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Tin (IV) Chloride-promoted Synthesis of 4-Aminopyridines and 4-Aminoquinolines

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Abstract: Ortho-aminobenzonitriles 1 react with β-ketoesters and alkyl malonates, in the presence of stoichiometric amounts of tin(IV) chloride, to give 4-aminoquinolines **2** and 4-amino-2-quinolones **3** respectively. Similarly β-enaminonitriles **7** afford 4-aminopyridines **8** and 4-amino-2-pyridones **9**.

The metal-promoted reactions of β-dicarbonyl compounds with nitriles afford β-enaminodiones resulting from the formation of a new carbon-carbon bond between the nitrile cyano group and the intercarbonylic methylene group of β-dicarbonyls[1]. In some cases these compounds cyclize to pyrrolines[2] or dimerize to pyrimidines[3].

In order to further explore the scope and the synthetic utility of these reactions we have extended our investigations to nitriles bearing substituents suitable for obtaining heterocycles of medicinal interest. In this paper[4] we report the tin (IV) chloride-promoted reactions of aromatic *ortho*-aminonitriles **1** and β-enaminonitriles **7** with β-ketoesters and β-diesters and the intramolecular cyclization reaction of aromatic *ortho*-aminonitrile derivatives **4**, **5**, and β-enaminonitrile derivative **10**, bearing a β-dicarbonyl moiety linked to the amino group.

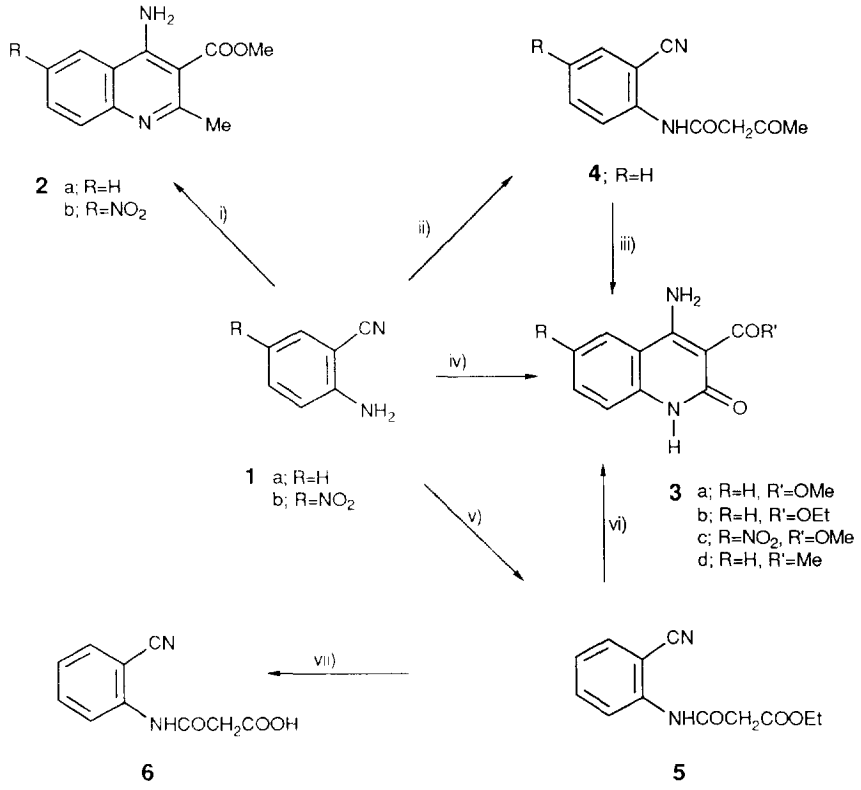
1. Reactions of *ortho*-aminobenzonitriles: Synthesis of 4-aminoquinolines (scheme 1)

The reactions of *ortho*-aminobenzonitriles with β-ketoesters and β-diesters were carried out in the presence of stoichiometric amounts of tin (IV) chloride and heating under reflux in toluene for 3-12 h; the reaction mixture was then treated with a saturated aqueous solution of sodium carbonate.

2-Aminobenzonitrile **1a** and the 5-nitro derivative **1b** reacted with methyl acetoacetate to give in good yield the 4-aminoquinolines **2a-b**. Similarly **1a,b** reacted with dialkyl malonates to afford in lower yield the 4-amino-2-quinolones **3a-c**.

In order to investigate an alternative intramolecular approach to quinolone derivatives **3**, we studied the cyclization of the acetoacetamide **4** and the malonyl ester amide **5**. Compound **4**, when heated under reflux in toluene in the presence of tin (IV) chloride, afforded the quinolone **3d** in low yield (35%); compound **5** under the same experimental conditions cyclized to the quinolone **3b** in only 5% yield. The cyclization in high yield of compounds **4** and **5** to quinolones **3d** and **3b** respectively was achieved by heating **4** and **5** under reflux in ethanol in the presence of stoichiometric amounts of sodium ethoxide. Compound **4** was cyclized to the

quinolone **3d** also by treatment with 1N sodium hydroxide, while compound **5** under the same experimental conditions afforded the acid derivative **6**.



i) CH_3COCH_2COOMe, $SnCl_4$; ii) diketene; iii) $SnCl_4$ or EtONa or NaOH;
iv) $CH_2(COOR')_2$, $SnCl_4$; v) $ClCOCH_2COOEt$; vi) EtONa; vii) NaOH

SCHEME 1

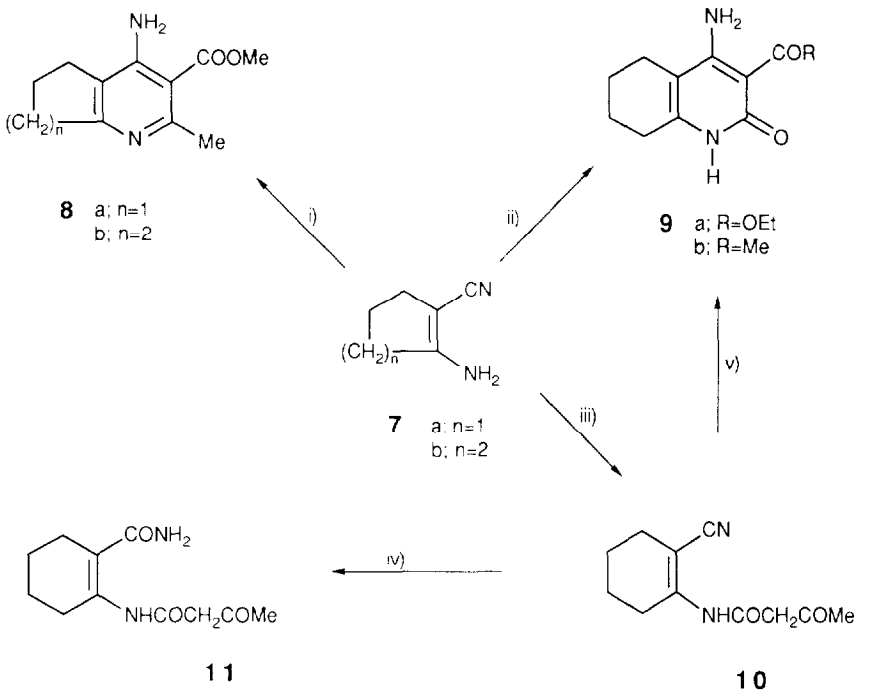
2. Reactions of β-enaminonitriles: synthesis of 4-aminopyridines (scheme 2)

The reactions of β-enaminonitriles with β-ketoesters and β-diesters were carried out in the presence of tin (IV) chloride under the same experimental conditions employed for the synthesis of quinolines.

The 4-aminopyridine derivatives **8a-b** were obtained in good yield by reaction of 1-amino-2-cyano-cyclopentene **7a** and 1-amino-2-cyano-cyclohexene **7b** with methyl acetoacetate while the 4-amino-2-pyridone **9a** was obtained in lower yield by the reaction of enaminonitrile **7b** with diethyl malonate.

In the alternative intramolecular cyclisation approach, when the acetoacetamide **10** was heated under reflux in the presence of tin (IV) chloride, the amido acetacetamide **11** was the only isolated compound.

Also in this case the cyclization of the acetoacetamide **10** to the pyridone **9b** was achieved by treatment with sodium ethoxide or sodium hydroxide.



i) CH_3COCH_2COOMe, $SnCl_4$; ii) $CH_2(COOEt)_2$, $SnCl_4$; iii) diketene; iv) $SnCl_4$; v) NaOH or EtONa

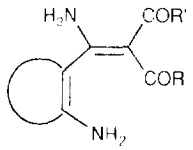
SCHEME 2

Discussion

The results obtained demonstrate that tin (IV) chloride is efficient in promoting the *intermolecular* reactions of aromatic *ortho*-aminonitriles and of β-enaminonitriles with β-ketoesters and β-diesters giving quinoline or pyridine derivatives respectively. Good yields of these heterocycles were obtained in the reactions of aminonitriles with β-ketoesters, while lower yields were obtained in the reactions with diesters.

According to our previous results[5] the heterocycles obtained are formed *via* the intermediate β-enaminodiones **12**, which were never isolated possibly because of their fast cyclization to heterocycles.

Tin (IV) chloride promotes these reactions possibly because of its well known ability to coordinate both β-dicarbonyl compounds[6] and nitriles[7], thus enhancing their nucleophilic and electrophilic character respectively.



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The *intramolecular* cyclization of acetoacetamide **4** and malonyl ester amide **5**, carried out in the presence of tin (IV) chloride, gave the quinolone derivatives only in low yield. In the same experimental conditions the acetoacetamide **10** failed to afford the expected pyridone **9b**. These results may be a consequence of steric and/or geometric factors inhibiting tin chloride activation, through coordination of both the β-dicarbonyl moiety and the cyano group of the same molecule. However the intramolecular cyclization of these compounds can be easily achieved in the presence of sodium ethoxide and in same cases also in the presence of sodium hydroxide.

The two different synthetic approaches are therefore complementary and allow an easy entry to 4-aminoquinoline and 4-aminopyridine derivatives, compounds of particular interest in medicinal chemistry[8].

Experimental

Mp.s were determined on open capillary tubes on a Buchi apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 157G spectrometer (values in cm^{-1}). NMR spectra were recorded on Brucker AC (200 MHz) spectrometer. Chemical shifts are given in ppm (δ) with respect to tetramethylsilane and coupling constants (J) are in Hertz. Merck Kieselgel (type 60) coated on glass plates were used for thin layer chromatography. Merck "Kieselgel 60" (70-230 mesh) was used for column chromatography.

1. Synthesis of 4-aminoquinolines

General procedure:

4-Amino-2-methyl-quinoline-3-carboxylic acid methyl ester **2a**

2-Amino-benzonitrile **1a** (1.18 g, 10 mmol) and $SnCl_4$ (2.3 ml, 20 mmol) were added to a stirred solution of methyl acetoacetate (1.08 ml, 10 mmol) in dry toluene (25 ml). The reaction mixture was stirred under nitrogen at room temperature for 30 min and then heated under reflux for 3 h. The solvent was removed under reduced pressure to give a residue, which was stirred for 30 min with a saturated aqueous solution of Na_2CO_3 (80 ml, pH *ca.*10). The suspension was extracted with ethyl acetate (3 x 50 ml) and filtered on Celite. The aqueous layer was extracted with ethyl acetate (2 x 20 ml) and the combined extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give the quinoline **2a** (1.24 g, 74%) as pale yellow crystals, mp 158-160°C; IR (KBr): 3360, 3160 (br), 1670, 1615, 1550, 1260; ^1H NMR ($CDCl_3$): δ 2.80 (s, 3H, Me), 3.90 (s, 3H, Me), 7.08 (br, 2H, NH_2), 7.4 -7.9 (m, 4H, Ph); ^{13}C NMR ($CDCl_3$): δ 27.9 (q, J=128 Hz, Me), 51.6 (q, J=148 Hz, OMe), 102.1 (s, C-3), 116.9 (s, Ar), 120.6 (d, J= 158 Hz, Ar), 124.9 (d, J=161 Hz, Ar), 129.0 (d, J=163 Hz, Ar), 131.3 (d, J= 162 Hz, Ar), 147.5 (s, Ar), 153.7 (C-4), 159.5 (s, C-2), 169.9 (s, COO). Found: C, 66.5; H, 5.4; N, 12.9. $C_{12}H_{12}N_2O_2$ requires C, 66.6; H, 5.6; N, 12.9.

Following this general procedure, with modification reported below, the following compounds were obtained:

4-Amino-2-methyl-6-nitro-quinoline-3-carboxylic acid methyl ester **2b**: obtained in 59% yield from 2-amino-5-nitro-benzonitrile **1b** and methyl acetoacetate as colourless crystals, mp 203-205°C (EtOH); IR(KBr): 3460, 3340, 3100 (br), 1730, 1680, 1640, 1550, 1240; ^1H NMR (DMSO-d_6): δ 2.61 (s, 3H, Me), 3.89 (s, 3H, Me), 7.80 (d, J=8.9 Hz, 1H, Ar), 8.12 (br, 2H, NH_2), 8.35 (dd, J=8.9 and 1.8 Hz, 1H, Ar), 8.39 (d, J=1.8 Hz, 1H, Ar). Found: C, 54.71; H, 4.26; N, 16.28. $C_{12}H_{11}N_3O_4$ requires C, 55.17; H, 4.24; N, 16.09.

4-Amino-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methylester **3a**: obtained in 24% yield from 2-amino-benzonitrile **1a** and dimethyl malonate. The reaction mixture was heated under reflux for 12 h: colourless crystals, mp 236-238°C; IR (KBr): 3380-3200, 1670, 1640, 1620, 1280; ^1H NMR (DMSO-d_6): two species are present: i) the main species corresponds to the amidic tautomer (80%): δ 3.74 (s, 3H, Me), 7.09-

7.21 (m, 2H, Ar), 7.49-7.57 (m, 1H, Ar), 8.11 (d, J=9 Hz, 1H, Ar), 8.43 (br, 2H, NH_2), 10.92 (br, 1H, NH); ii) the minor species (20%) corresponds to an enolic tautomer: δ 3.51 (s, 3H, Me), 7.37 (m, 2H, Ar), 7.64 (m, 1H, Ar), 8.27 (m, 1H, Ar), 8.8 (br, 1H, NH), 9.9 (br, 1H, NH), 16.1 (br, 1H, OH). Found: C, 60.3; H, 4.5; N, 12.6. $C_{11}H_{10}N_2O_3$ requires C, 60.55; H, 4.62; N, 12.84.

4-Amino-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid ethyl ester **3b**: obtained in 31% yield from 2-amino-benzonitrile **1a** and diethyl malonate. The reaction mixture was heated under reflux for 12 h: colourless crystals, mp 247-250°C; IR (KBr): 3350-2800, 1660, 1640, 1630, 1600 (br), 1250; ^{1}H NMR (DMSO-d_6): δ 1.27 (t, J=7.0 Hz, 3H, Me), 4.23 (q, J=7.0 Hz, 2H, OCH_2), 7.08-7.22 (m, 2H, Ar), 7.52 (t, J=7.6 Hz, 1H, Ar), 8.09 (d, J=8.2 Hz, 1H, Ar), 8.33 (br, 2H, NH_2), 10.86 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 14.2 (q, J=126 Hz, Me), 59.4 (t, J=147 Hz, OCH_2), 93.2 (s, C-3), 112.1 (s, C-4a, Ar), 115.2 (d, J=164 Hz, CH, Ar), 120.7 (d, J=164 Hz, CH, Ar), 123.6 (d, J=160 Hz, CH, Ar), 132.3 (d, J=164 Hz, CH, Ar), 139.3 (s, C-8a, Ar), 156.8 (s, C-4), 159.8 (s, C-2), 168.8 (s, COO). Found: C, 62.2; H, 5.3; N, 12.2. $C_{12}H_{12}N_2O_3$ requires C, 62.06; H, 5.21; N, 12.06.

4-Amino-6-nitro-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid methyl ester **3c**: obtained in 24% yield from 2-amino-5-nitro-benzonitrile **1b** and dimethyl malonate. The reaction mixture was heated under reflux for 12 h: brown crystals, mp 280-285°C (ethyl acetate); IR (KBr): 3430, 3340, 3240, 1710, 1625, 1500, 1455, 1320, 1070; ^{1}H NMR (DMSO-d_6): two species are present: the main species (85%) corresponds to an amidic tautomer: δ 3.75 (s, 3H, OMe), 7.3 (d, J=9.1 Hz, 1H, Ar), 8.35 (dd, J=9.1 and 1.7 Hz, 1H, Ar), 8.7 (br, 2H, NH_2), 9.17 (d, J=1.7 Hz, 1H, Ar), 11.5 (br, 1H, NH). The minor species (15%) corresponds to an enolic tautomer and shows absorptions at δ 3.51 (OMe) and at 15.6 (OH). Found: C, 50.9; H, 3.3; N, 16.1. $C_{11}H_9N_3O_5$ requires C, 50.20; H, 3.45; N, 15.97.

N-(2-Cyano-phenyl)-3-oxo-butanamide **4**

A mixture of 2-amino-benzonitrile (0.50 g, 4.2 mmol) and diketene (0.36 ml, 4.65 mmol) was heated at 60°C for 6 h. The resulting solid was suspended in ethyl ether and stirred for 0.5 h: the separated crystals were filtered and dried (P_2O_5) to give 0.814 g (yield 96%) of **4**, colourless crystals, mp 115-118°C; IR (KBr): 3200-3000, 2210, 1710, 1680, 1600, 1290; ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H, Me), 3.70 (s, 2H, CH_2), 7.15-7.23 (m, 1H, Ph), 7.53-7.61 (m, 2H, Ph), 8.24-8.33 (m, 1H, Ph), 9.93 (br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 31.1 (q, J=128 Hz, Me), 49.1 (t, J=128 Hz, CH_2), 103.0 (s, C-CN, Ph), 116.3 (s, CN), 121.8 (d, J=167 Hz, Ph), 124.5 (d, J=165 Hz, Ph), 132.5 (d, J=159 Hz, Ph), 133.9 (d, J=162 Hz, Ph), 140.2 (s, C-NH, Ph), 164.3 (s, NHCO), 204,8 (s, CO). Found: C, 65.5; H, 4.8; N, 13.7. $C_{11}H_{10}N_2O_2$ requires C, 65.34; H, 4.98; N, 13.85.

Cyclisation of compound **4** *to 3-acetyl-4-amino quinolin-2-one* **3d**

a) in the presence of tin(IV) chloride: $SnCl_4$ (0.35 ml, 3 mmol) was added to a solution of compound **4** (0.55 g, 2.5 mmol) in toluene (10 ml). The reaction mixture was heated under reflux for 12 h, concentrated under reduced pressure to give a residue, which was stirred for 30 min with a saturated aqueous solution of sodium carbonate (pH *ca.*10). The resulting suspension was extracted with ethyl acetate (3 x 50 ml), the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give 0.188 g (35%) of the quinolone **3d**; colourless crystals, mp 308-310°C; IR (KBr): 3360, 3260, 3000, 2880, 1670, 1610, 1520, 1480; ^{1}H NMR (DMSO-d_6): δ 2.6 (s, 3H, Me), 7.1-7.25 (m, 2H, Ar), 7.52-7.60 (m, 1H, Ar), 8.16 (d, J=7.0 Hz, 1H, Ar), 8.6 (br, 1H, NH), 10.8 (br, 1H, NH), 10.9 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 33.1 (q, J=127 Hz, Me), 101.0 (s, C-3), 112.5 (s, C-4a), 115.4 (d, J=163 Hz, Ar), 120.9 (d, J=155 Hz, Ar), 124.0 (d, 149 Hz, Ar), 132.9 (d, J = 163 Hz, Ar), 139.5 (s, C-8a), 158.1 (s, C-4), 162.4 (s, C-2), 200.4 (s, CO). Found: C, 65.4, H, 4.7; N, 13.8; $C_{11}H_{10}N_2O_2$ requires C, 65.34; H, 4.98; N, 13.85.

b) in the presence of sodium ethoxide: A 1M solution of sodium ethoxide (2.5 ml, 2.5 mmol) was added to a suspension of **4** (0.50 g, 2.47 mmol) in ethanol (1 ml). The reaction mixture was heated at 50°C in an oil bath for 24 h and then cooled. The separated colourless crystals were filtered, washed with ethanol and dried under reduced pressure (P_2O_5) to give the quinolone **3d**: 0.260 g (yield 86%).

c) In the presence of sodium hydroxide: Compound **4** (0.404 g, 2 mmol) was added to a 1M solution of sodium hydroxide. The reaction mixture was stirred at room temperature for 8 h: the separated crystals were washed with water and dried under reduced pressure (P_2O_5) to give the quinolone **3d**: 0.327 g (yield 82%).

3-Oxo-3-(2-cyanophenylamino)-propanoic acid ethyl ester **5**

To a solution of anthranilonitrile **1a** (0.59 g, 5 mmol) in dichloromethane (10 ml) ethyl malonyl chloride (0.77 ml, 6 mmol) and a saturated aqueous solution of sodium carbonate (12 ml, pH>10) were added. The reaction mixture was stirred for 3 h. The two layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give compound **5**: 1.07 g (yield 92%), pale yellow crystals, mp 93-95°C. IR (KBr): 3250, 2235, 1750, 1670, 1250; ^{1}H NMR ($CDCl_3$): δ 1.32 (t, J=7.2 Hz, 3H, Me), 3.58 (s, 2H, CH_2), 4.30 (q, J=7.2 Hz, 2H, O-CH_2), 7.19 (t, J=7.7 Hz, 1H, Ph), 7.54-7.52 (m, 2H, Ph), 8.35 (d, J=8.3 Hz, 1H, Ph), 9.92 (br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 13.8 (q, J=127 Hz, Me), 41.4 (t, J=131 Hz, CH_2), 62.0 (t, J=144 Hz, OCH_2), 102.6 (s, C-CN, Ph), 116.0 (s, CN), 121.4 (d, J=168 Hz, CH, Ph), 124.3 (d, J=166 Hz, CH, Ph), 132.3 (d, J=160 Hz, CH, Ph), 133.8 (d, J=163 Hz, CH, Ph), 140.0 (s, C-NH, Ph), 163.6 (s, NH-CO), 169.0 (s, COOEt). Found C, 62.2; H, 5.1; N, 12.2. $C_{12}H_{12}N_2O_3$ requires C, 62.06; H, 5.21, N, 12.06.

Cyclisation of compound **5** *to quinolinone* **3b**

a) In the presence of tin(IV) chloride: A 1M solution of $SnCl_4$ in dichloromethane (1.2 ml, 1.2 mmol) was added to a solution of compound **5** (0.232 g, 1 mmol) in dichloromethane (3 ml). The reaction mixture was heated under reflux for 24 h and treated as described in the general procedure. The ^{1}H NMR spectrum of obtained oil showed that the quinoline **3b** was formed in *ca.* 5% yield.

b) in the presence of sodium ethoxide: A 1M solution of sodium ethoxide in ethanol (1.5 ml, 1.5 mmol) was added to a solution of compound **5** (0.232 g, 1 mmol) in ethanol (2 ml). The reaction mixture was heated under reflux for 24 h, cooled at room temperature and poured into iced water. The separated crystals were filtered, washed with ethanol and dried (P_2O_5) to give the quinoline **3b**: 0.075 g (yield 32%).

3-Oxo-3 (2-cyanophenylamino)-propanoic acid **6**

Compound **5** (0.232 g, 1 mmol), stirred with 1N sodium hydroxide (1.2 ml, 1.2 mmol) at room temperature for 24 h, after treatment with 1N hydrochloric acid (pH *ca.* 1), gave the acid derivative **6** in 60% yield: colourless crystals, mp 114-116°C; IR (KBr): 3320, 3250-2500, 2220, 1730, 1650, 760; ^{1}H NMR (DMSO-d_6): δ 3.46 (s, 2H, CH_2), 7.30-7.38 (m, 1H, Ph), 7.59-7.80 (m, 2H, Ph), 7.81-7.83 (m, 1H, Ph), 10.40 (s, 1H, NH), 12.7 (br, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 42.9 (t, J=129 Hz, CH_2) 106.0 (s, C-CN, Ph), 116.5 (s, CN), 124.7 (d, J=163 Hz, CH, Ph), 125.5 (d, J=164 Hz, CH, Ph), 133.2 (d, J=164 Hz, CH, Ph), 133.7 (d, J=145 Hz, CH, Ph), 139.7 (s, C-NH, Ph), 165.1 (s, CO), 169.0 (s, CO). Found: C, 58.9; H, 3.8; N, 13.6. $C_{10}H_8N_2O_3$ requires C, 58.82; H, 3.95; N, 13.72.

2.Synthesis of 4-aminopyridines

General procedure: 2-Methyl-4-amino-5,6-trimethylene-pyridine -3-carboxylic acid methyl ester **8a**

1-Amino-2-cyano-cyclopentene **7a**[9] (1.08 g, 10 mmol) and $SnCl_4$ (2.3 ml, 20 mmol) were added to a stirred solution of methyl acetoacetate (1.08 ml, 10 mmol) in dry toluene (25 ml). The reaction mixture was stirred under nitrogen at room temperature for 30 min and then heated under reflux for 3 h. The solvent was

removed under reduced pressure to give a residue, which was stirred for 30 min with a saturated aqueous solution of Na_2CO_3 (80 ml, pH *ca.*10). The suspension was extracted with ethyl acetate (3 x 50 ml) and the combined extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give the pyridine **8a** (1.24 g, 60%) as pale yellow crystals, mp 113-115°C; IR (Nujol): 3425, 3340-3260, 3220-3160, 1690, 1610, 1250. ^1H NMR ($CDCl_3$): δ 2.2 (m, 2H, CH_2), 2.65 (s, 3H, Me), 2.70 (t, J=6.1 Hz, 2H, CH_2), 2.95 (t, J=6.1 Hz, 2H, CH_2), 3.89 (s, 3H, Me), 5.7 (br, 1H, NH), 7.3 (br, 1H, NH). Found: C, 63.8; H, 6.7; N, 13.4. $C_{11}H_{14}N_2O_2$ requires: C, 64.06; H, 6.84; N, 13.58.

According to this general procedure, with the modification reported below, the following compounds were synthesized:

2-Methyl-4-amino-5,6-tetramethylene-pyridine -3-carboxylic acid methyl ester **8b**: obtained in 50% yield in the reaction of 1-amino-2-cyano-cyclohexene **7b**[9] with methyl acetoacetate; pale yellow crystals, mp 96-98°C, IR (KBr): 3400-3200, 1680, 1610, 1220; ^1H NMR ($CDCl_3$): 1.60-1.65 (m, 4H, two CH_2), 2.33-2.38 (m, 2H, CH_2), 2.61 (s, 3H, Me), 2.74-2.80 (m, 2H, CH_2), 3.69 (s, 3H, OMe), 5.97 (br, 2H, NH_2).

2-Oxo-4-amino-5,6-tetramethylene 1-H-pyridine-3-carboxylic acid ethyl ester **9a**: obtained in 32% yield from 1-amino-2-cyano-cyclohexene **7b** and diethyl malonate in dichloromethane at room temperature for 24 h: colourless crystals, mp 222-225°C; IR (KBr): 3410, 3290, 1660, 1620 (br), 1530, 1270,1190, 1090; ^1H NMR ($CDCl_3$): δ 1.40 (t, J=7.1 Hz, 3H, Me), 1.79 (m, 4H, two CH_2), 2.30 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 4.34 (q, J=7.1 Hz, O-CH_2), 5-10 (2H, NH_2), 11.7 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 14.3 (q, J=125 Hz, Me), 20.7 (t, J=123 Hz, CH_2), 21.1 (t, J=123 Hz, CH_2), 21.5 (t, J=129 Hz, CH_2), 26.3 (t, J=126 Hz, CH_2), 58.8 (t, J=146 Hz, OCH_2), 91.6 (s, C-5), 101.6 (s, C-3), 145.5 (s, C-6), 160.2 (s, C-4 and C-2), 169.3 (s, COO). Found: C, 61.2; H, 6.90; N, 11.65. $C_{12}H_{16}N_2O_3$ requires C, 61.00; H, 6.83; N,11.86.

3-Oxo-N-(2-cyanocyclohexyl)-butanamide **10**

A mixture of 1-amino-2-cyano-cyclohexene **7b** (0.488 g, 4 mmol) and diketene (0.388 ml, 4.4 mmol) was heated on a oil bath at 60°C for 18 h. The obtained oil was purified by column chromatography (ethyl acetate-light petroleum 1:2): colourless crystals of **10**, mp 62-64°C, 0.758 g (yield 92%); IR (KBr): 3250, 2220, 1725, 1670, 1630,1160; ^1H NMR ($CDCl_3$): δ 1.61-1.72 (m, 4H, two CH_2), 2.28-2.34 (m, 2H, CH_2), 2.30 (s, 3H, Me), 2.72-2.76 (m, 2H, CH_2), 3.59 (s, 2H, CH_2), 9.31 (br, 1H, NH); ^{13}C NMR ($CDCl_3$): 20.9 (t, J=120 Hz, CH_2), 21.4 (t, J=117 Hz, CH_2), 25.8 (t, J=129 Hz, CH_2), 28.0 (t, J= 129 Hz, CH_2), 31.0 (q, J=127 Hz, CH_3), 49.6 (t, J=127, CH_2), 93.2 (s, C-CN), 117.8 (s, CN), 150.7 (s, C-NH), 163.8 (s, CONH), 204.21 (s, CO). Found: C, 64.2; H, 6.9; N, 13.7. $C_{11}H_{14}N_2O_2$ requires C, 64.06; H, 6.84; N, 13.58.

Cyclisation of compound **10** to **9b**

a) in the presence of sodium hydroxide: A solution of compound 10 (0.412 g, 2 mmol) in 1N NaOH (3 ml, 3 mmol) was stirred at room temperature for 24 h: the separated crystals were filtered, washed with water and dried (P_2O_5): colourless crystals of **9b**, 0.224 g (yield 55%), mp 300-302°C; IR (KBr): 3360, 3180, 3000-2700, 1630, 1530; ^1H NMR ($CDCl_3$): 1.65 (m, 4H, two CH_2), 2.17 (m, 2H, CH_2), 2.38 (m, 2H, CH_2), 2.49 (s, 3H, Me), 7.01 (br, 1H, NH), 10.28 (br, 1H, NH), 10.50 (br, 1H, NH); ^{13}C NMR ($CDCl_3$): 20.7 (t, J=127 Hz, CH_2), 20.8 (t, J=127 Hz, CH_2), 21.4 (t, J=124 Hz, CH_2), 26.4 (t, J= 131 Hz, CH_2), 32.8 (q, J=127 Hz, Me), 100.9 (s, C-5), 102.15 (s, C-3), 146.1 (C-NH), 160.4 (C-NH_2), 162.8 (CO-NH), 199.4 (CO). Found: C, 64.0; H, 6.9; N 13.7. $C_{11}H_{14}N_2O_2$ requires C, 64.06; H, 6.84; N, 13.68.

b) in the presence of sodium ethoxide: A solution of **10** (0.412 g, 2 mmol) in 1M solution of sodium ethoxide in ethanol (3 ml, 3 mmol) was heated under reflux for 24 h: the pyridinone **9b** was obtained in 44% yield togheter with the amide **11** (10% yield).

3-Oxo-N-(2-carboxamidocyclohexyl)-butanamide **11**

A 1M solution of $SnCl_4$ in dichloromethane (2.6 ml, 2.6 mmol) was added to a solution of **10** (0.412 g, 2 mmol) in dichloromethane (5 ml). The reaction mixture was heated at reflux for 48 h and worked up as described in the general procedure. The obtained oil was purified by column chromatography (chloroform-methanol, 9:1) to give the amide **5** as colourless oil, 0.250 g (62%). IR (neat): 3515, 3410, 1640 (br), 1340, 1310, 900; ^1H NMR ($CDCl_3$): 1.65 (m, 4H, two CH_2), 2.25 (m, 2H, CH_2), 2.28 (s, 3H, Me), 2.94 (m, 2H, CH_2), 3.45 (s, 2H, CH_2), 5.9 (br, 1H, NH), 6.3 (br, 1H, NH), 12.8 (br, 1H, NH); ^{13}C NMR ($CDCl_3$): 21.5 (t, J=128 Hz, CH_2), 21.5 (t, J=128 Hz, CH_2), 24.8 (t, J=125 Hz, CH_2), 28.1 (t, J=128 Hz, CH_2), 30.3 (q, J=127 Hz, Me), 53.8 (t, J=128 Hz, CH_2), 105,4 (s, =C-CO), 149.7 (s, =C-NH), 164.3 (s, CONH), 172.5 (s, CONH), 202.1 (s, CO). Found: C, 58.8; H, 7.3; N, 12.4. $C_{11}H_{16}N_2O_3$ requires C, 58.91; H, 7.19; N, 12.49.

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