Thermal Cyclization of 3-Acyl-4-azidopyridines to Isoxazolo[4,3-*c*]pyridines [1]

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Abstract. 4-Azidopyridines such as 3-acetyl-4-azido-2-pyridones **3** or 4-azido-3-ethoxycarbonylpyridine **7** with reactive *ortho*-acyl substituents were obtained from the 4-hydroxy-2-pyridones **1**, resp. **5** *via* 4-tosyloxy-2-pyridones **2** or the 2,4-dichloropyridine **6**. DSC-assisted thermolysis of the azides **3** and **7** resulted in electrocyclization and elimination of nitrogen to the isoxazolo[4,3-*c*]pyridines **4** and **8**.

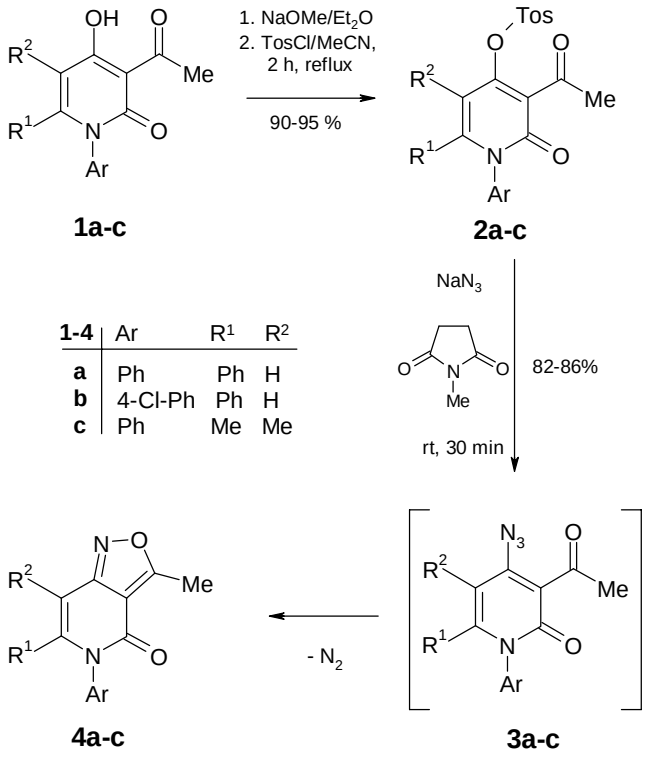
Isoxazoles are known as a class of compounds with interesting biological properties (*e.g.* [2]). Recently, we reported that fused azidoarenes or azidohetarenes with *ortho*-acyl substituents gave on thermolysis the corresponding isoxazolo derivatives [1, 3]. In the present work we extended this reaction to pyridones as fused ring partners, a ring system which is part of many natural products (*e.g.* [4]) or has interesting biological activities (*e.g.* [5]). Another point of interest was to study the thermal cyclization of *ortho*-acyl azidoarenes by means of differential scanning calorimetry (DSC), a method which makes possible the determination of the thermal reaction conditions [6], besides safety aspects, a fact which is important in synthetic azide chemistry.

Results and Discussion

As starting materials for the synthesis of 4-azidopyridines **3** and **7** 3-acyl-4-hydroxy-2-pyridones **1** and **5** were used, which were obtained by two different methods. 3-Acetyl-4-hydroxy-pyridones **1** were obtained in a two step reaction from diethyl malonate and azomethines, which were prepared in turn in a two step reaction from the appropriate ketones *via* aminonitriles by elimination of hydrogen cyanide adopting known methods [7, 8].

The conversion of the 4-hydroxy compounds **1** to 4-chloro derivatives, which could be transformed to the azido compounds, failed, probably because of strong hydrogen bondings between the hydroxy- and the acyl group. Also the use of bases such as triethyl amine during the chlorination, a method previously employed successfully in similar systems [9] gave no results. However, tosylation of the sodium salts of **1** [1,3a,d,e] furnished the reactive intermediates **2**.

Reaction of quinoline and phenalene tosylates with sodium azide gave at room temperature stable azido compounds [3d,e]; according to the DSC diagrams the peaks indicated in these cases exothermic reaction at 50–120 °C [1, 3a]. However, the azides **3**, formed from 4-tosyloxypyridones **2**, lost nitrogen already at room temperature and cyclized to isoxazolo[4,3-*c*]pyridones **4**. Attempts to isolate the azides **3** by reaction below room temperature failed too.



Scheme 1 Cyclization of 3-acetyl-4-tosyloxypyridones **2** *via* azides **3** to isoxazolo[4,3-*c*]pyridones **4**

Ethyl 4-hydroxy-6-methyl-2-oxo-pyridine-3-carboxylate (**5**) was obtained from ethyl β-aminocrotonate and diethyl malonate by an improved literature proce-

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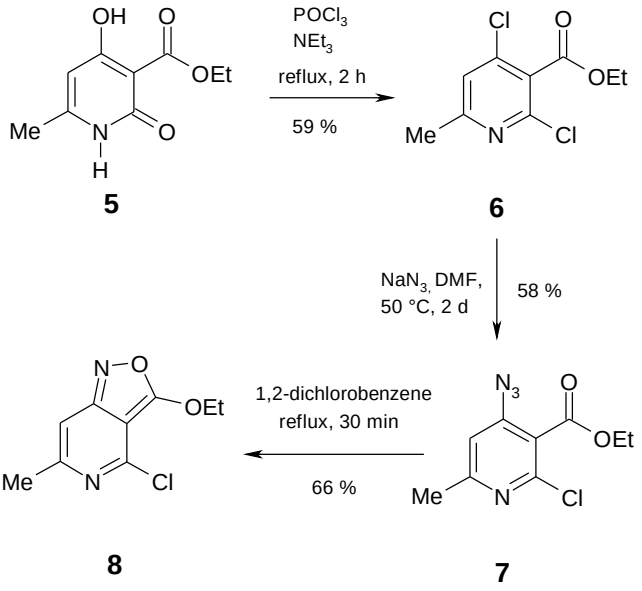
dure [10, 11]. Ethyl 2,4-dichloro-6-methylpyridine-3-carboxylate (**6**) was synthesized in 59% yield by reaction of **5** with excess of phosphorous oxychloride in the presence of triethylamine to break the hydrogen bondings. Similar reactions without addition of triethylamine were reported to afford yields below 30% [12, 13] or to require sealed tube techniques [14]. Selective exchange of the 4-chloro atom against azide was performed by reaction of **6** with sodium azide in dimethylformamide at 50 °C. Spectral data confirmed structure **7** [15]. Attempts to obtain the 2-azido isomer in acidic medium in the manner found recently for dichloroquinolines [15] failed.



Scheme 2 Cyclization of 4-azidopyridine-3-carboxylate **7** to 3-ethoxy-6-methyl-isoxazolo[4,3-*c*]pyridine **8**

Data of the azido compound **7** obtained by differential scanning calorimetry showed a broad exothermic reaction/decomposition peak starting at about 120–130 °C with a maximum at about 160 °C without any endothermic melting area. A reaction enthalpy of about –515 J/g was determined. Although the shape of the reaction peak indicated possible subsequent decomposition reactions, we found that the preparative thermolysis of **7** had to be performed at temperatures higher than the peak maximum of the DSC diagram; best results were obtained in refluxing 1,2-dichlorobenzene. Other solvents (*e.g.* dimethylformamide or bromobenzene) required longer reaction times and afforded by-products. Hence, the isoxazole **8** was prepared in 66% yield by thermolysis of **8** for 20–30 minutes in refluxing 1,2-dichlorobenzene.

Attempted replacement of the 4-hydroxygroup of esters **9** [16] by azide was unsuccessful. Tosylation of **9a**

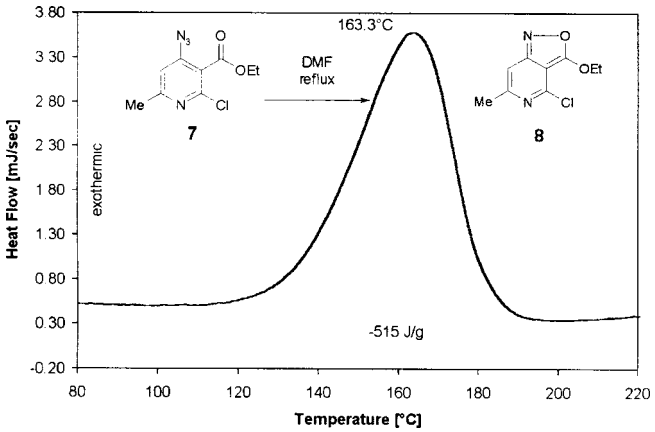
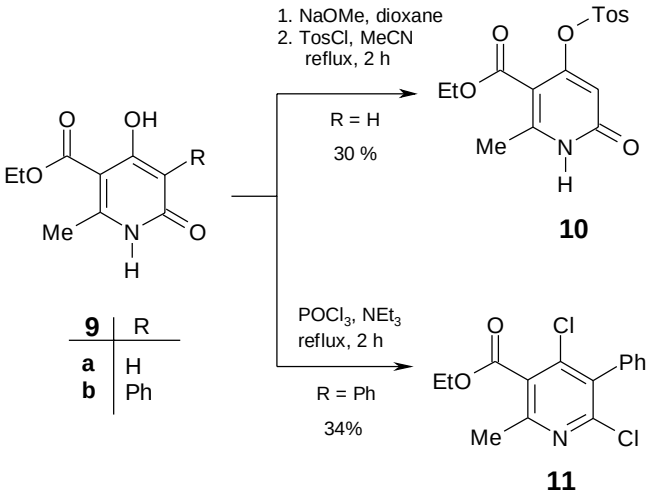


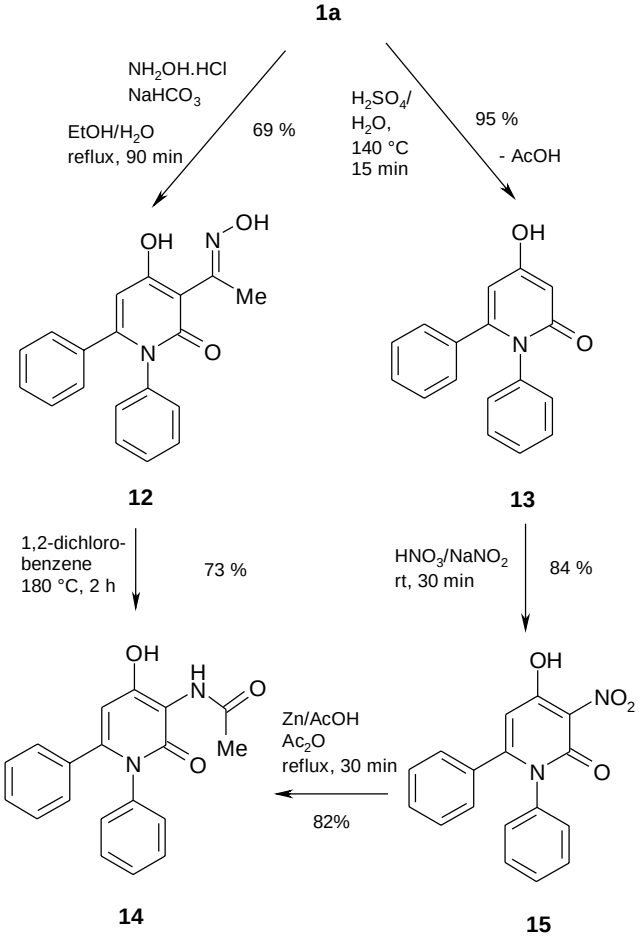
Fig. 1 Differential scanning calorimetry diagram of ethyl 4-azido-2-chloro-6-methylpyridine-3-carboxylate (**7**) (2.190 mg in a sealed aluminium crucible) between 50 and 350 °C with a heating rate of 5 °C/min in static air as environment

in the manner applied for compounds **1** gave in 30% yield the 4-tosylate **10** which did not react at room temperature with sodium azide. At higher temperatures mixtures of compounds were obtained. Chlorination of the 4-hydroxypyridone **9a** was unsuccessful. Under different conditions mixtures of three compounds were obtained in low yields. Chlorination of the pyridone **9b** with phosphorus oxychloride in the presence of triethylamine gave the dichloropyridine **11** in 34% yield. Reaction of this compound with sodium azide was again unsuccessful.



Scheme 3 Reactive derivatives of pyridine-5-carboxylates **9**

In an attempt to prepare an isoxazolo[4,5-*c*]pyridine isomeric to the isoxazolo[4,3-*c*]pyridines **4** and **8** we tried a cyclodehydration of the ketoxime **12**, which was synthesized from 3-acetyl-4-hydroxypyridone **1a** [17]. However, in all experiments – *e.g.* heating in various



Scheme 4 Beckmann rearrangement of 3-(1-hydroxyiminoethyl)-pyridinone **12** to 3-acetylaminopyridone **14**

solvents with or without acid catalysis – only 3-acetylamino-4-hydroxypyridone **14**, the product of a Beckmann rearrangement was isolated.

3-Acetylaminopyridone (**14**) was independently prepared from **1a**. In the first step the 3-acetyl group was removed by heating **1a** in 90% sulfuric acid. The product **13** was nitrated to 3-nitropyridone **15**. Reduction with zinc in a mixture of acetic acid and acetanhydride afforded the 3-acetylaminopyridone **14**. Attempts [3d] to cyclize **14** to 2-methyl-6,7-diphenyloxazolo[4,5-*c*] pyridin-5-one failed.

The results obtained reveal that thermal cyclization of 4-azido-3-acylpyridines is a viable method for the synthesis of isoxazolo[4,3-*c*]pyridines. The cyclization temperatures depend strongly on the structure of acyl substituent and substitution pattern of the pyridine nucleus. DSC measurements make possible the determination of the thermolysis temperature.

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Experimental

Melting points: Gallenkamp Melting Point Apparatus, Mod. MFB-595 in open capillary tubes. – IR: Perkin-Elmer 298 or Galaxy Series FTIR 7000. – ^{1}H NMR: Varian Gemini 200 or Bruker AM 360 (internal tetramethylsilane standard). – ^{13}C NMR: Bruker AM 360. – Microanalyses: Fisons elemental analyzer, Mod. EA 1108, within ±0.4% of the theoretical percentages. – DSC: Rheometric Scientific DSC-Plus instrument with the DSC software V5.42; temperature range: 25–500 °C, heating rate: 2–10 °C/min, compound amount: 1.5–3 mg in sealed aluminium crucibles (11 bar). – All reactions were monitored by thin layer chromatography on 0.2 mm silica gel F-254 (MERCK) plates using uv light (254 and 366 nm) for detection.

3-Acetyl-4-hydroxy-1,6-diphenylpyridin-2(1H)-one (**1a**)

A: 2-Phenyl-2-(phenylamino)propanenitril. To a cold (5 °C) mixture of acetophenone (36.0 g, 0.30 mol) and $PhNH_2$ (33.5 g, 0.36 mol) in AcOH (125 ml) NaCN (26.7 g, 0.53 mol)) was added in portions. After 12 h at 5 °C, ice/H_2O (250 ml) was added. Filtration (attention: the mother liquor contains still NaCN) and washing of the residue with H_2O (500 ml) and *n*-hexane (500 ml) yielded 57.9 g (87%) of colorless microprisms; *m.p.* 158–160 °C (lit. *m.p.* 155 °C [18]).

B: N[1]-Diphenyl-1-ethanimine. To a solution of the nitrile of step A (57.9 g, 0.26 mol) in boiling MeOH (300 ml) a solution of KOH (58.4 g) in MeOH (500 ml) was added. After boiling for 1 h, H_2O (800 ml) was added and the mixture was extracted with *n*-hexane (4 × 150 ml). Usual workup and crystallization at 4 °C afforded 46.0 g (91%) of pale yellow prisms; *m.p.* 42.6–43 °C (lit. m.p. 38–39 °C [18]).

C: 4-Hydroxy-6,7-diphenyl-pyrano[3,2-c]pyridine-2,5(6H)-dione. A mixture of the azomethine of step B (13.7 g, 0.070 mol), diethyl malonate (22.4 g, 0.14 mol) and Ph_2O (35 g) was heated at reflux in a distillation apparatus equipped with a 20 cm Vigreux column. During ca. 75 min, EtOH (about 15 ml) distilled off. After cooling to about 20 °C the precipitate was suspended in MeOH (100 ml). Filtration and washing of the residue with MeOH and Et_2O yielded 14.6 g (63%) of orange-yellow prisms; *m.p.* 294–296 °C. – IR (KBr): ν/cm^{-1} = 1720 s (2-C=O), 1670–1660 s, b (5-C=O). – ^{1}H NMR (CF_3COOH): δ/ppm = 5.90 (s, H-3), 6.80 (s, H-8), 7.00–7.40 (m, 10 ArH).

$C_{20}H_{13}NO_4$	Calcd.:	C 72.50	H 3.95	N 4.23
(331.3)	Found:	C 72.43	H 3.88	N 4.22.

D: 3-Acetyl-4-hydroxy-1,6-diphenylpyridin-2(1H)-one. A mixture of the pyrane of step C (14.9 g, 0.045 mol) in 1,2-dihydroxyethane (270 ml) and of KOH (18 g, 0.45 mol) in H_2O (30 ml) was heated to gentle boiling for 1 h. The hot reaction mixture was poured into ice/H_2O (1.5 l) and acidified with conc. HCl. The precipitate was filtered by suction and washed with H_2O; the yield was 12.8 g (93%) of colorless prisms; *m.p.* 120–121 °C (ligroin). – IR (KBr): ν/cm^{-1} = 1670 s (C=O). – ^{1}H NMR (DMSO-d_6): δ/ppm = 2.55 (s, CH_3), 6.25 (s, H-5), 7.15–7.35 (m, 10 ArH).

$C_{19}H_{15}NO_3$	Calcd.:	C 74.74	H 4.95	N 4.59
(305.3)	Found:	C 74.37	H 4.84	N 4.67.

3-Acetyl-1-(4-chlorophenyl)-4-hydroxy-6-phenyl-pyridin-2(1H)-one (**1b**)

A: 2-(4-Chlorophenylamino)-2-phenylpropanenitrile. The reaction of acetophenone (7.2 g, 0.06 mol), 4-chloroaniline (7.7 g, 0.06 mol) and NaCN (4.9 g, 0.10 mol) in AcOH (25 ml) as described for step A of **1a** yielded 10.9 g (71%) of colorless prisms; *m.p.* 147.5–147.8 °C. – IR (KBr): ν/cm^{-1} = 3 380 s (NH), 2 230 w (CN). – ^{1}H NMR ($CDCl_3$): δ/ppm = 1.95 (s, CH_3), 4.35 (s, br, NH), 6.45–5.55 (m, 2ArH), 7.00–7.10 (m, 2ArH), 7.35–7.50 (m, 3ArH), 7.55–7.70 (m, 2ArH).

$C_{15}H_{13}ClN_2$	Calcd.:	C 70.18	H 5.10	N 10.91
(356.7)	Found:	C 69.94	H 5.14	N 10.89.

B: N^1-(4-Chlorophenyl)-1-phenyl-1-ethanimine. The reaction of the nitrile of step A (10.45 g, 0.041 mol) in MeOH (50 ml) and KOH (5.6 g) in MeOH (50 ml) as described for step B of **1a** yielded 8.25 g (88%) of pale lightbrown microprisms; *m.p.* 75–76 °C. – IR (KBr): ν/cm^{-1} = 1 630 m (C=N), 1 590 (C=C). – ^{1}H NMR ($CDCl_3$): δ/ppm = 2.25 (s, CH_3), 6.75 (m, 2ArH), 7.30 (m, 2ArH), 7.40–7.50 (m, 3ArH), 7.90–8.00 (m, 2ArH).

$C_{14}H_{12}ClN$	Calcd.:	C 73.20	H 5.27	N 6.10
(229.7)	Found:	C 73.39	H 5.43	N 6.06.

C: 6-(4-Chlorophenyl)-4-hydroxy-7-phenyl-pyrano[3,2-c]pyridine-2,5(6H)-dione. The reaction of the azomethine of step B (7.88 g, 0.034 mol) and diethyl malonate (11.2 g, 0.070 mol) in Ph_2O (20 ml) as described for step B of **1a** yielded 6.2 g (49%) of yellow prisms; *m.p.* 265–265.5 °C (dioxane). – IR (KBr): ν/cm^{-1} = 1 725 s (2-C=O), 1 675 m (5-C=O), 1 665 m. – ^{1}H NMR (DMSO-d_6): δ/ppm = 5.60 (s, H-3), 6.85 (s, H-8), 7.20–7.55 (m, 9ArH).

$C_{20}H_{12}ClNO_4$	Calcd.:	C 65.67	H 3.31	N 3.83
(365.8)	Found:	C 65.27	H 3.70	N 3.49.

D: 3-Acetyl-1-(4-chlorophenyl)-4-hydroxy-6-phenyl-pyridin-2(1H)-one. The reaction of the pyrane of step C (6.08 g, 0.017 mol) in 1,2-dihydroxyethane (100 ml) and KOH (6.0 g) in H_2O (10 ml) as described for step D of **1a** yielded 5.1 g (90%) of colorless prisms; *m.p.* 179 °C (EtOH). – IR (KBr): ν/cm^{-1} = 1 680 s (C=O). – ^{1}H NMR (DMSO-d_6): δ/ppm = 2.60 (s, CH_3), 6.25 (s, H-5), 7.20–7.40 (m, 9ArH).

$C_{19}H_{14}ClNO_3$	Calcd.:	C 67.16	H 4.15	N 4.12
(339.8)	Found:	C 66.90	H 4.38	N 4.06.

3-Acetyl-4-hydroxy-5,6-dimethyl-1-phenylpyridin-2(1H)-one (**1c**)

A: 2-Methyl-2-(phenylamino)butanenitrile. The reaction of 2-butanone (4.3 g, 0.06 mol), $PhNH_2$ (7.7 g, 0.06 mol) and NaCN (4.9 g, 0.10 mol) in AcOH (25 ml) was performed as described for step A of **1a**. Dilution with ice/H_2O formed two layers, which were separated; to the upper layer *n*-hexane (10 ml) was added; cooling (4 °C) for 10 min, filtration and washing with cold *n*-hexane afforded 7.4 g (71%) of colorless prisms; *m.p.* 48.2–48.5 °C. – IR: ν/cm^{-1} = 3 360 s (NH), 2 240 w (CN), 1 605 s (C=C). – ^{1}H NMR ($CDCl_3$): δ/ppm = 1.15 (t, J = 7 Hz, CH_3), 1.60 (s, CH_3), 1.85 (q, *J* = 7 Hz, CH_2), 6.85–7.00 (m, 3ArH), 7.20–7.30 (m, 2ArH).

$C_{11}H_{14}N_2$	Calcd.:	C 75.82	H 8.10	N 16.08
(174.3)	Found:	C 75.80	H 8.11	N 16.08.

B: N^2-Phenyl-2-butanimine. The reaction of the nitrile of step A (6.0 g, 0.034 mol) in MeOH (30 ml) and KOH (5.6 g) in MeOH (50 ml) as described for step B of **1a** afforded after removal of the solvent a yellow solid (3.4 g, 67%), which was immediately used without further purification.

C: 4-Hydroxy-7,8-dimethyl-6-phenyl-pyrano[3,2-c]pyridine-2,5(6H)-dione. The reaction of the azomethine of step B (3.4 g, 0.023 mol) and diethyl malonate (7.4 g, 0.046 mol) in Ph_2O (20 ml) as described for step C of **2a** afforded 1.35 g (21%) of orange prisms; *m.p.* 270–271 °C (dioxane). – IR (KBr): ν/cm^{-1} = 1 730 s (2-C=O), 1 670 s (5-C=O). – ^{1}H NMR (DMSO-d_6): δ/ppm = 2.05 (s, 5-CH_3), 2.20 (s, 6-CH_3), 5.50 (s, H-3), 7.35–7.45 (m, ArH), 7.50–7.70 (m, ArH).

$C_{16}H_{13}NO_4$	Calcd.:	C 67.84	H 4.63	N 4.94
(283.3)	Found:	C 67.58	H 4.81	N 4.87.

D: 3-Acetyl-4-hydroxy-5,6-dimethyl-1-phenylpyridine-2 (1H)-one. The reaction of the pyrane of step C (1.24 g, 0.0044 mol) in 1,2-dihydroxyethane (20 ml) and KOH (2.0 g) in H_2O (2 ml) as described for step D of **1a** yielded 0.9 g (80%) of colorless prisms; *m.p.* 159 °C (cyclohexane). – IR (KBr): ν/cm^{-1} = 1 665 s (C=O). – ^{1}H NMR (DMSO-d_6): δ/ppm = 1.95 (s, 5-CH_3), 2.0 (s, 6-CH_3), 2.6 (s, acetyl-CH_3), 7.20–7.30 (m, 2ArH), 7.45–7.60 (m, 3ArH).

$C_{15}H_{15}NO_3$	Calcd.:	C 70.02	H 5.88	N 5.44
(257.3)	Found:	C 70.09	H 5.73	N 5.33.

3-Acetyl-1,6-diphenyl-4-(4-toluenesulfonyloxy)-pyridin-2(1H)-one (**2a**)

A: **1a**-*sodium salt.* Hydroxypyridone **1a** (2.0 g, 0.0066 mol) in dry Et_2O (50 ml) was combined with NaOMe, prepared from Na (0.23 g, 0.010 mol) in MeOH (10 ml). Cooling (4 °C) for 12 h, filtration and washing with dry Et_2O afforded 2.06 g (96%) of a light brown powder.

B: Tosylation of **1a**-*sodium salt.* Powdered **1a**-sodium salt (2.06 g, 0.0063 mol) and 4-tosylchloride (1.24 g, 0.0065 mol) in dry MeCN (25 ml) was heated at reflux for 2 h and then poured into ice/H_2O (250 ml). The oily product solidified on stirring; filtration and washing with H_2O afforded 2.75 g (95%) of pale yellow microprisms; m.p. 200–201 °C (PhMe). – IR (KBr): ν/cm^{-1} = 1 695 s (C=O). – ^{1}H NMR (DMSO-d_6): δ/ppm = 2.30 (s, tosyl-CH_3), 2.40 (s, acetyl-CH_3), 6.0 (s, H-5), 7.10–7.45 (m, 10ArH), 7.55 (m, 2ArH), 7.90 (m, 2ArH).

$C_{26}H_{21}NO_5S$	Calcd.:	C 67.96	H 4.61	N 3.05
(459.5)	Found:	C 68.34	H 4.65	N 2.86.

3-Acetyl-1-(4-chlorophenyl)-6-phenyl-4-(4-toluenesulfonyloxy)-pyridin-2(1H)-one (**2b**)

A: **1b**-*sodium salt.* The reaction of the hydroxypyridone **1b** (1.0 g, 0.0020 mol) in Et_2O (30 ml) and Na (0.07 g) in MeOH (5 ml) as described for **2a** afforded 0.95 g (90%) of a light-brown powder.

B: Tosylation of **1b**-*sodium salt.* The reaction of **1b**-sodium salt (0.95 g, 0.0026 mol) in MeCN (10 ml) with 4-tosylchloride (0.51 g, 0.0027 mol) as described for **2a** yielded 1.07 g (83%) of light yellow prisms; *m.p.* 212–213 °C (PhMe). – IR (KBr): ν/cm^{-1} = 1 695 s (C=O). – ^{1}H NMR (DMSO-d_6): δ/ppm = 2.30 (s, tosyl-CH_3), 2.45 (s, acetyl-CH_3), 6.05 (s, H-5), 7.10–7.40 (m, 9ArH), 7.55–765 (m, 2ArH), 7.85–7.95 (m, 2ArH).

$C_{26}H_{20}ClNO_5S$	Calcd.:	C 63.22	H 4.08	N 2.84
(494.0)	Found:	C 63.53	H 4.33	N 2.79.

3-Acetyl-5,6-dimethyl-1-phenyl-4-toluenesulfonyloxy-pyridin-2(1H)-one (**2c**)

A: **1c**-*sodium salt*. The reaction of hydroxypyridone **1c** (0.74 g, 0.0029 mol) in Et_2O (30 ml) and Na (0.07 g) in MeOH (5 ml) as described for **1a** afforded 0.68 g (85%) of a light brownish powder.

B: 3 B: Tosylation of ***1c****-sodium salt.* The reaction of **1c**-sodium salt (0.63 g, 0.0023 mol) in MeCN (10 ml) with 4-tosylchloride (0.48 g, 0.0025 mol) as described for **1a** yielded 0.86 g (91%) of light yellowish prisms; *m.p*. 177 °C (EtOH). – IR (KBr): ν/cm^{-1} = 1 690 m (C=O). – ^{1}H NMR (DMSO-d_6): δ/ppm = 1.75 (s, 5-CH_3), 1.90 (s, 6-CH_3), 2.35 (s, tosyl-CH_3), 2.48 (s, acetyl-CH_3), 7.30–7.40 (m, 2ArH), 7.50–7.65 (m, 5ArH), 7.85–7.95 (m, 2ArH).

$C_{22}H_{21}NO_5S$	Calcd.:	C 64.22	H 5.14	N 3.40
(411.5)	Found:	C 64.22	H 5.11	N 3.35.

3-Methyl-5,6-diphenyl-isoxazolo[4,3-c]pyridin-4-one (**4a**)

Tosyloxypyridone **2a** (2.64 g, 0.0052 mol) in 1-methylpyrrolidone (40 ml) and NaN_3 (1.3 g, 0.020 mol) was stirred at about 20 °C until the N_2 evolution had stopped (about 30 min) and then poured into ice/H_2O (400 ml). Filtration of the precipitate yielded 1.35 g (86%) of colorless prisms; *m.p*. 195 °C (EtOH). – IR (KBr): ν/cm^{-1} = 1 680 s (C=O). – ^{1}H NMR (DMSO-d_6): δ/ppm = 2.80 (s, 3-CH_3), 6.50 (s, H-7), 7.10–7.35 (m, 10 ArH).

$C_{19}H_{14}N_2O_2$	Calcd.:	C 75.48	H 4.67	N 9.27
(302.3)	Found:	C 75.26	H 4.77	N 9.07.

5-(4-Chlorophenyl)-3-methyl-6-phenyl-isoxazolo[4,3-c]pyridine-4-one (**4b**)

Reaction of the tosyloxypyridone **2b** (0.97 g, 0.00196 mol) and NaN_3 (0.65 g, 0.010 mol) in 1-methylpyrrolidone (20 ml) and quenching with H_2O (100 ml) as described for **4a** yielded 0.65 g (85%) of colorless prisms; *m.p*. 168–169 °C (1-PrOH). – IR (KBr): ν/cm^{-1} = 1 685 s (C=O), 1 660 m. – ^{1}H NMR (DMSO-d_6): δ/ppm = 2.80 (s, 3-CH_3), 6.50 (s, H-7), 7.10–7.40 (m, 9ArH).

$C_{19}H_{13}ClN_2O_2$	Calcd.:	C 67.76	H 3.89	N 8.32
(336.8)	Found:	C 67.59	H 4.22	N 8.42.

3,6,7-Trimethyl-5-phenyl-isoxazolo[4,3-c]pyridin-4-one (**4c**)

The reaction of the tosyloxypyridone **2c** (0.75 g, 0.0018 mol) and NaN_3 (0.65 g, 0.010 mol) in 1-methylpyrrolidone (20 ml) and quenching with H_2O (100 ml) as described for **4a** yielded 0.38 g (82%) of colorless prisms; *m.p*. 174–176 °C (EtOH). – IR (KBr): ν/cm^{-1} = 1680 s (C=O), 1640 s. – ^{1}H NMR (DMSO-d_6): δ/ppm = 1.80 (s, 6-CH_3), 2.20 (s, 7-CH_3), 2.80 (s, 3-CH_3), 7.25–7.35 (m, 2ArH), 7.45–7.65 (m, 3ArH). – ^{13}C NMR (DMSO-d_6): δ/ppm = 10.2 (7-CH_3), 13.2 (3-CH_3), 15.9 (6-CH_3), 104.5 (C-3a), 108.2 (C-7), 125.5- 140.1 (Ar-C), 145.9 (C-6), 152.8 (C-7a), 160.9 (C-4), 168.9 (C-3).

$C_{15}H_{14}N_2O_2$	Calcd.:	C 70.85	H 5.55	N 11.02
(254.3)	Found:	C 70.82	H 5.52	N 11.37.

Ethyl 4-Hydroxy-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (**5**)

NaOEt, obtained from Na (2.76 g, 0.12 mol) and abs. EtOH (36 ml), diethyl malonate (15 ml, 0.10 mol) and ethyl-β-aminocrotonate (12.9 g, 0.1 mol) were heated slowly to 140–160 °C and kept at this temperature for 17 h. The cooled mixture was poured into ice/H_2O (250 g) and then brought to pH = 1.5 with 2N HCl. Cooling (4 °C) for 24 h and filtration yielded 14.97 g (76%) of colorless prisms; *m.p*. 209–211 °C (EtOH); lit. *m.p*. [11] 208–210 °C.

Ethyl 2,4-dichloro-6-methylpyridine-3-carboxylate (**6**)

Pyridine-3-carboxylate **5** (10.0 g, 0.051 mol) in $POCl_3$ (100 ml) and NEt_3 (10 ml, 0.072 mol) was heated under reflux for 2 h, concentrated to the half volume and poured into ice/H_2O. The brown oil was stirred until solid and then brought to pH = 5–6 with NaOH. Filtration after 12 h yielded 7.0 g (59%) of grey-white crystals; *m.p*. 57–58 °C (EtOH/H_2O). – IR (KBr): ν/cm^{-1} = 1 740 s (C=O). – ^{1}H NMR (DMSO-d_6): δ/ppm = 1.40 (t, *J* = 7 Hz, ester-CH_3), 2.55 (s, 6-CH_3), 4.45 (q, *J* = 7 Hz, CH_2), 7.20 (s, H-5).

$C_9H_9Cl_2NO_2$	Calcd.:	C 46.18	H 3.88	N 5.98	Cl 30.29
(234.1)	Found:	C 45.98	H 3.96	N 6.01	Cl 30.36.

Ethyl 4-azido-2-chloro-6-methylpyridine-3-carboxylate (**7**)

Dichloropyridine **6** (5.0 g, 0.021 mol) and NaN_3 (2.0 g, 0.031 mol) in DMF (70 ml) was stirred for 4 d at 50 °C, cooled and poured into ice/H_2O (200 ml). Filtration after 2 h yielded 3.0 g (58%) of grey-white crystals; *m.p*. 46.7–47.2 °C (acetone/H_2O). – IR (KBr): ν/cm^{-1} = 2 140 s (N_3), 1740 s (C=O). DSC-data for thermolysis: onset temperature 135.0 °C, peak maximum 163.3 °C, $\Delta H = -515$ *J*/g, no further reaction/decomposition until 350 °C.

$C_9H_9ClN_4O_2$	Calcd.:	C 44.92	H 3.77	N 23.28	Cl 14.73
(240.7)	Found:	C 44.86	H 3.82	N 23.16	Cl 14.55.

4-Chloro-3-ethoxy-6-methyl-isoxazolo[4,3-c]pyridine (**8**)

Azidopyridine **8** (1.0 g, 0.0042 mol) in 1,2-dichlorobenzene (15 ml) was heated under reflux for 30 min and taken to dryness under reduced pressure. Triturating the residual oil with cyclohexane yielded 0.6 g (66%) of pale brownish prisms; *m.p*. 115–116 °C (cyclohexane). – IR (KBr): ν/cm^{-1} = 1 610 m, 1 590 s. – ^{1}H NMR (DMSO-d_6): δ/ppm = 1.45 (t, *J* = 7 Hz, ethyl-CH_3), 2.70 (s, 6-CH_3), 4.22 (q, *J* = 7 Hz, ethyl-CH_2), 7.30 (s, H-7). – ^{13}C NMR (DMSO-d_6): δ/ppm = 14.5 (ethyl-CH_3), 16.8 (6-Me), 63.5 (ethyl-CH_2), 89.1 (C-3a), 104.6 (C-7), 152.0 (C-6), 153.1 (C-7a), 159.5 (C-4), 165.2 (C-3).

$C_9H_9ClN_2O_2$	Calcd.:	C 50.84	H 4.27	N 13.17
(212.6)	Found:	C 51.20	H 4.27	N 13.50.

Ethyl 4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridine-5-carboxylate (**9a**)

This compound was prepared from ethyl β-aminocrotonate and bis-2,4,6-trichlorophenyl malonate according to ref. [16].

Ethyl 4-Hydroxy-6-methyl-3-phenyl-2-oxo-1,2-dihydropyridine-5-carboxylate (**9b**)

Ethyl β-aminocrotonate (10.24 g, 0.080 mol) and diethyl phenylmalonate (18.96 g, 0.080 mol) was heated to 220 °C for 3 h; EtOH formed in the reaction was distilled off. Triturating the residue with PhMe and EtOH yielded 11.29 g (52%) of colorless prisms; *m.p*. 282–285 °C (1-BuOH); lit. *m.p*. 270–272 °C [16].

Ethyl 6-methyl-2-oxo-4-(4-toluenesulfonyloxy)-1,2-dihydropyridine-5-carboxylate (**10**)

*A: **9a**-sodium salt.* NaOMe from Na (0.29 g, 0.013 mol) and MeOH (7.6 ml) was added to pyridine-5-carboxylate **9a** (2.0 g, 0.010 mol) in dry boiling dioxane (50 ml). Cooling (4 °C) for 12 h and filtration yielded 1.20 g (54%) of a light brown powder.

*B: Tosylation of **9a**-sodium salt.* **9a**-Sodium salt (1.20 g, 0.005 mol) in dry MeCN (15 ml) and tosylchloride (1.04 g, 0.0055 mol) was heated for 24 h under reflux and poured into ice/H_2O (150 ml). The yield was 0.98 g (56%) of a brownish gum-like solid. Tlc showed a pure product, but further purification was not possible.

Ethyl 2,4-dichloro-6-methyl-3-phenylpyridine-5-carboxylate (**11**)

Pyridine-5-carboxylate **9b** (10.0 g, 0.037 mol), $POCl_3$ (100 ml) and NEt_3 (9.4 ml, 0.11 mol) were heated for 2 h under reflux, concentrated to the half volume, poured into ice/H_2O (100 ml) and brought to pH 5–6 with NaOH. Filtration after 3 h yielded 3.81 g (34%) of a grey-white solid; *m.p.* 95.0–96.6 °C (acetone/H_2O). – IR (KBr): ν/cm^{-1} = 1720 s (C=O). – ^{1}H NMR (DMSO-d_6): δ/ppm = 1.35 (t, J = 8 Hz, ester-CH_3), 2.52 (s, 6-CH_3), 4.43 (q, J = 8 Hz, CH_2), 7.39–7.51 (m, 5 ArH).

$C_{15}H_{13}Cl_2NO_2$	Calcd.:	C 58.08	H 4.22	N 4.52	Cl 22.86
(310.2)	Found:	C 58.47	H 4.40	N 4.51	Cl 22.48.

4-Hydroxy-3-(1-hydroxyiminoethyl)-1,6-diphenylpyridin-2(1H)-one (**12**)

Acetylpyridone **1a** (5.0 g, 0.016 mol), $NH_2OH \cdot HCl$ (1.35 g, 0.020 mol) and $NaHCO_3$ (1.65 g, 0.020 mol) in EtOH (100 ml) and H_2O (50 ml) were heated under reflux for 90 min. Filtration after 2 h afforded 3.64 g (69%) of colorless prisms; *m.p.* 213 °C (EtOH). – IR (KBr): ν/cm^{-1} = 1640 s (C=O). – ^{1}H NMR (DMSO-d_6): δ/ppm = 2.23 (s, 6-CH_3), 6.02 (s, H-5), 7.09-7.24 (m, 10 ArH), 11.20 (s, OH), 13.00 (s, NH).

$C_{19}H_{16}N_2O_3$	Calcd.:	C 71.24	H 5.03	N 8.74	
(320.4)	Found:	C 71.08	H 5.19	N 8.54.	

4-Hydroxy-1,6-diphenyl-pyridine-2(1H)-one (**13**)

Acetylpyridone **1a** (41.8 g, 0.420 mol) in 90% H_2SO_4 (60 ml) was heated for 15 min to 140 °C and then poured onto ice (1.2 l). Filtration after 2 h and washing with H_2O afforded 34.2 g (95%) of light brown prisms; *m.p.* 295–296 °C (EtOH); lit. *m.p.* 286 °C [19].

3-Acetylamino-4-hydroxy-1,6-diphenyl-pyridin-2(1H)-one (**14**)

Method A: Beckmann Rearrangement. The oxime **12** (0.55g) in 1,2-dichlorobenzene (10 ml) was heated for 2 h under reflux and taken to dryness under reduced pressure. Triturating with cyclohexane and filtration yielded 0.4 g (73%) of colorless prisms; m.p. 251–252 °C (EtOH).

Method B: Reduction. To the nitropyridone **15** (4.0 g, 0.013 mol) in boiling AcOH (120 ml) and Ac_2O (8 ml), Zn powder (about 17 g, 0.26 mol) was added at reflux temperature in small portions until the brown color changed to green. After further 30 min refluxing, the insoluble parts were filtered still hot and the filtrate taken to dryness under reduced pressure. The residual yellow oil was dissolved in 1N NaOH solution, filtered and acidified with conc. HCl to give after filtration 3.39 g (82%) of colorless prisms; *m.p.* 250.4–251.7 °C (PhMe). – IR (KBr): ν/cm^{-1} = 1640 s (C=O). – ^{1}H NMR (DMSO-d_6): δ/ppm = 2.15 (s, acetyl-CH_3), 6.04 (s, H-5), 7.14–7.24 (m, 10 ArH), 9.45 (s, NH).

$C_{19}H_{16}N_2O_3$	Calcd.:	C 71.24	H 5.03	N 8.74	
(320.4)	Found:	C 70.99	H 4.99	N 8.51.	

4-Hydroxy-3-nitro-1,6-diphenyl-pyridine-2(1H)-one (**15**)

Pyridone **13** (8.0 g, 0.0114 mol) in AcOH (21 ml), conc. HNO_3 (2.1 ml) and $NaNO_2$ (0.06 g, 0.0009 mol) was stirred for 30 min at about 20 °C and then poured into ice/H_2O (75 ml). Filtration after 1 h yielded 9.95 g (84%) of yellow-orange prisms; *m.p.* 221–222 °C (EtOH). – IR (KBr): ν/cm^{-1} = 1630 m (C=O). – ^{1}H NMR (DMSO-d_6): δ/ppm = 6.20 (s, H-5), 7.0–7.35 (m, 10 ArH).

$C_{17}H_{12}N_2O_4$	Calcd.:	C 66.23	H 3.92	N 9.09	
(308.3)	Found:	C 66.32	H 4.10	N 9.06.	

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