

General Method for the Preparation of Substituted 2-Amino-4H,5H-pyrano[4,3-*b*]pyran-5-ones and 2-Amino-4H-pyrano[3,2-*c*]pyridine-5-ones

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Abstract: Reaction of 4-hydroxy-6-methyl-2-pyrone (**1a**) as well as 4-hydroxy-6-methyl-2(1*H*)-pyridones (**1b-d**) with arylmethylene malononitriles or arylmethylene methyl cyanoacetates (**2a-h**) leads to the formation of the very stable 5,6-fused bicyclic 2-amino-4*H*-pyran derivatives **3a-3af**.

Keywords: pyrano[4,3-*b*]pyran, pyrano[3,2-*c*]pyridine, arylmethylene malononitrile, arylmethylene cyanoacetate, *Michael* addition.

Introduction

Wiener *et al.* first published [1] that 4-hydroxycoumarin cyclized through *Michael* addition to benzylidene malononitrile in pyridine as solvent to give a derivative of 2-aminopyrano[3,2-*c*]benzopyran (**A**) (Figure 1). Later, Junek and Aigner [2] found a second case of this heterocyclization *via* addition of 4-hydroxy-6-methyl-2-pyrone (**1a**, “triacetic acid lactone”, Scheme 1) to tetracyanoethylene, thus preparing a substituted 2-amino-4*H*,5*H*-pyrano[4,3-*b*]pyran (**B**). Many years thereafter, Shaker [3] re-

ported several applications of this reaction where he also used 4-hydroxycoumarin and α,β -unsaturated nitriles in order to prepare **A** and some of its analogues without, however, referring to either of the preceding publications [1, 2].

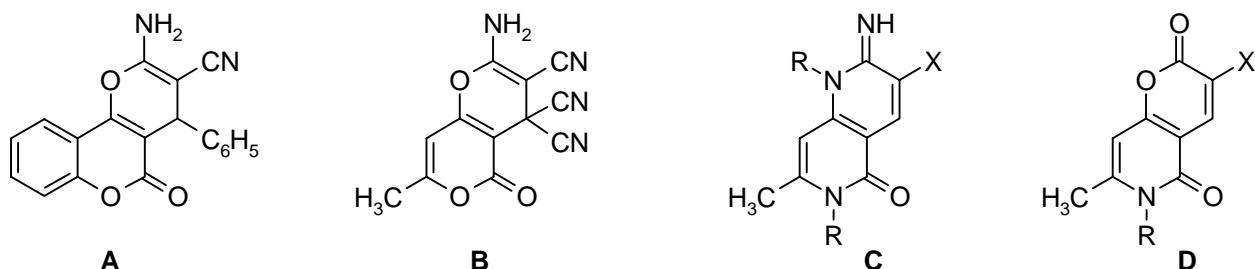
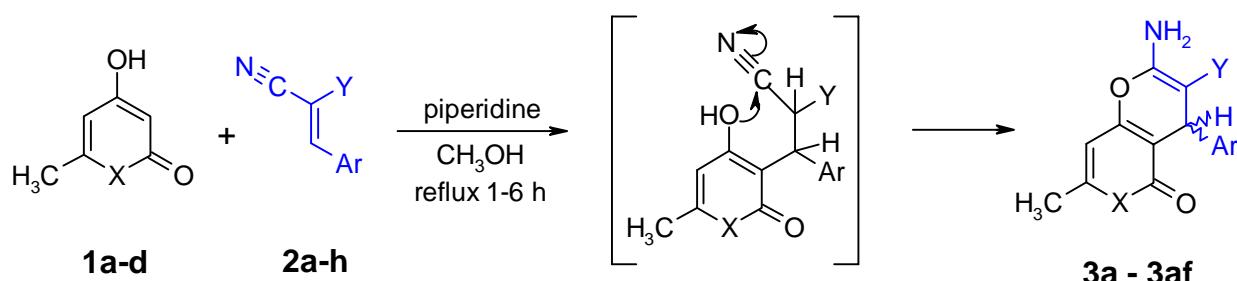


Figure 1.

In the course of our recent studies on the synthesis and the antituberculosis activity of 2-imino-7-methyl-1,6(6*H*)-naphthyridine derivatives (**C**) [4] and of 2*H*-pyrano[3,2-*c*]pyridines (**D**) as their oxygen analogues [5], we needed to obtain some structurally similar representatives of the 2-amino-4*H*,5*H*-pyrano[4,3-*b*]pyrans and the 2-amino-4*H*-pyrano[3,2-*c*]pyridines. For that purpose we successfully extended the known reaction, discussed above, to a general method for their preparation.

Meanwhile, two further communications on the same subject appeared in the literature. *Mekheimer et al.* [6] reported the cyclization of 4-hydroxy-6-methyl-2(1*H*)-pyridone (**1b**) with arylmethylene malononitriles and arylmethylene cyanoacetic esters to the corresponding pyrano[3,2-*c*]pyridines (**3f** and their analogues, Scheme 1), thus independently covering a small part of our results. Also *Piao* and *Imafuku* [7] published a preliminary paper dealing with the preparation in a similar way of some novel 4*H*,5*H*-pyrano[4,3-*b*]pyran-5-ones of type **B** from triacetic acid lactone without, however, giving spectral and analytical characterization of their products.

We now wish to report the general procedure for the preparation of both compound classes and to fully characterize the numerous new substances synthesized by us.



Scheme 1.

Table 1.

1	X	3	X	Y	Ar
a	O	a	O	COOCH ₃	C ₆ H ₅
b	N-H	b	N-H	COOCH ₃	C ₆ H ₅
c	N-CH ₂ -C ₆ H ₅	c	N-CH ₂ -C ₆ H ₅	COOCH ₃	C ₆ H ₅
d	N-CH ₂ -CH ₂ -C ₆ H ₅	d	N-CH ₂ -CH ₂ -C ₆ H ₅	COOCH ₃	C ₆ H ₅
2	Ar	Y	i	COOCH₃	C₆H₄-NO₂-m
a	C ₆ H ₅	COOCH ₃	j	N-H	COOCH ₃
b	C ₆ H ₅	CN	k	N-CH ₂ -C ₆ H ₅	COOCH ₃
c	C ₆ H ₄ -NO ₂ -m	COOCH ₃	l	N-CH ₂ -CH ₂ -C ₆ H ₅	COOCH ₃
d	C ₆ H ₄ -NO ₂ -m	CN	m	O	CN
e	C ₆ H ₄ -NO ₂ -p	COOCH ₃	n	N-H	CN
f	C ₆ H ₄ -NO ₂ -p	CN	o	N-CH ₂ -C ₆ H ₅	CN
g	C ₆ H ₄ -OCH ₃ -p	COOCH ₃	p	N-CH ₂ -CH ₂ -C ₆ H ₅	CN
h	C ₆ H ₄ -OCH ₃ -p	CN	q	O	COOCH ₃
			r	N-H	COOCH ₃
			s	N-CH ₂ -C ₆ H ₅	COOCH ₃
			t	N-CH ₂ -CH ₂ -C ₆ H ₅	COOCH ₃
			u	O	CN
			v	N-H	CN
			w	N-CH ₂ -C ₆ H ₅	CN
			x	N-CH ₂ -CH ₂ -C ₆ H ₅	CN
			y	O	COOCH ₃
			z	N-H	COOCH ₃
			aa	N-CH ₂ -C ₆ H ₅	COOCH ₃
			ab	N-CH ₂ -CH ₂ -C ₆ H ₅	COOCH ₃
			ac	O	CN
			ad	NH	CN
			ae	N-CH ₂ -C ₆ H ₅	CN
			af	N-CH ₂ -CH ₂ -C ₆ H ₅	CN

Results and Discussion

The starting compounds **1a-d** react with the *Knoevenagel* products **2a-h** [8] in an equimolar ratio by refluxing in methanol for 1-6 h in the presence of small amounts of piperidine. Both reaction steps, the *Michael* addition of C-3 of **1** to the β -position of **2** and the nucleophilic intramolecular addition of the 4-hydroxy group to the cyano group, occur as one-pot process. The products **3a-3af** (Table 1) usually crystallize on cooling and can be easily isolated to give yields in the range from 56 to 95%. Beside 4-hydroxy-6-methyl-2(1*H*)-pyridone (**1b**), its *N*-substituted derivatives **1c,d** were also successfully employed in the reaction.

In contrast with the reported statement that the ethyl α -cyanoacrylic esters react only in refluxing pyridine as solvent [6], we found that the methyl esters **2a,c,e,g** ($Y = COOCH_3$) did give good to excellent yields of the corresponding products **3** by using the same general procedure as for the malononitriles (reflux in methanol, piperidine).

The structure of the products **3** could be unambiguously deduced from their spectral properties. The primary amino group showed two IR absorption bands at 3357-3500 and 3133-3330 cm^{-1} and a sharp 2H-singlet at $\delta = 6.92$ -7.83 ppm in their 1H -NMR spectra (*cf.* [6]). In the IR spectra, all 3-carbonitriles absorbed at 2181-2217 cm^{-1} (CN) whereas the methyl 3-carboxylates gave bands in the range 1657-1696 cm^{-1} for ester carbonyl group. The mass spectra of **3** confirmed the corresponding molecular masses.

The stability of the compounds **3** with respect to opening of the 2-aminopyran ring was examined on the product **3f** as a model compound (no ester function, stable lactam ring). Surprisingly, it turned out that **3f** is rather stable under hydrolytic conditions (diluted or concentrated sulphuric and hydrochloric acid, mixture of acetic and hydrochloric acid, ethanolic potassium hydroxide). Our trials to perform some chemical transformations of **3f**, similar to those described in the literature [3,6], also failed.

Experimental

General

Melting points were determined in open capillary tubes with a Büchi 535 melting point apparatus (Switzerland). IR spectra (nujol) were recorded on a Shimadzu FTIR 8101M spectrometer (Japan), ν in cm^{-1} . Mass spectra were measured on a Varian MAT 711 spectrometer (Germany) at 70 eV (direct inlet). 1H NMR were recorded on a Bruker DRX-250 spectrometer at 250 MHz (Germany), δ (ppm) referenced to TMS (internal). Microanalyses were carried out in the Microanalytical Laboratory of the Institute of Organic Chemistry and Isotope Research, University of Stuttgart, Germany. TLC-monitoring: pre-coated aluminium sheets Merck, 0.2 mm layer of silica gel F₂₅₄, eluted by hexane-acetone/methanol (5:3:2, vol. parts), detection by Camag UV-lamp (254/366 nm). Yields of isolated, TLC-homogeneous products are given.

Spectral data for compounds **3f**, **3n**, **3v**, **3ad** have been reported earlier [6]; preparation of compounds **3a**, **3e** and **3ac** has been published [7] without preparative, spectral and analytical details.

General procedure for preparation of compounds **3a-3af**

Into a stirred mixture of 4-hydroxy-6-methyl-2-pyrone (**1a**; 126 mg, 1.0 mmol) or of the corresponding 4-hydroxy-2(1*H*)-pyridone (**1b-d**; 1.0 mmol) and the α,β -unsaturated nitrile (**2a-h**, 1.0 mmol) in methanol (5.0 ml), 1-2 drops of piperidine were added and the mixture was refluxed under stirring for a period of time given below for each product. After cooling to 20-25°C, the separated crystals were filtered, washed with cold methanol and air-dried to give the corresponding product **3a**-

3af. The product's purity was controlled by TLC. When necessary the crude product was recrystallized from the corresponding solvent given below.

Methyl 2-amino-7-methyl-5-oxo-4-phenyl-4H,5H-pyrano[4,3-b]pyran-3-carboxylate (3a)

Reflux 1 h. Colourless crystals (methanol), m.p. 197-199°C. Yield 68% (lit. [7]: yield 83%).

IR: 3428, 3299, 1717, 1688, 1620, 1603, 1507.

^1H NMR ($\text{d}_6\text{-DMSO}$): 2.15 (s, 7- CH_3), 3.45 (s, OCH_3), 4.48 (s, 4-H), 6.22 (s, 8-H), 7.07-7.18 (m, 5H arom.), 7.65 (s, NH_2).

EI MS (%): 313 (19, M^+); 254 (3); 236 (100); 204 (52); 162 (5); 127 (1); 102 (1); 77 (2); 43 (18); 18 (5).

Anal. Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_5$ (313.30): C, 65.17; H, 4.83; N, 4.47. Found: C, 65.25; H, 4.85; N, 4.45.

Methyl 2-amino-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carboxylate (3b)

Reflux 1 h. Colourless crystals (methanol), m.p. 230-232°C. Yield 84%.

IR: 3474, 3330, 1684, 1651, 1638, 1593, 1522.

^1H NMR ($\text{d}_6\text{-DMSO}$): 2.07 (s, 7- CH_3), 3.46 (s, OCH_3), 4.62 (s, 4-H), 5.82 (s, 8-H), 6.99-7.17 (m, 5H arom.), 7.54 (s, NH_2), 11.38 (s, NH).

EI MS (%): 312 (18, M^+); 235 (100); 203 (60); 175 (5); 126 (3); 84 (3); 42 (3); 28 (8); 18 (2).

Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4$ (312.32): C, 65.38; H, 5.16; N, 8.97. Found: C, 65.32; H, 5.15; N, 8.9.

Methyl 2-amino-6-benzyl-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carboxylate (3c)

Reflux 1 h. Colourless crystals (methanol), m.p. 214-216°C. Yield 60%.

IR: 3374, 3230, 1688, 1651, 1601, 1576, 1530.

^1H NMR ($\text{d}_6\text{-DMSO}$): 2.23 (s, 7- CH_3), 3.53 (s, OCH_3), 4.77 (s, 4-H), 5.04 and 5.33 (AB-q, $J = 16.0$ Hz, 2H, CH_2Ph), 6.12 (s, 8-H), 6.98-7.31 (m, 10H arom.), 7.63 (s, NH_2).

EI MS (%): 402 (15, M^+); 370 (2); 343 (2); 325 (100); 311 (2); 293 (24); 279 (3); 251 (1); 185 (1); 91 (60); 65 (2); 18 (8).

Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_4$ (402.44): C, 71.63; H, 5.51; N, 6.96. Found: C, 71.57; H, 5.52; N, 6.95.

Methyl 2-amino-7-methyl-5-oxo-6-phenethyl-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carboxylate (3d)

Reflux 1 h. Colourless crystals (methanol), m.p. 183-185°C. Yield 64%.

IR: 3391, 3285, 1682, 1651, 1605, 1583, 1516.

^1H NMR ($\text{d}_6\text{-DMSO}$): 2.13 (s, 7- CH_3), 2.74 (m, CH_2Ph), 3.47 (s, OCH_3), 3.85-4.04 (m, NCH_2), 4.71

(s, 4-H), 5.95 (s, 8-H), 7.01-7.21 (m, 10H arom.), 7.55 (s, NH₂).

EI MS (%): 416 (18, M^+); 384 (1); 357 (1); 339 (100); 307 (21); 279 (1); 253 (1); 235 (14); 203 (15); 175 (2); 128 (1); 105 (30); 79 (4); 28 (5); 18 (3).

Anal. Calcd for C₂₅H₂₄N₂O₄ (416.47): C, 72.10; H, 5.81; N, 6.73. Found: C, 72.25; H, 5.82; N, 6.73.

2-Amino-7-methyl-5-oxo-4-phenyl-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (3e)

Reflux 1 h. Colourless crystals, m.p. 236-238°C. Yield 79% (lit. [7]: yield 92%).

IR: 3401, 3324, 2199, 1713, 1674, 1646, 1615, 1591.

¹H NMR (d₆-DMSO): 2.16 (s, 7-CH₃), 4.22 (s, 4-H), 6.21 (s, 8-H), 7.11-7.28 (m, 7H, C₆H₅ and NH₂).

EI MS (%): 280 (21, M^+); 237 (2); 213 (10); 203 (100); 171 (1); 161 (13); 102 (6); 77 (1); 66 (8); 43 (30); 28 (12); 18 (8).

Anal. Calcd for C₁₆H₁₂N₂O₃ (280.28): C, 68.57; H, 4.32; N, 9.99. Found: C, 68.40; H, 4.33; N, 9.96.

2-Amino-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (3f)

Reflux 1 h. Colourless crystals, m.p. 291-293°C. Yield 94%. (Lit. [6]: m.p. 293-295 °C; yield 93%).

2-Amino-6-benzyl-7-methyl-5-oxo-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (3g)

Reflux 1 h. Colourless crystals, m.p. 275-277°C. Yield 74%.

IR: 3403, 3283, 3133, 2184, 1659, 1615, 1570.

¹H NMR (d₆-DMSO): 2.19 (s, 7-CH₃), 4.33 (s, 4-H), 5.02 and 5.21 (AB-q, J = 16.1 Hz, 2H, CH₂Ph), 6.05 (s, 8-H), 6.94-7.25 (m, 12H, two C₆H₅ and NH₂).

EI MS (%): 369 (40, M^+); 292 (90); 278 (47); 236 (1); 195 (4); 146 (5); 91 (100); 65 (8); 28 (14); 18 (8).

Anal. Calcd for C₂₃H₁₉N₃O₂ (369.42): C, 74.78; H, 5.18; N, 11.37. Found: C, 74.39; H, 5.33; N, 11.20.

2-Amino-7-methyl-5-oxo-6-phenethyl-4-phenyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (3h)

Reflux 1 h. Colourless crystals, m.p. 257-259°C. Yield 83%.

IR: 3455, 3300, 2193, 1673, 1617, 1599, 1576.

¹H NMR (d₆-DMSO): 2.16 (s, 7-CH₃), 2.6-2.8 (m, CH₂Ph), 2.75-4.05 (m, NCH₂), 4.33 (s, 4-H), 5.95 (s, 8-H), 6.95 (s, NH₂), 7.06-7.27 (m, 10H arom., two C₆H₅).

EI MS (%): 383 (30, M^+); 339 (1); 306 (42); 279 (28); 235 (1); 202 (100); 184 (1); 105 (19); 79 (5); 66 (2); 28 (8).

Anal. Calcd for C₂₄H₂₁N₃O₂ (383.44): C, 75.18; H, 5.52; N, 10.96. Found: C, 75.25; H, 5.59; N, 11.08.

Methyl 2-amino-7-methyl-4-(3-nitrophenyl)-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carboxylate (3i)

Reflux 1 h. Pale yellow crystals (methanol), m.p. 223-225°C (dec.). Yield 76%.

IR: 3465, 3322, 1715, 1660, 1628, 1597, 1531.

¹H NMR (d₆-DMSO): 2.16 (s, 7-CH₃), 3.44 (s, OCH₃), 4.60 (s, 4-H), 6.27 (s, 8-H), 7.50 (dd, J = 7.8 Hz, 5-H arom.), 7.59-7.62 (m, 6-H arom.), 7.78 (s, NH₂), 7.90 (m, 2-H arom.), 7.95-8.00 (m, 4-H arom.).

EI MS (%): 358 (15, M⁺); 327 (1); 299 (2); 251 (1); 236 (100); 204 (35); 162 (5); 126 (1); 101 (1); 85 (2); 59 (3); 43 (18); 28 (15); 18 (4).

Anal. Calcd for C₁₇H₁₄N₂O₇ (358.31): C, 56.99; H, 3.94; N, 7.82. Found: C, 56.86; H, 3.99; N, 7.94.

Methyl 2-amino-7-methyl-4-(3-nitrophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carboxylate (3j)

Reflux 1 h. Pale yellow crystals (methanol), m.p. 243-244°C. Yield 80%.

IR: 3434, 3297, 1696, 1651, 1620, 1595, 1522.

¹H NMR (d₆-DMSO): 2.09 (s, 7-CH₃), 3.45 (s, OCH₃), 4.72 (s, 4-H), 5.87 (s, 8-H), 7.43-7.50 (m, 5-H arom.), 7.57-7.61 (m, 6-H arom.), 7.68 (s, NH₂), 7.90-7.95 (m, 2H, 2-H and 4-H arom.), 11.47 (s, NH).

EI MS (%): 357 (12, M⁺); 325 (5); 298 (6); 257 (2); 235 (100); 203 (50); 175 (5); 125 (1); 84 (2); 59 (6); 44 (3); 28 (68); 18 (27).

Anal. Calcd for C₁₇H₁₅N₃O₆ (357.33): C, 57.14; H, 4.23; N, 11.76. Found: C, 57.38; H, 4.38; N, 11.48.

Methyl 2-amino-6-benzyl-7-methyl-4-(3-nitrophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carboxylate (3k)

Reflux 1 h. Pale yellow crystals (methanol), m.p. 231-233°C. Yield 57%.

IR: 3364, 3260, 1686, 1657, 1609, 1590, 1528.

¹H NMR (d₆-DMSO): 2.24 (s, 7-CH₃), 3.51 (s, OCH₃), 4.86 (s, 4-H), 5.05 and 5.28 (AB-q, J = 16.0 Hz, CH₂Ph), 6.16 (s, 8-H), 6.95-7.00 (m, 2H arom. from C₆H₅), 7.17-7.30 (m, 3H arom. from C₆H₅), 7.52 (m, 5-H from C₆H₅NO₂), 7.63-7.70 (m, 6-H from C₆H₅NO₂), 7.77 (s, NH₂), 7.96-8.03 (m, 2H arom., 2-H and 4-H from C₆H₅NO₂).

EI MS (%): 447 (22, M⁺); 430 (9); 415 (4); 388 (1); 356 (1); 325 (100); 293 (20); 215 (3); 165 (1); 91 (75); 65 (3); 31 (28); 18 (10).

Anal. Calcd for C₂₄H₂₁N₃O₆ (447.45): C, 64.42; H, 4.73; N, 9.39. Found: C, 64.20; H, 4.78; N, 9.32.

Methyl 2-amino-7-methyl-4-(3-nitrophenyl)-5-oxo-6-phenethyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carboxylate (3l)

Reflux 1 h. Pale yellow crystals (methanol), m.p. 215-217°C. Yield 87%.

IR: 3473, 3322, 1657, 1626, 1605, 1578, 1526.

^1H NMR ($\text{d}_6\text{-DMSO}$): 2.14 (s, 7-CH₃), 2.6-2.9 (m, CH₂Ph), 3.46 (s, OCH₃), 3.8-4.1 (m, NCH₂), 4.79 (s, 4-H), 6.00 (s, 8-H), 6.95-7.05 (m, 2H arom. from C₆H₅), 7.05-7.22 (m, 3H arom. from C₆H₅), 7.48 (m, 5-H from C₆H₅NO₂), 7.55 (m, 6-H from C₆H₅NO₂), 7.69 (s, NH₂), 7.90-7.97 (m, 2H arom., 2-H and 4-H from C₆H₅NO₂).

EI MS (%): 461 (20, M^+); 444 (11); 412 (1); 357 (23); 339 (100); 307 (18); 235 (50); 175 (1); 105 (25); 79 (2); 59 (2); 18 (48).

Anal. Calcd for C₂₅H₂₃N₃O₆ (461.48): C, 65.07; H, 5.02; N, 9.11. Found: C, 64.91; H, 5.06; N, 9.15.

2-Amino-7-methyl-4-(3-nitrophenyl)-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (3m)

Reflux 1 h. Pale yellow crystals (ethanol), m.p. 234-236°C. Yield 67%.

IR: 3397, 3326, 2199, 1715, 1674, 1646, 1615, 1526.

^1H NMR ($\text{d}_6\text{-DMSO}$): 2.22 (s, 7-CH₃), 4.55 (s, 4-H), 6.30 (s, 8-H), 7.34 (s, NH₂), 7.62 (dd, J = 7.8 Hz, 5-H arom.), 7.68-7.74 (m, 6-H arom.), 8.03 (m, 2-H arom.), 8.08-8.13 (m, 4-H arom.).

EI MS (%): 325 (21, M^+); 308 (1); 278 (1); 242 (1); 203 (100); 161 (11); 133 (1); 85 (1); 66 (3); 43 (30); 28 (4).

Anal. Calcd for C₁₆H₁₁N₃O₅ (325.28): C, 59.08; H, 3.41; N, 12.92. Found: C, 59.49; H, 3.58; N, 13.07.

2-Amino-7-methyl-4-(3-nitrophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (3n)

Reflux 1 h. Pale yellow crystals, m.p. 310-311°C. Yield 95%. (Lit. [6]: m.p. 309-310 °C; yield 92%).

2-Amino-6-benzyl-7-methyl-4-(3-nitrophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (3o)

Reflux 1 h. Pale yellow crystals, m.p. 284-285°C. Yield 90%.

IR: 3370, 3168, 2203, 1665, 1619, 1582, 1530.

^1H NMR ($\text{d}_6\text{-DMSO}$): 2.26 (s, 7-CH₃), 4.62 (s, 4-H), 5.05 and 5.23 (AB-q, J = 16.1 Hz, CH₂Ph), 6.15 (s, 8-H), 6.95-7.00 (m, 2H arom. from C₆H₅), 7.20 (s, NH₂), 7.22-7.29 (m, 3H arom. from C₆H₅), 7.61 (dd, J = 7.8 Hz, 5-H arom.), 7.66-7.72 (m, 6-H arom.), 7.98 (m, 2-H arom.), 8.05-8.10 (m, 4-H arom.).

EI MS (%): 414 (23, M^+); 397 (20); 367 (1); 323 (10); 292 (52); 91 (100); 66 (14); 28 (32); 18 (13).

Anal. Calcd for $C_{23}H_{18}N_4O_4$ (414.42): C, 66.66; H, 4.38; N, 13.52. Found: C, 66.58; H, 4.46; N, 13.55.

2-Amino-7-methyl-4-(3-nitrophenyl)-5-oxo-6-phenethyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (3p)

Reflux 1 h. Pale yellow crystals, m.p. 248–250°C. Yield 81%.

IR: 3357, 3169, 2191, 1661, 1613, 1570, 1580, 1524.

1H NMR (d_6 -DMSO): 2.21 (s, 7-CH₃), 2.70–2.83 (m, CH₂Ph), 3.85–4.10 (m, NCH₂), 4.60 (s, 4-H), 6.04 (s, 8-H), 7.08–7.13 (m, 2H arom. from C₆H₅), 7.15 (s, NH₂), 7.18–7.28 (m, 3H arom. from C₆H₅), 7.61 (dd, J = 7.8 Hz, 5-H arom.), 7.66–7.71 (m, 6-H arom.), 7.99 (m, 2-H arom.), 8.05–8.10 (m, 4-H arom.).

EI MS (%): 428 (8, M^+); 364 (1); 324 (31); 305 (17); 260 (1); 229 (10); 202 (100); 153 (30); 126 (15); 104 (80); 84 (6); 28 (32).

Anal. Calcd for $C_{24}H_{20}N_4O_4$ (428.45): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.35; H, 4.76; N, 13.23.

Methyl 2-amino-7-methyl-4-(4-nitrophenyl)-5-oxo-4H,5H-pyran-3-carboxylate (3q)

Reflux 1 h. Pale yellow crystals (methanol), m.p. 196–198°C. Yield 59%.

IR: 3461, 3322, 1730, 1694, 1636, 1599, 1525, 1516.

1H NMR (d_6 -DMSO): 2.21 (s, 7-CH₃), 3.48 (s, OCH₃), 4.64 (s, 4-H), 6.31 (s, 8-H), 7.44 (d, J = 8.7 Hz, 2H, 2-H and 6-H arom.), 7.83 (s, NH₂), 8.10 (d, J = 8.7 Hz, 2H, 3-H and 5-H arom.).

EI MS (%): 358 (20, M^+); 327 (1); 299 (3); 236 (100); 204 (33); 162 (4); 85 (2); 59 (1); 43 (19); 28 (21); 18 (12).

Anal. Calcd for $C_{17}H_{14}N_2O_7$ (358.31): C, 56.99; H, 3.94; N, 7.82. Found: C, 56.86; H, 4.00; N, 7.66.

Methyl 2-amino-7-methyl-4-(4-nitrophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carboxylate (3r)

Reflux 1 h. Pale yellow crystals (methanol), m.p. 233–235°C. Yield 66%.

IR: 3387, 3285, 1678, 1646, 1634, 1593, 1522.

1H NMR (d_6 -DMSO): 2.13 (s, 7-CH₃), 3.49 (s, OCH₃), 4.75 (s, 4-H), 5.90 (s, 8-H), 7.42 (d, J = 8.7 Hz, 2H, 2-H and 6-H arom.), 7.72 (s, NH₂), 8.08 (d, J = 8.7 Hz, 2H, 3-H and 5-H arom.).

EI MS (%): 357 (14, M^+); 325 (5); 298 (3); 257 (1); 235 (70); 203 (32); 175 (9); 152 (1); 136 (10); 98 (5); 84 (12); 68 (15); 59 (20); 44 (33); 31 (100); 18 (20).

Anal. Calcd for $C_{17}H_{15}N_3O_6$ (357.33): C, 57.14; H, 4.23; N, 11.76. Found: C, 56.60; H, 4.56; N, 11.44.

Methyl 2-amino-6-benzyl-7-methyl-4-(4-nitrophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carboxylate (3s)

Reflux 1 h. Pale yellow crystals (methanol), m.p. 237-239°C. Yield 72%.

IR: 3360, 3250, 1682, 1657, 1584, 1514.

^1H NMR (d_6 -DMSO): 2.24 (s, 7-CH₃), 3.51 (s, OCH₃), 4.84 (s, 4-H), 5.03 and 5.30 (AB-q, $J = 16.5$ Hz, CH₂Ph), 6.14 (s, 8-H), 6.95-7.00 (m, 2H arom. from C₆H₅), 7.20-7.29 (m, 3H arom. from C₆H₅), 7.45 (d, $J = 8.8$ Hz, 2H, 2-H and 6-H arom. from C₆H₄NO₂), 7.77 (s, NH₂), 8.09 (d, $J = 8.8$ Hz, 2H, 3-H and 5-H arom. from C₆H₄NO₂).

EI MS (%): 447 (25, M^+); 415 (1); 356 (4); 325 (100); 293 (18); 232 (15); 175 (2); 136 (5); 109 (3); 91 (98); 59 (20); 31 (62); 18 (22).

Anal. Calcd for C₂₄H₂₁N₃O₆ (447.45): C, 64.42; H, 4.73; N, 9.39. Found: C, 64.22; H, 4.78; N, 9.33.

Methyl 2-amino-7-methyl-4-(4-nitrophenyl)-5-oxo-6-phenethyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carboxylate (3t)

Reflux 1 h. Pale yellow crystals (methanol), m.p. 237-239°C. Yield 70%.

IR: 3378, 3264, 1688, 1657, 1605, 1584, 1534, 1516.

^1H NMR (d_6 -DMSO): 2.21 (s, 7-CH₃), 2.7-2.9 (m, CH₂Ph), 3.51 (s, OCH₃), 3.85-4.10 (m, NCH₂), 4.83 (s, 4-H), 6.04 (s, 8-H), 7.05-7.11 (m, 2H arom. from C₆H₅), 7.15-7.30 (m, 3H arom. from C₆H₅), 7.45 (d, $J = 8.8$ Hz, 2H, 2-H and 6-H arom. from C₆H₄NO₂), 7.74 (s, NH₂), 8.09 (d, $J = 8.8$ Hz, 2H, 3-H and 5-H arom. from C₆H₄NO₂).

EI MS (%): 461 (25, M^+); 430 (1); 402 (2); 357 (30); 339 (100); 325 (2); 307 (18); 235 (60); 203 (23); 175 (3); 104 (50); 79 (9); 44 (5); 28 (26); 18 (10).

Anal. Calcd for C₂₅H₂₃N₃O₆ (461.48): C, 65.07; H, 5.02; N, 9.11. Found: C, 64.97; H, 5.07; N, 9.11.

2-Amino-7-methyl-4-(4-nitrophenyl)-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carbonitrile (3u)

Reflux 1 h. Pale yellow crystals (ethanol), m.p. 216-218°C. Yield 67%.

IR: 3497, 3316, 3158, 2203, 1705, 1678, 1653, 1622, 1595, 1520.

^1H NMR (d_6 -DMSO): 2.22 (s, 7-CH₃), 4.49 (s, 4-H), 6.30 (s, 8-H), 7.33 (s, NH₂), 7.55 (d, $J = 8.7$ Hz, 2H, 2-H and 6-H arom. from C₆H₄NO₂), 8.15 (d, $J = 8.7$ Hz, 2H, 3-H and 5-H arom. from C₆H₄NO₂).

EI MS (%): 325 (23, M^+); 308 (1); 278 (1); 242 (1); 203 (100); 161 (8); 126 (2); 85 (2); 66 (8); 43 (35); 28 (5); 18 (2).

Anal. Calcd for C₁₆H₁₁N₃O₅ (325.28): C, 59.08; H, 3.41; N, 12.92. Found: C, 59.00; H, 3.46; N, 12.96.

2-Amino-7-methyl-4-(4-nitrophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (3v)

Reflux 1 h. Pale yellow crystals, m.p. 291-292°C. Yield 91%. (Lit. [6]: m.p. 290-201°C, yield 62%).

2-Amino-6-benzyl-7-methyl-4-(4-nitrophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (3w)

Reflux 1 h. Pale yellow crystals, m.p. 274-276°C. Yield 82%.

IR: 3428, 3297, 3173, 2182, 1665, 1615, 1590, 1518.

¹H NMR (d₆-DMSO): 2.26 (s, 7-CH₃), 4.57 (s, 4-H), 5.04 and 5.25 (AB-q, J = 16.2 Hz, CH₂Ph), 6.14 (s, 8-H), 6.95-7.02 (m, 2H arom. from C₆H₅), 7.19 (s, NH₂), 7.19-7.32 (m, 3H arom. from C₆H₅), 7.46 (d, J = 8.7 Hz, 2H, 2-H and 6-H arom. from C₆H₄NO₂), 8.16 (d, J = 8.7 Hz, 2H, 3-H and 5-H arom. from C₆H₄NO₂).

EI MS (%): 414 (27, M⁺); 323 (25); 292 (40); 277 (2); 215 (24); 199 (22); 169 (2); 153 (10); 126 (11); 109 (8); 91 (100); 66 (73); 51 (3); 28 (20); 18 (12).

Anal. Calcd for C₂₃H₁₈N₄O₄ (414.42): C, 66.66; H, 4.38; N, 13.52. Found: C, 66.52; H, 4.46; N, 13.22.

2-Amino-7-methyl-4-(4-nitrophenyl)-5-oxo-6-phenethyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (3x)

Reflux 1 h. Pale yellow crystals, m.p. 245-247°C. Yield 86%.

IR: 3376, 3325, 3193, 2199, 1671, 1588, 1520.

¹H NMR (d₆-DMSO): 2.23 (s, 7-CH₃), 2.7-2.85 (m, CH₂Ph), 3.72-4.10 (m, NCH₂), 4.56 (s, 4-H), 6.04 (s, 8-H), 7.08-7.30 (m, 7H, 5H arom., C₆H₅ and 2H, NH₂), 7.45 (d, J = 8.8 Hz, 2H, 2-H and 6-H arom. from C₆H₄NO₂), 8.17 (d, J = 8.8 Hz, 2H, 3-H and 5-H arom. from C₆H₄NO₂).

EI MS (%): 428 (1, M⁺); 324 (4); 306 (2); 229 (2); 202 (11); 169 (3); 153 (5); 126 (5); 104 (8); 38 (11); 28 (30); 18 (15).

Anal. Calcd for C₂₄H₂₀N₄O₄ (428.45): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.22; H, 4.75; N, 13.07.

Methyl 2-amino-4-(4-methoxyphenyl)-7-methyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-3-carboxylate (3y)

Reflux 6 h. Colourless crystals (methanol), m.p. 180-182°C. Yield 56%.

IR: 3488, 3316, 1717, 1626, 1584, 1559, 1510.

¹H NMR (d₆-DMSO): 2.19 (s, 7-CH₃), 3.50 (s, COOCH₃), 3.67 (s, OCH₃ arom.), 4.47 (s, 4-H), 6.26 (s, 8-H), 6.78 (d, J = 8.7 Hz, 2H, 3-H and 5-H arom.), 7.06 (d, J = 8.7 Hz, 2H, 2-H and 6-H arom.).

7.66 (s, NH₂).

EI MS (%): 343 (40, M^+); 311 (7); 284 (8); 236 (100); 217 (10); 204 (30); 186 (5); 162 (4); 145 (2); 117 (2); 85 (2); 59 (8); 43 (17); 28 (23); 18 (2).

Anal. Calcd for C₁₈H₁₇NO₆ (343.33): C, 62.97; H, 4.99; N, 4.08. Found: C, 62.83; H, 5.00; N, 4.09.

Methyl 2-amino-4-(4-methoxyphenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carboxylate (3z)

Reflux 6 h. Colourless crystals (methanol), m.p. 241-243°C. Yield 62%.

IR: 3428, 3316, 1690, 1651, 1636, 1532, 1509.

¹H NMR (d₆-DMSO): 2.21 (s, 7-CH₃), 3.50 (s, COOCH₃), 3.66 (s, OCH₃ arom.), 4.61 (s, 4-H), 5.85 (s, 8-H), 6.73 (d, J = 8.7 Hz, 3-H and 5-H arom.), 7.07 (d, J = 8.7 Hz, 2-H and 6-H arom.), 7.54 (s, NH₂), 11.39 (s, NH).

EI MS (%): 342 (40, M^+); 325 (2); 310 (100); 281 (30); 255 (30); 235 (100); 203 (40); 186 (18); 158 (4); 121 (12); 108 (25); 84 (22); 59 (17); 42 (15); 31 (55); 28 (46).

Anal. Calcd for C₁₈H₁₈N₂O₅ (342.35): C, 63.15; H, 5.30; N, 8.18. Found: C, 62.35; H, 5.50; N, 8.04.

Methyl 2-amino-6-benzyl-4-(4-methoxyphenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carboxylate (3aa)

Reflux 6 h. Colourless crystals (methanol), m.p. 193-194°C. Yield 59%.

IR: 3374, 3268, 1682, 1657, 1586, 1510.

¹H NMR (d₆-DMSO): 2.21 (s, 7-CH₃), 3.52 (s, COOCH₃), 3.66 (s, OCH₃ arom.), 4.70 (s, 4-H), 5.03 and 5.32 (AB-q, J = 16.0 Hz, CH₂Ph), 6.09 (s, 8-H), 6.75 (d, J = 8.7 Hz, 3-H and 5-H arom. from C₆H₄-OCH₃), 6.95-7.03 (m, 2H arom. from C₆H₅), 7.09 (d, J = 8.7 Hz, 2-H and 6-H arom. from C₆H₄OCH₃), 7.18 - 7.30 (m, 3H arom. from C₆H₅), 7.57 (s, NH₂).

EI MS (%): 432 (45, M^+); 415 (1); 400 (15); 373 (7); 341 (12); 325 (100); 309 (20); 293 (16); 281 (4); 265 (2); 217 (10); 186 (8); 158 (2); 91 (95); 59 (12); 28 (23); 18 (3).

Anal. Calcd for C₂₅H₂₄N₂O₅ (432.48): C, 69.43; H, 5.59; N, 6.48. Found: C, 69.19; H, 5.67; N, 6.41.

Methyl 2-amino-4-(4-methoxyphenyl)-7-methyl-5-oxo-6-phenethyl-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carboxylate (3ab)

Reflux 6 h. Colourless crystals (methanol), m.p. 211-213°C. Yield 66%.

IR: 3453, 3324, 1659, 1628, 1605, 1580, 1509.

¹H NMR (d₆-DMSO): 2.18 (s, 7-CH₃), 2.70-2.85 (m, CH₂Ph), 3.52 (s, COOCH₃), 3.66 (s, OCH₃ arom.), 3.85-4.15 (m, NCH₂), 4.70 (s, 4-H), 5.98 (s, 8-H), 6.75 (d, J = 8.7 Hz, 2H, 3-H and 5-H arom. from C₆H₄OCH₃), 7.09 (d, 2H, J = 8.7 Hz, 2-H and 6-H arom. from C₆H₄OCH₃), 7.05-7.30 (m, C₆H₅), 7.57 (s, NH₂).

EI MS (%): 446 (50, M^+); 414 (4); 387 (6); 339 (100); 307 (14); 283 (5); 235 (17); 186 (12); 158 (2); 105 (32); 59 (14); 28 (19); 18 (5).

Anal. Calcd for $C_{26}H_{26}N_2O_5$ (446.51): C, 69.94; H, 5.87; N, 6.27. Found: C, 69.51; H, 6.01; N, 6.14.

2-Amino-4-(4-methoxyphenyl)-7-methyl-5-oxo-4H,5H-pyran-3-carbonitrile (3ac)

Reflux 5 h. Colourless crystals, m.p. 205-207°C. Yield 57% (lit. [7]: yield 87%).

IR: 3455, 3312, 3168, 2186, 1728, 1676, 1646, 1607, 1510.

1H NMR (d_6 -DMSO): 2.20 (s, 7-CH₃), 3.71 (s, OCH₃), 4.21 (s, 4-H), 6.24 (s, 8-H), 6.84 (d, J = 8.7 Hz, 2H, 3-H and 5-H arom.), 7.08 (d, J = 8.7 Hz, 2H, 2-H and 6-H arom.), 7.12 (s, NH₂).

Anal. Calcd for $C_{17}H_{14}N_2O_4$ (310.31): C, 65.80; H, 4.55; N, 9.03. Found: C, 65.58; H, 4.58; N, 9.12.

2-Amino-4-(4-methoxyphenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyran-3-carbonitrile (3ad)

Reflux 5 h. Colourless crystals, m.p. 248-250°. Yield 86%. (Lit. [6]: m.p. 250-251°C, yield 84%).

2-Amino-6-benzyl-4-(4-methoxyphenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyran-3-carbonitrile (3ae)

Reflux 5 h. Colourless crystals, m.p. 273-275°C. Yield 52%.

IR: 3397, 3291, 3169, 2182, 1665, 1615, 1614, 1588, 1512.

1H NMR (d_6 -DMSO): 2.23 (s, 7-CH₃), 3.70 (s, OCH₃), 4.33 (s, 4-H), 5.04 and 5.27 (AB-q, J = 16.0 Hz, CH₂Ph), 6.08 (s, 8-H), 6.82 (d, J = 8.6 Hz, 2H, 3-H and 5-H arom. from C₆H₄OCH₃), 6.96 (s, NH₂), 7.00 (m, 2H arom. from C₆H₅), 7.07 (d, J = 8.6 Hz, 2H, 2-H and 6-H arom. from C₆H₄OCH₃), 7.17-7.30 (m, 3H arom. from C₆H₅).

EI MS (%): 399 (30, M^+); 332 (15); 308 (50); 292 (23); 242 (2); 215 (7); 184 (12); 141 (1); 114 (1); 91 (100); 66 (60); 28 (70); 18 (12).

Anal. Calcd for $C_{24}H_{21}N_3O_3$ (399.45): C, 72.17; H, 5.30; N, 10.52. Found: C, 72.11; H, 5.33; N, 10.38.

2-Amino-4-(4-methoxyphenyl)-7-methyl-5-oxo-6-phenethyl-5,6-dihydro-4H-pyran-3-carbonitrile (3af)

Reflux 5 h. Colourless crystals, m.p. 263-265°C. Yield 84%.

IR: 3370, 3285, 3156, 2187, 1661, 1613, 1582, 1512.

1H NMR (d_6 -DMSO): 2.21 (s, 7-CH₃), 2.70-2.85 (m, CH₂Ph), 3.70 (s, OCH₃), 3.84-4.10 (m, NCH₂), 4.32 (s, 4-H), 5.98 (s, 8-H), 6.83 (d, J = 8.7 Hz, 2H, 3-H and 5-H arom. from C₆H₄OCH₃), 6.93 (s, NH₂), 7.07 (d, J = 8.7 Hz, 2H, 2-H and 6-H arom. from C₆H₄OCH₃), 7.05-7.30 (m, C₆H₅).

EI MS (%): 413 (14, M^+); 347 (10); 309 (11); 256 (7); 229 (14); 202 (22); 184 (82); 141 (12); 104 (62); 84 (14); 66 (100); 55 (8); 39 (17); 28 (23).

Anal. Calcd for $C_{25}H_{23}N_3O_3$ (413.48): C, 72.62; H, 5.61; N, 10.16. Found: C, 72.55; H, 5.64; N, 10.00.

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Samples Availability: Samples are available from the authors and from MDPI.