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Cyanide Mediated Decarboxylation of 1-Substituted-4-oxoquinoline and 4-oxo-1,8-naphthyridine-3-carboxylic Acids

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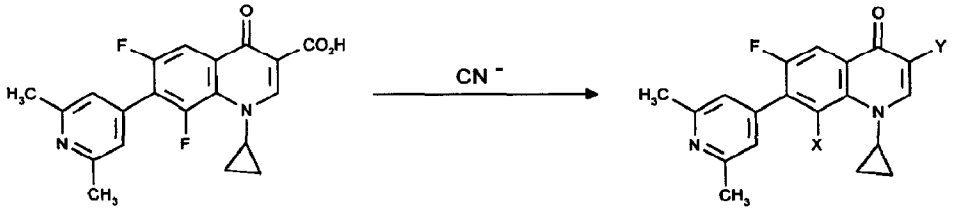
Abstract: Electron deficient 3-quinolinecarboxylic acids undergo ready decarboxylation in the presence of cyanide ion. This reaction most likely requires the addition of CN^- to the 2-position of the quinoline (or naphthyridine) nucleus to provide a β-keto acid intermediate that rapidly decarboxylates to give the 3-H substituted product.

The preparation of naturally occurring 4-oxoquinoline derivatives has attracted the attention of a number of research groups.[1] Among the available methods for the synthesis of 4-oxopyridinone derivatives, there are few that involve the direct decarboxylation of the corresponding acids.[2,3,7b,10] One attempt to effect this decarboxylation by heating in DMF, quinoline, or in the presence of various copper reagents met with failure.[3] We would like to report here a serendipitous finding of a simple method for the decarboxylation of 4-oxo-3-quinolinecarboxylic acids.

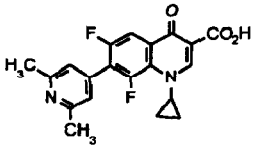
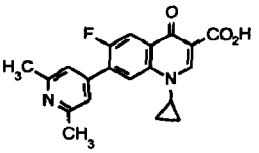
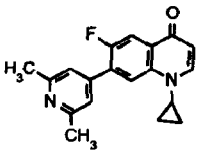
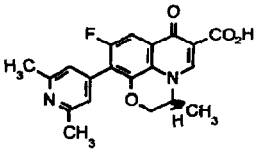
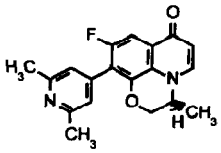
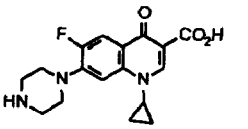
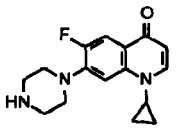
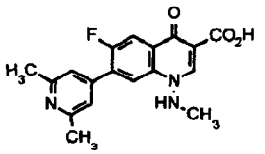
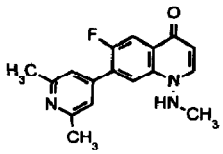
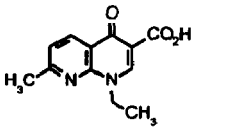
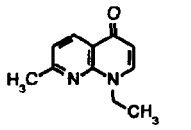


1a

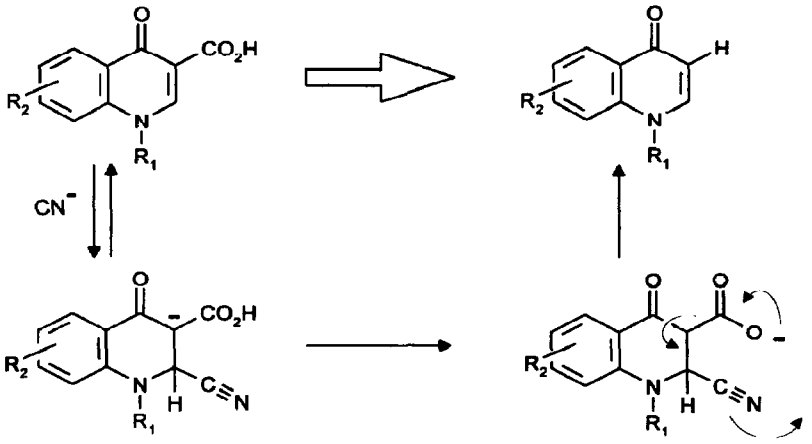
1b X = F, Y = H
1c X = CN, Y = H
1d X = CN, Y = CO_2H

For our work in topoisomerase inhibitors we wanted to prepare the 8-cyano derivative **1d**. Uno and coworkers[4] demonstrated the reactivity of the 8-fluoro substituent on a substituted 6,8-difluoro-3-quinolinecarboxylic acid toward nucleophilic displacement. In their study, the use of $NaSCH_3$ or $NaOCH_3$ as nucleophiles gave the corresponding 8-thiomethyl or 8-methoxy derivatives. Based on this work, we thought that the 8-fluoro substituent of **1a** might be reactive to displacement by other nucleophiles, such as CN^-, to give **1d**. Instead of providing **1d**, treatment of **1a** with NaCN in hot DMF gave **1b** and **1c** as a 60:40 mixture. Apparently decarboxylation[5] of **1a** and **1d** is competitive with displacement to form **1d**. When other 4-oxo-3-quinolinecarboxylic acids, or the 1,8-naphthyridine **6a**, were subject to treatment with NaCN or KCN, in most cases, they underwent ready decarboxylation to give the corresponding 3-H compounds in good yield. It is noteworthy that when an electron poor ring is fused to the 4-oxopyridine nucleus, the decarboxylation reaction is fairly rapid. When the fused ring contains electron donating groups, the decarboxylation reaction is slower and requires either higher temperatures or longer reaction times, illustrated with **3a** and **4a**. In a competition

Table Decarboxylation of Substituted-4-oxoquinoline and 4-oxo-1,8-naphthyridine-3-carboxylic Acids

Carboxylic Acid	Products	Conditions	Yield
 **1a**[6]	**1b**[11], **1c**[11] (60/40 mixt)	NaCN (5eq), DMF 5 min, 150 - 160 °C	90 %
	1b	Cu-Quinoline, 1 h, 200 °C	81 %
 **2a**[6]	 **2b**[11]	NaCN (5eq), DMF 12h, 120 °C	75 %
 **3a**[6]	 **3b**[11]	NaCN (5eq), DMF 24 h, 120 °C	52 %
 **4a**[7a]	 **4b**[7b]	NaCN (1eq), DMSO 5 h, 180 °C	77 %
		Cu-Quinoline 3 h, 230 °C	Decomp
 **5a**[8]	 **5b**[11]	NaCN (1eq), DMSO 1 h, 170 °C	81 %
		Cu-Quinoline 3 h, 230 °C	Decomp
 **6a**[9a]	 **6b**[9b]	KCN (5eq), DMSO 14 h, 100 °C	84 %

experiment equimolar amounts of **1a** and **2a** were combined in DMF, the mixture was equilibrated to 120 °C, 5 equivalents of NaCN was added, followed by workup of an aliquot after 5 minutes. Analysis of the product mixture by GC mass spec indicated the ratio (**1b** + **1c**):**2b** was 9:1. When the same competition experiment was conducted using an equimolar mixture of **2a** and **3a**, the product ratio of **2b**:**3b** was 99:1. Furthermore, treatment of oxolinic acid[10] with NaCN afforded only traces of the anticipated decarboxylation product. This reactivity behavior appears consistent with a Michael addition to the 2,3 double bond of the pyridinone ring system to give a transient adduct which decomposes to the 3-H compound. Conceivably, the HCN generated in this reaction may also play a role by protonation of the substrate prior to cyanide addition. When we compared the cyanide mediated decarboxylation with that of copper-quinoline, **1a** was cleanly converted to **1b** without the formation of by products. When examples **4a** and **5a** were subject to Cu-quinoline treatment, only products resulting from decomposition of the starting materials were found.



A general experimental procedure follows: A solution of the oxopyridinone carboxylic acid is combined with NaCN or KCN in the solvent indicated in the table and heated for the specified time. The reaction mixture is allowed to cool, poured into water, and extracted with ethylacetate or chloroform, dried, and concentrated to give the yield stated in the table. As an example, 0.50g (2.15 mmol) of Nalidixic acid, **6a**, was combined with 0.70g (10.7 mmol) of KCN in 5 mL of DMSO. The mixture was heated in an oil bath at 100 °C for 14h, allowed to cool to room temperature, poured into water and extracted with EtOAc. The extracts were dried ($MgSO_4$), filtered and concentrated to give **6b**, 0.34g (1.8 mmol, 84 %). ^1H NMR 300 MHz ($CDCl_3$) δ 8.58 (d, 1H), 7.63 (d, 1H), 7.18 (d, 1H), 6.30 (d, 1H), 4.42 (q, 2H), 2.65 (s, 3H), 1.45 (t, 3H).

In examples where the copper-quinoline method for decarboxylation of acids is unsuccessful, as with **4a** and **5a** in this report, the cyanide mediated decarboxylation described in this communication may provide an alternative.

Acknowledgments

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11 Data for new products: **1b**, mp 234-6 °C, Anal Calcd for $C_{19}H_{16}F_2N_2O$, C-69.93, H-4.94, N-8.58, found C-69.74, H-4.94, N-8.57; **1c**, mp 282-5 °C, Anal Calcd for $C_{20}H_{16}FN_3O$, C-72.06, H-4.84, N-12.60, found C-72.10, H-4.81, N-12.58; **1d**, mp 269-272 °C, Anal Calcd for $C_{21}H_{16}FN_3O_3$, C-66.84, H-4.27, N-11.14, found C-66.94, H-4.22, N-11.07; **2b**, mp 251-3°C, Anal Calcd for $C_{19}H_{17}FN_2O$, C-74.01, H-5.56, N-9.09, found C-73.78, H-5.39, N-9.16; **3b**, mp 283-4.5 °C, $\alpha_D^{25} = -86.2$ ($CHCl_3$), Anal Calcd for $C_{19}H_{17}FN_2O_2$, C-70.36, H-5.28, N-8.64, found C-70.52, H-5.40, N-8.71; **5b**, mp 228-9 °C, Anal Calcd for $C_{17}H_{16}FN_3O$, C-68.67, H-5.42, N-14.13, found C-69.07, H-5.61, N-14.40.

12 We will miss the companionship of George Lesher. Deceased March 17, 1990.

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