A Convenient Synthesis of 4-Hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide Derivatives

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Received 25 August 2008; revised 30 September 2008

Abstract: A simple method for synthesizing 1-aryl-4-hydroxy-*N*,*N*-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamides has been developed. Thus, 3-(2-chloropyridin-3-yl)-*N*,*N*-dimethyl-3-oxopropanamide, easily prepared by treating ethyl 2-chloropyridine-3-carboxylate with lithium enolate of *N*,*N*-dimethylacetamide, smoothly reacts with a range of aryl isocyanates in the presence of two molar amounts of sodium hydride to provide the desired products in moderate yields.

Key words: carbanions, fused-ring system, isocyanates, naphthyridines, tandem reaction

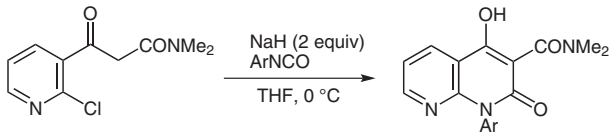
3-Substituted 4-hydroxy-1,8-naphthyridin-2(1*H*)-one derivatives are an important class of molecules in medicinal chemistry.[1] Among them, 4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamides have been reported to exhibit useful biological activities.[2] 3-Substituted 4-hydroxy-1,8-naphthyridin-2(1*H*)-one derivatives have been prepared by the reactions of 2-methyl-4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one with active methylene compounds.[1] However, no general procedures are available to prepare 4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamides directly from readily available compounds, though 3-carboxylate derivatives have been converted into the corresponding 3-carboxamide derivatives.[2] On the other hand, we previously reported a method to prepare (*Z*)-2-(2-oxo-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-ylidene)acetamide derivatives, which was based on the reaction of (*Z*)-3-amino-2-(chloro-6-methylpyridin-3-yl)propenamide derivatives with aryl isocyanates in the presence of sodium hydride.[3] In continuation of this study, we became interested in examining the reaction of 3-(2-chloropyridin-3-yl)-3-oxopropanamides with isocyanates. We envisaged that if the addition of the enolate anions of 3-(2-chloropyridin-3-yl)-3-oxopropanamides to isocyanates would occur at the carbon, the reaction should lead to construction of 4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamides. In this report, we wish to report the results of our study, which provide a facile method for the synthesis of 1-aryl-4-hydroxy-*N*,*N*-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamides **2** from 3-(2-chloropyridin-3-yl)-*N*,*N*-dimethyl-3-oxopropanamide (**1**) and aryl isocyanates.

SYNTHESIS 2009, No. 3, pp 0375–0378
Advanced online publication: 09.01.2009
DOI: 10.1055/s-0028-1083307; Art ID: F18508SS

The starting material, 3-(2-chloropyridin-3-yl)-*N*,*N*-dimethyl-3-oxopropanamide (**1**) was prepared by the reaction of 2-chloropyridine-3-carboxylate with lithium enolate of *N*,*N*-dimethylacetamide in 76% yield. We first conducted the reaction of compound **1** with phenyl isocyanate in DMF in the presence of two molar amounts of sodium hydride at 0 °C. These conditions are the same as those used previously in the preparation of (*Z*)-3-amino-2-(chloro-6-methylpyridin-3-yl)propenamide derivatives.[3] TLC monitoring of the progress of the reaction revealed that it was complete within 30 minutes. Unfortunately, however, aqueous extractive work up gave only a trace amount of the desired product **2a**. All other efforts to isolate **2a** in satisfactory yields were unsuccessful. Then, we conducted the reaction in THF as shown in Table 1. It also proceeded smoothly and was complete in one hour. Successive addition of chloroform and saturated aqueous ammonium chloride to the reaction mixture allowed **2a** to precipitate (see experimental section). Collection and subsequent recrystallization of this precipitate gave pure **2a** in satisfactory yield. The reactions of **1** with other aryl isocyanates were carried out in a manner similar to that described above and the resulting 1-aryl-4-hydroxy-*N*,*N*-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamides **2b–j** were isolated in a similar way. Yields of the desired products are summarized in Table 1. The modest yields are ascribed to loss of the products during the work-up and purification procedures, as TLC analyses did not indicate formation of any distinct by-products. It should be noted that the reactions using aliphatic isocyanates, such as *n*-butyl isocyanate and *tert*-butyl isocyanate, did not give the corresponding desired products, and the starting keto amide **1** was recovered almost quantitatively in each case. Unfortunately, we have no explanation of the reason for this result.

When an equimolar amount of sodium hydride was used, considerable amounts of the starting material was recovered and rather decreased yields of the desired products were obtained. The necessity of two molar amounts of sodium hydride may be explained as shown in Scheme 1. Thus, addition of sodium enolate of the keto amide **1**, generated by deprotonation of the active methylene with the first equivalent of sodium hydride, to an isocyanate generates the amide anion intermediate **3**. Presumably, proton transfer converts this intermediate into the much more stable enolate intermediate **4**, whose NH hydrogen is deprotonated by the second equivalent of sodium hydride to

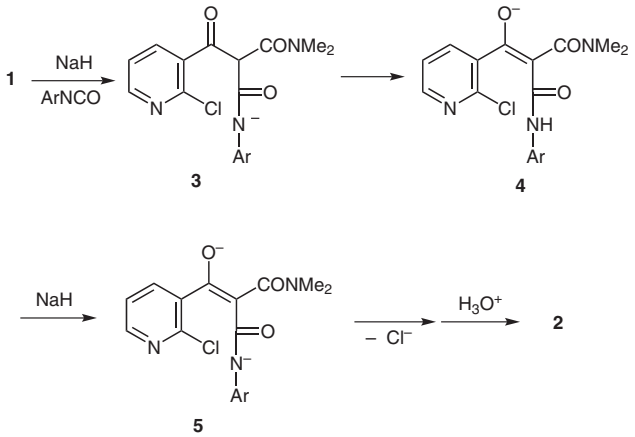
Table 1 Products and Yields of the Reaction of Keto Amide **1** with Aryl Isocyanates



1 2

Product	Ar	Yield (%)
2a	Ph	58
2b	2-MeC_6H_4	33
2c	3-MeC_6H_4	40
2d	3-ClC_6H_4	51
2e	4-ClC_6H_4	55
2f	3-Cl-4-MeC_6H_3	57
2g	2,4-$Cl_2C_6H_3$	52
2h	4-BrC_6H_4	52
2i	3-$MeOC_6H_4$	59
2j	1-naphthyl	54

generate the dianion intermediate **5**. This undergoes intramolecular substitution to afford, after aqueous workup, the product **2**.



Scheme 1

In summary, we have developed a simple and efficient method for the direct preparation of 4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide derivatives based on the reaction of the readily available starting material, 3-(2-chloropyridin-3-yl)-*N*,*N*-dimethyl-3-oxopropanamide, with various aryl isocyanates. The present method should be of use in synthesizing this class of heterocycles because of the ease of operations.

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 using TMS as an internal reference on a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. The ^{13}C NMR spectra were recorded in DMSO-d_6 using TMS as an internal reference on a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra were measured with a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use. Ethyl 2-chloropyridine-3-carboxylate was prepared according to the reported procedure.[4] All other chemicals used in this study were commercially available.

3-(2-Chloropyridin-3-yl)-*N*,*N*-dimethyl-3-oxopropanamide (1)
To a stirred solution of LDA (5.4 mmol; prepared by the standard method) in THF (7 mL) at –78 °C was added DMA (0.24 g, 2.7 mmol) dropwise. After 15 min, a solution of ethyl 2-chloropyridine-3-carboxylate (0.50 g, 2.7 mmol) in THF (2 mL) was added, and stirring was continued for an additional 15 min at the same temperature. H_2O (10 mL) was added and the mixture was neutralized by adding 10% aq HCl. The organic materials were extracted with Et_2O (3 × 10 mL), and the combined extracts were washed with brine (10 mL) and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by chromatography on silica gel (THF–hexane, 1:2) to give **1** as a white solid; yield: 0.46 g (76%); mp 51–52 °C (hexane–Et_2O); exists as a tautomeric mixture with the corresponding enol amide (ca. 2:8 in $CDCl_3$).

IR (KBr): 3495, 1643, 1601 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.97 (s, 1.2 H), 3.07 (s, 4.8 H), 4.16 (s, 0.4 H), 5.88 (s, 0.8 H), 7.32 (dd, *J* = 7.3, 4.6 Hz, 0.8 H), 7.36 (dd, *J* = 7.8, 4.6 Hz, 0.2 H), 7.99 (dd, *J* = 7.3, 2.3 Hz, 0.8 H), 8.05 (dd, *J* = 7.8, 1.8 Hz, 0.2 H), 8.42 (dd, *J* = 4.6, 2.3 Hz, 0.8 H), 8.49 (dd, *J* = 4.6, 1.8 Hz, 0.2 H), 11.14 (br s, 0.8 H).

Anal. Calcd for $C_{10}H_{11}ClN_2O_2$: C, 52.99; H, 4.89; N, 12.36. Found: C, 52.87; H, 5.00; N, 12.24.

4-Hydroxy-*N*,*N*-dimethyl-2-oxo-1-phenyl-1,2-dihydro-1,8-naphthyridine-3-carboxamide (2a); Typical Procedure
To a stirred suspension of NaH (60% in oil; 54 mg, 1.4 mmol) in THF (3 mL) at 0 °C was added dropwise a solution of **1** (0.15 g, 0.68 mmol) in THF (2 mL). After 15 min, PhNCO (81 mg, 0.68 mmol) was added, and stirring was continued for an additional 1 h before the successive addition of $CHCl_3$ (7 mL) and sat. aq NH_4Cl (5 mL). The resulting precipitate was collected by suction and recrystallized from Et_2O–EtOH to give **2a** as a white solid; yield: 0.12 g (58%); mp 197–203 °C (dec.).

IR (KBr): 3398, 1620 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.59 (br s, 3 H), 2.91 (br s, 3 H), 6.86 (t, *J* = 7.8 Hz, 1 H), 7.21 (t, *J* = 7.8 Hz, 2 H), 7.25 (dd, *J* = 6.9, 5.0 Hz, 1 H), 7.51 (d, *J* = 6.9 Hz, 1 H), 7.57 (d, *J* = 7.8 Hz, 2 H), 8.20 (d, *J* = 5.0 Hz, 1 H), 12.75 (br s, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 309 (25, [M$^+$]), 265 (38), 217 (100).

Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 65.86; H, 5.01; N, 13.36.

4-Hydroxy-*N*,*N*-dimethyl-1-(2-methylphenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide (2b)
White solid; mp 160–164 °C (Et_2O–EtOH).

IR (KBr): 3227, 1615 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.26 (s, 3 H), 2.60 (br s, 3 H), 2.96 (br s, 3 H), 6.77 (t, *J* = 7.3 Hz, 1 H), 7.04 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.10 (d, *J* = 7.3 Hz, 1 H), 7.24 (dd, *J* = 7.3, 4.9 Hz, 1 H), 7.52 (d, *J* = 7.3

Hz, 1 H), 8.17 (dd, *J* = 4.9, 1.8 Hz, 1 H), 8.45 (d, *J* = 7.8 Hz, 1 H), 12.54 (s, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 323 (36, [M$^+$]), 217 (54), 191 (100).

Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.80; H, 5.19; N, 12.99.

4-Hydroxy-*N*,*N*-dimethyl-1-(3-methylphenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide (2c)
White solid; mp 145–148 °C (Et_2O–EtOH).

IR (KBr): 3194, 1612 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.23 (s, 3 H), 2.57 (s, 3 H), 2.92 (s, 3 H), 6.65 (d, *J* = 7.3 Hz, 1 H), 7.06 (t, *J* = 7.3 Hz, 1 H), 7.22 (dd, *J* = 7.6, 4.6 Hz, 1 H), 7.31 (d, *J* = 7.6 Hz, 1 H), 7.41 (s, 1 H), 7.49 (d, *J* = 7.3 Hz, 1 H), 8.16 (dd, *J* = 4.6, 1.5 Hz, 1 H), 12.69 (s, 1 H).

MS (CI): *m*/*z* (%) = 324 (100, [M + 1]$^+$).

Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.82; H, 5.51; N, 12.96.

1-(3-Chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide (2d)
White solid; mp 140–142 °C (Et_2O–EtOH).

IR (KBr): 3421, 1616 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.60 (s, 3 H), 2.95 (s, 3 H), 6.88 (d, *J* = 7.9 Hz, 1 H), 7.17–7.27 (m, 3 H), 7.51 (d, *J* = 7.3 Hz, 1 H), 8.02 (s, 1 H), 8.19 (dd, *J* = 4.9, 1.4 Hz, 1 H), 13.00 (s, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 343 (19, [M$^+$]), 299 (20), 217 (100).

Anal. Calcd for $C_{17}H_{14}ClN_3O_3$: C, 59.40; H, 4.10; N, 12.22. Found: C, 59.20; H, 4.18; N, 12.09.

1-(4-Chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide (2e)
White solid; mp 213–215 °C (dec.) (Et_2O–EtOH).

IR (KBr): 3371, 1620 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.58 (br s, 3 H), 2.92 (br s, 3 H), 7.21–7.26 (m, 3 H), 7.51 (d, *J* = 7.3 Hz, 1 H), 7.60 (d, *J* = 8.6 Hz, 2 H), 8.19 (d, *J* = 5.5 Hz, 1 H), 12.93 (br s, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 343 (9.8, [M$^+$]), 217 (61), 191 (100).

Anal. Calcd for $C_{17}H_{14}ClN_3O_3$: C, 59.40; H, 4.10; N, 12.22. Found: C, 59.28; H, 4.20; N, 12.07.

1-(3-Chloro-4-methylphenyl)-4-hydroxy-*N*,*N*-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide (2f)
White solid; mp 235–237 °C (dec.) (Et_2O–EtOH).

IR (KBr): 3412, 1616 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.23 (s, 3 H), 2.49 (s, 3 H), 2.93 (s, 3 H), 7.09 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.15 (d, *J* = 7.8 Hz, 1 H), 7.23 (dd, *J* = 7.3, 4.9 Hz, 1 H), 7.49 (d, *J* = 7.3 Hz, 1 H), 7.99 (d, *J* = 1.8 Hz, 1 H), 8.17 (dd, *J* = 4.9, 1.8 Hz, 1 H), 12.84 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 18.83, 34.29, 38.33, 100.84, 116.88, 118.28, 121.98, 126.52, 130.90, 132.93, 137.18, 139.44, 140.63, 146.96, 147.15, 166.02, 171.10, 175.06.

MS (EI, 70 eV): *m*/*z* (%) = 357 (40, [M$^+$]), 312 (49), 217 (100).

Anal. Calcd for $C_{18}H_{16}ClN_3O_3$: C, 60.42; H, 4.51; N, 11.74. Found: C, 60.24; H, 4.54; N, 11.58.

1-(2,4-Dichlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide (2g)
White solid; mp 170–171 °C (Et_2O–EtOH).

IR (KBr): 3423, 1624 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.59 (s, 3 H), 2.93 (s, 3 H), 7.22–7.25 (m, 2 H), 7.48 (d, *J* = 2.4 Hz, 1 H), 7.51 (d, *J* = 7.3 Hz, 1 H), 8.17 (dd, *J* = 4.3, 1.8 Hz, 1 H), 8.71 (d, *J* = 9.2 Hz, 1 H), 13.12 (s, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 377 (40, [M$^+$]), 333 (100).

Anal. Calcd for $C_{17}H_{13}Cl_2N_3O_3$: C, 53.99; H, 3.46; N, 11.11. Found: C, 53.92; H, 3.32; N, 11.08.

1-(4-Bromophenyl)-4-hydroxy-*N*,*N*-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide (2h)
White solid; mp 214–217 °C (dec.) (Et_2O–EtOH).

IR (KBr): 3415, 1611 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.49 (s, 3 H), 2.84 (s, 3 H), 7.15 (dd, *J* = 7.3, 4.9 Hz, 1 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 7.41 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.44 (d, *J* = 8.5 Hz, 2 H), 8.08 (dd, *J* = 4.9, 1.8 Hz, 1 H), 12.83 (s, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 387 (10, [M$^+$]), 217 (100).

Anal. Calcd for $C_{17}H_{14}BrN_3O_3$: C, 52.60; H, 3.63; N, 10.82. Found: C, 52.49; H, 3.62; N, 11.81.

4-Hydroxy-1-(3-methoxyphenyl)-*N*,*N*-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide (2i)
White solid; mp 199–202 °C (dec.) (Et_2O–EtOH).

IR (KBr): 3413, 1614 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.64 (br s, 3 H), 2.94 (br s, 3 H), 3.71 (s, 3 H), 6.42 (d, *J* = 7.9 Hz, 1 H), 6.95 (d, *J* = 7.9 Hz, 1 H), 7.08 (t, *J* = 7.9 Hz, 1 H), 7.23 (dd, *J* = 6.9, 3.8 Hz, 1 H), 7.40 (s, 1 H), 7.50 (d, *J* = 6.9 Hz, 1 H), 8.17 (d, *J* = 3.8 Hz, 1 H), 12.79 (s, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 339 (13, [M$^+$]), 217 (48), 191 (100).

Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.69; H, 5.35; N, 12.38.

4-Hydroxy-*N*,*N*-dimethyl-1-(naphthalen-1-yl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide (2j)
White solid; mp 212–215 °C (dec.) (Et_2O–EtOH).

IR (KBr): 3253, 1614 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.62 (s, 3 H), 2.98 (s, 3 H), 7.26 (dd, *J* = 7.3, 4.9 Hz, 1 H), 7.37 (t, *J* = 7.9 Hz, 1 H), 7.42 (d, *J* = 7.9 Hz, 1 H), 7.48–7.52 (m, 2 H), 7.57 (d, *J* = 7.3 Hz, 1 H), 7.85 (d, *J* = 7.9 Hz, 1 H), 8.20 (dd, *J* = 4.9, 1.8 Hz, 1 H), 8.37 (d, *J* = 8.7 Hz, 1 H), 8.61 (d, *J* = 8.2 Hz, 1 H), 13.63 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 34.31, 38.36, 101.72, 114.19, 120.15, 121.66, 121.96, 124.42, 125.21, 125.42 (2 C), 126.22, 128.26, 133.76, 137.07, 139.48, 147.05, 147.14, 166.21, 171.23, 174.97.

MS (EI, 70 eV): *m*/*z* (%) = 359 (45, [M$^+$]), 314 (100).

Anal. Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69. Found: C, 70.03; H, 4.80; N, 11.70.

Acknowledgment

We are grateful to Mrs. Miyuki Tanmatsu of this university for determining mass spectra and performing combustion analyses.

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