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ENAMINO ESTERS IN THE SYNTHESIS OF HETEROCYCLIC SYSTEMS. TRANSFORMATION OF DIMETHYL ACETONE-1,3-DICARBOXYLATE INTO POLYSUBSTITUTED 1,6-NAPHTHYRIDINE-8-CARBOXYLATES

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Dedicated to Professor Dr. Albert Padwa, Emory University, Atlanta, GA, USA, on the occasion of his 75th birthday

Abstract – A simple two-step synthesis of 1,6-naphthyridine derivatives is described. Methyl 2-(2-methoxy-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**3**), prepared from dimethyl acetone-1,3-dicarboxylate (**1**) and propyolic acid amide (**2**) according to the known procedure, was transformed with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) first into 2-[1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl]-6-oxo-1,6-dihydropyridine-3-dicarboxylate (**4**). This was followed by reaction with monosubstituted hydrazines **5a-h** to afford substituted 1,6-naphthyridine-8-carboxylates **7a-h**.

INTRODUCTION

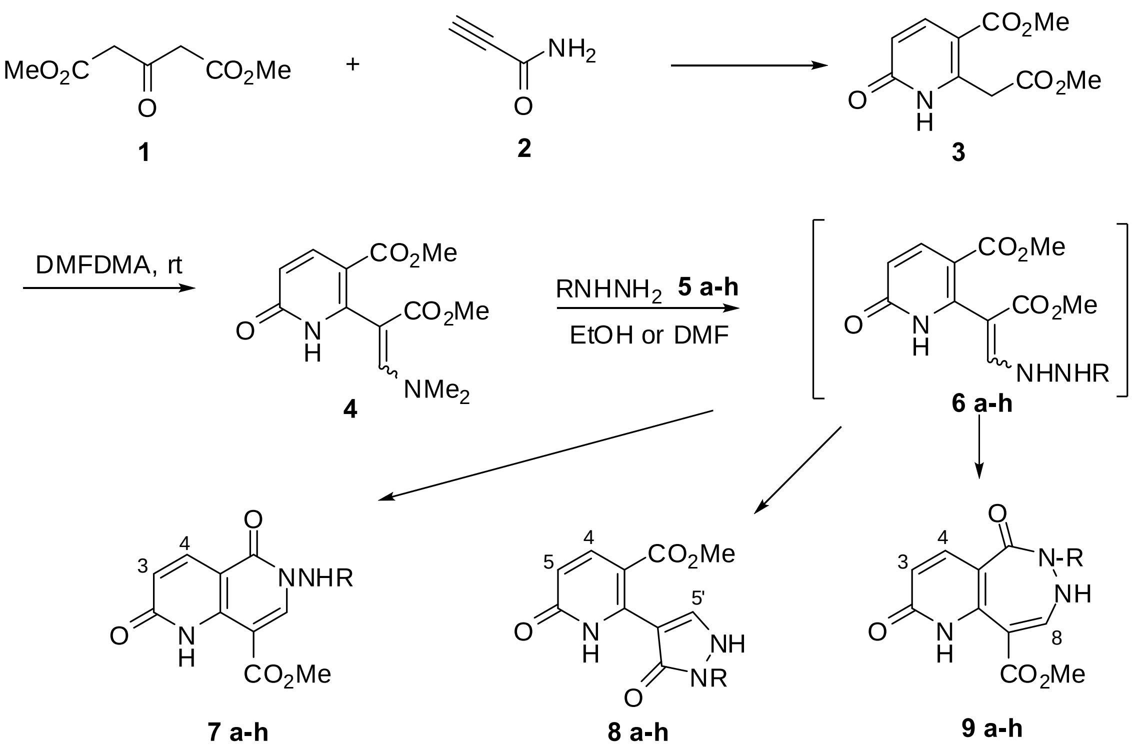
In the context of our interest in the development of new useful strategies for the synthesis of heterocyclic systems, we report that 1,6-naphthyridine derivatives can be efficiently synthesiszed from dimethyl acetone-1,3-dicarboxylates. As an extension of our research in the field of enaminones as building blocks for the preparation of various heterocyclic systems and some natural products we have demonstrated the usefulness of dialkyl acetone-1,3-dicarboxylates and their mono- and bis(dimethylamino)methylidene derivatives as versatile building blocks in the construction of many five- and six-membered heterocyclic systems, their fused analogues, such as polysubstituted pyridines, pyrimidines, pyrazolopyridines, pyridopyrimidines, pyranopyrane-diones, pyrazolodiazepines, and others.[1] Recently, we have prepared also derivatives of pyrido[4,3-*d*]pyrimidine-8-carboxylates,[2] (pyrido[1,2-*a*]-pyrimidin-3-yl)thiazole-5-carboxylates,[3] thiazolo[5,4-*c*]pyridine-7-carboxylates,[4] and 2,7-naphthyridine-4-carboxylates.[5]

In this paper we describe the synthesis of methyl 6-substituted amino)-2,5-dioxo-1,2,5,6-tetrahydro-1,6-naphthyridine-8-carboxylates. The chemistry of naphthyridiens has been reviewed several times.[6] 1,6-Naphthyridines have been prepared also by palladium(0)/copper(I)-catalyzed coupling[7] and by some other efficient syntheses published recently.[8] Various naphthyridine derivatives have received considerable attention over the past years because of their wide range of biological activities, including antitumor, antiinflamatory and antifungal properties.[9]

RESULTS AND DISCUSSION

Methyl 2-(2-methoxy-2-oxoethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**3**), prepared from dimethyl acetone-1,3-dicarboxylate (**1**) and propiolamide (**2**) according to the known procedure,[10] was transformed with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) first into methyl 2-[1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl]-6-oxo-1,6-dihydropyridine-3-carboxylate (**4**). By further treatment with monosubstituted aliphatic, aromatic or hetroaromatic hydrazines **5a-h** substitution of the dimethylamino group gave enehydrazine intermediates **6a-h**, which could give by cyclization either substituted 1,2,5,6-tetrahydro-1,6-naphthyridine-8-carboxylates **7a-h**, (1*H*-pyrazol-4-yl)-1,6-dihydro-pyridine-3-carboxylates (**8a-h**) or pyrido[3,2-*d*]-[1,2]diazepine-9-carboxylates **9a-h** (Scheme 1).

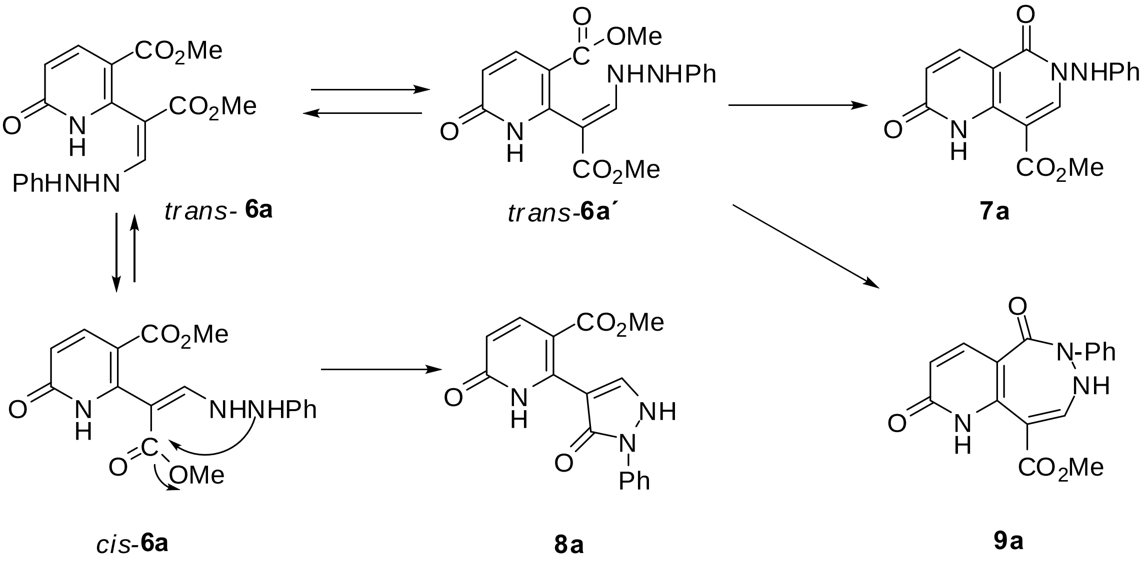
The structures of the products were determined on the basis of elemental analyses for C, H, and N, and IR, ^{1}H, ^{13}C NMR, MS, and HRMS spectra. In the reaction of compound **4** with monosubstittued hydrazines **5a-h** the enehydrazino intermediates **6a-h** were not isolated, since the cyclization took place under relatively mild conditions. By cyclization three types of products could be formed: 1,6-naphthyridines **7a-h** from (*E*)-**6a´**, pyrazolylpyridine derivatives **8a-h** from (*Z*)-**6a**, and/or pyrido[3,2-*d*][1,2]diazepin derivatives **9a-h** from (*E*)-**6a´** (Scheme 2). First, the comparison of the ^{1}H NMR spectral characteristics was taken into account. Appart from the signals for R groups, three signals are significant for all compounds: two doublets in the range of $\delta = 6.49 – 6.62$ ppm and $\delta = 7.99 – 8.11$ ppm with a coupling constant $J = 9.5 – 9.7$ Hz for two *ortho* protons of the pyridine part of the molecule, and a singlet at $\delta = 8.40 – 8.60$ ppm, which could correspond to H_7 of compounds **7a-h**, $H_{5'}$ of compounds **8a-h**, or H_8 of compounds **9a-h**. Compound derived from ethyl hydrazinoacetate (**5f**) exhibits besides these signals also a doublet integrating for two protons at $\delta = 3.90$ ppm with a coupling constant $J = 4.1$ Hz, and a triplet integrating for one proton at $\delta = 7.21$ ppm with a coupling constant $J = 4.1$ Hz. This corresponds to the -NHCH$_2$- structural element, which is compatible only with the 1,6-naphthyridines **7f.** Similarly, compound derived from cyclohexylhydrazine (**5g**) exhibits a doublet at δ = 5.92 ppm, with a coupling constant *J* = 3.6 Hz. This is compatible only with 1,6-naphthyridine derivative **6g**. Furthermore, the structures of compounds **3** (Figure 1) and **7d** (Figure 2) were confirmed by X-ray analysis.



Scheme 1

Table 1. Methyl 6-(substituted-amino)-2,5-dioxo-1,2,5,6-tetrahydro-1,6-naphthyridine-8-carboxylate **7a-h**

Compound 7	R	Yield [%]	mp [°C]	^{1}H NMR δ (ppm)		
				H_3	H_4	H_7
a	C_6H_5	64	235-236	8.00	6.50	8.58
b	4-MeO-C_6H_4	75	182-184	7.99	6.49	8.58
c	3-Cl-C_6H_4	61	245-246	8.09	6.62	8.53
d	4-F-C_6H_4	34	240-242	8.00	6.50	8.60
e	*t*-Bu	17	147-151	8.11	6.57	8.40
f	CH_2CO_2Et	61	139-140	8.03	6.47	8.69
g	cyclohexyl	16	158-161	8.11	6.57	8.40
h	phthalazinyl-1	79	288-289	8.07	6.50	8.48



Scheme 2

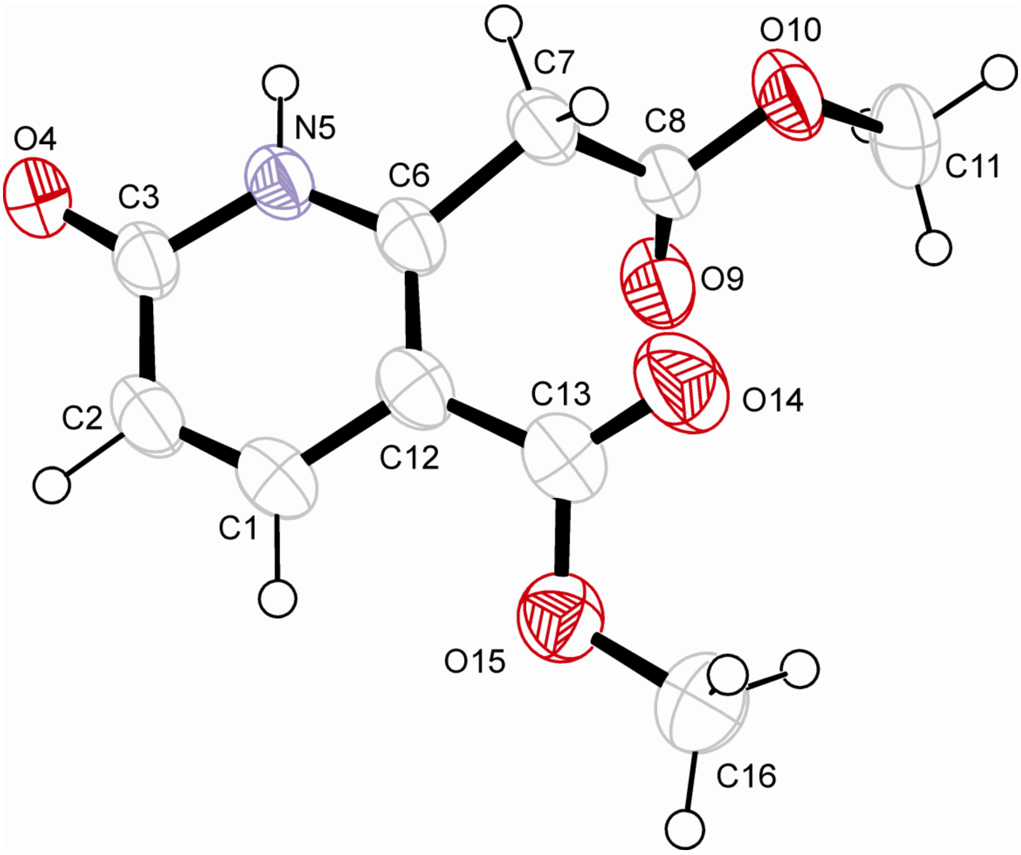


Figure 1. Ortep view of the asymmetric unit of compound **3** with labeling of nonhydrogen atoms (Ellipsoids are drawn at 50% probability level)

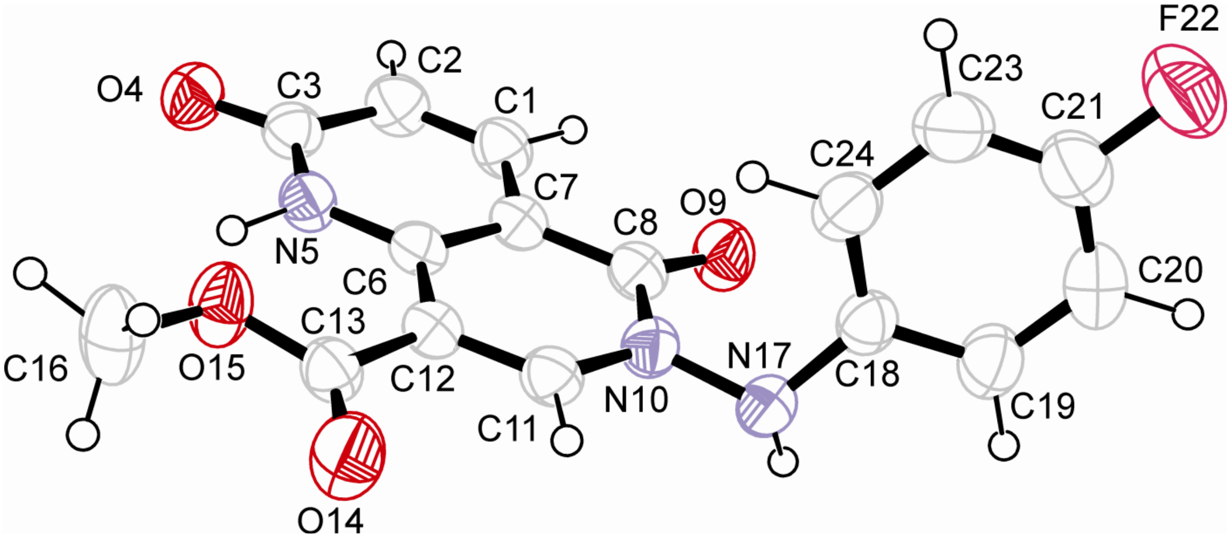


Figure 2. Ortep view of the asymmetric unit of compound **7d** with labeling of nonhydrogen atoms (Ellipsoids are drawn at 50% probability level)

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The NMR spectra were obtained on a Bruker Advance DPX 300 (300 MHz) spectrometer in DMSO-d_6 or $CDCl_3$ with TMS as the internal standard, MS spectra on a Q-Tof Premier spectrometer, IR spectra on a Perkin-Elmer 1310 infrared spectrophotometer and elemental analyses for C, H and N on a Perkin-Elmer CHN Analyser 2400.

Methyl 2-(2-methoxy-2-oxyethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (3)

This compound was prepared from dimethyl acetone-1,3-dicarboxylate (**1**; 17.42 g, 0.1 mol) and propynamide (**2**, 9.97 g, 0.115 mol) according to the literature procedure.[10] Yield: 7.32 g (33%) of white solid; mp 150-152 °C, (lit.,[10] mp 145-146 ˚C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.84 (3H, s, O*Me*); 3.72 (3H, s, O*Me*); 3.99 (2H, s, CH_2); 6.91 (1H, d, J = 9.7 Hz, H_4); 7.84 (1H, d, J = 9.7 Hz, H_5); 11.5 (1H, s, N*H*); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 168.8, 164.6, 162.4, 149.0, 140.7, 117.7, 107.2, 107.0, 52.0, 51.7. IR (KBr): ν_{max} (cm^{-1}) 3154, 3004, 2954, 2789, 1748, 1718, 1654, 1612, 1560, 1481, 1458, 1435, 1418, 1372, 1335, 1285, 1211, 1169, 1132, 1092, 1007, 971, 844, 766, 728, 638. Anal. Calcd for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.51; H, 4.73; N, 6.03. ESI-HMRS: m/z = 225.0633 (M$^+$); $C_{10}H_{11}NO_5$ requires: m/z = 225.0637 (M$^+$).

Methyl 2-[1-(dimethylamino)-3-methoxy-3-oxoprop-1-en-2-yl]-6-oxo-1,6-dihydropyridine-3-carboxylate (4)

To a solution of methyl 2-(2-methoxy-2-oxyethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (**3**; 135 mg, 0.6 mmol) in CH_2Cl_2 (2 mL), *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) (79 mg, 0.7 mmol) was added and the mixture was stirred at rt for 36 h. The volatile components were evaporated *in vacuo* and the crude solid residue was recrystallized from EtOAc. Yield: 127 mg (76%), mp 242-244 °C (white solid from EtOAc). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.78 (1H, s, N*Me*$_2$); 3.48 (1H, s, O*Me*); 3.65 (1H, s, O*Me*); 6.23 (1H, d, *J* = 9.6 Hz, H$_4$); 7.42 (1H , s, C=C*H*-NMe$_2$); 7.79 (1H, d, *J* = 9.6 Hz, H$_5$); 11.76 (1H, s, N*H*). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 166.9, 164.6, 162.3, 150.9, 148.9, 140.6, 117.0, 109.7, 90.7, 51.3, 50.6, 41.9. IR (KBr): ν (cm^{-1}) 3118, 2953, 2830, 1720, 1698, 1651, 1607, 1554, 1438, 1401, 1312, 1285, 1265, 1218, 1192, 1135, 1115, 1082, 1041, 963, 902, 853, 817, 759, 586. Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.40; H, 5.80; N, 9.73. ESI-HRMS: *m/z* = 280.1063; $C_{13}H_{16}N_2O_5$ (M^+) requires: 280.1059.

Methyl 6-(substituted-amino)-2,5-dioxo-1,2,5,6-tetrahydro-1,6-naphthyridine-8-carboxylate 7a-h. General Procedure

To compound **4** (150 mg, 0.535 mmol) dissolved in dry MeOH (2 mL) or DMF (2 mL) a monosubstittued hydrazine hydrochloride **5a-h** (1.605 mmol) was added and the mixture was heated in an argon atmosphere at reflux temperature (MeOH) or at 120 °C (DMF) for 5 min. The volatile components were evaporated *in vacuo.* The crude product was purified by column chromatography (Fluka Silicagel 60, EtOAc/petroleum ether 2:1). The solid residue was, after evaporation of solvents recrystallized from EtOH.

The following compounds were prepared accordingly:

Methyl 6-(phenylamino)-2,5-dioxo-1,2,5,6-tetrahydro-1,6-naphthyridine-8-carboxylate (7a)

This compound was prepared from **4** (150 mg, 0.535 mmol) and phenylhydrazine hydrochloride (**5a**; 232 mg, 1.605 mmol). Yield: 107 mg (64%), mp 235-236 °C (white crystals from EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.88 (3H, s, O*Me*); 6.50 (1H, d, *J* = 9.7 Hz, H$_4$); 6.69 – 7.21 (5H, m, Ph); 8.00 (1H, d, *J* = 9.7 Hz, H$_3$); 8.58 (1H, s, H$_7$); 9.50 (1H, s, N*H*); 11.21 (1H, s, N*H*). IR (KBr): ν (cm^{-1}) 3303, 3185, 3114, 1695, 1679, 1642, 1545, 1403, 1297, 1270, 1214, 1140, 1115, 799, 755, 694. Anal. Calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.72; H, 3.98; N, 13.44. ESI-HRMS: *m/z* = 311.0911 (M^+); $C_{16}H_{13}N_2O_4$ requires: *m/z* = 311.0906 (M^+).

Methyl 6-(4-methoxyphenylamino)-2,5-dioxo-1,2,5,6-tetrahydro-1,6-naphthyridine-8-carboxylate (7b)

This compound was prepared from **4** (150 mg, 0.535 mmol) and 4-methoxyphenylhydrazine hydrochloride (**5b**; 280 mg, 1.605 mmol). Yield: 140 mg (75%), mp 182-184 °C (white crystals from EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.67 (3H, s, O*Me*); 3.88 (1H, s,O*Me*); 6.49 (1H, d, *J* = 9.7 Hz, H$_4$); 6.68 (2H, m, *J* = 9.0 Hz, Ph); 6.80 (2H, m, *J* = 9.0 Hz, Ph); 7.99 (1H, d, *J* = 9.7 Hz, H$_3$); 8.58 (1H, s, H$_7$); 9.21 (s, 1H, N*H*); 11.28 (1H, s, N*H*). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 165.2, 160.9, 158.3, 154.6, 154.2, 145.1, 140.6, 138.9, 117.2, 115.1, 114.2, 106.9, 96.9, 55.3, 52.6. IR (KBr): ν (cm^{-1}) 3330, 3222, 1681, 1664, 1637, 1609, 1558, 1510, 1443, 1303, 1236, 1217, 838, 808, 706, 655, 608, 503. Anal. Calcd for $C_{17}H_{15}N_3O_5$: C, 59.82; H, 4.43; N, 12.31. Found: C, 59.84; H, 4.24; N, 12.39. ESI-HRMS: *m/z* = 341.1004 (M^+); $C_{17}H_{15}N_3O_5$ requires: *m/z* = 341.1012 (M^+).

Methyl 6-(3-chlorophenylamino)-2,5-dioxo-1,2,5,6-tetrahydro-1,6-naphthyridine-8-carboxylate (7c)

This compound was prepared from **4** (150 mg, 0.535 mmol) and 3-chlorophenylhydrazine hydrochloride (**5c**; 285 mg, 1.605 mmol). Yield: 120 mg (61%), mp 245-246 °C (white crystals from EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96 (3H, s, O*Me*); 6.62 (1H, d, *J* = 9.7 Hz, H_4); 6.69 – 7.21 (4H, m, arom.); 7.47 (1H, s, N*H*); 8.09 (1H, d, *J* = 9.7 Hz, H_3); 8.53 (1H, s, H_7), 11.52 (1H, s, N*H*). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 165.1, 160.7, 158.1, 148.6, 148.4, 145.2, 137.7, 133.6, 130.7, 120.4, 119.7, 112.6, 111.7, 106.9, 97.5, 52.5. IR (KBr): ν (cm^{-1}) 3261, 3066, 1685, 1646, 1598, 1555, 1437, 1353, 1299, 1279, 1211, 1144, 1042, 802, 782. Anal. Calcd for $C_{16}H_{12}ClN_3O_4$: C, 55.58; H, 3.50; N, 12.15. Found; C, 55.22; H, 3.25; N, 11.95. ESI-HRMS): *m/z* = 345.0522 (M^+); $C_{16}H_{12}ClN_3O_4$ requires: *m/z* = 345.0516 (M^+).

Methyl 6-(4-fluorophenylamino)-2,5-dioxo-1,2,5,6-tetrahydro-1,6-naphthyridine-8-carboxylate (7d)

This compound was prepared from **4** (150 mg, 0.535 mmol) and 4-fluorophenylhydrazine hydrochloride (**5d**; 261 mg, 1.605 mmol). Yield: 60 mg (35%), mp 240-242 °C (white crystals from EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (3H, s, O*Me*); 6.50 (1H, d, *J* = 9.7 Hz, H_4); 6.74 – 7.09 (4H, m, arom.); 8.00 (1H, d, *J* = 9.7 Hz, H_3), 8.60 (1H, s, H_7), 9.50 (1H, s, N*H*), 11.30 (1H, s, N*H*). IR (KBr): ν (cm^{-1}) 3292, 3201, 3031, 1726, 1689, 1677, 1640, 1545, 1505, 1299, 1209, 1139, 1115, 835, 800. Anal. Calcd for $C_{16}H_{12}FN_3O_4$: C, 58.36; H, 3.67; N, 12.76**.** Found: C, 58.51; H, 3.46; N, 12.87. ESI-HRMS: *m/z* = 329.0816 (M^+); $C_{16}H_{12}FN_3O_4$ requires: 329.0812 (M^+).

Methyl 6-(*tert*-butylamino)-2,5-dioxo-1,2,5,6-tetrahydro-1,6-naphthyridine-8-carboxylate (7e)

This compound was prepared from **4** (150 mg, 0.535 mmol) and *tert*-butylhydrazine hydrochloride (**5e** 200 mg, 1.605 mmol). Yield: 26 mg (17%), mp 147-151 °C (white crystals from EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (9H, s, *CMe₃*); 3.94 (3H, s, O*Me*); 6,17 (1H, s, N*H*); 6.57 (1H, dd, *J* = 9.7, H_4); 8.11 (1H, d, *J* = 9.7 Hz, H_3); 8.40 (1H, s, H_7); 11.44 (1H, s, N*H*). IR (KBr): ν (cm^{-1}) 3297, 3265, 2971, 2930, 1696, 1683, 1657, 1557, 1438, 1366, 1344, 1293, 1267, 1242, 1206, 1180, 1038, 811, 800. Anal. Calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.77; H, 5.69; N, 14.25. ESI-HRMS: *m/z* = 291.1222 (M^+); $C_{14}H_{17}N_3O_4$ requires: 291,1219 (M^+).

Methyl 6-(2-ethoxy-2-oxoethylamino)-2,5-dioxo-1,2,5,6-tetrahydro-1,6-naphthyridine-8-carboxylate (7f)

This compound was prepared from **4** (313 mg, 1.116 mmol) and ethyl hydrazinoacetate hydrochloride (**5f**; 106 mg, 0.898 mmol). Yield: 134 mg (61%), mp 139-140 °C (white crystals from EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.18 (3H, t, *J* = 7.0 Hz, CH_2*Me*); 3.89 (6H, s, 2 x O*Me*); 3.90 (2H, d, *J* = 4.1 Hz, NHC*H₂*C=O); 4.09 (2H, q, *J* = 7.0 Hz, C*H₂*Me); 6.47 (1H, dd, *J* = 9.7; 1.1 Hz , H_4); 7.21 (1H, t, *J* = 4.0 Hz, N-N*H*CH_2); 8.03 (1H, d, *J* = 9.7 Hz, H_3); 8.69 (1H, s, H_7), 11.21 (1H, d, *J* = 1.1 Hz, N*H*). ^{13}C NMR (75.5

MHz, DMSO-d_6): δ 169.9, 165.1, 160.7, 158.2, 147.6, 144.7, 137.6, 119.4, 106.0, 95.4, 60.4, 52.4, 50.3, 13.8. IR (KBr): ν (cm^{-1}) 3246, 2992, 2959, 2931, 1746, 1676, 1696, 1555, 1497, 1435, 1336, 1296, 1250, 1211, 1031, 798. Anal. Calcd for $C_{14}H_{15}N_3O_6$: C, 52.34; H, 4.71; N, 13.08. Found: C, 52.12; H, 4.51. N, 12.92. ESI-HRMS: *m/z* = 322.0688 (MH$^+$); $C_{14}H_{16}N_3O_6$ requires: 322.0961 (MH$^+$).

Methyl 6-(cyclohexylamino)-2,5-dioxo-1,2,5,6-tetrahydro-1,6-naphthyridine-8-carboxylate (7g)

This compound was prepared from **4** (150 mg, 0.535 mmol) and cyclohexylhydrazine hydrochloride (**5g**, 242 mg, 1.605 mmol). Yield: 27 mg (16%), mp 158-161 °C (white crystals from EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 – 3.93 (11H, m, cyclohexyl); 3.94 (3H, s, O*Me*); 5.92 (1H, d, *J* = 3.6 Hz, N-N*H*), 6.57 (1H, dd, *J* = 9.7, 1.7 Hz, H_4); 8.11 (1H, d, *J* = 9.7 Hz, H_3); 8.40 (1H, s, H_7); 11.45 (1H, d, N*H*). IR (KBr): ν (cm^{-1}) 3290, 3229, 2925, 2853, 1721, 1689, 1668, 1640, 1540, 1429, 1296, 1259, 1217, 1132, 841, 802, 718. Anal. Calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.91, H, 5.74; N, 12.81. (ESI-HRMS: *m/z* = 317.1383 (M$^+$); $C_{16}H_{19}N_3O_4$ requires: 317.1376 (M$^+$).

Methyl 6-(1-phthalazinylamino)-2,5-dioxo-1,2,5,6-tetrahydro-1,6-naphthyridine-8-carboxylate (7h)

This compound was prepared from **4** (207 mg, 0.74 mmol) and 1-hydrazinophthalazine hydrochloride (**5h**, 131 mg, 0.666 mmol). Yield: 190 mg (79%), mp 288-289 °C (white crystals from EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.86 (3H, s, O*Me*); 6.50 (1H, dd, *J* = 9.7, 2.0 Hz, H_4);), 8.07 (1H, d, *J* = 9.7 Hz, H_3); 8.48 (1H, s, H_7); 7.80 – 8.40 (5H, m, phthalazinyl); 11.30 (1H, d, *J* = 1.9 Hz, N*H*), 12.15 (1H, s, N*H*). IR (KBr): ν (cm^{-1}) 3290, 3254, 3167, 3079, 3006, 1692, 1683, 1658, 1632, 1616, 1598, 1557, 1539, 1481, 1430, 1298, 1271, 1206, 1028, 794, 757, 705, 684, 661. Anal. Calcd for $C_{18}H_{13}N_5O_4$: C, 59.50; H, 3.61; N, 19.28. Found: C, 59.47; H, 3.36; N, 19.51. ESI-HRMS: *m/z* = 363.0971 (M$^+$); $C_{18}H_{13}N_5O_4$ requires: *m/z* = 363.0968 (M$^+$).

X-Ray structure analysis

Diffraction data for compounds **3** and **7d** were collected on a Nonius Kappa CCD diffractometer with graphite monochromated Mo*Kα* radiation. The data were processed using DENZO[11] program. Structures were solved by direct methods using SIR971.[12] We employed full-matrix least-squares refinements on F magnitudes with anisotropic displacement factors for all non-hydrogen atoms using Xtal3.6.[13] H-atoms parameters were not refined. The resulting crystal data and details concerning data collection and refinement for both compounds are quoted in Table 1. Selected bond lengths and bond angles are listed in Table 2. ORTEP[14] drawings of the content of asymmetric units of both compounds showing the atom-labeling scheme are presented in Figures 1 and 2. The final atomic and geometrical parameters, crystal data and details concerning data collection and refinement for both compounds have also been deposited with the Cambridge Crystallographic Data Center as supplementary material with the deposition numbers: CCDC 810326 & 810327, respectively. These data can be obtained, free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html.

Table 2. Crystal data, data collection and structure refinement for compounds **3** and **7d**

	compound **3**	compound **7a**
Formula	$C_{10}H_{11}N_1O_5$	$C_{16}H_{12}F_1N_3O_4$
Rel. formula weight	225.2	329.29
Crystal System	Monoclinic	Orthorhombic
Space group	$P2_1/c$	*Pcab*
a (Å)	8.8003 (3)	9.6343 (2)
b (Å)	11.1268 (4)	13.2974 (2)
c (Å)	10.8312 (4)	22.6298 (5)
β (˚)	100.313 (2)	90.00
V ($Å^3$)	1043.45 (6)	2899.13 (10)
Z	4	8
ρ (Mg m^{-3})	1.433	1.509
μ (mm^{-1})	0.117	0.119
Color of crystal	colorless	yellow
Shape of crystal	prism	plate
Dimensions (mm)	0.55 × 0.50 × 0.50	0.72 × 0.20 × 0.06
Temperature (K)	293	293
Wavelength (Å)	0.71073	0.71073
θ_{max} (°)	27.5	27.5
No. of integrated refl.	15340	28150
No. of independent refl.	2326	6156
R_{int}	0.028	0.038
No. of observed refl.	2012	2327
Threshold criterion	$F^2 > 2.0\sigma(F^2)$	$F^2 > 2.0\sigma(F^2)$
No. of contributing refl.	2213	2893
No. of parameters.	145	217
Final R and R_w	0.044, 0.045	0.047, 0.045
$(\Delta/\sigma)_{max}$	0.0001	0.0003
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)	0.19, -0.16	0.30, -0.24

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REFERENCES AND NOTES

1. For a review see: B. Stanovnik and U. Grošelj, *Adv. Heterocycl.Chem.*, 2010, **100**, 145.
2. S. Zupančič, J. Svete, and B. Stanovnik, *Heterocycles*, 2009, **77**, 899.
3. M. Žugelj, A. Albreht, U. Uršič, J. Svete, and B. Stanovnik, *ARKIVOC*, 2009, **VI**, 137.
4. A. Albreht, U. Uršič, J. Svete, and B. Stanovnik, *Heterocycles*, 2009, **78**, 2343.
5. K. Pirnat, P. Šimunek, U. Uršič, J. Bezenšek, U. Grošelj, A. Golobič, A. Meden, J. Svete, and B. Stanovnik, *ARKIVOC*, 2011, **VI**, 120.
6. a) C. F. H. Allen, *Chem. Rev.*, 1950, **47**, 275; b) W. W. Paudler and T. J. Kress, *Adv. Heterocycl. Chem.*, 1970, **11**, 123; c) W. W. Paudler and R. M. Sheets, *Adv. Heterocycl. Chem.*, 1983, **33**, 147; d) P. A. Lowe, In “*Compreh. Heterocycl. Chem.*”, ed. by A. J. Boulton and A. Mc Killop, Pergamon Press, New York, 1984; Vol. 2, p. 581; e) S. P. Stanforth, In “*Compreh. Heterocycl. Chem. II*”, ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Pergamon Press, New York, 1996; Vol. 7, p. 527; f) A. P. Dobbs, In “*Compreh. Heterocycl. Chem. III*´, ed. by A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, and R. J. K. Taylor, Elsevier, New York, 2008; Vol. 10, p. 713; g) P.-W. Phuan and M. C. Kozlowski, Product Class 8: Naphthyridines, In: *Science of Synthesis*, Georg Thieme Verlag, Stuttgart 2006, Vol. 15, p. 947.
7. a) Q. Huang, J. A. Hunter, and R. C. Larock, *Org. Lett.*, 2001, **3**, 2973; b) A. Numata, Y. Kondo, and T. Sakatomo, *Synthesis*, 1999, 306.
8. a) D. Guiadeen, S. Konthandaraman, L. Yang, S. G. Mills, and M. McCoss, *Tetrahedron Lett.*, 2008, **49**, 6368; b) Z.-G. Han, S.-J. Tu, B. Jiang, S. Yan, X.-H. Zhang, S.-S. Wu, W.-J. Hao, X.-D. Cao, F. Shi, G. Zhang, and N. Ma, *Synthesis*, 2009, 1639; c) F. Yang, L. Zheng, J. Xiang, Q. Dang, and X. Bai, *J. Comb. Chem.*, 2010, **12**, 478; d) P. S. Lemport, G. V. Bodrin, A. I. Belyakov, P. V. Petrovskii, A. V. Vologzhanina, and E. E. Nifant´ev, *Mendeleev Commun.*, 2009, **19**, 303; e) Z.-G. Han, C.-B. Miao, F. Shi, N. Ma, G. Zhang, and S.-J. Tu, *J. Comb. Chem.*, 2010, **12**, 16; f) S. Vanlaer, A. Voet, C. Gielens, M. De Maeyer, and F. Compernolle, *Eur. J. Org. Chem.*, 2009, 643.
9. a) H. J. El-Subbagh, S. M. Abu-Zaid, M. A. Mahran, F. A. Badria, and A. M. Al-Obaid, *J. Med. Chem.*, 2000, **43**, 2915; b) A. E. G. Hammam, M. A. Sharaf, and N. A. Abd El-Hafez, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2001, **40**, 213; c) A. Gangjee, Y. Zheng, J. J. McGuire, and R. L. Kisliuk, *J. Med. Chem.*, 2002, **45**, 5173; d) J.-C. Jaton, K. Roulin, K. Rose, F. M. Sirotnak, A. Lewenstein, G. Brunner, C. P. Franhauser, and U. Burger, *J. Nat. Prod.*, 1997, **60**, 356; e) Y. Morimoto, F. Matsuda, and H. Shirahama, *Tetrahedron*, 1996, **52**, 10609.
10. S. Feng, X. He, G. Yu, Y. Xia, and D. Bai, *Org. Prep. Proced. Int.*, 2004, **36**, 129.
11. Z. Otwinowski and W. Minor, *Methods Enzymol.*, 1997, **276**, 307.
12. A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. Moliterni,

G. Polidori, and R. Spagna, *J. Appl. Cryst*., 1999, **32**, 115.

13. S. R. Hall, D. J. du Boulay, and R. Olthof-Hazekamp, Eds.; Xtal3.6 System, University of Western Australia.

14. C. K. Johnson, ORTEPII. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA, 1976.