ON THE MECHANISM OF FORMATION OF PYRIDINES FROM α,β-UNSATURATED NITRILES AND ACTIVE CYANO COMPOUNDS

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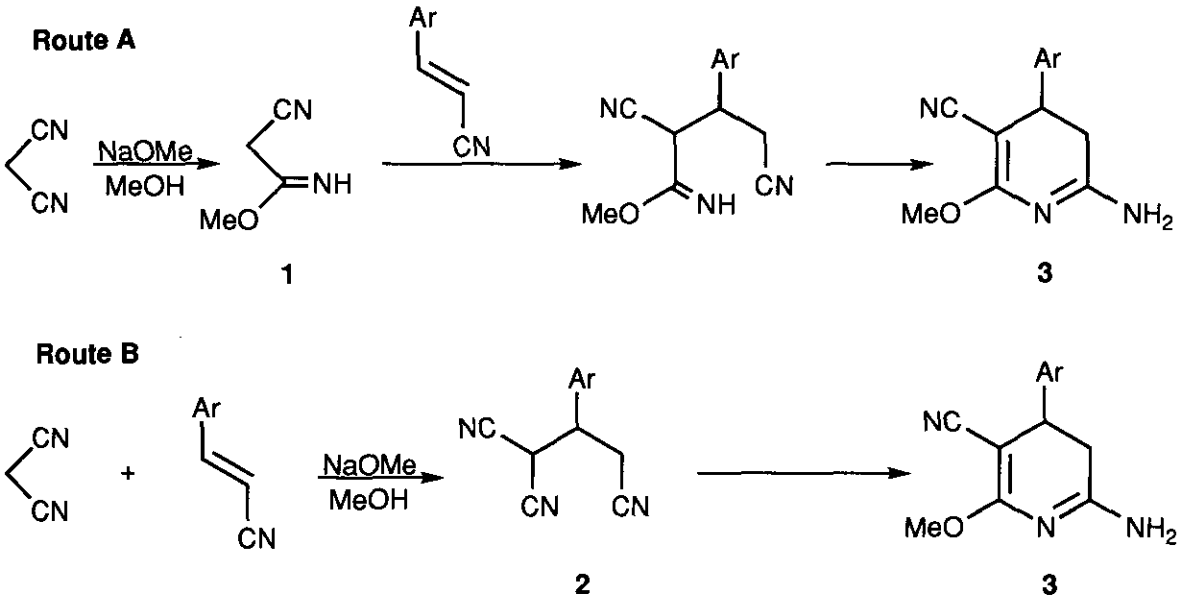
Abstract- The mechanism of formation of pyridines from α,β-unsaturated nitriles and active cyano compounds has been investigated. These processes proceed through a Michael adduct which undergoes a regioselective cyclization to the corresponding heterocyclic compound. The regioselectivity of the heterocyclization processes is justified.

A synthesis of heterocyclic compounds from α,β-unsaturated nitriles is a useful tool in heterocyclic chemistry.[1-5] We have previously described [6] the synthesis of 3,4-dihydropyridines (**3**) from the reaction of malononitrile with cinnamonitriles in sodium methoxide-methanol. Two posible routes for the formation of the 3,4-dihydropyridines can be devised. One of them involves intervention of the malononitrile methyl imidate (**1**) as an intermediate (route A) whereas in the other, a Michael adduct (**2**) is proposed (route B) (Scheme 1).

With the purpose of studying the mechanism of the formation of 3,4-dihydropyridines (**3**) we performed the reaction of malononitrile methyl imidate (**1**) with cinnamonitrile in sodium methoxide-methanol which did not afford the corresponding 3,4-dihydropyridine (**3**). We then synthesized the 2-phenyl-1,1,3-propanotricarbonitrile (**2 a**) from malononitrile and cinnamonitrile in dimsyl sodium-dimethyl sulfoxide. By heating at reflux a methanolic solution of **2 a** with sodium methoxide, 2-amino-5-cyano-6-methoxy-4-phenyl-3,4-dihydropyridine (**3 a**) was obtained as the

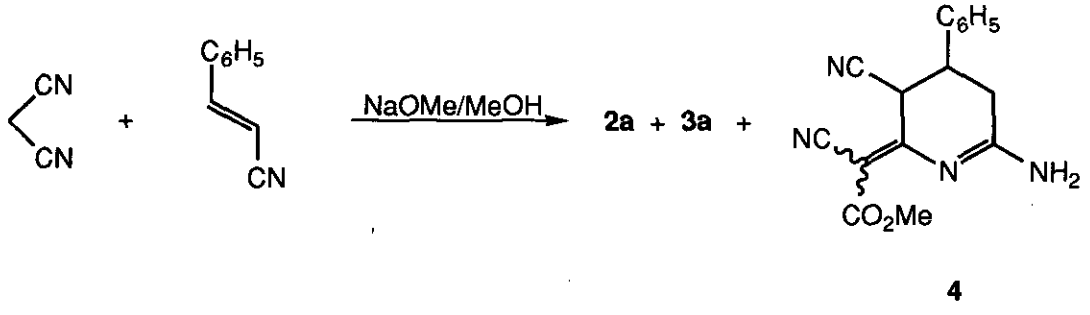
sole product.

Scheme 1



Reinvestigation of the previously described reaction [6] of cinnamonitrile with malononitrile in sodium methoxide-methanol led to the isolation of the 3,4-dihydropyridine (**3 a**), and 2-phenyl-1,1,3-propanotricarbonitrile (**2 a**) and 6-amino-3-cyano-2-(cyanomethoxycarbonylmethylidene)-4-phenyl-2,3,4,5-tetrahydropyridine (**4**) as side-products.

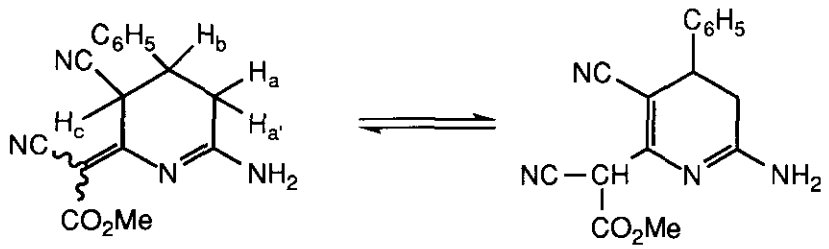
Scheme 2



Formation of the tetrahydropyridine (**4**) can be explained by reaction of the dihydropyridine (**3 a**) with methyl cyanoacetate formed in turn from malononitrile. The structure of **4** was characterized from spectrocopic data. In dimethyl sulfoxide solution the predominant tautomeric form is **4 a** which exists as a diastereomeric racemic mixture. Thus the ^{1}H-nmr spectrum of **4** in this solvent shows a

doublet which is attributed to proton H-3 and complex multiplets for protons H-4 and H-5. The ir spectrum (KBr) shows the presence of stretching bands at 2259 (w) and 2215 (s) cm^{-1}, attributed to non-conjugated and conjugated cyano group respectively. The absorption of the methoxycarbonyl group at 1749 (s) cm^{-1} establishes that in the solid state the predominant tautomeric form is **4b**.

Scheme 3

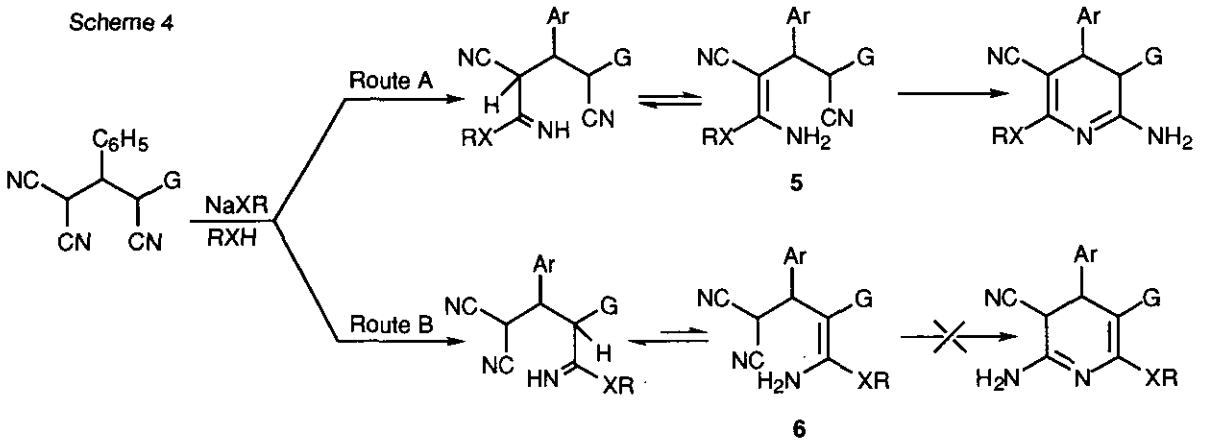


4a **4b**

Concluding from these results we can say that the formation of the 3,4-dihydropyridines (**3**) proceeds through a Michael adduct which undergoes a regioselective cyclization.

Previously we reported [7-10] the synthesis of other 3,4-dihydropyridines by regioselective cyclization of non-symmetrical 1,1,3-propanotricarbonitriles. This regioselectivity can be explained by the fact that the tautomerization to the ketene-aminohemiketal (**5**) (route A), proposed as an intermediate of the cyclization process, is favoured by the cyano group. In the literature[11,12] it has been described that imidates with a cyano group in the α-position are in equilibrium with the enamine like ketene-aminohemiketal.

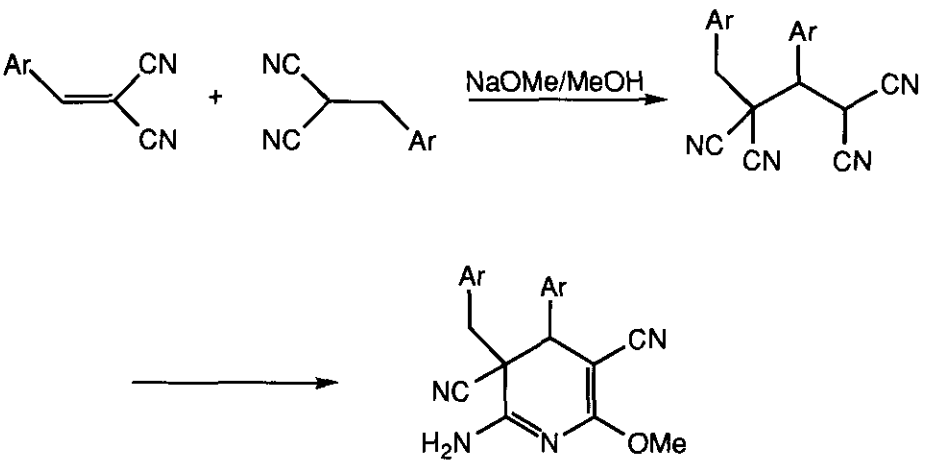
Scheme 4



This tautomerization is a fundamental factor in the cyclization process. Thus the 1,2-diphenyl-1,3-

propanedicarbonitrile does not cyclize to the corresponding 3,4-dihydropyridine by treatment with sodium methoxide in methanol. As additional evidence, regioselective formation[7,9] of the 3,4-dihydropyridines (**7**) is an experimental confirmation of these assumptions because the formation of the other isomer is precluded by the lack of α-hydrogens.

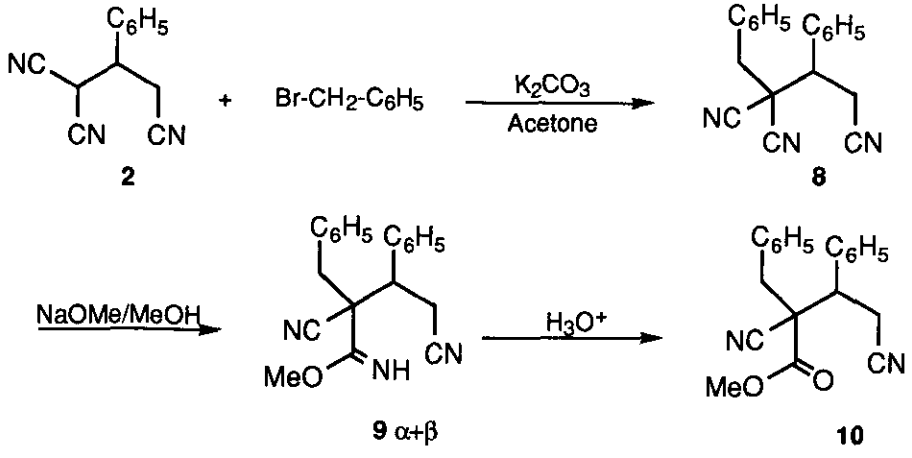
Scheme 5



7

In order to obtain further confirmation of this hypothesis we synthetized the 1,3-diphenyl-2,2,4-butanetricarbonitrile (**8**) which was treated with sodium methoxide in methanol at reflux. Purification of the crude reaction mixture afforded the methyl imidate (**9**) as a diastereomeric racemic mixture (arbitrarily designed as α and β). In this case methyl imidate (**9**) does not undergo cyclization because it can't tautomerize to the ketene aminohemiketal.

Scheme 6



2 **8**

9 α+β **10**

Assignment of relative configurations of both diastereomeric racemates (α+β) was carried out by a radiocrystallographic study of the ester (**1 0**) (Scheme 6) obtained by acid hydrolysis of **9**α. Thus the relative configuration of **9**α is *RR, SS* and that of **9**β is *RS,SR*.

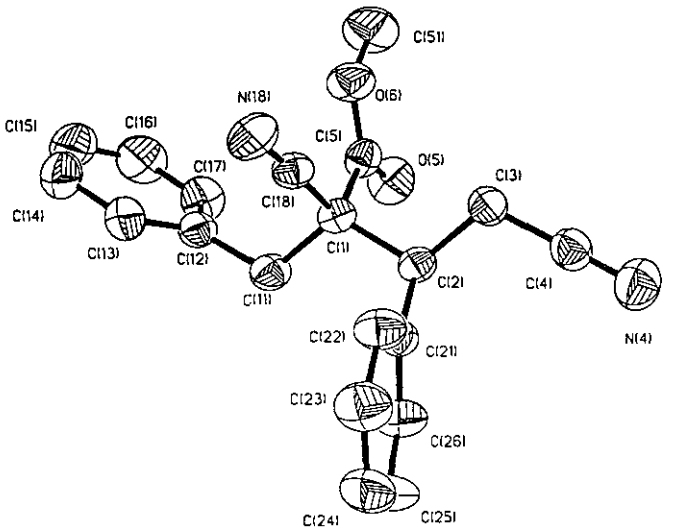


Figure 1. Ortep view of **1 0** with crystallographic numbering

Table 1. Selected geometric parameters for compound (**1 0**).

Bond lengths (Å)

C(1)-C(18)	1.479(3)	C(3)-C(4)	1.462(4)	C(2)-C(3)	1.535(3)
C(1)-C(11)	1.564(3)	O(6)-C(5)	1.325(3)	C(18)-N(18)	1.136(3)
C(2)-C(21)	1.514(3)	C(1)-C(5)	1.526(3)	O(6)-C(51)	1.454(4)
C(12)-C(11)	1.509(3)	C(1)-C(2)	1.567(3)	N(4)-C(4)	1.142(3)

Bond angles (°)

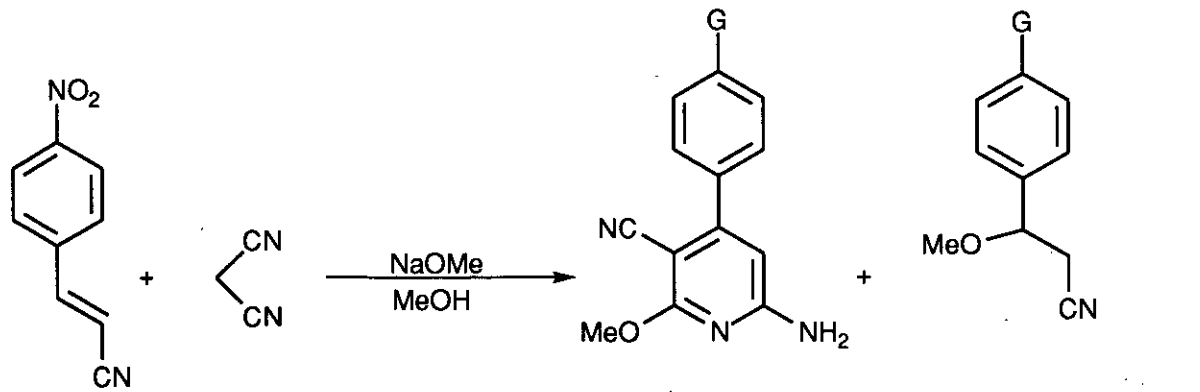
C(18)-C(1)-C(5)	110.8(2)	C(22)-C(21)-C(2)	122.1(2)	C(11)-C(1)-C(2)	110.9(2)
C(5)-C(1)-C(11)	107.5(2)	C(5)-O(6)-C(51)	115.6(3)	C(21)-C(2)-C(1)	113.8(2)
C(5)-C(1)-C(2)	108.0(2)	N(4)-C(4)-C(3)	179.0(3)	C(4)-C(3)-C(2)	111.5(2)
C(21)-C(2)-C(3)	112.2(2)	O(5)-C(5)-C(1)	122.1(2)	C(12)-C(11)-C(1)	112.7(2)
C(3)-C(2)-C(1)	110.7(2)	C(18)-C(1)-C(11)	108.2(2)	O(5)-C(5)-O(6)	124.5(2)
N(18)-C(18)-C(1)	176.5(3)	C(18)-C(1)-C(2)	111.4(2)	O(6)-C(5)-C(1)	113.4(2)

Torsion angles (°)

C1-C2-C21-C22	-76.6(3)	C5-C1-C2-C21	-172.8(2)
C1-C2-C3-C4	-171.6(2)	C11-C1-C2-C21	-55.2(3)
C1-C2-C21-C26	105.3(3)	C11-C1-C2-C3	177.3(2)
C2-C1-C11-C12	-177.4(2)	C11-C1-C5-O5	-58.5(3)
C2-C1-C5-O5	61.2(3)	C13-C12-C11-C1	-91.9(3)
C3-C2-C21-C22	50.2(3)	C17-C12-C11-C1	86.2(3)
C3-C2-C21-C26	-128.0(3)	C18-C1-C11-C12	60.2(3)
C5-C1-C11-C12	-59.6(3)	C18-C1-C2-C21	65.3(3)
C5-C1-C2-C3	59.7(3)	C18-C1-C2-C3	-62.3(3)

In a previous paper [6] we described the synthesis of the 6-amino-3-cyano-2-methoxy-4-(4-nitrophenyl)pyridine (**11**) from malononitrile and 4-nitrocinnamonitrile in methanol-sodium methoxide. We have now reinvestigated this reaction and isolated, besides the pyridine (**11**), the 4-(4-aminophenyl)pyridine (**12**) and the 4-(4-methoxycarbonylaminophenyl)pyridine (**13**). The 3-aryl-3-methoxypropanonitriles (**14** and **15**) were also obtained as side-products.

Scheme 7



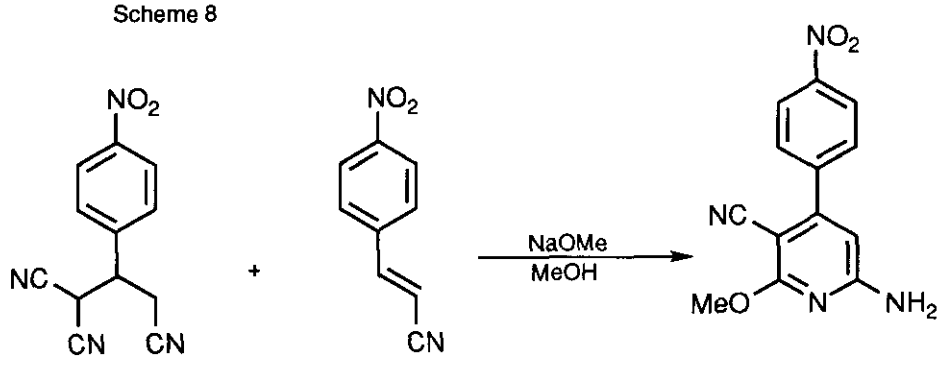
11; G = NO_2
12; G = NH_2
13; G = $NHCO_2Me$

14; G = NO_2
15; G = $NHCO_2Me$

The structure of the pyridine (**11**) is in agreement with its spectroscopic data and the relative position of the amino and methoxy groups was unequivocally established from the NOE effect between the amino group and H-5. The structures of the pyridines (**12**) and (**13**) were established from spectroscopical data and by reduction (hydrazine/Raney Ni) of **11** to the 4-(4-aminophenyl)pyridine (**12**) which was converted to the pyridine (**13**) by treatment with methyl

chloroformate. In order to investigate the mechanism of this reaction we synthesized the 2-(4-nitrophenyl)-1,1,3-propanetricarbonitrile (**16**) as a likely intermediate in the formation of the pyridine (**11**). Treatment of **16** with sodium methoxide in methanol did not give the expected pyridine (**11**). Howewer when the reaction was performed in the presence of 4-nitrocinnamonitrile the 4-(4-nitrophenyl)pyridine (**11**) was obtained.

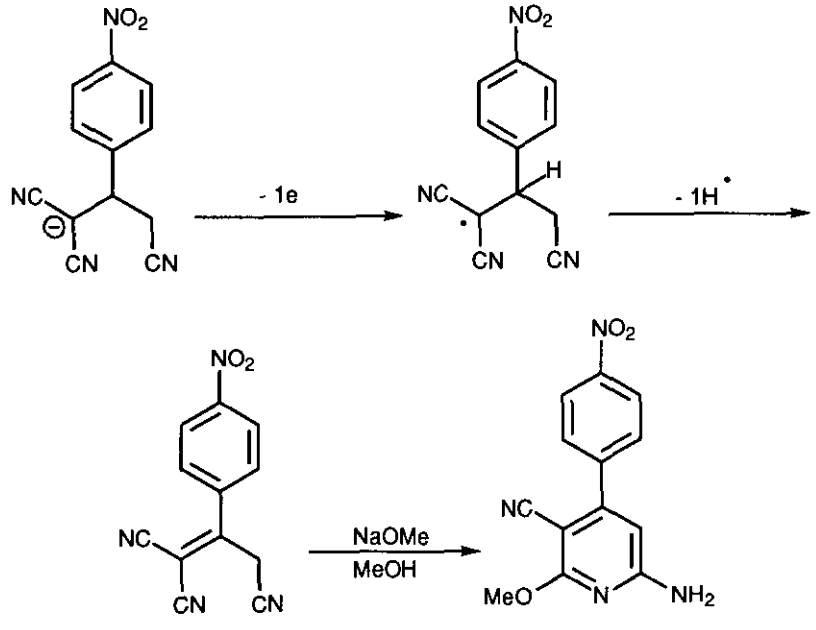
Scheme 8



16 **11**

These results suggest that the oxidation of the Michael adduct precedes the cyclization and that the 4-nitrocinnamonitrile is the oxidizing agent.

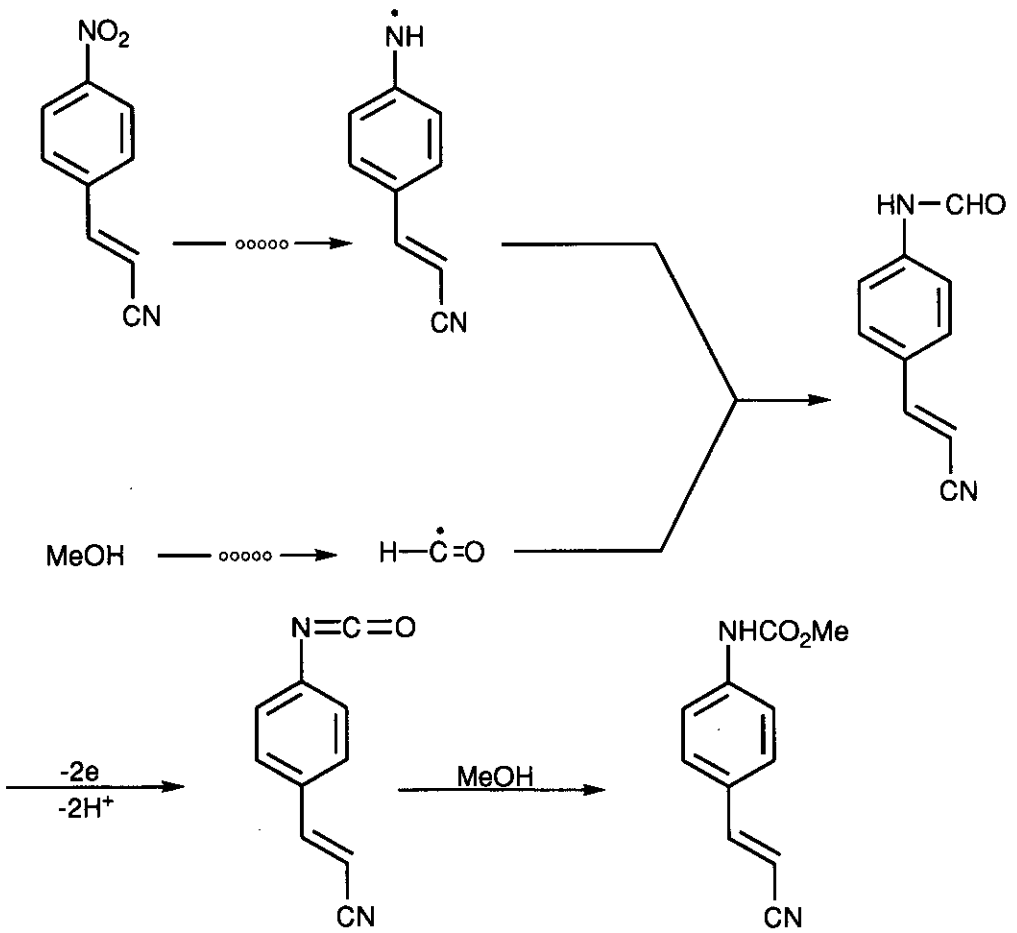
Scheme 9



11

Formation of the 4-(4-methoxycarbonylamino)pyridine (**13**) signifies an unusual methoxycarbonylation process which can be explained by the coupling of the radicals resulting from the reduction of the 4-nitrocinnamonitrile and oxidation of the methanol to yield a formamide. Further oxidation of this formamide to the isocyanate and subsequent addition of methanol yields the methyl carbamate.

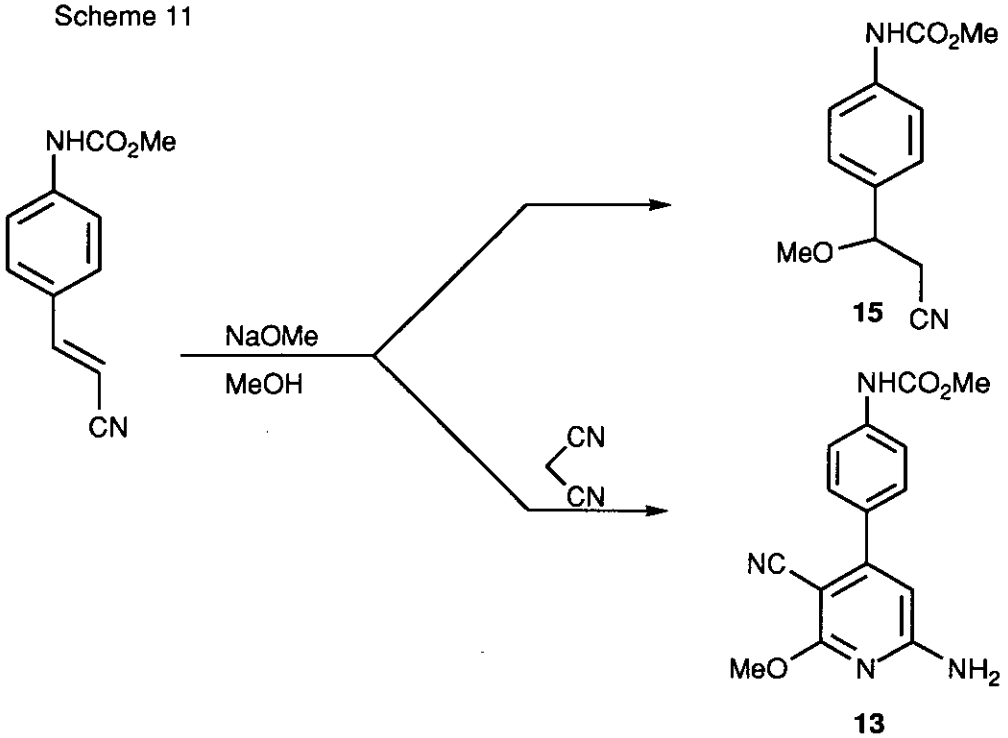
Scheme 10



Nyberg and Blum[13] have described a similar mechanism for the oxidation of tertiary formamides in methanol as a method for the synthesis of methyl carbamates.

The 4-methoxycarbonylaminocinnamonitrile evolves to the propanenitrile (**15**) and to the pyridine (**13**) according to the following process.

Scheme 11



The formation of the 4-(4-aminophenyl)pyridine (**12**) can be explained by reduction of the 4-(4-nitrophenyl)pyridine (**11**) or by reduction of the 2-(4-nitrophenyl)-1,1,3-propanetricarbonitrile (**16**) to the corresponding amino derivative and subsequent cyclization. An alternative route involving addition of malononitrile to the 4-aminocinnamonitrile followed by cyclization of the Michael adduct can be discarded because cinnamonitriles with electron-donor substituents do not undergo Michael addition.[6]

EXPERIMENTAL

All melting points were determined with a Büchi SMP-20 and are uncorrected. Ir spectra were recorded on a Perkin Elmer 883 spectrophotometer. Nmr spectra were measured on a Varian UNITY 300 spectrometer at 303 °K. Mass spectra were obtained with a Hewlett Packard HP-5988 at 70 eV. Microanalyses were performed in a Heraeus CHN. Flash column chromatographies were carried out on silica gel SDS 230-400 mesh. Malononitrile methyl imidate [14] and 4-nitrocinnamonitrile [15] were synthesized according to reported procedures.

2-Phenyl-1,1,3-propanetricarbonitrile (2a): To a suspension of dimsyl sodium in dimethyl sulfoxide (25 ml prepared from 16 mmol of sodium hydride), malononitrile (1.32 g, 20 mmol) and *E*-cinnamonitrile (1.72 g, 13 mmol) were added. The reaction mixture was stirred at room temperature for 4 h and then poured into ice-water (200 ml) and acidified with 10% hydrochloric

acid. The resulting precipitate was collected and recrystallized from 2-propanol affording **2 a**. Yield 1.78 g (70%); mp 98-99 °C; ir (KBr) υ 2250, 1601, 1497, 1455, 1421 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.95-3.15 (m, 2H, CH_2CN), 3.6-3.7 (m, 1H, CHPh), 4.19 (d, 1H, C1-H, J= 6.59 Hz), 7.24-7.36 (m, 2H arom), 7.44-7.48 (m, 3H arom); ms *m/z*: 195 (M^+, 67%), 155 (53), 140 (11), 131 (67), 130 (100), 129 (48), 128 (55), 127 (16), 115 (12), 104 (48), 103 (72), 102 (49), 101 (36), 89 (23), 78 (28), 77 (63). *Anal.* Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.53. Found: C, 73.4; H, 4.81; N, 21.71.

Cyclization of 2a: 2-Amino-5-cyano-6-methoxy-4-phenyl-3,4-dihydropyridine (3a): To a solution of sodium (46 mg, 2 mmol) in dry methanol (25 ml), 2-phenyl-1,1,3-propanetricarbonitrile (390 mg, 2 mmol) was added. The reaction mixture was heated at reflux for 8 h and then poured into ice-water. The solid thus obtained was filtered and recrystallized from ethanol affording 263 mg (58 %) of **3 a** ; lit.,[6] mp, 181-182 °C.

Reaction of *E*-cinnamonitrile with malononitrile. Synthesis of 2a, 3a and 4a: To a solution of sodium methoxide in dry methanol (400 ml) (prepared from sodium (460 mg, 20 mmol)), malononitrile (1.32 g, 20 mmol) and *E*-cinnamonitrile (2.58 g, 20 mmol) were added. This solution was heated at reflux for 8 h and then stirred at room temperature for a further 12 h. By pouring the reaction mixture into water (250 ml) a product precipitated which was filtered and recrystallized from ethanol affording 2.22 g (49 %) of **3 a**. The mother liquors were neutralized with 10% hydrochloric acid and extracted with dichloromethane (3x100 ml). The combined organic extracts were dried over magnesium sulfate, evaporated under reduced pressure and purified by flash column (diameter: 3 cm) chromatography on silica gel using hexane-ethyl acetate (8/1, v/v) as eluent. 2-Phenyl-1,1,3-propanetricarbonitrile (**2**) was obtained first (234 mg, 6%). With the same eluent 6-amino-3-cyano-2-(cyanomethoxycarbonylmethylidene)-4-phenyl-2,3,4,5-tetrahydropyridine (**4**) was obtained. Yield: 176 mg (3%); mp 234-236 °C; ir (KBr) υ 3381, 3349, 3239, 2215, 2199, 1748, 1662, 1548, 1453, 1434, 1339 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.95-3.18 (m, 2H, C5-H), 3.61 and 3.63 (2 s, 3H, CO_2Me), 3.89-3.94 (m, 1H, C4-H), 4.66 (d, 1H, J= 6.84 Hz, C3-H), 4.72 (d, 1H, J= 5.86 Hz, C3-H) 7.28-7.41 (m, 5H arom), 8.35 and 8.66 (2 br s, NH_2), 8.39 and 8.69 (2 br s, NH_2); ms *m/z*: 295 (M^++1, 4%), 235 (9), 196 (100), 170 (13), 169 (19), 156 (17), 144 (57), 140 (10), 131 (14), 130 (38), 129 (27), 128 (26), 117 (13), 115 (52), 104 (18), 103 (50), 102 (32), 91 (17), 89 (11), 79 (24), 78 (27), 77 (61). *Anal.* Calcd for $C_{16}H_{14}N_4O_2$: C, 65.3; H, 4.79; N, 19.04. Found: C, 65.5; H, 4.61; N, 18.82.

1,3-Diphenyl-2,2,4-butanetricarbonitrile (8): To a solution of 2-phenyl-1,1,3-propanetricarbonitrile (**2**) (675 mg, 3.46 mmol) in dry acetone (40 ml), anhydrous potassium carbonate (956 mg, 6.92 mmol) and benzyl bromide (604 mg, 3.46 mmol) were added. The reaction mixture was stirred at room temperature for 24 h and then the solvent was evaporated *in vacuo*. The solid thus obtained was dissolved in water and extracted with dichloromethane (3x75

ml). The combined extracts were dried over magnesium sulfate, concentrated to dryness and the resulting residue recrystallized from ethanol affording 804 mg (81 %) of **8**; mp 115-117 °C; ir ($CHCl_3$) υ 2250, 1602, 1494, 1450, 1416 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.86 (d, 1H, C$\underline{H}_2$Ph, J= 13.55 Hz), 3.05 (d, 1H, C$\underline{H}_2$Ph, J= 13.55 Hz), 3.21 (part A of the ABX syst., CH_2CN, J_{AB}= 16.48 Hz and J_{AX}= 10.62 Hz), 3.21 (part B of the ABX syst., CH_2CN, J_{AB}= 16.48 Hz, J_{BX}= 5.13 Hz), 3.53 (part X of the ABX syst., J_{AX}= 10.62 Hz, J_{BX}= 5.13 Hz, C$\underline{H}$Ph), 7.23-7.57 (m, 10H arom); ms *m/z*: 285 (M^+, 5 %), 131 (8), 130 (77), 128 (5), 103 (20), 92 (12), 91 (100), 77 (21). *Anal.* Calcd for $C_{19}H_{15}N_3$: C, 79.98; H, 5.3; N, 14.73. Found: C, 79.75; H, 5.57; N, 14.98.

Methyl 2-benzyl-2,4-dicyano-3-phenylimidobutanoate (9): To a solution of sodium (38 mg, 1.62 mmol) in dry methanol (20 ml), 1,3-diphenyl-2,2,4-butanetricarbonitrile (463 mg, 1.62 mmol) was added. The mixture was stirred at room temperature for 8 h and then poured into ice-water. The precipitate thus formed was filtered and purified by flash column (diameter: 3 cm) chromatography on silica gel using hexane-ethyl acetate (4/1, v/v) as eluent, affording 36 mg (7 %) of **9**α; mp 120-122 °C (hexane-ethyl acetate); ir ($CHCl_3$) υ 3335, 2248, 1660, 1498, 1457, 1443 cm^{-1}; ^1H nmr (acetone-d_6): δ 3.21-3.55 (m, 4H, CH_2CN and C$\underline{H}_2$Ph), 3.53 (s, 3H, OMe), 3.82 (dd, 1H, C$\underline{H}$Ph, J= 4.02 Hz, J'= 11.9 Hz), 7.29-7.45 (m, 10H arom); ms *m/z*: 317 (M^+, 0.6%), 226 (13), 187 (48), 130 (24), 115 (6), 104 (7), 103 (19), 102 (7), 91 (100), 77 (28). *Anal.* Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.24; H, 6.12; N, 13.69.

With the same eluent 293 mg (57 %) of **9**β were obtained; mp 123-125 °C (hexane-ether); ir ($CHCl_3$) υ 3332, 2249, 1657, 1496, 1450 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.53 (d, part A of the AB syst., C$\underline{H}_2$Ph, J_{AB}= 13.55 Hz), 2.71 (Part A of AMX syst., CH_2CN, J_{AM}= 16.85 Hz, J_{AX}= 4.76 Hz), 2.99 (d, part B of AB syst., C$\underline{H}_2$Ph, J_{AB}= 13.55 Hz), 3.01 (Part M of AMX syst., CH_2CN, J_{AM} = 16.85 Hz, J_{MX}= 10.98 Hz), 3.68 (part X of AMX syst., C$\underline{H}$Ph, J_{MX}= 10.98 Hz, J_{AX}= 4.76 Hz), 3.89 (s, 3H, OMe), 7.01-7.05 (m, 2H, arom), 7.23-7.26 (m, 2H, arom), 7.46-7.50 (m, 6H, arom), 7.75 (s, 1H, NH); ms *m/z*: 317 (M^+, 0.25 %), 226 (5), 187 (57), 171 (4), 155 (5), 140 (5), 130 (31), 115 (6), 103 (22), 91 (100), 77 (30). *Anal.* Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.82; H, 6.1; N, 13.53.

Methyl 2-benzyl-2,4-dicyano-3-phenylbutanoate (10): A solution of **9**α (158 mg, 0.5 mmol) in methanol (30 ml) was acidified with 10 % hydrochloric acid. The reaction mixture was stirred at room temperature for 8 h and then the solvent was removed at reduced pressure. The resulting residue was purified by recrystallization from hexane-ethyl acetate (1/1, v/v) affording 129 mg (81 %) of **10**; mp 129-130 °C; ir (KBr) υ 2246, 1741, 1601, 1583, 1496, 1450, 1355, 1305 cm^{-1}; ^1H nmr (acetone-d_6): δ 2.58 (d, part A of AB syst., C$\underline{H}_2$Ph, J_{AB}= 13.55 Hz), 3.05 (part A of AMX syst., CH_2CN, J_{AM} = 16.85 Hz, J_{AX}= 5.49 Hz), 3.24 (d, part B of AB syst., C$\underline{H}_2$Ph, J_{AB}= 13.55 Hz), 3.28 (part M of AMX syst., CH_2CN, J_{AM} = 16.85 Hz, J_{MX}= 10.62 Hz), 3.70 (s, 3H, OMe), 3.83 (dd, part X of AMX syst., C$\underline{H}$Ph, J_{AX}= 5.49 Hz, J_{MX}= 10.62 Hz), 7.10-7.13 (m, 2H, arom), 7.26-7.31

(m, 3H, arom), 7.45-7.54 (m, 3H arom), 7.62-7.65 (m, 2H arom); ms *m/z*: 318 (M^+, 0.31 %), 188 (7),130 (45), 115 (4), 104 (5), 103 (18), 91 (100), 77 (20). *Anal.* Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.7; N, 8.8. Found: C, 75.71; H, 5.84; N, 9.02.

X-Ray crystallography

Table 2. Crystal and X-Ray structural analysis data for compound (**1 0**)

Empirical formula	C20H18N202
Molecular weight	318.36
Temperature	293(2) K
Wavelength	0.7107 Å
Crystal colour/habit	Yellow-pale; hexagonal
Crystal system; Space group	Monoclinic; $P2_1/c$
Unit cell dimensions	a= 11.403(3) Å
	b= 8.470(4) Å, β= 99.14(3)°
	c= 17.891(8) Å
Volume	1706(1) $Å^3$
Z	4
D_c/ gcm^{-3}	1.239
Absorption coefficient	0.81 cm^{-1}
Crystal size	1.5x0.3x0.15 mm
F(000)	672
θ range for data collection	2 to 28
Range of hkl	$-15<h<0$, $-11<k<0$, $-23<l<23$
Reflections collected	4481
Independent reflections	4193 (R_{int} = 0.0434)
Observed reflections I> 2σ(I)	2299
Absorption correction	N/A
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4181/0/289
Goodness of fit on F^2	1.039
Final R indices [I>2σ(I)]	R1= 0.0493, wR2= 0.1288
R indices (all data)	R1= 0.1376, wR2= 0.1971

Data collection and processing. Enraf-Nonius CAD-4 diffractometer, graphite-monochromated Mo-

Kα radiation; 4481 reflections measured 2299 observed with I> 2σ(I). Two check reflections measured every 90 min showed no significant variation.

Structure analysis and refinement. The structure was solved by a combination of direct methods and Fourier synthesis , and refined (on F^2) by full matrix least-squares calculations. All the non hydrogen atoms were refined anisotropically. The hydrogen atoms were found in the difference Fourier synthesis and included in further refinement with fixed isotropic temperature factors. Final F= 0.176 and -0.212 eÅ^{-3}, R1= 0.0493 and wR2= 0.1288 with $R1 = \Sigma||Fo|-|Fc||/\Sigma|Fo|$, $wR2 = [\Sigma[W(Fo^2-Fc^2)^2/\Sigma[W(Fo^2)^2]^{1/2}$, $w=1/[\sigma^2(Fo^2)+(0.0852P)^2+0.6599P]$ and $P=(Fo^2+2Fc^2)/3$. Calculations were performed with the SHELXS-86 [16] program on an ALPHA AXP Digital workstation.

Reaction of 4-nitrocinnamonitrile with malononitrile: *To a solution of sodium* (173 mg, 7.5 mmol) in dry methanol (40 ml), malononitrile (495 mg, 7.5 mmol) and 4-nitrocinnamonitrile (1.3 g, 7.5 mmol) were added. The reaction mixture was heated at reflux for 8 h and then stirred at room temperature for 12 h. By pouring the reaction mixture into water (400 ml) a product precipitated which was filtered and the mother liquors were extracted with dichloromethane affording an additional amount of product. The combined fractions were purified by flash column (diameter: 3 cm) chromatography on silica gel. On elution with hexane-ethyl acetate (3/1, v/v) a mixture of the propanenitriles (**14**) and (**15**) was obtained. With hexane-ethyl acetate (2/1, v/v) as eluent, 523 mg (26 %) of **11** were obtained. lit.,[6] mp, 283-285 °C. With the same eluent 18 mg (1 %) of **12** were obtained which were recrystallized from ethanol; mp 219-220 °C; ir (KBr) υ 3392, 3300, 3224, 2209, 1648, 1585, 1531, 1456, 1420 cm^{-1}; ^1H *nmr* (DMSO-d_6): δ 3.85 (s, 3H, OMe), 5.49 (s, 2H, NH_2), 6.02 (s, 1H, C5-H), 6.60 (part AA of AA'BB' syst., J= 7.23 Hz, 2H arom), 6.93 (br s, 2H, NH_2), 7.21 (part BB' of AA'BB' syst., J= 7.23 Hz, 2H arom); ms *m/z*: 240 (M^+, 100 %), 239 (34), 211 (19), 209 (7), 155 (16), 143 (8), 142 (8), 128 (6), 93 (6), 89 (6), 77 (6). *Anal.* Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.22. Found: C, 65.23; H, 5.11; N, 23.69. With the same eluent 36 mg (1.6 %) of **13** were obtained; mp 229-231 °C (ethyl acetate); ir (KBr) υ 3346, 2208, 1725, 1593, 1529, 1451 cm^{-1}; ^1H nmr (acetone-d_6): δ 3.71 (s, 3H, CO_2Me), 3.92 (s, 3H, OMe), 6.26 (s, 1H, C5-H), 6.45 (br s, 2H, NH_2), 7.53 (part AA' of AA'BB' syst., J= 8.79 Hz, 2H arom), 7.68 (part BB' of AA'BB' syst., J= 8.79 Hz, 2H arom), 8.91 (br s, 1H, NH); ms *m/z*: 298 (M^+, 100%), 297 (13), 267 (9), 266 (34), 265 (27), 240 (10), 239 (13), 238 (11), 237 (13), 224 (14), 155 (10). *Anal.* Calcd for $C_{15}H_{14}N_4O_3$: C, 60.4; H, 4.73; N, 18.78. Found: C, 61.28; H, 4.9; N, 18.45.

The mixture of **14** and **15** was separated by column chromatography on alumina using hexane-ethyl acetate (6/1, v/v) as eluent, affording 161 mg (11 %) of **14**; bp (3 mm) 175 °C; ir ($CHCl_3$) υ 2254, 1603, 1519, 1343 cm^{-1}; ^1H nmr (acetone-d_6): δ 2.94 (*dd*, 1H, CH_2CN, J= 6.59 Hz, J'= 16.87

Hz), 3.03 (dd, 1H, CH_2CN, J= 5.13 Hz, J'= 16.87 Hz), 4.8 (dd, 1H, CHAr, J= 6.59 Hz, J'= 5.13 Hz), 7.73 (part AA' of AA'BB' syst., J= 8.79 Hz, 2H arom), 8.28 (part BB' of AA'BB' syst., J= 8.79 Hz, 2H arom); ms (CI) *m/z*: 207 (M^++1, 100 %), 175 (3), 167 (8), 166 (82). *Anal.* Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.59; H, 4.83; N, 13.44. With the same eluent 112 mg (6.4 %) of **15** were obtained; mp 99-101 °C (ethyl acetate); ir (KBr) ν 3330, 2253, 1745, 1604, 1543 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.66 (dd, 1H, CH_2CN, J= 5.68 Hz, J'= 16.66 Hz), 2.75 (dd, 1H, CH_2CN, J= 6.96 Hz, J'= 16.66 Hz), 3.26 (s, 3H, NCO_2Me), 3.78 (s, 3H, OMe), 4.41 (dd, 1H, CHPh, J= 5.68 Hz, J'= 6.96 Hz), 6.66 (s, 1H, NH), 7.27 (part AA' of AA'BB' syst., J= 8.42 Hz, 2H arom), 7.42 (part BB' of AA'BB' syst., J= 8.42 Hz, 2H arom); ms *m/z*: 234 (M^+, 7 %), 202 (7), 195 (15), 194 (100), 178 (5), 163 (13), 162 (98), 134 (5), 120 (5), 119 (6), 104 (4), 92 (11), 89 (12), 77 (9). *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.87; H, 6.15; N, 11.64.

Reduction of the 4-nitrophenylpyridine 11. Synthesis of the 4-aminophenylpyridine 12: To a suspension of Raney Ni (50 mg) in methanol (20 ml) containing 100 % hydrazine hydrate (96 mg, 3 mmol) heated at reflux and then a solution of the 4-nitrophenylpyridine (**11**) (168 mg, 0.6 mmol) in methanol (50 ml) was added dropwise. The reaction mixture was heated at reflux for an additional 40 min and then filtered through celite. The filtrate was evaporated *in vacuo* and the residue recrystallized from ethanol affording 116 mg (81 %) of **12**.

Reaction of the 4-aminophenylpyridine 12 with methyl chloroformate. Synthesis of the 4-methoxycarbonylaminophenylpyridine 13: To a solution of **12** (122 mg, 0.5 mmol) in the minimal volume of dry acetone, methyl chloroformate (290 mg, 3 mmol) and anhydrous potassium carbonate (846 mg, 6.12 mmol) were added. The reaction mixture was heated at reflux for 24 h and then the solvent was evaporated under reduced pressure to afford a solid which was treated with water and extracted with dichloromethane (3x50 ml). The combined extracts were evaporated *in vacuo* and the residue purified by flash column (diameter: 2 cm) on silica gel using hexane-ethyl acetate-triethylamine (4/6/1, v/v/v) as eluent, to afford 8 mg (5 %) of **13**.

2-(4-Nitrophenyl)-1,1,3-propanetricarbonitrile (16): To a suspension of dimsyl sodium in dimethyl sulfoxide (15 ml, prepared using 1.8 mmol of sodium hydride), malononitrile (109 mg, 1.64 mmol) and 4-nitrocinnamonitrile (286 mg, 1.64 mmol) were added. The mixture was stirred at room temperature for 24 h and then poured into water and acidified with 10% hydrochloric acid. The precipitate thus obtained was filtered and purified by flash column chromatography on silica gel using hexane-ethyl acetate (3/1, v/v) as eluent affording 122 mg (31 %) of **16**; mp 164-165 °C (2-propanol); ir (KBr) ν 2258, 1606, 1522, 1449 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.21-3.28 (m, 2H, CH_2CN), 4.45-4.49 (m, 1H, CH-Ar), 5.51 (d, 1H, $CH(CN)_2$, J= 5.37 Hz), 7.65 (part AA' of AA'BB' syst., J= 8.79 Hz, 2H arom), 8.25 (part BB' of AA'BB' syst., J= 8.79 Hz, 2H arom); ms *m/z*: 240 (M^+, 23 %), 213 (7), 194 (4), 167 (6), 140 (27), 136 (100), 128 (10), 116 (14), 106 (34), 102 (12), 89

(32), 78 (27). *Anal.* Calcd for $C_{12}H_8N_4O_2$: C, 60; H, 3.36; N, 23.32. Found: C, 59.87; H, 3.49; N, 23.61.

Reaction of 16 with 4-nitrocinnamonitrile. Synthesis of 11: To a solution of sodium (23 mg, 1 mmol) in dry methanol (30 ml), 2-(4-nitrophenyl)-1,1,3-propanetricarbonitrile (120 mg, 0.5 mmol) and 4-nitrocinnamonitrile (87 mg, 0.5 mmol) were added. The reaction mixture was heated at reflux for 12 h, poured into water and extracted with dichloromethane. The crude product obtained after evaporating the solvent was purified by flash column (diameter: 2 cm) chromatography on silica gel using hexane-ethyl acetate (2/1, v/v) as eluent affording, 58 mg (43 %) of **11**.

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