The Preparation of Ethyl 7-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-5-methyl-4-oxo-1,8-naphthyridine-3-carboxylate

John S. Kiely

Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company,
Ann Arbor, Michigan 48105
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Ethyl 7-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-5-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid has been prepared by a route involving masking of the $C_{2,3}$ double bond through reduction, followed by regioselective deprotonation of the C_5 position and methylation and then regeneration of the $C_{2,3}$ double bond via selenation, oxidation, and syn-elimination.

A recent report from our laboratories has shown that in 1-cyclopropyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids (quinolone-type antibacterials) inclusion of a 5-methyl substitutent resulted in an increase in *in vitro* activity, while the homolog 5-ethyl decreased activity [1]. In our continued development of a structure activity relationship for the closely related 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid antibacterials, we wished to follow up these observations and assess the effect of incorporation of a methyl group at C_5 of the 1,8-naphthyridine ring. We wish to report here a straightforward synthesis of this compound.

Two approaches to preparing the key intermediate to antibacterials of this type, 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-5-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid, **3**, seemed possible and were initially considered. The first approach being the preparation of a 2,6-dichloro-5-fluoro-4-methylnicotinic acid, **1**, suitable for elaboration into the proper 1,8-napthyridine, **3**. Published methods for constructing the necessary 5-fluorinated nicotinic acids did not seem directly amenable to incorporating a 4-methyl substituent [2,3,4]. The second conceptual route was through direct methylation of the 1,8-naphthyridine ring system, **2** via regioselective deprotonation of the C_5 position followed by methylation. In such an approach, the desired regioselective deprotonation would be aided by stabilization of the intermediate anion from both the *ortho* fluorine and the carbonyl oxygen in the peri position.

Exploration of this second route was undertaken initially. Attempts to employ a hindered amide base to effect selective deprotonation of the C_5 position of ethyl 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, **4**, followed by methylation was wholly unsuccessful, giving only indescipherible mixtures [5]. The potential of employing alkyllithium reagents as an alternative base to achieve deprotonation seemed unfavorable based on our previous work which demonstrated that alkyl- or aryl- lithium species could add in a 1,4 fashion to the 1,8-naphthyridine C_2 position giving 2-alkylated-1,8-naphthyridines [6].

These results seemed to indicate that it was probably

Figure 1
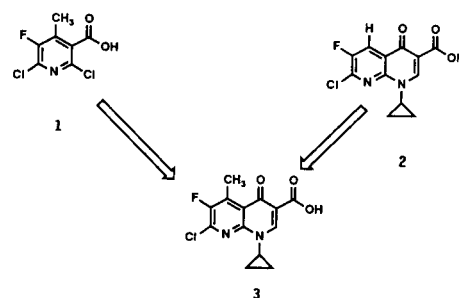
necessary to protect/mask the C_2 position in some manner prior to attempting to deprotonate at C_5. It occurred to us that reduction of the 2,3 double bond could be an excellent way to achieve this protection. This idea was reinforced by the knowledge that reintroduction of the double bond could be readily accomplished [6]. Using the sequence of "masking" the $C_{2,3}$ double bond by reduction, C_5-deprotonation, and methylation, successfully produced the desired 5-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid, **8**.

Figure 2
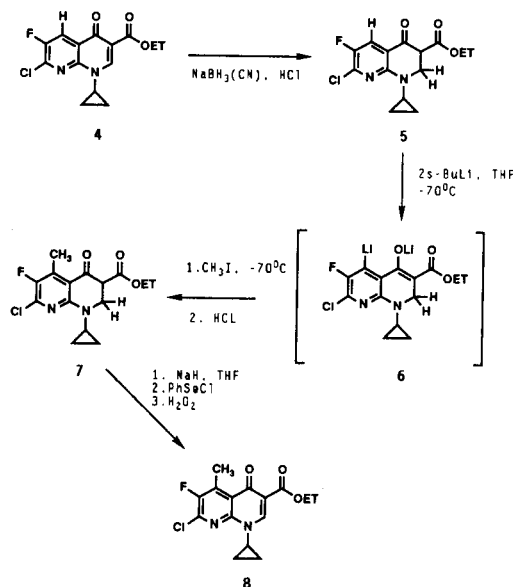
Selective reduction of the $C_{2,3}$ double bond is readily accomplished by an hydrochloric acid-catalyzed sodium cyanoborohydride reduction giving **5** in 72% yield. Using 200 mole percent *sec*-butyllithium as the base we carried out C_5-deprotonation selectively at low temperature to give in a formal sense compound **6**. In this reaction the initial deprotonation of the β-ketoester functionality served to protect the carbonyl and ester moieties from nucleophilic attack by the *sec*-butyllithium. The *ortho* fluorine and β-ketoester anion located in a peri relationship to C_5 likely are providing stabilization to the C_5 anion. While maintaining $-70°$, *in situ* methylation was accomplished using methyl iodide which gave the intermediate **7** (85% yield).

Reintroduction of the $C_{2,3}$ double bond was accomplished by the previously described methodology [6]; deprotonation of the β-ketoester with sodium hydride, addition of phenylselenyl chloride to effect C_3-selenation, followed by oxidation of the selenium with 30% hydrogen peroxide, and *in situ* syn-elimination of the phenyl selenoxide gave **8** (64%).

This sequence then readily produces the desired C_5-methylated 1,8-naphthyridine intermediate. Microbiologically, fully elaborated compounds containing 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-5-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid are equipotent with the unmethylated analogs in parallel with the original observations [1].

EXPERIMENTAL

Infrared spectra were determined on a Nicolet FT RI SX-20 with 2 cm⁻¹ resolution. Proton magnetic resonance spectra were recorded on a Varian XL-200 spectrometer. Chemical shifts are reported in delta units relative to tetramethylsilane. Mass spectra were recorded on a VG Analytical 7070E/HF with an 11/250 data system. All concentrations of solutions were performed under reduced pressure on a Buchi rotary evaporator. The CHN elemental analyses were performed on a Control Equipment Corp. Model 240X Elemental Analyzer and halogen determinations were performed by the closed flask combustion method, employing a titrimetric determination. Melting points are uncorrected.

Ethyl 7-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate, **4**.

7-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid [7] (20.0 g, 0.071 mole) and dimethylformamide (0.5 ml) were added to methylene chloride (750 ml) to give a light tan suspension. Over 1 minute oxalylchloride (7.4 ml, 0.085 mole) was added and the mixture stirred for 90 minutes during which time the suspension dissolved to give a homogeneous solution. The reaction progress was monitored by removing an aliquot and quenching with methanol then checking for the presence of starting acid by tlc (silica gel, 4/1 v/v methylene chloride-ethanol). An additional 2.0 ml of oxalyl chloride was required to consume all the starting acid. To the reaction was added ethanol (7.4 ml, 0.078 mole) and stirring continued for 4

hours. After storing overnight in the cold, the reaction was stirred at room temperature for an additional 3 hours after addition of 2.0 ml of ethanol. The reaction was evaporated to a brown solid and dissolved in hot tetrahydrofuran, filtered while hot, reheated, and allowed to cool and stand overnight at 0°. Filtration gave **4** as fine colorless needles (11.1 g, 50%) mp 174-176°; ¹H nmr (deuteriochloroform): ppm 8.67 (s, 1H), 4.40 (q, 2H, J = 7.0 Hz), 8.44 (d, 1H, J_{HF} = 7.4 Hz), 4.40 (q, 2H, J = 7.2 Hz), 3.70-3.60 (m, 1H), 1.40 (t, 3H, J = 7.2 Hz), 1.35-1.25 (m, 2H), 1.10-1.02 (m, 2H); ms: M⁺ = 310, 265, 238 (base); ir (potassium bromide): 3100-2750, 1728, 1697, 1625, 1480, 1264.

Anal. Calcd. for $C_{14}H_{12}ClFN_2O_3$: C, 54.11; H, 3.89; N, 9.02; F, 6.12. Found: C, 54.29; H, 3.89; N, 9.00; F, 6.32.

Ethyl 7-Chloro-1-cyclopropyl-6-fluoro-1,2,3,4-tetrahydro-4-oxo-1,8-naphthyridine-3-carboxylate, **5**.

The naphthyridine ester, **4**, (3.00 g, 0.01 mole) was suspended in absolute ethanol (200 ml) and sodium cyanoborohydride (0.70 g, 0.01 mole) was added. To this slurry was added three drops of concentrated hydrochloric acid immediately turning the reaction mixture bright yellow. At thirty minute intervals additional acid was added until tlc showed that the reaction was complete (approximately 6 hours). The reaction mixture was added to water (300 ml) and extracted with methylene chloride (4 x 100 ml). The methylene chloride layers were combined, dried (magnesium sulfate), and evaporated to a yellow solid. This solid was purified by flash chromatography to give **5** (2.2 g, 73%) mp 117-119°; ¹H nmr (deuteriochloroform): ppm 11.98 (s, 1H), 7.52 (d, 1H, J_{HF} = 7.9 Hz), 7.27 (s, 1H), 4.30 (q, 2H, J = 7.1 Hz), 4.27 (s, 2H overlapping quartet at 4.30), 2.53-2.44 (m, 1H), 1.35 (t, 3H, J = 7.1 Hz), 0.95-0.86 (m, 2H), 0.65-0.57 (m, 2H); ms: M⁺ = 312, 297, 265, 251 (base), 239, 225; ir (potassium bromide): 2974, 1673, 1629, 1560, 1496, 1463, 1268, 1052.

Anal. Calcd. for $C_{14}H_{14}ClFN_2O_3$: C, 53.77; H, 4.51; N, 8.96. Found: C, 53.69; H, 4.03; N, 8.87.

Ethyl 7-Chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-5-methyl-4-oxo-1,8-naphthyridine-3-carboxylate, **8**.

Compound **5** was dissolved in tetrahydrofuran (170 ml) and cooled to $-70°$ (internal) and the *sec*-butyllithium (1.3M, 22.2 ml, 0.028 moles) was added dropwise over 30 minutes while maintaining the temperature at $-70°$. The resulting orange solution was stirred for 1 hour at $-70°$ followed by the addition of methyliodide (0.90 ml, 0.014 moles) and stirring continued at $-70°$ for 7 hours. The reaction was then allowed to slowly warm over 17 hours to $-25°$. At this time no starting material was detectible by tlc. The reaction was quenched by the addition of saturated ammonium chloride solution (50 ml). This mixture was diluted with methylene chloride (150 ml) and the layers separated. The organic layer was washed with saturated sodium chloride solution, dried (magnesium sulfate), and evaporated to an orange oil,

7. This oil was purified by flash chromatography (Grace 60 230-400 mesh silica gel, methylene chloride) to give the product as an orange oil (3.91 g, 86%). This oil was used as in the following oxidation step; ¹H nmr (deuteriochloroform): ppm (mixture of keto and enol forms) 12.62 (s, enol), 4.35 and 4.25 (quartets), 3.95 (dd), 3.75 (dd), 3.49 (m), 2.62 (d, J_{HF} = 2.2 Hz), 2.55 (d, J_{HF} = 2.4 Hz), 1.38 (t), 1.27 (t); ms: M⁺ = 326, 311, 279, 265 (base), 239.

A solution of oil-free sodium hydride (0.10 g of 60% by weight) in tetrahydrofuran (50 ml) was prepared and to this was added **7**

(0.68 g, 0.002 mole) to give a yellow solution. Phenylselenyl chloride (0.44 g, 0.002 mole) was added as a solution in tetrahydrofuran causing the color to discharge. The reaction was diluted with an equal volume of ether and washed successively with solutions of saturated potassium bicarbonate and sodium chloride, followed by drying over sodium sulfate and evaporation to a solid. This solid was dissolved in methylene chloride (15 ml) and 30% hydrogen peroxide (0.3 ml) was added and allowed to react for 0.5 hour. The mixture was washed successively with solutions of saturated potassium bicarbonate and sodium chloride, followed by drying over sodium sulfate and evaporation to a solid, **8** (0.66 g). The solid was crystallized from isopropyl ether to give **8** as off-white needles (0.44 g, 64%); ^{1}H nmr (deuteriochloroform): ppm 8.67 (s, 1H), 4.40 (q, 2H, J = 7 Hz), 3.67-3.56 (m, 1H), 2.93 (d, 3H, J_{HF} = 2.6 Hz), 1.40 (t, 3H, J = 7 Hz), 1.35-1.25 (m, 2H), 1.10-0.95 (m, 2H); ms: M$^+$ = 324, 278, 250 (base); ir (potassium bromide): 3650-3100, 1728, 1644, 1476, 1264.

Anal. Calcd. for $C_{15}H_{14}ClFN_2O_3$: C, 55.47; H, 4.34; N, 8.63. Found: C, 55.21; H, 4.30; N, 8.70.

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