One-Step Synthesis of Aminopyrimidines from 5-Oxo-4*H*-Benzopyrans

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Received November 7, 2003

Novel 4-amino-6-aryl-2-phenylpyrimidine-5-carbonitriles have been prepared in one step procedure from the readily available 4-aryl-2-amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-benzopyrans. The mass spectroscopy study under EI conditions shows molecular peaks with high intensity corresponding to the loss of benzonitrile from the C2 position of the pyrimidine ring. Semiempirical (AM1 and PM3) and *ab initio* HF/6-31G* calculations reveal a favored distorted geometry where the three rings are not in the same plane.

J. Heterocyclic Chem., **41**, 509 (2004).

Introduction.

The synthesis of 1,4-dihydropyridines (1,4-DHPs) **1** has attracted much attention along the last three decades due the calcium modulator effect they display [1]. It is well-established that the pharmacological activity of this family of compounds is determined by their structural features [2-4], and major efforts have been devoted to the preparation of novel derivatives and to the definition of the structure-activity relationship based on crystallographic studies. Related structures with more pharmacological interests [5-8] and 1,4-DHP sub-structures fused to one carbocyclic ring as **2** [9] were also reported and evaluated.

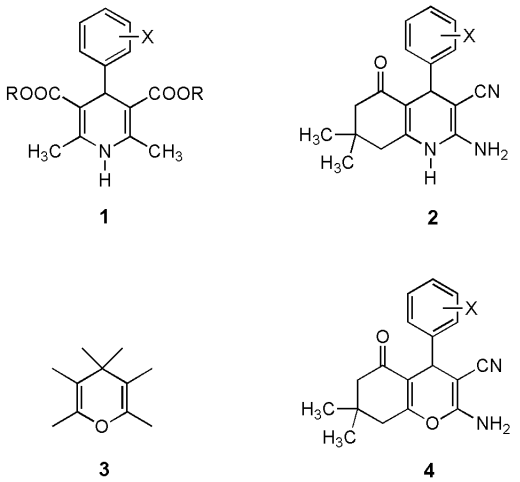
The 4*H*-pyran ring **3** can be considered as the oxa-analogue of the biologically active 1,4-dihydropyridine system. Therefore, we have reported the synthesis of a wide variety of 4*H*-pyran derivatives [10-12] as well as their study by mass spectrometry [13,14] and NMR spectroscopy [15,16]. In addition, the X-ray crystal structure of some monocyclic 4*H*-pyran derivatives showed that their geometrical features were similar to those found for the biologically active 1,4-DHPs [17-19].

In order to determine the influence of the presence of a fused carbocyclic ring on the structure of the 4*H*-pyran ring, we reported an X-ray crystallographic study of substituted tetrahydrobenzo-4*H*-pyrans **4** [20].

As a part of our studies aimed at determining the reactivity of 2-amino-3-cyano-5-oxo-4*H*-benzopyran derivatives (**4**), in this paper we report on the reaction of these compounds with benzamidine. The reaction yielded the respective 4-amino-6-aryl-2-phenylpyrimidine-5-carbonitrile derivatives.

The synthesis of substituted aryl pyrimidines from α-substituted cinnamonitrile derivatives and benzamidine hydrochloride has been previously reported [21,22]. Although very early we have reported the synthesis of aminocyano substituted pyrimidines from the corresponding 4*H*-pyrans [23], the procedure now reported is, to the best of our knowledge, a new approach to the synthesis of a pyrimidine ring with a different substitution pattern. The pyrimidine ring is a skeleton of particular interest provided that it is present in many compounds exhibiting biological and pharmaceutical activity [24]. The present methodology allows preparing new pyrimidine derivatives in two steps from acyclic readily available starting materials involving: i) formation of 5-oxo-4*H*-benzopyrans and ii) further ring transformation to the pyrimidine system by reaction with benzamidine.

Chart 1

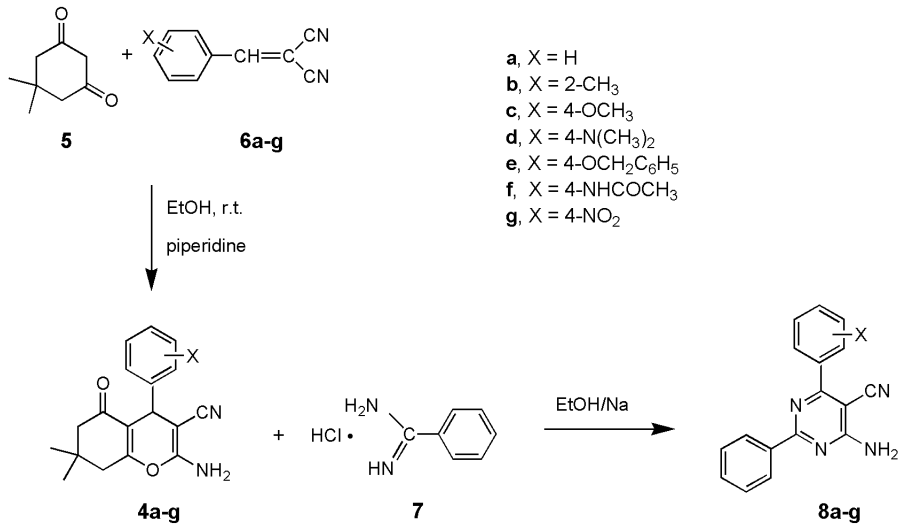


Some representative 1,4-DHPs and 4*H*-pyrans.

Discussion.

2-Amino-4-aryl-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrobenzo-4*H* pyrans (**4a-g**) were synthesized by following the general procedure from dimedone (**5**) and the corresponding arylidenmalononitrile (**6a-g**) by an 6-*exo-dig* cyclization of δ-oxonitriles firstly reported by our group [11,20] (See Scheme 1).

Scheme 1

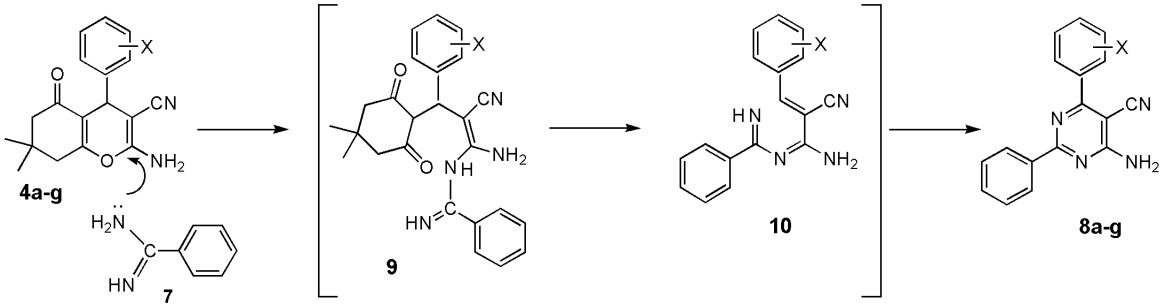


Compounds **4a-g** were obtained as crystalline solids after recrystallization from ethanol and their structures were confirmed by spectroscopic methods (see Experimental part). Thus, compounds **4a-g** show in the FTIR spectra the bands corresponding to the C≡N and C=O groups at 2220 and 1680 cm^{-1}, respectively. The ^1H nmr spectra of compounds **4** show the proton on C4 as a singlet at δ=4.6–4.0 ppm. The two protons on C6 appear as an AB system with a coupling constant of J = 16 Hz, indicating that these two geminal protons are not equivalents. The protons on C8 appear as a broad singlet at δ=2.4–2.5 ppm. The ^{13}C nmr spectra show two olefinic double bonds between C2 (δ=156-159 ppm) and C3 (δ=57-68 ppm), and C8a (δ=159-164 ppm) and C4a (δ=110-118 ppm) in compounds **4a-g**, clearly showing the presence of a *push-pull* effect which is responsible for the δ values found for these olefinic carbon atoms. This finding has been previously observed in other related molecules [25-28]. All signals were unambiguously assigned by DEPT 90° and 135° and HMQC experiments. A further support to the spectroscopic assignment was based on the HMBC, NOE and COSY experiments (see Experimental section).

Further reaction of the corresponding 5-oxobenzopyran (**4a-g**) with an excess of benzamidine (**7**), prepared from benzamidine hydrochloride immediately before its use by treatment under basic conditions, led to the respective 4-amino-6-aryl-2-phenylpyrimidine-5-carbonitrile (**8a-g**) (See Scheme 1).

The formation of compounds **8a-g** is not straightforward and can be accounted for by assuming the reaction steps depicted in Scheme 2. A nucleophilic attack by the benzamidine to the C2 of the benzopyran ring in **4a-g** promotes a ring opening, leading to intermediate **9**. Elimination of a

Scheme 2



dimedone molecule generates **10**, the cyclization of which affords the final products **7a-g**, that are obtained as stable crystalline solids in good yields (69 to 79%) after a simple work-up.

The FTIR spectra of compounds **8a-g** show the NH_2 group as two bands at around 3470 and 3380 cm^{-1}, the conjugated cyano group at *ca*. 2200 cm^{-1} and several bands in the aromatic region. The ^1H nmr spectra show the NH_2 protons as a singlet at δ=7.9–7.7 ppm and the expected signals corresponding to the protons of the monosubstituted and disubstituted benzene ring. The ^{13}C nmr spectra of these compounds (**8a-g**) exhibit signals corresponding to the cyano and aromatic regions (see Table 1). In order to assign unequivocally the signals corresponding to the heterocyclic ring, we used 1D and 2D techniques: DEPT(135°), HMQC and HMBC. The cyano group appears at δ=116–18 ppm. As shown in Table 1, the signals corresponding to the heterocyclic system (C2, C4, C5, C6) are relatively insensitive to the nature of the substituent on the aryl ring. The rest of the signals are in agreement with the nature of the aromatic carbon atoms (see Experimental part).

Table 1

^{13}C nmr Spectroscopic Data of Compounds **8a-g**

Compound	C6	C4	C2	CN	C5
8a	168.0	164.5	163.9	116.2	84.3
8b	167.4	164.9	164.2	117.2	84.3
8c	167.2	164.8	164.0	116.7	83.3
8d	167.6	165.9	164.4	118.3	82.5
8e	168.0	165.5	164.7	117.6	84.2
8f	168.1	165.3	164.7	118.2	83.4
8g	168.6	166.7	164.8	118.5	82.5

In order to establish the fragmentation pathway of compounds **8a-g**, we have recorded the mass spectra generated under EI conditions. The principal peaks are listed in Table 2.

Table 2

Significant Peaks in the Mass Spectra (EI) of Pyrimidines **8a-g**

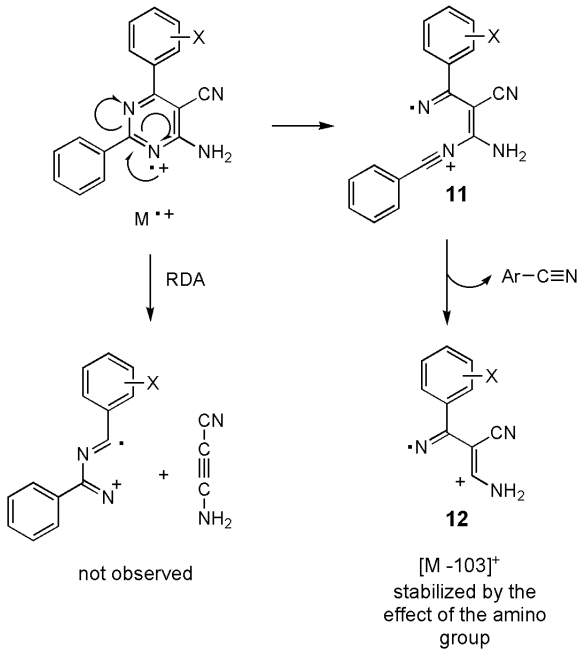
Compound	$M^{\cdot+}$	$M - C_6H_5CN$ (**12**)
8a (X = H)	272 (100)	169 (68)
8b (X = 2-CH_3)	286 (100)	183 (55)
8c (X = 4-OCH_3	302 (100)	199 (63)
8d (X = 4-$N(CH_3)_2$)	315 (100)	212 (15)
8e (X = 4-$OCH_2C_6H_5$)	378 (15)	91 ($C_7H_7^+$, 100)
8f (X = 4-$NHCOCH_3$	329 (100)	Not detected
8g (X 4-NO_2)	317 (100)	214 (46)

The molecular peaks of pyrimidines **8a-g** were detected at high intensity (See Scheme 3) with exception of compound **8e**, where the base peak was the tropilium ion (*m/z* = 91). It is known that pyrimidine forms easily $[M-H]^+$ ions [29-32]; however, for these compounds these fragments were not detected. Cleavage of the N1-C2 bond causes no change in mass, producing only a distonic radical ion (**11**). Subsequent cleavage of the N3-C4 with concomitant elimination of benzonitrile yields the most characteristic fragment of these compounds, the corresponding $[M-C_6H_5CN]^+$ (**12**) which is stabilized by the effect of the amino group.

It is important to note that the homologous elimination of 4-substituted benzonitrile was not observed. This difference can be explained because the cyano group is not able to stabilize the corresponding odd-electron ion. On the other hand, no fragments from a retro Diels-Alder reaction were detected. The stability of the possible diazodiene formed in the RDA process is too low and the reaction does not take place. This fragmentation pattern is similar to that previously found in the mass spectra of cycloalkane fused pyrimidines [33].

In order to gain a better understanding of the novel compounds, we have calculated their structures at *ab initio* and semiempirical levels.

Scheme 3



Mass spectrometry fragmentation pattern of pyrimidines **8a-g**.

In previous works we have widely used theoretical calculations for determining the conformational features of 1,4-DHPs and 3,4-dihydropyridone derivatives [34-36] and we have proved that *ab initio* and semiempirical calculations (at AM1 level) reproduce adequately the geometry of this type of compounds.

In the case of model compound **8a**, calculations were performed using both semiempirical AM1 and PM3 methods and *ab initio* HF/6-31G* method for comparison sake. Figure 1 shows the most stable conformation of **8a** calculated by semiempirical AM1 and HF/6-31G* *ab initio* method.

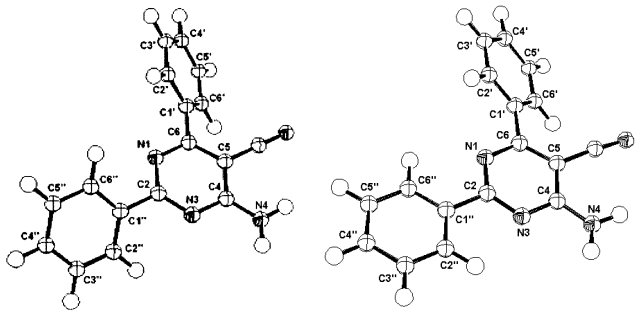


Figure 1. Most stable conformation for compound **8a** calculated by (a) AM1 and (b) HF/6-31G* showing the atomic numbering scheme.

Table 3

Heat of Fortmation and Most Relevant Bond Distances, Bond Angles and Dihedral Angles for Compound **8a**; Bond Distances are given in Å and Angles in Degrees

	AM1	PM3	HF/6-31G*
ΔH°_{f}	133.0 [a]	121.9 [a]	-868.58669 [b]
Bond distances			
C5-CN	1.411	1.417	1.432
C4-N4	1.373	1.401	1.339
C2-N3	1.361	1.360	1.320
C2-N1	1.374	1.370	1.325
C6-C1'	1.476	1476	1.489
C2-C1"	1.489	1.474	1.487
Bond angles			
N1-C2-N3	126.2	121.9	125.7
C2-N1-C6	117.1	119.9	118.3
C4-N3-C2	117.0	119.3	117.6
C4-C5-CN	120.4	121.0	118.4
C5-C4-N4	120.6	123.7	121.8
N1-C6-C1'	118.2	117.0	116.0
N3-C2-C1"	116.9	119.1	117.3
H-N4-H	119.0	113.8	119.3
Dihedral angles			
N3-C2-N1-C6	0.1	-0.1	-0.2
C2-N1-C6-C5	-0.6	0.3	-1.3
N1-C6-C5-C4	1.0	0.3	1.7
C6-C5-C4-N3	-0.9	-1.2	-0.7
C5-C4-N3-C2	0.5	1.4	-0.7
C4-N3-C2-N1	-0.1	-0.7	1.2
C2'-C1'-C6-N1	50.2	89.7	38.5
C2"-C1"-C2-N3	-39.0	-26.8	3.4
N3-C4-C5-CN	178.1	178.6	176.7
C6-C5-C4-N4	177.7	173.8	179.4

[a] Energy in kcal/mol; [b] Electronic energy in Hartree.

Table 3 shows the most relevant bond distances, valence angles and dihedral angles predicted for the minimum energy conformation of **8a** calculated by AM1, PM3 and HF/6-31G* methods.

Theoretical calculations show that the system formed by these three aromatic rings is not fully planar, due to the steric interaction of phenyl rings with the pyrimidine ring. Torsion angle C2"-C1"-C2-N3 is -39.0º, -26.8º and 3.4º by mean of AM1, PM3 and *ab initio* HF/6-31G* methods, respectively; while C2'-C1'-C4-N3 is 50.2º, 89.7º, 38.5º by AM1, PM3 and HF/6-31G*, respectively. Taking *ab initio* HF/6-31G* results as a reference, phenyl ring at C2 is nearly planar with respect to the pyrimidine ring, while phenyl group at C6 shows a clear loss of planarity and hence, the loss of electronic delocalization between both aromatic rings. The high deviation from coplanarity of the phenyl at C6 compared to coplanarity of the phenyl at C2 is due to the presence of the cyano group on C5 position. AM1 and PM3 methods overestimate the steric repulsion between both the phenyl and the pyrimidine rings. Nevertheless, AM1 method appears to be slightly closer to the HF/6-31G* results than PM3.

The bond angle H-N4-H for amino group is 119.0º and 119.3º for AM1 and *ab initio* HF/6-31G* optimized geometries. This fact indicates an sp^2 hybridization, due to the delocalization of the nitrogen lone-pair electrons through the aromatic pyrimidine ring. PM3 predict and sp^3 hybridization for the amine nitrogen since the bond angle H-N4-H is 113.8º in compound **8a**. In this case, PM3 do not reproduce the possible delocalization of the nitrogen lone-pair electrons through the aromatic ring, which can be confirmed by the longer C4-N4 bond distance predicted for PM3 (1.401 Å), while AM1 and *ab initio* HF/6-31G* methods gave 1.373 and 1.339 Å, respectively. For this particular bond distance, even when both semiempirical methods seems to overestimate the possible value, AM1 method appears to give more reliable values than PM3.

The remaining synthesized compounds **8b-g** were then studied by using the AM1 semiempirical method which shows more reliable results and the calculations reveal for compounds **8b-g** similar results. The most relevant geometrical data calculated for these compounds (**8b-g**) are collected in Table 4.

Conclusions.

In summary, we have carried out the one-step synthesis and characterization of substituted 4-amino-6-aryl-2-phenylpyrimidine-5-carbonitriles from the readily available 2-amino-4-aryl-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-benzopyrans. The structure of the compounds have been calculated by theoretical methods at the semiempirical and *ab initio* levels. Structural characterization has been completed by means of the fragmentation pattern of these heterocyclic compounds by mass spectrometric study under EI conditions.

Table 4

Most Relevant Bond Distances, Bond Angles Dihedral Angles for Compound **8b-g** Calculated by AM1 Semiempirical Method; Bond Distances are Given in Å and Angles in Degrees

	8b	**8c**	**8d**	**8e**	**8f**	**8g**
ΔH°_{f} [a]	127.0	94.6	141.1	123.7	96.0	137.4
Bond distances						
C5-CN	1.410	1.410	1.41	1.411	1.411	1.411
C4-N4	1.373	1.371	1.372	1.371	1.371	1.369
C2-N3	1.361	1.361	1.361	1.361	1.361	1.360
C2-N1	1.375	1.373	1.373	1.374	1.374	1.376
C6-C1'	1.479	1.474	1.472	1.474	1.475	1.479
C2-C1"	1.489	1.489	1.489	1.489	1.489	1.488
Bond angles						
N1-C2-N3	126.2	126.2	126.3	126.2	126.2	126.1
C2-N1-C6	117.0	117.1	117.2	117.1	117.1	117.0
C4-N3-C2	117.0	117.0	116.8	116.9	116.9	117.1
C4-C5-CN	120.6	120.3	120.2	120.27	120.4	120.5
C5-C4-N4	120.6	120.6	120.6	120.64	120.7	120.7
N1-C6-C1"	118.6	118.2	118.2	118.1	118.2	117.9
N3-C2-C1"	117.0	116.9	116.9	116.9	117.0	117.1
H-N4-H	119.2	119.7	119.6	119.7	119.7	119.6
Dihedral angles						
N3-C2-N1-C6	0.0	-0.3	-0.3	-0.3	0.3	0.0
C2-N1-C6-C5	-0.1	-0.5	-0.8	-0.5	0.6	-0.5
N1-C6-C5-C4	0.4	1.1	1.1	1.1	-0.9	0.6
C6-C5-C4-N3	-0.7	-0.8	-0.4	-0.8	0.5	-0.2
C5-C4-N3-C2	0.6	0.0	-0.5	0.0	0.2	-0.3
C4-N3-C2-N1	-0.2	0.6	1.0	0.6	-0.6	0.4
C2'-C1'-C6-N1	64.7	47.9	46.8	47.9	-48.1	51.4
C2"-C1"-C2-N3	-38.2	39.1	39.3	39.1	-39.2	38.7
N3-C4-C5-CN	178.8	177.9	178.1	178.0	-178.2	178.8
C6-C5-C4-N4	178.1	178.8	179.8	178.9	-179.5	179.9

[a] Energy in kcal/mol.

EXPERIMENTAL

Melting points were determined in a capillary tube in an Electrothermal C14500 apparatus and are uncorrected. The NMR spectra were recorded on a Bruker DPX300 spectrometer (300 MHz-^{1}H and 75.47 MHz-^{13}C). Chemical shifts are given as δ values against tetramethylsilane as the internal standard and *J* values are given in Hz. The IR spectra were measured with a Shimadzu FTIR 8300 instrument as potassium bromide pellets. Mass spectra were obtained with a Hewlett Packard 5989A spectrometer. Microanalyses were performed in a Perkin Elmer 2400 CHN by the Servicio de Microanálisis of Universidad Complutense de Madrid. The reactions were monitored by TLC performed on silica-gel plates (Merck $60F_{250}$) and using hexane:ethyl acetate (8:2) as eluent. Commercially available starting materials and reagents were purchased from commercial sources (BDH and Fluka) and were used without further purification. Semiempirical calculations (AM1 [37] and PM3 [38]) were carried out using the MOPAC 6.0 molecular orbitals set [39]. Previously, the molecular geometry was optimized by means of the Allinger´s Molecular Mechanics [40] with PCMODEL program [41]. *Ab initio* calculations were carried out with Gaussian 98 program [42]. Calculations were performed on an IBM-RS6000.

Synthesis of 3-Arylidenemalononitriles (**6a-g**).

These compounds were obtained by following the method previously reported in the literature [43].

General Procedure for Synthesis of 2-Amino-4-aryl-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-benzopyrans (**4a-g**).

A mixture of dimedone (5,5-dimethyl-1,3-cyclohexanedione) (40 mmol), the appropriate arylidenemalononitrile (40 mmol) and catalytic amount of piperidine in ethanol (40 mL) was stirred at room temperature. After 1 h, a precipitate was formed. The solid was collected by filtration. Further purification was accomplished by recrystallization from ethanol.

2-Amino-3-cyano-4-phenyl-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-benzopyran (**4a**).

This compound was obtained in 78 % yield, mp 224-225°; ir (KBr): 3396 and 3325 (NH_2), 2196 (CN), 1679 (C=O), 1660 and 1604 (C=C) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.29-7.09 (m, 5H, H2', H3', H4', H5', H6'), 6.99 (s, 2H, NH_2), 4.14 (s, 1H, H4), 2.38 (br s, 2H, H8), 2.24 (d, 1H, H6a, *J*=16.1 Hz), 2.14 (d, 1H, H6b, *J*=16.1 Hz), 1.01 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 195.7 (C5), 162.5 (C8a), 158.6 (C2), 144.8 (C1'), 128.4 (C2', C6'), 127.2 (C3', C5'), 126.6 (C4'), 119.8 (CN), 112.8 (C4a), 58.2 (C3), 50.1 (C6), 9.6 (C8), 5.6 (C4), 31.8 (C7), 28.5 (CH_3), 26.8 (CH_3); ms: m/z 294 (M^+, 66), 293 ($[M^+–H]^+$, 25), 217 ($[M^+–C_6H_5]^+$, 100), 161 (5).

Anal. Calcd. $C_{18}H_{18}N_2O_2$ (294.35): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.53; H, 6.31; N, 9.47.

2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(2'-methylphenyl)-5-oxo-4*H*-benzopyran (**4b**).

This compound was obtained in 88 % yield, mp 205-206°; ir (KBr): 3400 and 3330 (NH_2), 2194 (CN), 1679 (C=O), 1660 and 1620 (C=C) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.16-7.05 (m, 3H, H4', H5', H6'), 6.97 (d, 1H, H3' *J*=8.1 Hz), 6.93 (s, 2H, NH_2), 4.50 (s, 1H, H4), 2.56 (s, 3H, CH_3), 2.44 (br s, 2H, H8), 2.21 (d, 1H, H6a, *J*=16.3 Hz), 2.14 (d, 1H, H6b, *J*=16.3 Hz), 1.05 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 195.7 (C5), 162.4 (C8a), 158.2 (C2), 143.5 (C1'), 134.7 (C2'), 129.8 (C3'), 127.8 (C6'), 127.2 (C4'), 126.7 (C5'), 119.7 (CN), 113.4 (C4a), 58.2 (C3), 49.9 (C6), 39.4 (C8), 32.7 (C4), 31.8 (C7), 28.3 (CH_3), 26.7 (CH_3), 20.9 (CH_3); ms: m/z 308 (M^+, 90), 293 ($[M^+–CH_3]^+$ 30), 217 ($[M^+–C_6H_4\text{-}CH_3]^+$, 80); 161 (20).

Anal. Calcd. $C_{19}H_{20}N_2O_2$ (308.38): C, 74.00; H, 6.54; N, 9.08. Found: C, 74.36; H, 6.92; N, 9.43.

2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4'-methoxyphenyl)-5-oxo-4*H*-benzopyran (**4c**).

This compound was obtained in 82 % yield, mp 207-208°; ir (KBr): 3398 and 3317 (NH_2), 2187 (CN), 1683 (C=O), 1654 and 1606 (C=C) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.03 (d, 2H, H2', H6', *J*=8.6 Hz), 6.92 (s, 2H, NH_2), 6.82 (d, 2H, H3', H5', *J*=8.6 Hz), 4.10 (s, 1H, H4), 3.86 (s, 3H, OCH_3), 2.44 (br s, 2H, H8), 2.23 (d, 1H, H6a, *J*=16.3 Hz), 2.06 (d, 1H, H6b, *J*=16.3 Hz), 1.01 (s, 3H, CH_3), 0.93 (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 195.7 (C5), 162.2 (C8a), 158.4 (C4'), 157.9 (C2), 136.8 (C1'), 128.2 (C2', C6'), 119.8 (CN), 113.7 (C4a), 113.0 (C3', C5'), 58.7 (C3), 55.0 (OCH_3), 50.0 (C6), 40.7 (C8), 34.3 (C4), 32.8 (C7), 28.4 (CH_3), 26.8 (CH_3); ms: m/z 324 (M^+, 100), 293 ($[M^+–OCH_3]^+$,43), 217 ($[M^+–C_6H_4\text{-}OCH_3]$, 73), 161 (25).

Anal. Calcd. $C_{19}H_{20}N_2O_3$ (324.38): C, 70.35; H, 6.21; N, 8.64.

Found: C, 70.76; H, 6.52; N, 8.43.

2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4'-N,N-dimethylaminophenyl)-5-oxo-4*H*-benzopyran (**4d**).

This compound was obtained in 83 % yield, mp 216-217°; ir (KBr): 3388 and 3320 (NH_2), 2197 (CN), 1685 (C=O), 1650 and 1604 (C=C) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 6.93 (d, 2H, H2', H6', *J*=8.5 Hz), 6.87 (s, 2H, NH_2), 6.62 (d, 2H, H3', H5', *J*=8.5 Hz), 4.04 (s, 1H, H4), 2.52 (d, 1H, H8a, *J*=18.0 Hz), 2.42 (d, 1H, H8b, *J*=18.0 Hz), 2.83 (s, 6H, $2CH_3$), 2.23 (d, 1H, H6a, *J*=16.1 Hz), 2.06 (d, 1H, H6b, *J*=16.1 Hz), 1.04 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 195.7 (CO), 161.9 (C8a), 158.4 (C2), 149.3 (C4'), 132.6 (C1'), 127.8 (C2', C6'), 120.0 (CN), 113.3 (C4a), 112.4 (C3', C5'), 59.0 (C3), 50.1 (C6), 43.1 (CH_3), 42.9 (CH_3), 40.0 (C8), 34.3 (C4), 31.8 (C7), 28.6 (CH_3), 26.8 (CH_3); ms: m/z 337 (M^+, 100), 293 ($[M^+–N(CH_3)_2]^+$, 22), 217 ($[M^+–C_6H_4\text{-}N(CH_3)_2]^+$, 10), 161 (3).

Anal. Calcd. $C_{20}H_{23}N_3O_2$ (337.42): C, 71.19; H, 6.87; N, 12.45. Found: C, 71.46; H, 6.52; N, 12.53.

2-Amino-4-(4'-benzyloxyphenyl)-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-benzopyran (**4e**).

This compound was obtained in 86 % yield, mp 224-226°; ir (KBr): 3380 and 3310 (NH_2), 2189 (CN), 1688 (C=O), 1660 and 1610 (C=C) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 7.45-7.33 (m, 5H, H2", H3", H4", H5", H6"), 7.05 (d, 2H, H3', H5', *J*=8.7 Hz), 6.95 (s, 2H, NH_2), 6.91 (d, 2H, H2', H6', *J*=8.7 Hz), 4.11 (s, 1H, H4), 3.32 (s, 2H, CH_2), 2.46 (br s, 2H, H8), 2.24 (d, 1H, H6a, *J*=16.1 Hz), 2.08 (d, 1H, H6b, *J*=16.1 Hz), 1.02 (s, 3H, CH_3), 0.93 (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 195.4 (C5), 162.0 (C8a), 158.3 (C2), 156.9 (C4'), 137.0 (C1'), 136.9 (C1"), 128.2 (C3', C5'), 128.1 (C2", C6"), 127.6 (C3", C5"), 127.5 (C2', C6'), 119.6 (CN), 114.4 (1C), 112.8 (C4a), 69.1 (CH_2), 58.4 (C3), 49.9 (C6), 39.6 (C8), 34.7 (C4), 31.6 (C7), 28.2 (CH_3), 26.7 (CH_3); ms: m/z 400 (M^+, 20), 293 ($[M^+–OCH_2C_6H_5]^+$, 4), 217 ($[M^+–C_6H_4\text{-}OCH_2C_6H_5]^+$, 10), 161 (5), 91 (100).

Anal. Calcd. $C_{25}H_{24}N_2O_3$ (400.48): C, 79.98; H, 6.04; N, 7.00. Found: C, 79.48; H, 6.41; N, 7.43.

4-(4'-Acetamidophenyl)-2-amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-benzopyran (**4f**).

This compound was obtained in 86 % yield, mp 250-251°; ir (KBr): 3382 and 3303 (NH_2), 2191 (CN), 1683 (C=O), 1654 and 1606 (C=C) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 9.87 (s, 1H, NH), 7.44 (d, 2H, H3', H5', *J*=8.0 Hz), 7.03 (d, 2H, H2', H6', *J*=8.0), 6.97 (s, 2H, NH_2), 4.10 (s, 1H, H4), 2.47 (s, 2H, H8), 2.25 (d, 1H, H6a, *J*=16.0 Hz), 2.07 (d, 1H, H6b, *J*=16.0 Hz), 1.99 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.93 (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 195.4 (C5), 167.8 (C=O), 161.9 (C8a), 158.2 (C2), 139.1 (C1'), 137.5 (C4'), 127.1 (C3', C5'), 119.5 (CN), 118.8 (C2', C6'), 112.5 (C4a), 58.1 (C3), 49.7 (C6), 39.8 (C8), 34.7 (C4), 31.5 (C7), 28.1 (CH_3), 26.3 (CH_3), 23.6 (CH_3); ms: m/z 351 (M^+, 76), 293 ($[M^+–NHCOCH_3]^+$, 14), 217 ($[M^+–C_6H_4\text{-}NHCOCH_3]^+$, 100), 161 (15).

Anal. Calcd. $C_{20}H_{21}N_3O_3$ (351.41): C, 68.36; H, 6.02; N, 11.96. Found: C, 68.48; H, 6.33; N, 11.65.

2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4'-nitrophenyl)-5-oxo-4*H*-benzopyran (**4g**).

This compound was obtained in 81 % yield, mp 209-210°; ir (KBr): 3392 and 3327 (NH_2), 2198 (CN), 1685 (C=O), 1670 and 1637 (C=C), 1525 and 1350 (NO_2) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 8.16 (d, 2H, H3', H5', *J*=8.0 Hz), 7.43 (d, 2H, H2', H6', *J*=8.0 Hz), 7.19 (s, 2H, NH_2), 4.35 (s, 1H, H4), 2.52 (br s, 2H, H8), 2.25 (d, 1H, H6a, *J*=16.0 Hz), 2.08 (d, 1H, H6b, *J*=16.0 Hz), 1.02 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 195.7 (CO), 163.2 (C8a), 158.6 (C2), 152.3 (C1'), 146.3 (C4'), 128.7 (C3', C5'), 123.7 (C2', C6'), 119.4 (CN), 111.7 (C4a), 57.0 (C3), 49.7 (C6), 39.5 (C8), 35.5 (C4), 31.8 (C7), 28.3 (CH_3), 27.9 (CH_3); ms: m/z 339 (M^+, 65), 293 ($[M^+\text{-}NO_2]^+$, 18), 217 ($[M^+–C_6H_4\text{-}NO_2]^+$, 100), 161 (25).

Anal. Calcd. $C_{18}H_{17}N_3O_4$ (339.35): C, 63.71; H, 5.05; N, 12.38. Found: C, 63.86; H, 5.33; N, 12.51.

General Procedure of Synthesis of 4-Amino-6-aryl-2-phenylpyrimidine-5-carbonitrile (**8a-g**).

A solution of 144 mg (0.0063 at-g) sodium metallic in 20 mL dry ethanol was cooled with ice-water and benzamidine hydrochloride was added 0.889 g (5.7 mmol) with stirring during 15 minutes. The sodium chloride that precipitated was filtered off, and to the resulting solution 1.9 mmol of the corresponding tetrahydro-4*H*-benzopyran was added. The mixture was refluxed during 72 hours and the solid was collected by filtration. Further purification was accomplished by recrystallization from ethanol.

4-Amino-2,6-diphenylpyrimidine-5-carbonitrile (**8a**) [21].

This compound was obtained in 79 % yield, mp 158-159°; ir (KBr) 3470 and 3380 (N-H), 2202 (CN), 1660 and 1580 (C=C) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 8.31(m, 2H, H2" H6"), 7.92 (s, 2H, NH_2), 7.84 (m, 2H, H2', H6'), 7.45 (m, 6H, H3', H4', H5', H3", H4", H5"); ^{13}C nmr (dimethylsulfoxide-d_6): δ 168.0 (C6), 164.5 (C4), 163.9 (C2), 136.4 (C1"), 131.6 (C), 130.9(C), 128.6 (3C), 128.5 (3C), 128.4 (2C), 128.2 (C1'), 116.2 (CN), 84.3 (C5); ms: m/z 272 (100), 271 (72), 169 (76), 142 (15), 104 (27), 77 (26).

Anal. Calcd. $C_{17}H_{12}N_4$ (272.31): C, 74.98; H, 4.44; N, 20.57. Found: C, 74.88; H, 4.21; N, 20.32.

4-Amino-6-(2´-methylphenyl)-2-phenylpyrimidine-5-carbonitrile (**8b**).

This compound was obtained in 75 % yield, mp 201-202°; ir (KBr) 3450 and 3340 (N-H), 2200 (CN), 1650 and 1580 (C=C) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 8.28-8.05 (m, 2H, H2", H6"), 7.90 (s, 2H, NH_2), 7.44–7.32 (m, 3H, H3", H4", H5"), 7.21-7.11 (m, 3H, H3', H4', H5'), 7.01 (d, 1H, H3', *J*= 7.3 Hz), 2.47 (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 167.4 (C6), 164.9 (C4), 164.2 (C2), 138.2 (C1'), 136.7 (C1"), 135.2 (C2'), 129.6 (2C), 129.2 (2C), 128.8 (2C), 128.6 (2C), 128.4 (C), 117.2 (CN), 84.3 (C5), 20.9 (CH_3); ms: m/z 286 (100), 285 (62), 242 (15), 183 (55), 104 (25), 91 (10).

Anal. Calcd. $C_{18}H_{14}N_4$ (286.33): C, 75.50; H, 4.93; N, 19.57. Found: C, 75.62; H, 4.81; N, 19.72.

4-Amino-6-(4´-methoxyphenyl)-2-phenylpyrimidine-5-carbonitrile (**8c**).

This compound was obtained in 69 % yield, mp 215-216°; ir (KBr) 3375 and 3344 (N-H), 2118 (CN), 1639 and 1608 (C=C) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 8.40-8.29 (m, 2H, H2", H6"), 8.03-7.90 (d, 2H, H2', H6', *J*=11.3 Hz), 7.91 (s, 2H, NH_2), 7.53 (m, 3H, H3", H4", H5"), 7.14 (d, 2H, H6', H2', *J*=11.3 Hz), 3.87 (s, 3H, OCH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 167.2 (C6), 164.8 (C4), 164.0 (C2), 161.5 (C4'), 136.6 (C1"), 131.4

(C4"), 130.4 (C2', C6'), 128.7 (C1'), 128.4 (C3'', C5''), 128.3 (C2", C6"), 116.7 (CN), 113.8 (C5', C3'), 83.3 (C5), 55,4 (OCH_3); ms: m/z 302 (100), 301 (52), 258 (15), 199 (55), 104 (20).

Anal. Calcd. $C_{18}H_{14}N_4O$ (302.34): C, 71.51; H, 4.67; N, 18.53. Found: C, 71.68; H, 4.55; N, 18.37.

4-Amino-6-(4'-N,N-dimethylaminophenyl)-2-phenylpyrimidine-5-carbonitrile (**8d**) [22].

This compound was obtained in 72 % yield, mp 234-235°; ir (KBr) 3475 and 3305 (N-H), 2202 (CN), 1635 and 1616 (C=C) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 8.39-8.21 (m, 2H, H2", H6"), 8.02 (d, 2H, H2', H6', *J*=8.9 Hz), 7.72 (s, 2H, NH_2), 7.53-7.42 (m, 3H, H3", H4", H5"), 6.84 (d, 2H, H3', H5', *J*=8.9 Hz), 3.02 (s, 6H, $2CH_3$); ^{13}C nmr (dimethylsulfoxide-d_6): δ 167.6 (C6), 165.9 (C4), 164 4 (C2), 153.1 (C4'), 137.8 (C1"), 132.2 (C4"), 130.8 (C2', C6'), 129.3 (C5", C3"), 129.2 (C2", C6"), 123.7 (C1'), 118.3 (CN), 112.0 (C5', C3'), 82.5 (C5), 40.5 (CH_3), 40.4 (CH_3); ms: m/z 315 (100), 314 (63), 298 (12), 212 (16), 157 (10), 104 (14).

Anal. Calcd. $C_{19}H_{17}N_5$ (315.38): C, 72.36; H, 5.43; N, 22.21. Found: C, 72.65; H, 5.22; N, 22.32.

4-Amino-6-(4´-benzyloxiphenyl)-2-phenylpyrimidine-5-carbonitrile (**8e**).

This compound was obtained in 76 % yield, mp 265-266°; ir (KBr): 3385 and 3308 (N-H), 2190 (CN), 1660 and 1610 (C=C) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 8.42-8.24 (m, 2H, H2", H6"), 8.15 (d, 2H, H2', H6', *J*=9.7 Hz), 7.86 (s, 2H, NH_2), 7.58-7.38 (m, 8H, H3", H4", H5", Ph-CH_2), 7.22 (d, 2H, H3', H5', *J*=9.7 Hz), 5.23 (s, 2H, CH_2); ^{13}C nmr (dimethylsulfoxide-d_6): δ 168.0 (C6), 165.5 (C4), 164.7 (C2), 161.5 (C4'), 141.9 (C), 137.5 (C1"), 132.2 (2C), 131.3 (C), 129.7 (C), 129.4 (C), 129.3 (C2', C6'), 128.9 (C), 128.7 (2C), 128.4 (C1'), 128.1 (C), 127.8 (C), 117.6 (CN), 115.6 (C3', C5'), 84.2 (C5), 70.3 (CH_2); ms: m/z 378 (40), 377 (12), 353 (15), 319 (21), 275 (12), 104 (10), 91 (100).

Anal. Calcd. $C_{24}H_{18}N_4O$ (378.43): C, 76.17; H, 4.79; N, 14.80. Found: C, 76.83; H, 4.86; N, 14.58.

4-Amino-6-(4´-acetamidophenyl)-2-phenylpyrimidine-5-carbonitrile (**8f**).

This compound was obtained in 74 % yield, mp 243-244°; ir (KBr): 3930 and 3310 (N-H), 2202 (CN); 1680 (C=O), 1640 and 1620 (C=C) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 8.40-8.31 (m, 2H, H2", H6"), 7.92 (d, 2H, H3', H5', *J*=8.7 Hz), 7.81 (s, 2H, NH_2), 7.51 (d, 2H, H2', H6', *J*=8.7 Hz), 7.18-7.06 (m, 3H, H3", H4", H5"), 2.20 (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 169.1 (C=O), 168.1 (C6), 165.3 (C4), 164.7 (C2), 143.2 (C4'), 138.9 (C1"), 132.7 (C1'), 128.9 (C4"), 129.5 (C5", C3"), 127.7 (C2', C6'), 128.8 (C2", C6"), 118.2 (CN), 122.1 (C3', C5'), 83.4 (C5), 20.5 (CH_3); ms: m/z 329 (100), 328 (60), 203 (12), 104 (18).

Anal. Calcd. $C_{19}H_{15}N_5O$ (329.36): C, 69.29; H, 4.59; N, 21.26. Found: C, 69.42; H, 4.70; N, 21.32.

4-Amino-6-(4´-nitrophenyl)-2-phenylpyrimidine-5-carbonitrile (**8g**).

This compound was obtained in 76 % yield, mp 215-216°; ir (KBr): 3478 and 3300 (N-H), 2200 (CN); 1640, 1620 (C=C), 1540 and 1350 (NO_2) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 8.41 (m, 2H, H2", H6"), 8.14 (d, 2H, H3', H5', *J* = 7.9 Hz), 7.67 (s, 2H, NH_2), 7.62 (d, 2H, H2', H3', *J*=7.9 Hz), 7.28 (m, 3H, H3", H4", H5"); ^{13}C nmr (dimethylsulfoxide-d_6): δ 168.6 (C6), 166.7 (C4), 164.8 (C2), 150.2 (C4'), 145.8 (C1'), 139.2 (C1"), 129.5 (C4"), 130.3 (C5", C3"), 129.2 (C2", C6"), 128.9 (C2', C6'), 125.2 (C3', C5'), 118.5 (CN), 82.5 (C5); ms: m/z 317 (100), 316 (63), 283 (15), 214 (46), 104 (12).

Anal. Calcd. $C_{17}H_{11}N_5O_2$ (317.30): C, 64.35; H, 3.49; N: 22.07. Found: C, 64.61; H, 3.80; N, 22.36.

Acknowledgement.

Supports of this work by *Proyectos Alma Mater* (CUBA) and MCyT of Spain (BQU2002-00855 and BQU2000-0790) are gratefully acknowledged.

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