Tetrahedron Vol. 44, No. 18, pp. 5861 to 5868, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

A CONVENIENT, ONE STEP SYNTHESIS OF PYRANO[2,3-b]PYRIDINES[1]

Nazario Martín, Carlos Seoane and José L. Soto

Departamento de Química Orgánica. Facultad de Química,
Universidad Complutense. E-28040 Madrid, Spain

(*Received in UK* 24 *June* 1988)

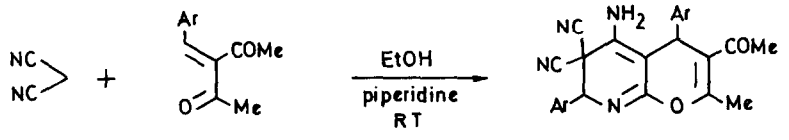
Abstract - A novel, one step synthesis of pyrano[2,3-b]pyridines from malononitrile and unsaturated ketones is reported. The reaction mechanism is discussed and takes place through an intermediate monocyclic 4H-pyran. Several derivatives with different substitution patterns are prepared.

INTRODUCTION

Although a great deal of work has been published on polycyclic pyridine-containing compounds[2], much less is known about pyranopyridine systems. [1]Benzo-pyrano[4,3-b]pyridines have been reported[3]. The parent 2H-pyrano[2,3-b]pyridine ring is known, as well as a number of azaflavones, azacoumarins and azachromones[4]. On the other hand, the 4H-pyrano[2,3-b]pyridine system is little known[2] and some proposed structures[5] proved latter to be wrong[6].

RESULTS AND DISCUSSION

We report in this paper a new, one step synthesis of pyrano-[2,3-b]pyridine systems (3) from 2-arylidene-1,3-diketones (2) which are easily accesible through a Knoevenagel condensation of aromatic aldehydes with 2,4-pentanedione.



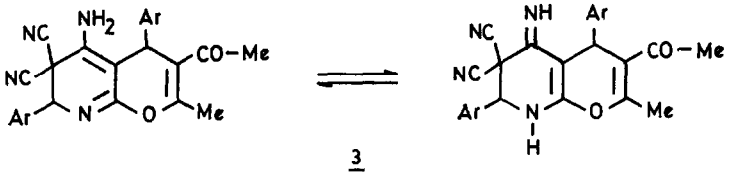
1 2 3a-c

The reaction is easily performed in ethanol at room temperature by stirring a mixture of malononitrile (1) with 2 for 24 hours in the presence of piperidine as basic catalyst. Pyranopyridines 3 are thus obtained in moderate yields.

Structural assignment of compound 3a was based on analytical and spectral data (M^+408, $C_{25}H_{20}N_4O_2$). The ^{1}H-nmr spectrum of 3a (d_6-DMSO, 300 MHz, 50°C) showed the following signals: δ 1.90 (3H, s), 2.09 (3H, d, J = 2.0 Hz), 4.48 (1H, s), 4.94 (1H, q, J = 2.0 Hz), 7.1-7.4 (10H, m, arom.) and a very broad signal at approx. δ = 8.0 (2H, NH_2), which disappeared on the addition of a

trace of deuterated trifluoroacetic acid. A double resonance experiment indicated that the proton at δ 4.94 (C_4 of the pyran ring) is coupled to the methyl group at δ 2.09 (substituent at position 2 of the pyran ring, ^5J = 2.0 Hz in a long range homoallylic coupling). The ^{13}C-nmr spectrum of 3a confirmed the proposed pyranopyridine structure.

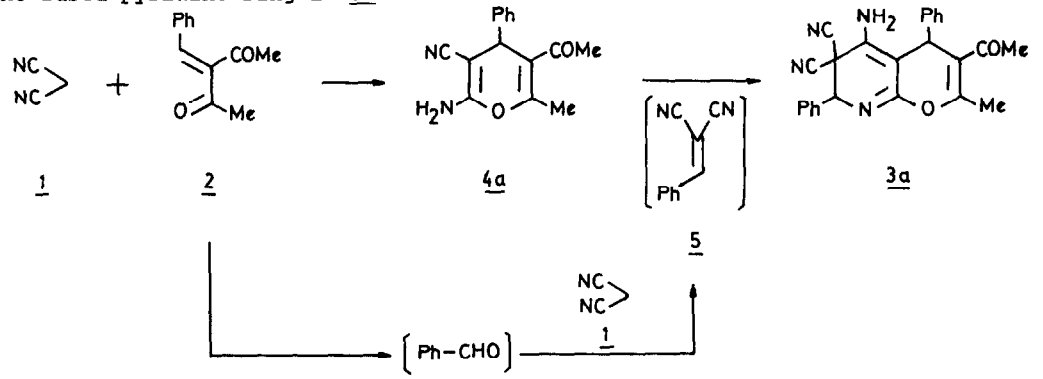
Assignement of the ^{13}C-NMR spectra required the examination of chemical shifts, SFORD multiplicities and J-modulated spin echo experiments. Compounds 3 present an equilibrium of tautomeric forms and the addition of a trace of trifluoroacetic acid to the sample was useful in order to get sharp peaks for some signals.



3

The five sp^3 carbons in the molecule appear at the following chemical shifts (SFORD multiplicities): 17.2 (q, CH_3), 29.7 (q, CH_3-CO), 48.1 (s, C6), 50.0, 50.8 (d, C4; d, C7). The seven sp^2 carbons with no hydrogen attached appear at 130.5, 134.5, 135.1, 139.4 (s, C2; s, C3; 2C, ipso phenyl carbons), 163.4, 168.1 (s, C8a; s, C5), 52.0 (s, C4a). The remaining ten sp^2 aromatic carbons bearing one hydrogen give rise to four peaks at 128.3 (2C), 128.4 (2C), 129.2 (4C) and 129.3 (2C). Finally the carbonyl and cyano groups appear at 201.5, 117.7 and 115.9 ppm. This assignement has been confirmed by the J-modulated spin echo spectrum. The signals corresponding to CH_3 and CH carbons appear as inverted peaks, whereas the other carbons remain in an upright position.

Formation of 3a can be interpreted through a two step process. Addition of malononitrile (1) to the unsaturated diketone (2) is followed by a spontaneous cyclization to 4H-pyran (4a) by attack of the carbonyl oxygen to a nitrile group. The presence in intermediate 4a of an amino and a cyano group next to one another allows the reaction with unsaturated dinitrile 5, which gives rise to the fused pyridine ring in 3a.

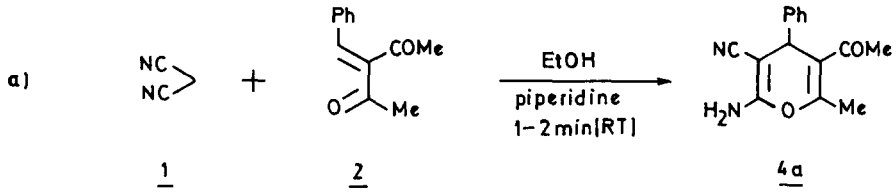


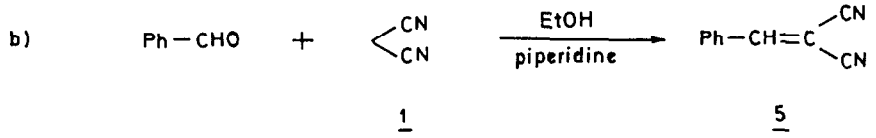
1 2 4a 5 3a

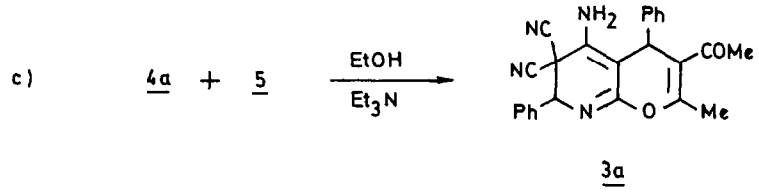
The apparent difficulty in this interpretation lies in the fact that compound 5 has not been added as a reactant. However, the presence of 5 in the reaction medium can be explained by admitting the easy decomposition of the starting material (2), consistent with the moderate yields of the reaction. The aldehyde thus formed could bring about a Knoevenagel condensation with 1 leading to unsaturated nitrile 5.

A number of experiments have been carried out in proof of this interpreta-

tion. The first one (a) involves the isolation of the proposed intermediate pyran 4a.

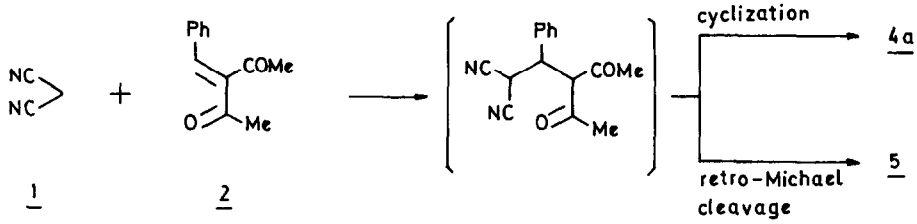




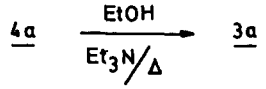


It is not easy, but can be achieved by stopping the reaction after 1-2 minutes[7]. This intermediate, therefore, does exist and can take part in the reaction mechanism. Secondly (b), dinitrile 5 can be obtained separately from aldehyde and malononitrile. When (c) the monocyclic pyran 4a is reacted with 5, the same pyranopyridine 3a is obtained in good yield, in proof of the proposed mechanism.

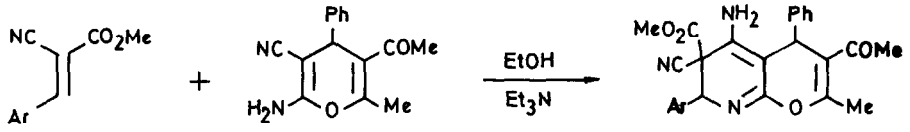
There is an objection to be made to this interpretation: the generation of aldehyde is difficult to admit in a non-aqueous medium. However, formation of dinitrile 5 can also result from an alternative mechanism involving a retro-Michael cleavage of the intermediate adduct leading to the monocyclic pyran, in which 5 is formed as a by-product.



This decomposition process is substantiated by the fact that pyranopyridine 3a can also be obtained by simply heating the intermediate pyran 4a in a basic medium. Reasonably enough, the yield in pyranopyridine is approximately halved in respect to the direct synthesis.

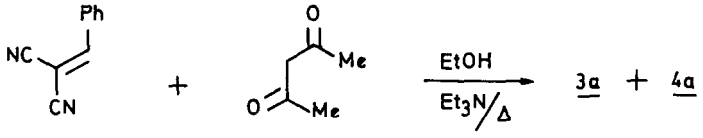


Several pyranopyridines 3 with a different substitution pattern were prepared by reaction of monocyclic pyran 4a with methyl α-cyanocinnamates (6) (Table).



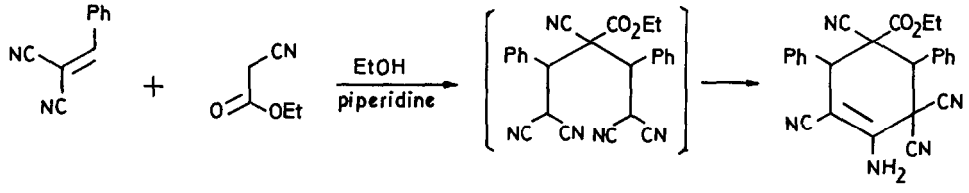
6 4a 3d-f

It is worth mentioning that if the reaction is carried out from α-cyanocinnamonitrile (5) and 2,4-pentanedione (7) as starting materials, a mixture of the monocyclic pyran 4a and the pyranopyridine 3a is obtained.



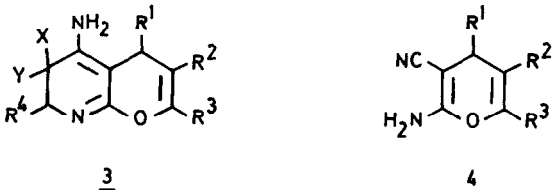
5 7

On the other hand, if α-cyanocinnamonitrile 5 is reacted with ethyl cyanoacetate (8), the reaction takes a different route, and does not afford any heterocyclic compound. A cyclohexene ring (9) is obtained instead, through a Thorpe-type cyclization of the previously formed bisadduct.



5 8 9

Table Pyrano 2,3-b pyridines 3 and 4H-pyrans 4



3 4

Table Pyrano[2,3-b]pyridines 3 and 4H-pyrans 4

Compound	R^1	R^2	R^3	R^4	X	Y	Yield (%)[a]	Molecular formula	Mp (°C) (solvent)
3a	C_6H_5	$COCH_3$	CH_3	C_6H_5	CN	CN	45[b] 59[c]	$C_{25}H_{20}N_4O_2$	293-295(d) (acetonitrile or ethanol)
3b	$pCH_3C_6H_4$	$COCH_3$	CH_3	$pCH_3C_6H_4$	CN	CN	43	$C_{27}H_{24}N_4O_2$	274-276(d) (acetonitrile or ethanol)
3c	$pCH_3OC_6H_4$	$COCH_3$	CH_3	$pCH_3OC_6H_4$	CN	CN	42	$C_{27}H_{24}N_4O_4$	210-213(d) (ethanol)
3d	C_6H_5	$COCH_3$	CH_3	C_6H_5	CN	CO_2CH_3	90	$C_{26}H_{23}N_3O_4$	268-270(d) (acetonitrile or ethanol)
3e	C_6H_5	$COCH_3$	CH_3	$pCH_3C_6H_4$	CN	CO_2CH_3	47	$C_{27}H_{25}N_3O_4$	262-264(d) (acetonitrile)
3f	C_6H_5	$COCH_3$	CH_3	$p\text{-}ClC_6H_4$	CN	CO_2CH_3	69	$C_{26}H_{22}N_3O_4Cl$	254-256(d) (acetonitrile)
4a	C_6H_5	$COCH_3$	CH_3	-	-	-	73	$C_{15}H_{14}N_2O_2$	158-160[d] (ethanol)
4b	$pCH_3C_6H_4$	$COCH_3$	CH_3	-	-	-	56	$C_{16}H_{16}N_2O_2$	135-137 (ethanol)
4c	$pCH_3OC_6H_4$	$COCH_3$	CH_3	-	-	-	57	$C_{16}H_{16}N_2O_3$	157-159 (ethanol)

a) Yield of isolated product. b) By using the general procedure.
c) Starting from pyran 4a (see experimental section). d) See reference 8.

EXPERIMENTAL SECTION

Melting points were determined in a Büchi apparatus in capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 and 781 spectrometer. Unless otherwise stated, ^{1}H-NMR spectra were determined in a Varian T-60A and a Varian FT-80 was used for the ^{13}C-NMR spectra. Reactions were monitored by TLC, using silica gel as the adsorbent and toluene-ethyl acetate as the eluent.

1,3-Pentanedione, malononitrile and ethyl cyanoacetate were obtained from Aldrich and used without further purification. Arylidene-1,3-diketones[9] and α-cyanocinnamonitriles[10] were prepared by condensation of aromatic aldehydes with either ß-diketones or malononitrile according to previously described procedures.

3-Acetyl-5-amino-4,7-diaryl-6,6-dicyano-2-methyl-6,7-dihydro-4H-pyrano[2,3-b]-pyridines (3a-c). General procedure. - Malononitrile (1) (5 mmol) and the appropriate propenone 2 (5 mmol) were suspended in ca. 20 ml of ethanol and 2-3 drops of piperidine were added. The reaction mixture was kept at room temperature for 24 hours. The solid that precipitates[11] after that time was collected by filtration and washed with ethanol. Compounds 3 can be recrystallized from either ethanol or acetonitrile. However, samples crystallized from the former solvent contain one molecule of ethanol per molecule of compound[12]. Compounds 3 could exist as two diastereomers, but only one is isolated.

3-Acetyl-5-amino-6,6-dicyano-2-methyl-4,7-diphenyl-6,7-dihydro-4H-pyrano[2,3-b]-pyridine (3a). - This compound was obtained in 45% yield; mp 293-295°C (d) (from acetonitrile); IR (KBr): 3400, 3000 (broad), 2250, 1705, 1680, 1660, 1540, 1290, 1280, 1240 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz, 50°): δ = 8.0 (b, 2H, NH_2; disappears upon addition of TFA; if the spectrum is registered at lower temperature, the amino group appears as two broad peaks at similar values as for 3b and 3c), 7.4-7.1 (m, 10H, arom.), 4.94 (q, 1H, CH, J = 2.0 Hz), 4.48 (s, 1H, CH), 2.09 (d, 3H, CH_3, J = 2.0 Hz; homoallylic coupling confirmed by a double resonance experiment), 1.90 (s, 3H, CH_3); MS: m/e = 408 (M^+, 55): 390 (11), 365 (34), 331 (11), 323 (10), 295 (5), 257 (11), 252 (10), 210 (12), 202 (100), 156 (44), 140 (7), 128 (37), 101 (40).
^{13}C-NMR (DMSO-d_6 with a trace of TFA, 100.6 MHz) (SFORD multiplicities): δ = 17.2 (q), 29.7 (q), 48.1 (s) 50.0 (d), 50.8 (d), 52.0 (s), 115.2 (s), 117.7 (s), 128.3 (2C), 128.4 (2C), 129.2 (4C), 129.3 (2C), 130.5 (s), 134.5 (s), 135.1 (s), 139.4 (s), 163.4 (s), 168.1 (s) and 201.5 (s).
Anal. calcd. for $C_{25}H_{20}N_4O_2$: C, 73.53; H, 4.90; N, 13.72. Found: C, 73.25; H, 5.05; N, 14.00.

3-Acetyl-5-amino-6,6-dicyano-2-methyl-4,7-bis(p-methylphenyl)-6,7-dihydro-4H-pyrano[2,3-b]pyridine (3b). - This compound was obtained in 43% yield; mp. 274-276°C (d) (from acetonitrile or ethanol; see below); IR (KBr): 3420, 3200, 3000 (broad), 2250, 1700, 1670, 1635, 1530, 1510, 1360, 1270 cm^{-1}. ^1H-NMR (DMSO-d_6): δ = 9.2 (b, 1H, NH); 7.3-6.7 (9H, arom., NH); 4.9 (b, 1H, CH), 4.5 (s, 1H, CH), 2.33 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.16 (d, 3H, CH_3), 2.06 (s, 3H, CH_3). MS: m/e = 436 (M^+, 100), 435 (19), 432 (39), 428 (34), 351 (10), 345 (33), 285 (15), 266 (13), 250 (12), 208 (9), 186 (8), 171 (8), 170 (71), 143 (15), 142 (22), 128 (22), 116 (9), 115 (30).
Anal. calcd. for $C_{27}H_{24}N_4O_2$: C, 74.31; H, 5.50; N, 12.84. Found: C, 74.42; H, 5.87; N, 12.54. Sample with EtOH of crystallization: Calcd. for $C_{27}H_{24}N_4O_2 \cdot C_2H_5OH$: C, 72.20; H, 6.22, N, 11.62. Found: C, 72.30; H, 6.37; N, 11.71.

3-Acetyl-5-amino-6,6-dicyano-2-methyl-4,7-bis(p-methoxyphenyl)-6,7-dihydro-4H-pyrano[2,3-b]pyridine (3c). - This compound was obtained in 42% yield; mp 210-212°C (d) (from ethanol); IR (KBr): 3500, 3000 (broad), 2240, 1700, 1670, 1640, 1610, 1580, 1515, 1280, 1260, 1190, 1030 cm^{-1}; ^1H-NMR (DMSO-d_6): δ = 9.1 (b, s, 1H, NH), 7.2-6.5 (m, 9H, arom., NH), 4.8 (b, 1H, CH): 4.35 (s, 1H, CH), 3.66 (s, 3H, CH_3O), 3.63 (s, 3H, CH_3O), 2.10 (b, s, 3H, CH_3), 2.0 (s, 3H, CH_3); MS: m/e = 468 (M^+, 100), 467 (14), 450 (18), 426 (35), 425 (72), 383 (13), 382 (12), 361 (16), 317 (26), 303 (30), 266 (15), 241 (10), 200 (10), 187 (18), 186 (84), 170 (9), 159 (17), 158 (24), 127 (17), 121 (43).
Anal. calcd. for $C_{27}H_{24}N_4O_4 \cdot C_2H_5OH$: C, 67.70; H, 5.83; N, 10.89. Found: C, 67.58; H, 5.60; N, 11.33.

5-Acetyl-2-amino-4-aryl-3-cyano-6-methyl-4H-pyrans (4). General procedure. - To a suspension of the appropriate 2-acetyl-3-aryl-1-methylpropenone (2) (10 mmol) in ca. 30 ml of ethanol, 10 mmol of malononitrile (1) and 2 - 3 drops of triethyl-amine were added. The reaction mixture was stirred until total solution occurs. Upon standing at room temperature, a solid precipitated[13] and was collected by filtration. Compounds 4 were obtained in pure form by recrystallization from ethanol.

5-Acetyl-2-amino-3-cyano-6-methyl-4-(p-methylphenyl)-4H-pyran (4b). - This compound was obtained in 56% yield; mp 135-137°C (from ethanol); IR (KBr): 3460, 3300, 3200, 2190, 1705, 1680, 1665, 1600, 1510, 1400, 1380, 1240, 1210 cm^{-1}; ^1H-NMR (DMSO-d_6): δ = 6.82 (b, s, 4H, arom.), 6.50 (bs, 2H, NH_2, disappears upon addition of TFA), 4.25 (s, 1H, CH), 2.16 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 1.95 (s, 3H, CH_3).
Anal. calcd. for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.44. Found: C, 71.55; H, 6.01; N, 10.35.

5-Acetyl-2-amino-3-cyano-6-methyl-4-(p-methoxyphenyl)-4H-pyran (4c). - This compound was obtained in 57% yield; mp 157-159°C (from ethanol); IR (KBr): 3460, 3300, 3170, 2180, 1695, 1660, 1600, 1510, 1370, 1270, 1250, 1220, 1180, 1030 cm^{-1}; ^1H-NMR (DMSO-d_6): δ = 6.95 (q, 4H, arom.); 6.72 (bs, 2H, NH_2), 4.40 (s, 1H, CH), 3.73 (s, 3H, CH_3O), 2.25 (s, 3H, CH_3), 2.08 (s, 3H, CH_3).
Anal. calcd. for $C_{16}H_{16}N_2O_3$: C, 67.60; H, 5.63; N, 9.86. Found: C, 67.77; H, 5.90; N, 10.00.

Reaction of 5-acetyl-2-amino-3-cyano-6-methyl-4-phenyl-4H-pyran (4a) with benzylydenemalononitrile (5). - Pyran 4a (1.27 g, 5 mmol) was suspended in ca. 30 ml of ethanol and 0.77 g (5 mmol) of benzylydenemalononitrile 5 were added, together with 2 - 3 drops of triethylamine. The reaction mixture was heated until total solution occurs and then refluxed for 5 hours. After that time a solid separated and was collected by filtration from the hot reaction mixture. The white solid thus obtained was identified as pure 3a by comparison with an authentic sample. Yield 59%.

Treatment of 5-acetyl-2-amino-3-cyano-6-methyl-4-phenyl-4H-pyran (4a) in basic medium. - 0.3 g of pyran 4a (1.2 mmol) was dissolved in 12 ml of hot ethanol and 2 drops of triethylamine. The reaction mixture was refluxed for 5 hours. The solid that separates was filtered off from the hot solution and was isolated as a pure crystalline solid identified as pyranopyridine 3a by comparison with an authentic sample. Yield 27%.

Reaction of benzylydene malononitrile (5) with acetylacetone (7). Benzylydenemalononitrile (5) (1.54 g, 10 mmol) and acetylacetone (7) (1 g, 10 mmol) were suspen-ded in ca. 30 ml of ethanol containing 3 drops of triethylamine. The reaction mixture was refluxed for 3 hours. After that time, the starting materials were totally dissolved. Upon cooling, a solid precipitated. It was filtered off and identified as 3a. Yield 18%. From the mother liquors, upon standing, another solid precipitated after 24 hours. When collected by filtration, it was identified as pyran 4a. Yield 40%.

3-Acetyl-7-aryl-5-amino-6-cyano-2-methyl-6-methoxycarbonyl-4-phenyl-6,7-dihydro-4H-pyrano[2,3-b]pyridines (3d-f). General procedure. - The appropriate methyl

arylydenecyanoacetate (6) (20 mmol) was added to a suspension of 20 mmol of pyran 4a in ca. 20 ml of ethanol and 3 drops of triethylamine. The reaction mixture was stirred at room temperature for 1-4 days. The solid that separated after that time was collected by filtration and recrystallized from acetonitrile.

3-Acetyl-5-amino-6-cyano-2-methyl-6-methoxycarbonyl-4,7-diphenyl-6,7-dihydro-4H-pyrano[2,3-b]pyridine (3d). - This compound was obtained in 90% yield; mp 268-270°C (from acetonitrile); IR (KBr): 3340, 3040 (broad), 2250, 1760, 1700, 1680, 1650, 1530, 1290, 1265 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 9.26, 8.41 (bs, NH_2), 7.4-6.9 (m, 10H, arom.), 5.03 (bs, 1H, CH), 4.3 (s, 1H, CH), 3.4 (s, 3H, CO_2CH_3), 1.98 (s, 3H, CH_3), 1.94 (s, 3H, CH_3). MS: m/e = 441 (M^+, 15), 440 (8), 399 (19), 398 (67), 397 (10), 382 (21), 156 (19), 128 (23), 91 (16).
Anal. calcd. for $C_{26}H_{23}N_3O_4$: C, 70.74; H, 5.21; N, 9.52. Found: C, 71.00; H, 5.40; N, 9.82.

3-Acetyl-5-amino-6-cyano-2-methyl-6-methoxycarbonyl-7-(p-methylphenyl)-4-phenyl-6,7-dihydro-4H-pyrano[2,3-b]pyridine (3e). - This compound was obtained in 47% yield; mp. 262-264°C (d) (from acetonitrile); IR (KBr): 3350, 3100 (b), 2250, 1750, 1700, 1680, 1650, 1530, 1290, 1270, 1230, 1100, 1080 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 8.66, 8.44 (bs, NH_2), 7.4-6.8 (m, 9H, arom.), 5.0 (bs, 1H, CH), 4.2 (s, 1H, CH), 3.46 (s, 3H, CO_2CH_3), 2.28 (s, 3H, CH_3), 1.97 (s, 3H, CH_3).
Anal. calcd. for $C_{27}H_{25}N_3O_4$: C, 71.20; H, 5.49; N, 9.23. Found: C, 71.58; H, 5.82; N, 9.11.

3-Acetyl-5-amino-7-(p-chlorophenyl)-6-cyano-2-methyl-6-methoxycarbonyl-4-phenyl-6,7-dihydro-4H-pyrano[2,3-b]pyridine (3f). - This compound was obtained in 69% yield; mp 254-256°C (from acetonitrile); IR (KBr): 3410, 3240 (b), 2250, 1740, 1700, 1650, 1600, 1520, 1280, 1100, 1020 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 9.23, 8.46 (bs, NH_2), 7.5-6.8 (m, 9H, arom.), 5.0 (bs, 1H, CH), 4.36 (s, 1H, CH), 3.5 (s, 3H, CO_2CH_3), 2.0 (s, 3H, CH_3), 1.96 (s, 3H, CH_3).
Anal. calcd. for $C_{26}H_{22}N_3O_4Cl$: C, 65.61; H, 4.62; N, 8.83. Found: C, 65.29; H, 4.69; N, 8.69.

1-Amino-2,4,6,6-tetracyano-4-ethoxycarbonyl-3,5-diphenylcyclohexene (9). - α-Cyanocinnaomonitrile (5) (10 mmol) was suspended in ca. 25 ml of dry ethanol and 10 mmol of ethylcyanoacetate (8) and three drops of piperidine were added. The reaction mixture was stirred until total solution was achieved and, then, kept at room temperature for 4 days. The solid that separates was collected by filtration. Yield: 30%; mp 224-226°C (from ethanol). IR (KBr): 3380, 3340, 3240, 2250, 2200, 1740, 1660, 1620, 1500 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ = 7.6 - 7.0 (m, 12H, arom., NH_2), 4.8 (s, 1H, CH), 4.6 (s, 1H, CH), 3.65 (q, 2H, CH_2), 0.65 (t, 3H, CH_3); MS: m/e = 421 (M^+, 6), 394 (3), 348 (10), 321 (15), 221 (19), 220 (100), 219 (12), 201 (15), 200 (9), 195 (14), 194 (19), 193 (13), 156 (10), 140 (5), 128 (9), 102 (5), 77 (9).
Anal. calcd. for $C_{25}H_{19}N_5O_2$: C, 71.26; H, 4.51; N, 16.62. Found: C, 71.59; H, 4.81; N, 16.57.

ACKNOWLEDGEMENTS

Support of this work by a grant from the Comisiòn Asesora de Investigaciòn Cientifica y tecnica de la Presidencia de Gobierno of Spain (Grant PB 86-0570) is gratefully acknowledged.

REFERENCES AND NOTES

(1) A previous account of part of this work was presented as a poster communication at ESOC V, Jerusalem (Israel), 1987.
(2) See, for example: Katritzky, A.R; Rees, C.W., "Comprehensive Heterocyclic Chemistry", vol. 2, Pergamon Press, 1984.
(3) Al Nakib, T.; Tyndall, D.V.; Meegan, M.J., J. Chem. Res. (S), 1987 (322).
(4) Bargar, T.M.; Wilson, T.; Daniel, J.K., J. Heterocyclic Chem., 1985, 22, 1583; Sliwa, H., Bull. Soc. Chim. France, 1970, 631; Sliwa, H.; Delaunay, L., J. Heterocyclic Chem., 1979, 16, 939; Maffett, R.B.; J. Org. Chem., 1970, 25, 3596; Bonnetand, D.; Queguiner, G.; Pastour, P., J. Heterocyclic Chem., 1972, 9, 165; Khalifa, M.A.; Elnagdi, M.H.; Indian J. Chem., 1974, 12, 46; Abdalla, M.; Essawy, A.; Deeb, A., Indian J. Chem., 1978, 16B, 332; Essawy, A.; El-Safty, M.; El-Gandy, M.A., Indian J. Chem., 1982, 21B, 769; Loewe, W., J. Heterocyclic Chem., 1977, 14, 931; Glozman, O.M.; Zagorevsk, D.V.; Zhmorenko, L.A., Khim. Geterotsikle. Soedin, 1978, 622, C.A. 89, 108959 w (1978).
(5) Degny, E.; Zard, S.Z.; Pastor, R.; Cambon, A., Tetrahedron Letters, 1981, 22, 2169.
(6) Manchand, P.S.; Todaro, L.J.; Manchand, R.S., J. Chem. Res. (S), 1984, 116.
(7) This kind of cyclization of ϒ-cyanoketones is not new and the formation of 2-aminopyrans from some intermediates of this type is known. For a review,

see: Quinteiro, M.; Seoane, C.; Soto, J.L., "Synthetic approaches to the 4H-pyran ring", Heterocycles, 1980, 14, 337.
(8) Ciller, J.A.; Martin, N.; Quinteiro, M.; Seoane, C.; Soto, J.L., Org. Prep. Proced. Int., 1986, 18, 227.
(9) Sekiya, M.; Suzuki, K., Chem. Pharm. Bull. Jpn., 1970, 18, 1530. Knoevenagel, E.; Ruschanpt, N., Ber., 1898, 31, 2775. Silver, R.F.; Louch, C.E.; Holmes, H.L.; Currie, D.T., Can. J. Chem., 1967, 45, 1001. Calmon, M.; Arnaud-Lejujeur, B.; Calmon, J.P., Bull. Soc. Chim. Fr., 1972, 179.
(10) Corson, B.; Stoughton, R., J. Am. Chem. Soc., 1928, 50, 2825. Cope, A.C.; Hoyle, K.E., J. Am. Chem. Soc., 1941, 63, 733.
(11) In the particular case of 3a (Ar=C_6H_5), a certain amount of pyran 4a can be isolated from the reaction if a solid initially formed is collected after a few minutes. The yield in pyran 4a varies widely (20-60%) depending upon concentration, reaction time and even the precise room temperature. In fact, this reaction has been previously reported as a preparation for pyran 4a[a].
(12) The same happens with n-butanol as the solvent. Further recrystallization of the samples from acetonitrile removes the alcohol.
(13) Usually, but not always, a certain amount of the corresponding compound 3 precipitates first and must be removed by filtration. Pyran 4 is then collected by precipitation from the mother liquor.