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### IMPROVED SYNTHESIS OF NITRILES OF QUINOLONE ANTIBIOTICS

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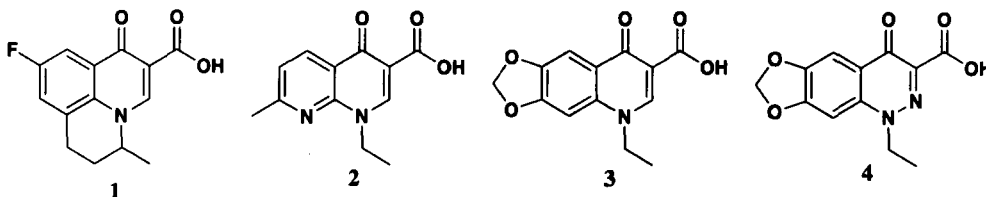
## IMPROVED SYNTHESIS OF NITRILES OF QUINOLONE ANTIBIOTICS

Submitted by Keith A. Korthals<sup>†</sup> and Thomas J. Delia<sup>††</sup>  
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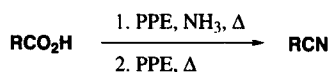
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The parasites that cause malaria (*Plasmodium vivax*, *Plasmodium falciparum*, and *Plasmodium malariae*) are becoming resistant to current treatment methods.<sup>1</sup> In the course of our studies toward the preparation of tetrazole<sup>2</sup> derivatives of commercially available antibiotics for potential application in the treatment of malaria, we required the corresponding nitrile derivatives.<sup>3</sup>



The quinolone antibiotics flumequine (1), nalidixic acid (2), oxolinic acid (3), and cinoxacin (4) were selected. In view of the fact that the structural features of the  $\beta$ -ketoacids would seem to preclude facile decarboxylation, it was surprising that the formation of the corresponding nitriles proved more challenging than anticipated. Initial attempts which included the following reactions: a) thermal cyclization of ethyl 3-[(3,4-methylenedioxyphenyl)amino]-2-cyanopropenoate to give the *desethyl* nitrile of dihydrooxolinic acid (3) directly, b) microwave irradiation of the carboxylic acids (1-4) in the presence of urea and sulfamic acid to generate the amide and to induce its dehydration to the nitriles, and c) the use of chlorosulfonyl isocyanate to induce the formation of amides with subsequent elimination to the nitrile, all gave low yields.<sup>4</sup> Conversion of oxolinic acid (3) to its acid chloride with thionyl chloride followed by treatment with ammonium hydroxide also failed to give the desired amide.

Success was achieved by utilizing the reagent polyphosphate ester (PPE) to generate the desired nitriles. Although PPE has previously been used for the formation of nitrile derivatives from acids,<sup>5</sup> it has not been reported for the quinoline series and may be of particular value in the case of problematic substrates. The equation below illustrates the optimized dehydration process in which the carboxylic acid is treated with PPE and ammonia gas. The resulting solid is then taken up in basic solution, filtered and dried. Subsequent treatment of the solid with additional PPE followed by heating and an acid work-up gave the product.



Although the conversion of acid to nitrile was reasonable for flumequine (1) and nalidixic acid (2), low yields of nitriles corresponding to oxolinic acid (3) and cinoxacin (4) were obtained and might be attributed to the instability of the methylenedioxy group to polyphosphate ester and the acid work-up.

The current procedure gave higher yields (68%) for the nitrile of nalidixic acid (2) compared with the literature preparation (42%). The literature preparation required multistep syntheses (in some cases as many as eleven steps) whereas the current procedure effectively requires one step from commercially available starting materials.<sup>6</sup> The previously unknown nitrile of flumequine (1) was prepared in an overall yield of 65%.

**Table.** Conversion of Quinolonecarboxylic Acids to Nitriles

Cmpd	Nitrile Yield (%)	mp. (°C) <sup>a</sup>	lit. mp. (°C)	Time (hrs) <sup>b</sup>
1	65	242-243	n/a	45/1.5
2	68	216-218	221-223 <sup>c</sup>	21/0.3
3	10	254-256	256-258 <sup>c</sup>	36/1
4	21	265-266	261-263 <sup>d</sup>	24/1

a) Powder from ethyl acetate and chloroform (7:3 by vol.) after column chromatography. b) Conversion to the nitrile was performed in two steps. The acid was treated with ammonia and PPE for the indicated time then filtered and treated again with PPE for the indicated time. c) Ref. 5a. d) Ref. 5b.

In conclusion, we have shown that the reagent PPE is useful for the formation of nitriles from quinolone carboxylic acids. This procedure should have subsequent usefulness for other similarly difficult substrates.

## EXPERIMENTAL SECTION

The literature preparation of PPE was followed.<sup>5</sup> Chloroform was dried over anhydrous calcium chloride, followed by distillation over phosphorus pentoxide. The remaining reagents were commercially available and were used as supplied. A Thomas Hoover capillary melting point

apparatus was used for all melting points which are uncorrected. All IR spectra were recorded on a Perkin Elmer 1600 using a matrix of KBr. The  $^1\text{H}$  NMR spectra were obtained using a General Electric QE-300. The mass spectra were determined using a Hewlett Packard 5995A MS instrument with a direct insertion probe (DIP).

**Typical Procedure.**- To a three necked 25 mL flask equipped with a mechanical stirrer and reflux condenser was added ( $\pm$ )-flumequine (1, 0.95 g, 3.6 mmoles), 3 mL of chloroform, and 5.14 g (11.9 mmoles) of PPE. The contents of the flask were cooled to  $0^\circ\text{C}$  and the atmosphere was replaced with gaseous ammonia. The flask was heated for 45 hrs and temperature controlled to remain at  $119\text{--}123^\circ\text{C}$  using a digital controller, leading to subsequent loss of chloroform. After cooling, 50 mL of 1 M NaOH was added and the resulting slurry was suction filtered and the solid was washed with water leading to a yellow powder after drying. The yellow powder and PPE (7.6 g, 17.6 mmoles) were added to a flask equipped with a mechanical stirrer. The flask was purged with nitrogen and heated for 90 minutes and temperature controlled to remain at  $120^\circ\text{C}$  with a digital controller. After cooling, 100 mL of 1 M HCl was added to the contents of the flask and the solid obtained was collected. The solid, mp.  $232\text{--}236^\circ\text{C}$ , (weight of 0.59 g) was purified by column chromatography (silica gel, ethyl acetate/chloroform 7:3) to give 0.57 g (65%) of product as a beige powder, mp.  $242\text{--}243^\circ\text{C}$ .  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz):  $\delta$  1.39 (d, 3 H), 2.10 (m, 2 H), 3.06 (m, 2 H), 4.65 (m, 1 H), 7.68 (m, 2 H), 8.88 (s, 1 H); IR (KBr pellet,  $\text{cm}^{-1}$ ) 3036.8, 2966.2, 2942.7, 2225.9, 1631.7, 1601.7; mass spectrum  $m/z$  (% rel intensity) 242 ( $\text{M}^+$ , 48), 228 (15), 227 (100), 226 (15), 213 (19).

*Anal.* Calcd for  $\text{C}_{14}\text{H}_{11}\text{FN}_2\text{O}$ : C, 69.41; H, 4.58; N, 11.56. Found: C, 69.33; H, 4.75; N, 11.51

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## REFERENCES

1. W. Peters, "Chemotherapy and Drug Resistance in Malaria", p 23, Academic Press: London and New York, 1970.
2. (a) F. Himo, Z. P. Demko, L. Noodleman, and K. B. Sharpless, *J. Am. Chem. Soc.*, **125**, 9983 (2003). (b) F. Himo, Z. P. Demko, L. Noodleman, and K. B. Sharpless, *J. Am. Chem. Soc.*, **124**, 12210 (2002). (c) Z. P. Demko and K. B. Sharpless, *Angew. Chem. Int. Edit.*, **41**, 2113 (2002). (d) Z. P. Demko and K. B. Sharpless, *Angew. Chem. Int. Edit.* **41**, 2110 (2002). (e) Z. P. Demko and K. B. Sharpless, *Org. Letters*, **4**, 2525 (2002). (f) Z. P. Demko and K. B. Sharpless, *J. Org. Chem.*, **66**, 7945 (2001). (g) Z. P. Demko and K. B. Sharpless, *Org. Letters*, **3**, 4091 (2001).
3. (a) K. Koguro, T. Oga, S. Mitsui, and R. Orita, *Synthesis*, 910 (1998). (b) R. N. Butler, "Advances in Heterocyclic Chemistry", Vol. 21, p. 323, Academic Press: New York, 1977.

4. (a) K. Korthals, Heterocyclic Antibiotics: Conversion of Carboxylic Acids to Nitriles, M.S. Thesis, Central Michigan University, Mount Pleasant, MI 2000. (b) D. S. Bose and B. Jayalakshmi, *J. Org. Chem.*, **64**, 1713 (1999). (c) J. C. Feng, B. Liu, Y. Liu, and C. C. Li, *Synth. Commun.*, **26**, 4545 (1996).
5. (a) Y. Kanaoka, T. Kuga, and K. Tanizawa, *Chem. Pharm. Bull.*, **18**, 397 (1970). (b) Y. Kanaoka, T. Hamada, and O. Yonemits, *Chem. Pharm. Bull.*, **18**, 587 (1970). (c) T. Imamoto, T. Takaoka, and M. Yokoyama, *Synthesis*, 142 (1983). (d) M. Yokoyama, S. Yoshida, and T. Imamoto, *Synthesis*, 591 (1982).
6. (a) P. M. Gilis, A. Haemers, and W. Bollaert, *Eur. J. Med. Chem.*, **15**, 499 (1980). (b) T. Nagasaki, Y. Katsuyama, and H. Minato, *J. Labelled Compd. Radiopharm.*, **12**, 409 (1976). (c) R. M. Carr and D. R. Sutherland, *J. Labelled Comp. Radiopharm.*, **34**, 961 (1994).

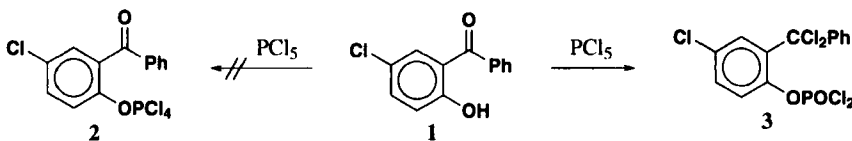
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## REACTION OF 5-CHLORO-2-HYDROXYBENZOPHENONE WITH PHOSPHORUS OXYCHLORIDE AND RELATED REACTIONS

Submitted by A. G. Pinkus\*, Tsung C. Chang, and Lily Y. C. Meng  
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5-Chloro-2-hydroxybenzophenone (**1**) has been shown<sup>1</sup> to react with phosphorus pentachloride to yield the substituted phenylphosphorodichloridate (**3**) rather than the tetrachlorophosphate (**2**) as would be expected<sup>2-4</sup> on the basis of previously reported reactions of  $\text{PCl}_5$  with phenols (*Scheme 1*). More conclusive substantiation of these findings is provided in the present communication.



**Scheme 1**

5-Chloro-2-hydroxybenzophenone (**1**) reacted at the hydroxy group with phosphorus oxychloride to give the phenylphosphorodichloridate (**4**) which, upon treatment with phosphorus pentachloride, afforded compound **3**. Reaction of **3** with phenol occurred at phosphorus to yield