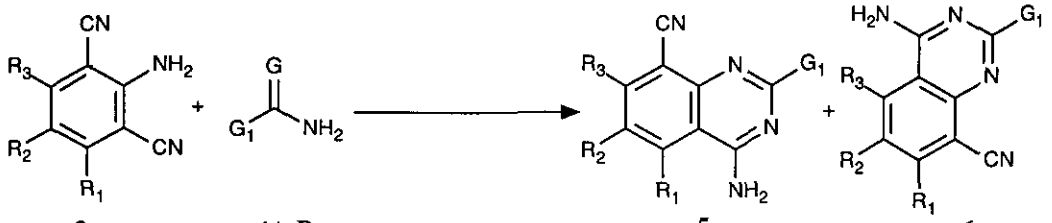
[ii] In this case, piperidine was used as the base instead of sodium methoxide.

Nevertheless, (*E*)-1,3-diphenylpropenone (**1f**) as an exception did not lead to the desired 2-aminobenzene-1,3-dicarbonitrile (**3f**) but to the pyridine (**2f**). However, compound (**3f**) was obtained when piperidine was used as the base instead of sodium methoxide, the formation of **2f** being thus precluded.

Once compounds (**3a-f**) were obtained, we studied their conversion into quinazolines by reaction with formamide or guanidine. Although compounds (**3**) may lead to two isomeric quinazolines depending on which cyano group undergoes the cyclization process, the treatment of **3a-f** with formamide yielded a single 4-amino-8-cyanoquinazoline whereas the reaction with guanidine gave a single 8-cyano-2,4-diaminoquinazoline (Table 2).

Thus **3c-f** afforded a single quinazoline by treatment with formamide or guanidine (Entries 1 to 7) due to the fact that both possible isomers (**5** and **6**) are the same compound when $R_1 = R_3$.

On the other hand, treatment of the unsymmetrical 2-amino-4-methylbenzene-1,3-dicarbonitrile (**3a**) (Entry 8, $R_1 \neq R_3$) with formamide afforded only one of the two possible isomers (Scheme 2). We have assigned to this product the less sterically hindered quinazoline structure (**5aA**). This structure has been unequivocally established by using the NOE technique. Upon irradiating the ^{1}H-nmr signal of the amino group an enhancement of one signal of the *AB* aromatic system (the one located at δ= 8.33 ppm) was observed, a result which is only compatible with the structure (**5aA**). A detailed study of the partially decoupled ^{13}C-nmr spectrum of **5aA** led to the same assignment.[5]



3 **4A-B** **5** **6**

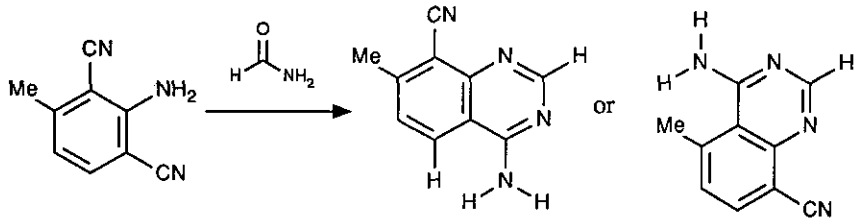
4A, formamide: G_1=H, G= O
4B, guanidine: G_1= NH_2, G= NH

A: G_1=H
B: G_1= NH_2

Table 2

Entry	Starting material	R_1	R_2	R_3	Reagent	G_1	final product	yield (%)
1	3c	H	Me	H	formamide	H	5cA=6cA	70
2	3d	H	Ph	H	formamide	H	5dA=6dA	75
3	3e	Me	H	Me	formamide	H	5eA=6eA	50
4	3f	Ph	H	Ph	formamide	H	5fA=6fA	50
5	3d	H	Ph	H	guanidine	NH_2	5dB=6dB	50
6	3e	Me	H	Me	guanidine	NH_2	5eB=6eB + 3e [i]	- -
7	3f	Ph	H	Ph	guanidine	NH_2	5fB=6fB	45
8	3a	H	H	Me	formamide	H	5aA	55

[i] The result was always a mixture of the starting material and the corresponding quinazoline.



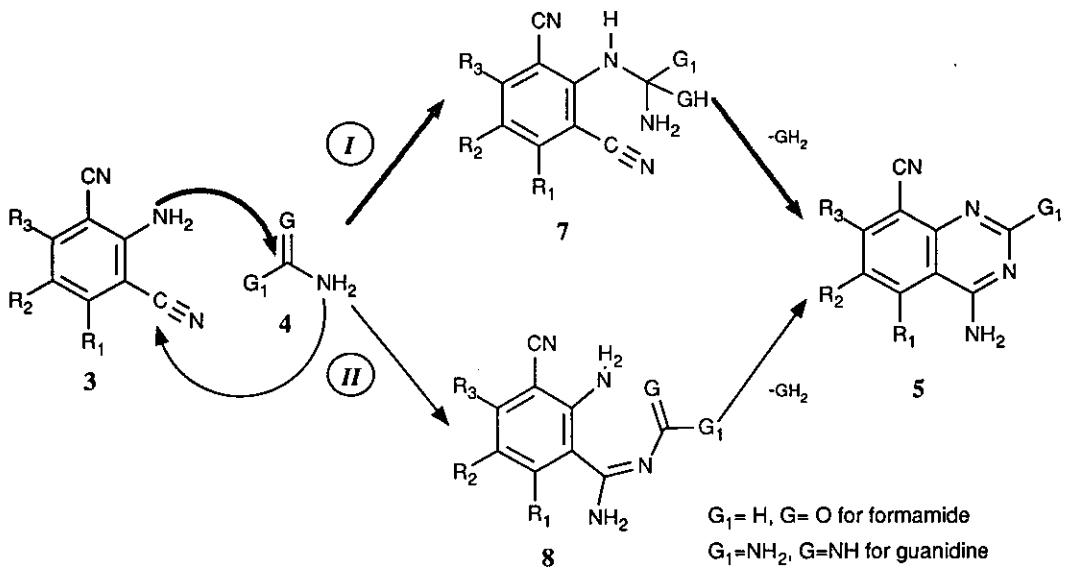
3a **5aA** **6aA**

Scheme 2

Two tentative mechanistic rationalizations for the formation of **5** are depicted in Scheme 3 (formation of **6** could be also rationalized in a similar way considering the other cyano group in **3**).

The first one (*pathway I*) involves addition of the amino group of **3** to the sp^2 carbon of **4**. This step is followed by intramolecular addition onto the cyano group and elimination of water (in the case of formamide GH_2 = H_2O) or ammonia (in the case of guanidine GH_2 = NH_3) to yield **5**. In the second one (*pathway II*) the order of the addition to the sp^2 carbon of **4** and the cyclization is reversed.

Although pathway I is most likely for formamide, the high nucleophilicity of the nitrogen atoms of guanidine



Scheme 3

rends difficult to consider the attack of the benzene amino group as the first step of the cyclization process, pathway II being in that case not rejectable. Further studies have been planned to confirm this hypothesis.

EXPERIMENTAL

Melting points were determined on a Büchi-Tottoli apparatus, and are uncorrected. The ir spectra were obtained in a Bomem Michelson-100 (FT-IR) or a Perkin-Elmer 683 apparatus. The ^{1}H-nmr spectra were recorded on Bruker AC-80 or Bruker AC-300 spectrometers in DMSO-d_6 unless otherwise stated. The ^{13}C-nmr spectra were recorded on Bruker AC-80, Bruker AC-300 or Varian XL-200/F-19 spectrometers in DMSO-d_6 unless otherwise stated. Chemical shifts are given in ppm (δ) and in the case of ^{1}H-nmr and partially decoupled ^{13}C-nmr signals are expressed as s (singlet), d (doublet), m (multiplet) or br s (broad signal). Mass spectra were obtained on Hewlett-Packard 5995 A or Hewlett-Packard 5998 A mass spectrometers. Microanalyses were performed on Carlo-Erba CHNS-O/EA 1106 or CHNS-O/EA 1108 analyzers. "Preparative column chromatography" refers to Flash chromatography using 230-400 mesh silica gel (Macherey-Nagel Reagent) unless otherwise stated. Uv spectra were recorded in a Perkin-Elmer Lambda 2 instrument. Carbonyl compounds (**1a**), (**1b**), (**1c**) and (**1f**) were obtained from Fluka. The remaining carbonyl compounds (**1d**)[6] and (**1e**)[7] were prepared following known procedures.

2-Aminobenzene-1,3-dicarbonitriles (3a-f):

General procedure for 3a-e: Propanedinitrile (13.2 g, 0.2 mol) in 25 ml of MeOH was added to a freshly prepared NaOMe solution at 0°C [4.6 g (0.2 mol) of sodium in 100 ml of MeOH]. After stirring for 5 min, 0.1 mol of the corresponding carbonyl compound (**1a-e**) in 25 ml of MeOH was added dropwise (2 h). The mixture

was refluxed for 90 min and the solvent was removed *in vacuo*. The resulting oil was dissolved in 250 ml of water and extracted with 10 x 50 ml of CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvent was removed. The desired product (**3a-e**) was purified by preparative column chromatography with CH_2Cl_2 as the eluent. In some cases, the corresponding 2-methoxypyridine-3-carbonitrile (**2**) is separated as a minor fraction that has the higher *Rf*.

2-Amino-4-methylbenzene-1,3-dicarbonitrile (**3a**); yield: 10%, mp 158-159 °C (lit.,[8] 158-159).

2-Amino-4-phenylbenzene-1,3-dicarbonitrile (**3b**); yield: 10%, mp 149-150 °C (lit.,[1] 149-150).

2-Amino-5-methylbenzene-1,3-dicarbonitrile (**3c**); yield: 5%, mp 178-179 °C (lit.,[9] 179).

2-Amino-5-phenylbenzene-1,3-dicarbonitrile (**3d**); yield: 10%, mp 233-234 °C (lit.,[1] 233-234).

2-Amino-4,6-dimethylbenzene-1,3-dicarbonitrile (**3e**); yield: 15%, mp 195-197 °C. Analytical data are in agreement with the reported ones.[10]

2-Amino-4,6-diphenylbenzene-1,3-dicarbonitrile (**3f**): A mixture of 20.8 g (0.1 mol) of (*E*)-1,3-diphenylpropenone (**1f**), 13.2 g (0.2 mol) of propanedinitrile and 300 ml of anhydrous ethanol was cooled to 2 °C. Then, 34 g (0.4 mol) of piperidine was added dropwise at a rate which maintains the temperature below 5 °C. The resulting mixture was warmed until room temperature and the stirring was maintained for 12 h. Then the solution was cooled at 0 °C for 2 h. The solid was filtered, washed with cold ethanol and recrystallized from ethanol to yield 5.9 g (20%) of **3f**; mp 223-224 °C (lit.,[12] 226). Spectroscopic and analytical data are in agreement with the reported ones.[11]

When the filtrate obtained in the recrystallization was chromatographed on column using CH_2Cl_2 as the eluent, 1.2 g (2.5 mmol, 5%) of *3-benzoyl-4-hydroxy-2,4,6-triphenyl-1,1-cyclohexanedicarbonitrile* were obtained; mp 212-214 °C (lit.,[13] 213-215). A change of the eluent to a CH_2Cl_2:AcOEt mixture (1:1) afforded an extra crop of **3f** (1.5 g, 5%).

4-amino-8-cyanoquinazolines:

General procedure for the reaction between 3 and formamide: A mixture of 6 mmol of the corresponding 2-aminobenzene-1,3-dicarbonitrile (**3**) and 20 ml (22.6 g, 0.5 mol) of formamide was heated at reflux for 24 h. The reaction mixture was cooled and poured in 50 ml of water. The solid formed was filtered, washed with water and recrystallized from ethanol using decolourising charcoal.

4-Amino-8-cyano-6-methylquinazoline (**5cA=6cA**); yield 70%; mp >300 °C. Ir (KBr): υ_{max}: 3400 cm^{-1}, 3340 (weak) and 3080 (N-H), 2240 (C≡N), 1665 (N-H), 1580, 1555 and 1510 (C=C and C=N). ^{1}H-Nmr (80 MHz): δ= 2.50 ppm (s, 3H, Me), 8.06 (br s, 2H, exchangeable with D_2O, NH_2), 8.19 (s, 1H, H-C5), 8.37 (s, 1H, H-C7), 8.48 (s, 1H, H-C2). ^{13}C-Nmr (50 MHz): δ= ppm 20.5 (Me), 109.5 (C8), 114.3 (C4a)*, 116.9 (CN)*, 128.2 (C5), 134.8 (C6), 139.8 (C7), 148.2 (C8a), 156.4 (C2), 161.3 (C4) (* Interchangeable assignments). Ms (70 eV): *m/z* (%): 184 (100.0) [M^+], 183 (6.1), 168 (9.2), 167 (2.0), 157 (47.7), 156 (41.1), 130 (4.1), 129 (10.3). Uv (MeOH): λ_{max}= 212 nm (log ϵ= 4.77), 233 (4.38), 295 (3.97), 339 (4.10). *Anal.* Calcd for $C_{10}H_8N_4$: C 65.21, H 4.38, N 30.42. Found: C 65.36, H 4.34, N 30.19.

4-Amino-8-cyano-6-phenylquinazoline (**5dA=6dA**); yield 75%; mp >300 °C. Ir (KBr): υ_{max}: 3405 cm^{-1}, 3320 and 3100 (N-H), 2240 (C≡N), 1670 (N-H), 1580, 1550, 1520, 1500 and 1480 (C=C and C=N), 695 and 760

(Ph). ^{1}H-Nmr (80 MHz): δ= 7.49-9.13 ppm (m, partially exchangeable with D_2O, 9H, H-C5 + H-C7 + Ph + NH_2), 8.61 (s, 1H, H-C2). ^{13}C-Nmr (50 MHz): δ= 110.5 ppm (C8), 114.8 (C4a)*, 117.0 (CN)*, 126.4-137.3 (Ph + C7 + C6 + C5), 149.2 (C8a), 157.3 (C2), 162.0 (C4) (* Interchangeable assignments). Ms (70 eV): *m/z* (%): 246 (100.0) [M$^+$], 245 (5.4), 230 (2.0), 219 (43.5), 192 (4.4), 191 (7.3). Uv (MeOH): λ_{max}= 211 nm (log ε= 4.67), 246 (4.48), 309 (4.09), 351 (3.96). *Anal.* Calcd for $C_{15}H_{10}N_4$: C 73.16, H 4.09, N 22.75. Found: C 73.46, H 4.21, N 22.48.

4-Amino-8-cyano-5,7-dimethylquinazoline (**5eA=6eA**); yield 50%; mp >300 °C. Ir (KBr): υ_{max}: 3490 cm^{-1}, 3330 and 3120 (N-H), 2230 (C≡N), 1640 (N-H), 1605, 1580, 1555 and 1550 (C=C and C=N). ^{1}H-Nmr (80 MHz, DMSO-d_6 + CF_3COOD): δ=2.67 ppm (s, 3H, Me), 2.92 (s, 3H, Me), 7.55 (s, 1H, H-C6), 8.61 (s, 1H, H-C2). ^{13}C-Nmr (50 MHz, DMSO-d_6 + CF_3COOD):.δ= 20.5 and 23.4 ppm (Me), 129.7 (C6), 156.4 (C2). Ms (70 eV): *m/z* (%): 198 (100.0) [M$^+$], 197 (32.0), 181 (41.7), 180 (5.5), 171 (20.8), 170 (20.8), 143 (8.2), 144 (2.5). Uv (MeOH): λ_{max}= 219 nm (log ε= 4.67), 239 (4.33), 302 (3.99), 332 (4.09). *Anal.* Calcd for $C_{11}H_{10}N_4$: C 66.65, H 5.08, N 28.26. Found: C 66.37, H 4.93, N 28.00.

4-Amino-8-cyano-5,7-diphenylquinazoline (**5fA=6fA**); yield 50%; mp 260-261 °C. Ir (p. KBr): υ_{max}: 3480 cm^{-1}, 3285 and 3140 (N-H), 2230 (C≡N), 1640 (N-H), 1585, 1555 and 1490 (C=C and C=N), 780, 770, 710 and 700 (Ph). ^{1}H-Nmr (80 MHz): δ= 7.39-8.27 ppm (m, partially exchangeable with D_2O, 13H, H-C6 + Ph + Ph + NH_2), 8.59 (s, 1H, H-C2). ^{13}C-Nmr (50 MHz): δ= 110.6 ppm (C8), 116.5 and 116.6 (C4a, CN), 127.0-138.5 (Ph + Ph + C6), 149.6 (C8a)*, 153.2 (C7)*, 156.3 (C2), 161.0 (C4), (* Interchangeable assignments). Ms (70 eV): *m/z* (%): 322 (73.4) [M$^+$], 321 (100), 305 (1.6), 294 (1.1), 267 (1.5). Uv (MeOH): λ_{max}= 203 nm (log ε= 4.55), 254 (4.26), 415 (3.99). *Anal.* Calcd for $C_{21}H_{10}N_4$: C 78.24, H 4.38, N 17.38. Found: C 77.92, H 4.61, N 17.26.

4-Amino-8-cyano-7-methylquinazoline (**5aA**); yield 55%; mp >300 °C. Ir (KBr): υ_{max}: 3430 cm^{-1}, 3340 and 3060 (N-H), 2220 (C≡N), 1665 (N-H), 1610, 1580 and 1560 (C=C and C=N). ^{1}H-Nmr (300 MHz): δ= 2.60 ppm (s, 3H, Me), 7.45 (d, $^3J_{HH}$= 8.5 Hz, 1H, H-C6), 8.03 (br s, 2H, exchangeable with D_2O, NH_2), 8.33 (d, $^3J_{HH}$= 8.5 Hz, 1H, H-C5), 8.44 (s, 1H, H-C2). ^{13}C-Nmr (75 MHz): δ= 20.9 ppm (Me), 109.5 (C8), 112.4 (C4a), 116.2 (CN), 127.1 (C6), 128.2 (C5), 149.3 (C7), 150.7 (C8a), 157.4 (C2), 161.8 (C4). ^{13}C-Nmr (75 MHz, with ^{1}H completely coupled): δ= 20.9 (qxd, $^1J_{Me\text{-}CH_3}$= 128.4 Hz, $^3J_{Me\text{-}H6}$= 4.2 Hz, Me), 109.5 (m, $^3J_{C8\text{-}CH_3}$= 5.5 Hz, $^4J_{C8\text{-}H5}$= 1.5 Hz, $^3J_{C8\text{-}H6}$= 7.2 Hz, C8), 112.4 (dxd, $^3J_{C4a\text{-}H5}$= 8.0 Hz, $^3J_{C4a\text{-}NH_2}$= 4.9 Hz, C4a), 116.2 (s, CN), 127.1 (qxd, $^1J_{C6\text{-}H6}$= 160.5 Hz, $^3J_{C6\text{-}CH_3}$= 4.9 Hz, C6), 128.2 (dxd, $^1J_{C5\text{-}H5}$= 162.8 Hz, $^2J_{C5\text{-}H6}$= 1.1 Hz, C5), 149.3 (m, $^2J_{C7\text{-}CH_3}$= 6.1 Hz, $^3J_{C7\text{-}H5}$= 8.9 Hz, $^2J_{C7\text{-}H6}$= 1.9 Hz, C7), 150.7 (dxd, $^3J_{C8a\text{-}H2}$= 10.8 Hz, $^3J_{C8a\text{-}H5}$= 6.3 Hz, C8a), 157.4 (d, $^1J_{C2\text{-}H2}$= 197.8 Hz, C2), 161.8 (dxd, $^3J_{C4\text{-}H2}$= 9.9 Hz, $^3J_{C4\text{-}H5}$= 3.3 Hz, C4). Ms (70 eV): *m/z* (%): 184 (100.0) [M$^+$], 183 (21.0), 168 (5.4), 167 (2.4), 157 (37.8), 156 (17.3). Uv (MeOH): λ_{max}= 216 nm (log ε= 4.35), 233 (4.09), 248 (4.15), 297 (3.71), 330 (3.94). *Anal.* Calcd for $C_{10}H_8N_4$: C 65.21, H 4.38, N 30.42. Found: C 65.02, H 4.25, N 30.39.

8-cyano-2,4-diaminoquinazolines:

8-Cyano-2,4-diamino-6-phenylquinazoline (**5dB=6dB**): 0.9 g (5.0 mmol) of guanidine carbonate were added to a mixture of 0.24 g (10.4 mmol) of sodium in 20 ml of methanol. The resulting mixture was stirred for 10 min and then was heated at reflux for 30 min. The sodium carbonate formed was filtered and washed with 40 ml of

methanol. 1.2 g (5.4 mmol) of **3d** were added to the filtrate and the resulting solution was heated at reflux for 24 h. The precipitate formed was filtered, washed with water and recrystallized from ethanol to yield 710 mg (50%) of **5dB=6dB**, mp >300 °C. Ir (KBr): υ_{max}: 3480 cm^{-1}, 3440, 3360 and 3260 (N-H), 2230 (C≡N), 1675, 1650, 1620, 1570 and 1520 (N-H, C=C and C=N), 750 and 690 (Ph). ^{1}H-Nmr (80 MHz, DMSO-d_6 + CF_3COOD): δ= 7.35 - 9.14 ppm (m, H-C5 + H-C7 + Ph). ^{13}C-Nmr (50 MHz, DMSO-d_6 + CF_3COOD): δ= 106.5 ppm (C8), 111.2 (C4a), 118.2 (CN), 126.3-138.0 (C5 + C6 + C7 + Ph), 153.1 (C8a), 161.9 (C2)*, 162.6 (C4)*, (* Interchangeable assignments). Ms (70 eV): *m/z* (%): 261 (100.0) [M^+], 260 (3.5), 219 (23.0), 193 (10.3), 192 (7.5), 191 (9.7), 165 (8.9), 164 (13.4). Uv (MeOH): λ_{max}= 201 nm (log ε= 4.62), 248 (4.57), 306 (4.30), 380 (3.85). *Anal.* Calcd for $C_{15}H_{11}N_5$: C 68.95, H 4.24, N 26.80. Found: C 68.97, H 4.41, N 26.70.

8-Cyano-2,4-diamino-5,7-diphenylquinazoline (**5fB=6fB**): Procedure as described for **3e** but using 0.86 g (2.9 mmol) of **3f**. The reaction mixture was heated at 140 °C for 24 h to yield 440 mg (45%) of **5fB=6fB**, mp 267-8 °C. Ir (KBr): υ_{max}: 3510 cm^{-1}, 3480, 3350 and 3060 (N-H), 2225 (C≡N), 1660, 1620, 1570 and 1500 (N-H, C=C and C=N), 775 and 700 (Ph). ^{1}H-Nmr (80 MHz): δ= 3.37 and 6.64 ppm (br s, 2H, exchangeable with D_2O, NH_2), 6.89 (s, 1H, H-C6), 7.58 (s, 10H, Ph + Ph). ^{13}C-Nmr (20 MHz): δ= 104.8 ppm (C8), 107.5 (C4a), 117.3 (CN), 123.4 (C6), 128.6 - 139.8 (Ph + Ph + C5), 143.8 (C7), 149.0 (C8a), 161.2 (C2)*, 161.8 (C4)*, (* Interchangeable assignments). Ms (70 eV): *m/z* (%): 337 (100.0) [M^+], 336 (84.3), 294 (2.0), 268 (1.0), 267 (2.1), 240 (1.7). Uv (MeOH): λ_{max}= 204 nm (log ε= 4.74), 265 (4.63), 316 (4.49). *Anal.* Calcd for $C_{21}H_{15}N_5$: C 74.76, H 4.48, N 20.76. Found: C 74.61, H 4.44, N 20.79.

ACKNOWLEDGEMENTS

We are grateful to the *Fundació J. Salañer* for a fellowship granted to one of us (A. V.-F.).

REFERENCES AND NOTES

1. P. Victory, J. I. Borrell, and A. Vidal-Ferran, *Heterocycles*, **1993**, *36*, in press.
2. See for example:
   a) B. Kokel, G. Menchini, and M. Hubert-Habart, *Tetrahedron Lett.*, **1984**, *25*, 1557.
   b) E. C. Taylor and A. L. Borror, *J. Org. Chem.*, **1961**, *26*, 4967.
   c) E. C. Taylor, A. McKillop, and S. Vromen, *Tetrahedron*, **1967**, *23*, 885.
   d) E. C. Taylor, A. McKillop, and R. N. Warrener, *Tetrahedron*, **1967**, *23*, 891 and references cited therein.
3. See for example: A. Rosowsky and E. J. Modest, *J. Org. Chem.*, **1966**, *31*, 2607.
4. The reaction crude material is mainly formed by propanedinitrile polymers (see A. J. Fatiadi, *Synthesis*, **1978**, 165) from which the corresponding 2-aminobenzene-1,3-dicarbonitrile (**2**) is easily separated. Nevertheless, a GC-MS analysis of the reaction crude material of **1b** (Hewlett-Packard 5890 Series 2 gas chromatograph coupled with a Hewlett-Packard 5989 mass spectrometer) has shown the presence of the Knoevenagel adduct of propanedinitrile and **1b** in diferent levels of hydrogenation. Although other carbonyl compounds can lead to **3a** and **3b** by this procedure, we have only mentioned those that afford these 2-aminobenzene-1,3-dicarbonitriles in higher yields.

5. ^{1}H coupled ^{13}C-nmr spectra showed the signal of the carbon atom that bears the amino group (C4) as a doublet of doublets (J_{CH}= 3.3 Hz and J_{CH}= 9.9 Hz). An irradiation at the frequency corresponding to H-C2 (8.44 ppm) caused the coupling corresponding to 9.9 Hz to be eliminated, the signal of C4 being converted into a doublet of J_{CH}= 3.3 Hz ($^{3}J_{C4H2}$= 9.9 Hz). On the other hand, irradiation at δ 8.33 ppm (one of the signals of the *AB* aromatic system) eliminated the coupling corresponding to 3.3 Hz ($^{3}J_{C4H5}$= 3.3 Hz). These results are only compatible with the structure (**5aA**) because there is no possibility in the structure (**6aA**) to have a measurable coupling constant between one of the signals of the *AB* aromatic system and C4. It is interesting to note that the reaction between guanidine and the 2-aminobenzene-1,3-dicarbonitrile obtained from (*E*)-4-phenyl-3-buten-2-one (R_1= Ph, R_2= H, R_3= Me) affords a mixture of the corresponding 2,4-diaminoquinazolines (**5B** and **6B**) as it is pointed out in the ^{13}C-nmr spectrum of the resulting material by the signals at 20.6 and 23.6 ppm respectively. The major character of the less hindered structure (**5B**) togheter with the sole formation of **5aA** seem to indicate that the direction of the ring-closure is mainly governed by the steric hindrance.
6. I. Crossland, *Org. Synth.*, **1976**, *60*, 6.
7. H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **1966**, *31*, 3128.
8. N. A. Vaydia, W. J. Nixon, A. A. Fatmi, and C. De Witt, *J. Org. Chem.*, **1982**, *47*, 2483.
9. N. Detzer, O. Burkhard, H. Schaffrin, and W. Liptay, *Z. Naturforsch., Teil B*, **1987**, *42B*, 1129.
10. B. Rigerte and E. Gudriniece, *Latv. PSR Zinat. Akad. Vestis. Kim. Ser.*, **1975**, 371 [*Chem. Abstr.*, **1975**, *83*, 113891y].
11. P. Victory, J. I. Borrell, A. Vidal-Ferran, C. Seoane, and J. L. Soto, *Tetrahedron Lett.*, **1991**, *32*, 5375.
12. K. Gewald and W. Schill, *J. Prak. Chem.*, **1971**, *313*, 678.
13. J. L. Soto, C. Seoane, and J. A. Ciller, *An. Quim. Ser. C*, **1980**, 281.

Received, 15th March, 1993