Synthesis of a 1,8-Naphthyridin-5-one Derivative *via* an Intramolecular 1,3-Dipolar Cycloaddition Reaction

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Synthesis of a 1,8-naphthyridin-5-one derivative [(5,6,7,8-tetrahydro-(3-chloro-6-hydroxymethyl-8-methyl)-1,8-naphthyridin-5-one (**9**)] is described starting from 2-chloronicotinic acid using an intramolecular 1,3-dipolar cycloaddition reaction as the key step.

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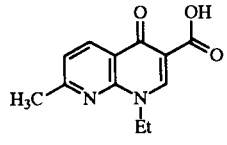
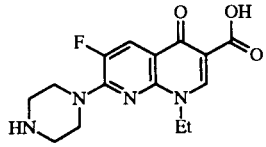
Intramolecular 1,3-dipolar cycloaddition reactions provide a powerful method for the construction of fused heterocycles, and this has been exploited extensively with *ortho* substituted benzenes [1-3]. This versatile reaction has also enjoyed considerable success in the synthesis of fused heterocyclic systems [3-9] which may then be further elaborated to provide a variety of functional groups attached to the heterocycle [10-11].

The discovery of the antibacterial agent nalidixic acid led to the synthesis of many 1,8-naphthyridin-5-one derivatives including the potent antibacterial enoxacin [12-13]. Different synthetic methods to prepare these heterocyclic systems have been reviewed [13-14]. In this paper we report an alternative method for the preparation of a 1,8-naphthyridin-5-one derivative using an intramolecular 1,3-dipolar cycloaddition reaction between a pyridine 3-nitrile oxide and an alkene dipolarophile tethered to the 2-position of the pyridine ring. A similar strategy was employed recently to prepare a pyridopyrimidinone derivative [7].

Our synthesis began with the reaction of 2-chloronicotinic acid (**1**) with thionyl chloride followed by treatment with sodium borohydride which gave the corresponding alcohol **2** [15] in 80% yield (Scheme 1). Oxidation of **2** with pyridinium chlorochromate provided 2-chloro-3-formylpyridine (**3**) in 81% yield [16]. Reaction of **3** with *N*-methylallylamine in the presence of triethylamine in refluxing THF led to the isolation of **4** in 87% yield. Reaction of **4** with hydroxylamine gave the corresponding oxime **5** in 35% yield.



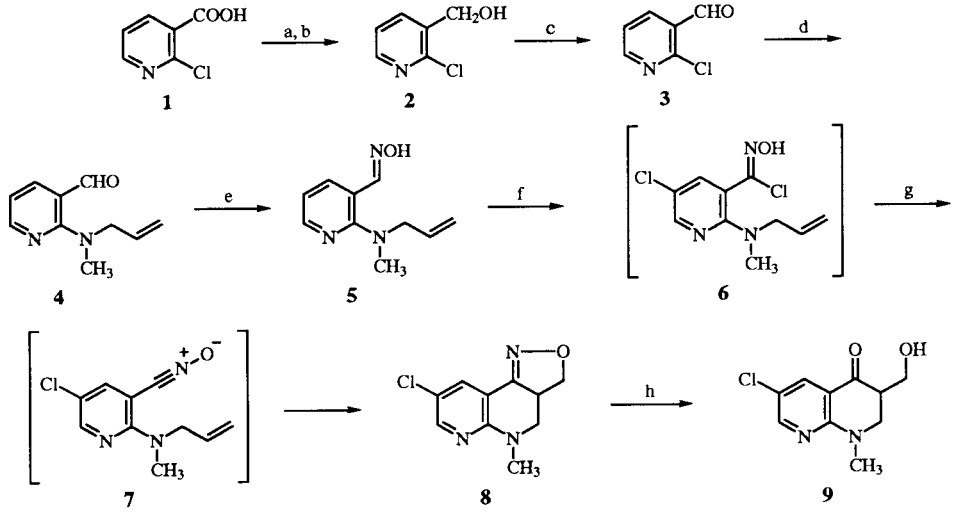
Nalidixic Acid



Enoxacin

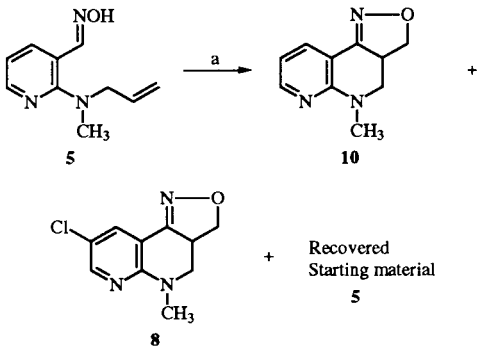
Treatment of the oxime **5** with one equivalent of freshly prepared *tert*-butyl hypochlorite followed by reaction with triethylamine gave a 1:1 mixture of the cycloadducts **8** and **10** together with recovered starting material **5** (Scheme 2). Evidently, aromatic chlorination of the pyri-

Scheme 1



(a) $SOCl_2$, Δ; (b) $NaBH_4$, H_2O, 10°C; (c) PCC, CH_2Cl_2; (d) $CH_3NHCH_2CH{=}CH_2$, Et_3N, THF, Δ; (e) $NH_2OH.HCl$, pyridine, EtOH, Δ; (f) *t*-BuOCl (2.3 equiv), CH_2Cl_2, 5°C; (g) Et_3N, 5°C to rt.; (h) Raney nickel, MeOH, AcOH, H_2O, H_2, rt, 1 atm.

Scheme 2



(a) *t*-BuOCl (1 eq), CH_2Cl_2, 5°C followed by Et_3N, 5°C to rt.

dine ring competes with chlorination *alpha* to the oxime. We therefore decided to react **5** with 2.3 equivalents of *tert*-butyl hypochlorite which provided the chloro oxime **6**; this was not isolated but instead treated *in situ* with triethylamine to generate the nitrile oxide **7** which underwent an intramolecular 1,3-dipolar cycloaddition reaction and provided the chlorinated cycloadduct **8** in 86% yield. Reaction of **8** with Raney nickel and hydrogen in aqueous methanol in the presence of acetic acid at atmospheric pressure gave the β-hydroxy ketone **9** in 88% yield. Thus, we have demonstrated a novel approach to the 5,6,7,8-tetrahydro-1,8-naphthyridin-5-one system containing a 6-hydroxymethyl substituent which could, in principle, be further elaborated to provide a variety of analogs.

EXPERIMENTAL

Melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are uncorrected. The proton (300 MHz) and carbon (75 MHz) nmr spectra were recorded on a Varian VXR-300 spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from internal tetramethylsilane. Column chromatography was performed on Merck silica gel 60 (240-400) mesh; silica gel plates were routinely used for tlc determinations. Elemental analyses were performed by Desert Analytics, Tucson, AZ, and were within ±0.4% of the theoretical values.

2-Chloro-3-hydroxymethylpyridine (**2**).

A mixture of 2-chloronicotinic acid (**1**, 50.0 g, 0.317 mole) and thionyl chloride (200 ml) was heated at reflux for 1.5 hours. The excess thionyl chloride was removed by evaporation under reduced pressure. The solid residue was added in portions to a well stirred solution of sodium borohydride (43.22 g, 1.14 moles) in water (500 ml) cooled to 10°. The reaction was maintained at 10-15° during the addition and then allowed to warm to room temperature. The reaction mixture was saturated with sodium chloride and extracted with diethyl ether (3 x 300 ml). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed by evaporation under reduced pressure to give 36.37 g (80%) of a colorless solid, mp 62-63°, (lit [15] mp 63-64°); ^{1}H nmr (deuteriochloroform): δ 3.25 (br s, 1H), 4.79 (s, 2H), 7.26 (dd, J = 5.0, 7.5 Hz, 1H), 7.89 (dd, J = 2.0, 7.5 Hz, 1H), 8.24 (dd, J = 2.0, 5.0 Hz, 1H), 8.24; ^{13}C nmr (deuteriochloroform): δ 61.3, 122.8, 135.3, 136.9, 148.0, 149.0.

2-Chloro-3-formylpyridine (**3**).

Pyridinium chlorochromate (27.12 g, 0.126 mole) was added to a solution of 2-chloro-3-hydroxymethylpyridine (**2**, 15.12 g, 0.107 mole) in anhydrous methlyene chloride (200 ml). The mixture was stirred at room temperature for 2 hours. Anhydrous diethyl ether (600 ml) was added and the mixture decanted. The residue was washed several times with diethyl ether. The solvent was removed by evaporation under reduced pressure and the residue was chromatographed using a short silica gel pad eluting with 80% ethyl acetate in hexanes to give 24.26 g (81%) of a colorless solid, mp 48-50° (lit [16] mp 42-43°); ^{1}H nmr (deuteriochloroform): δ 7.41 (dd, J = 5.0, 7.5 Hz, 1H), 8.23 (dd, J = 2.0, 7.5 Hz, 1H), 8.60 (dd, J = 2.0, 5.0 Hz, 1H),10.44 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 123.2, 128.9, 138.1, 153.7, 154.2, 189.2.

3-Formyl-2-(*N*-methyl)allylaminopyridine (**4**).

2-Chloro-3-formylpyridine (**3**, 15.5 g, 0.1104 mole), THF (80 ml), *N*-methylallylamine (8.0 g, 0.112 mole) and triethylamine (25 ml, 0.118 mole) were placed in a sealed container and heated in a sand bath at 100° for 24 hours. After allowing to cool to room temperature, water (300 ml) was added and the mixture was extracted with ethyl acetate (3 x 150 ml). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with 50% ethyl acetate in hexanes. The fractions containing the pure product were combined and the solvent was removed under reduced pressure to give 17.83 g (87%) of a pale yellow oil; ^{1}H nmr (deuteriochloroform): δ 2.98 (s, 3H), 4.08 (m, 2H), 5.19 (m, 1H), 5.89 (m, 2H), 6.73 (dd, J = 4.5, 7.6 Hz, 1H), 7.9 (dd, J = 2.0, 7.6 Hz, 1H), 8.26 (dd, J = 2.0, 4.5 Hz, 1H), 9.92 (s, 1H). ^{13}C nmr (deuteriochloroform): δ 39.5, 56.7, 113.9, 117.5, 133.8, 141.0, 152.2, 160.5, 189.7.

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.43; H, 7.15; N, 16.03.

2-(*N*-Methyl)allylamino-3-oximinomethylpyridine (**5**).

A mixture of 3-formyl-2-(*N*-methyl)allylaminopyridine (**4**, 17.83 g, 0.1 mole), hydroxylamine hydrochloride (6.96 g, 0.1 mole), pyridine (15 ml, 0.186 mole) and ethanol (110 ml) was heated at reflux for 1 hour. The solvent and excess pyridine were removed *in vacuo* and the residue was partitioned between ethyl acetate and water. The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure. The residue was recrystallized from ethanol/water mixture to give 6.81 g (35%) of a crystalline solid, mp 72-74°; ^{1}H nmr (deuteriochloroform): δ 2.19 (s, 3H), 3.83 (d, J = 5.6 Hz, 2H), 5.27 (m, 2H), 5.92 (m, 1H), 6.85 (dd, J = 4.9, 7.5 Hz, 1H), 7.89 (dd, J = 1.9, 7.6 Hz, 1H), 8.25 (s, 1H), 8.26 (dd, J = 1.7, 4.9 Hz, 1H), 8.80 (br s, 1H). ^{13}C nmr (deuteriochloroform): δ 33.8, 58.0, 116.4, 117.4, 134.5, 136.5, 148.1, 148.4, 160.8.

Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.44; H, 6.87; N, 21.79.

8-Chloro-5-methyl [4,5-*b*][1,8]-3a,4-dihydronaphthyridine (**8**).

To a well stirred solution of **5** (3.1 g, 0.015 mole) in anhydrous methylene chloride (40 ml) cooled to 5° was added dropwise a mixture of freshly prepared *tert*-butyl hypochlorite [17] (3.74 g, 0.035 mole) in methylene chloride over a period of 10 minutes. The mixture was stirred at 5° for 20 minutes and a mixture of triethylamine (2.62 ml, 0.019 mole) in methylene chloride (10 ml) was added dropwise over a 20 minute period. The solution was stirred for a further 45 minutes while allowing it to warm to room temperature. The reaction mixture was washed with saturated sodium chloride solution and the organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with 50% ethyl acetate in hexanes to give 3.03 g (86%) of a colorless solid, mp 69-71°; ^{1}H nmr (deuteriochloroform): δ 3.11 (s, 3H), 3.41 (t, J = 11.5 Hz, 1H), 3.67 (dd, J = 5.8, 11.5 Hz, 1H), 3.82-4.20 (m, 2H), 4.70 (dd, J = 7.3, 9.1 Hz, 1H), 7.84 (d, J = 2.5 Hz, 1H), 8.11 (d, J = 2.5 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 37.3, 45.1, 52.8 ,72.4, 107.3, 120.3, 132.5, 149.3, 153.9, 154.5.

Anal. Calcd. for $C_{10}H_{10}ClN_3O$: C, 53.72; H, 4.51; N, 18.80. Found: C, 53.58; H, 4.44; N, 18.44.

5,6,7,8-Tetrahydro-(3-chloro-6-hydroxymethyl-8-methyl)-1,8-naphthyridin-5-one (**9**).

A mixture of W-2 Raney nickel (washed well with water and then with methanol; approximately 1.0 g), the cycloadduct **8** (2.924 g, 0.013 mole), methanol (100 ml), acetic acid (2 ml) and water (2 ml) was stirred vigorously at room temperature under one atmosphere of hydrogen for 30 hours. The mixture was filtered through a pad of Celite which was washed well with methanol. The filtrate was evaporated under reduced pressure. The residue was dissolved in methylene chloride and washed with saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure to give 2.62 g (88%) of a pale yellow solid, mp 73-75°; ^{1}H nmr (deuteriochloroform): δ 2.65 (br s, 1H), 2.90 (m, 1H), 3.17 (s, 3H), 3.50 (m, 2H), 3.90 (d, J = 5.7 Hz, 2H), 7.93 (d, J = 2.5 Hz, 1H), 8.22 (d, J = 2.5 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 36.8, 47.4, 50.5, 60.2, 114.2, 120.4, 135.2, 153.4, 158.1, 194.8.

Anal. Calcd. for $C_{10}H_{11}ClN_2O_2$: C, 53.02; H, 4.89; N, 12.36. Found: C, 53.10; H, 4.84; N, 12.10.

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