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General methodology for synthesis of fused tricyclic oxazino-2-quinolones under phase-transfer catalyzed conditions

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Abstract—A one-pot synthesis of substituted oxazino-2-quinolones is described. The cornerstone of this methodology involves PTC catalyzed addition of an ethylene dihalide to a quinol to generate the corresponding *O*-alkylated intermediate in situ followed by ring closing and subsequent formation of a carbonyl group in the oxazinoquinolone in a one-pot sequence.

Quinolone antibiotics have gained wide acceptance for the treatment of various bacterial infections.[1] Their mode of action is believed to involve inhibition of bacterial DNA gyrase, an enzyme essential for DNA replication.[2–6] Recent trends in drug research includes interest in preparing and testing analogues or enantiomers of drugs that are known to exert their pharmacological action via specific receptors or enzymes.[7] Since the discovery of nybomycin,[8,9] a number of quinolone antibacterials has been developed. The core moieties of these analogues, in general, are either 2-quinolones or 4-quinolones, and few fused tricyclic analogues have been found to possess useful antibacterial activity. Some of the more prominent exceptions are nybomycin[10–12] (**1**), methyl flumequine[13] (**2**), and ofloxacin[14–16] (**3**). Among these, nybomycin (**1**) and ofloxacin (**3**) contain fused 1,4-oxazolo- and 1,4-oxazino-ring systems, respectively. The most striking structural feature in these heterocycles is the saturated linkage between a nitrogen and an oxygen, which is uncommon in the literature. The published route adopted for the preparation of these molecules is rather lengthy.[11,17] Industry requires the development of methodologies exhibiting high yields, low cost, operational simplicity, mild reaction conditions, and environmental care[18] and it has been recognized that PTC reactions can be a potential and efficient methodology to achieve these characteristics.[19–21]

In continuation of our search for newer molecules for DNA topoisomerase I and II activity,[22,23] we came across a novel finding that may be exploited for the preparation of 2-quinolone analogues of greater potency and with fewer side effects. In the present communication, we disclose methodology for a one-pot synthesis of 1,4-oxazino-2-quinolones from 8-hydroxyquinoline **4** and its 5-chloro- **5**, 5,7-dibromo- **6**, and 2-methyl- **7** analogues, as model substrates and 1,2-dichloroethane as solvent *cum* reactant (Schemes 1 and 2) The reactions were carried out using catalytic amounts of a commercially available quaternary ammonium halide as PTC in the presence of an inorganic base. A literature survey revealed few reports on the synthesis of fused tricyclic 2-quinolones. Most of the methodologies involve multi-step sequences and rely on the *O*-alkylation of 8-hydroxy-2-quinolone forming an intermediate, which on subsequent intramolecular nucleophilic substitution affords the fused quinolone.[11] In our approach, we reacted 8-hydroxyquinoline **4** with 1,2-dichloroethane in 10% sodium hydroxide in the presence of tetrabutylammonium bromide. The product **8**[24] was obtained in fairly good yield (42%) as a single isomer and was deduced to have the molecular formula $C_{11}H_9NO_2$ by elemental and mass spectral analysis. The IR spectrum exhibited a strong absorption band at 1666 cm^{-1} suggesting an amide carbonyl group in the molecule. The ^1H NMR spectrum of **8** displayed signals

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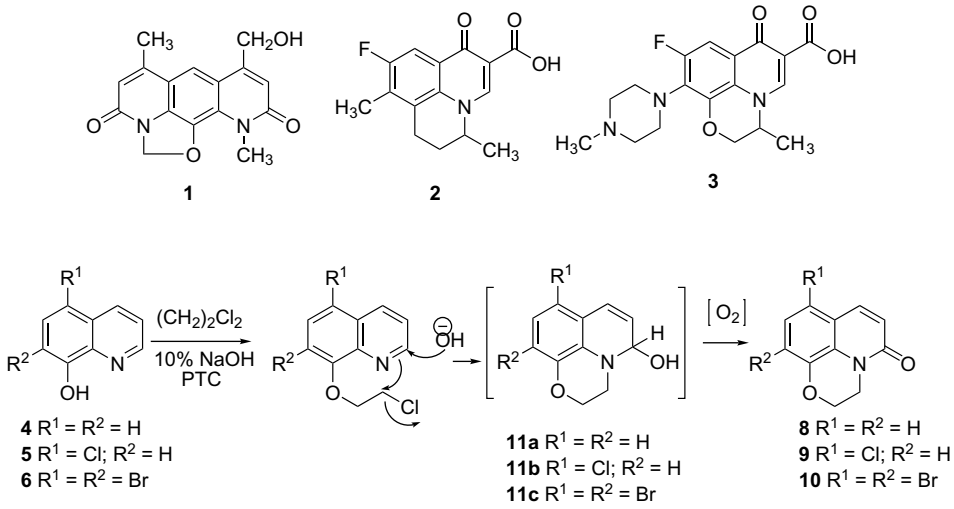
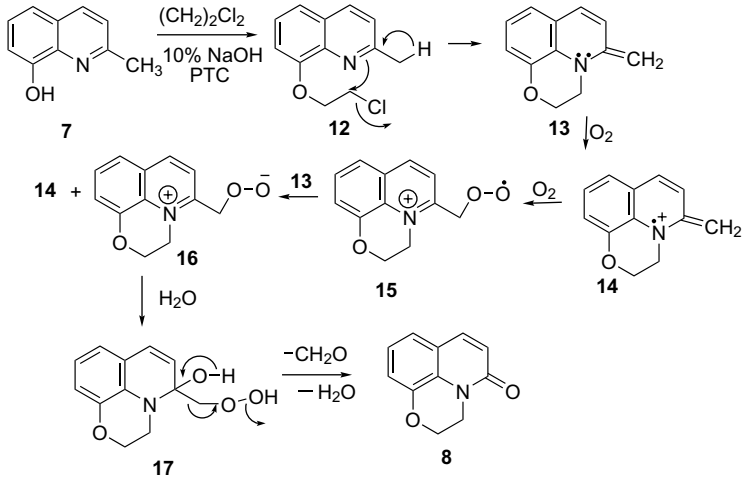


Scheme 1.



Scheme 2.

corresponding to two methylenes, as two distinct triplet like signals at δ 4.28 and 4.38. The presence of two sp^3 methylene signals at δ 40.5 and 64.1 and a quaternary carbonyl signal at δ 160.5 in the ^{13}C NMR spectrum of **8** suggested the linking of one methylene with nitrogen and the other with oxygen. A careful comparison of the observed chemical shifts with those of closely related compounds[12] suggested the formation of a bridged quinolone, that is, a novel oxazino-2-quinolone.

A plausible mechanism for the formation of the novel oxazinoquinolone is shown in Scheme 1. We presume that the formation of **8** involves the condensation of 8-hydroxyquinoline **4** with 1,2-dichloroethane to produce the intermediate **11**, which on aerial oxidation may lead to **8**. It is worthy of mention that no reaction was observed in the absence of a PTC, and the addition of a catalytic amount of PTC produced a dramatic transformation in this reaction system.

To establish the generality of this reaction, substituted 8-quinolinols were studied as substrates. Thus, carrying out the reaction with **5** and **6**, following the same reaction parameters as that of **4**, afforded substituted oxazino-2-quinolones **9**[25] and **10**[26] in ~32% and 35% yields, respectively[27] (Scheme 1). However, when the reaction was attempted with 2-methyl-8-hydroxyquinoline **7** following the same reaction parameters as with **4**, **5**, and **6**, the product formed (yield, 50%) displayed no aromatic methyl signal in its ^1H and ^{13}C NMR spectrum; rather it displayed signals of two methylenes and an amide carbonyl carbon. To our surprise, all the characteristic signals in its IR, ^1H and ^{13}C NMR, and mass spectrum were found to be identical with those of **8**, formed from **4** (spectral comparison). It may be mentioned that Arrault et al.[28] carried out a similar reaction of 2-methyl-8-hydroxyquinoline with 2,3-dibromopropanoate in acetone under reflux conditions in the presence of potassium carbonate and obtained a mixture of two uncyclized products.

The mechanism of formation of **8** from **7** most likely involves the participation of aerial oxygen, but a photochemical route appeared unlikely. Indeed the reaction

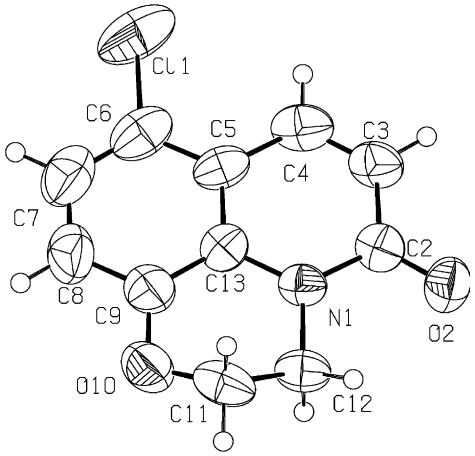


Figure 1. ORTEP-representation of 8-chloro-2*H*,3*H*,5*H*-1,4-oxazino-[6,5,4-*i*,*j*]quinolin-5-one **9**; the displacement ellipsoids are drawn at a probability of 50%.

was found to proceed equally well in the dark, though the product was not formed when the reaction was carried out under argon. A literature survey revealed that the reaction of steroidal dienamines with oxygen has been studied mechanistically and a free radical chain process was suggested to occur.[29] The reaction was found to be catalyzed by metal ions like Cu^{2+} and Fe^{3+}, which are able to accept an electron from the enamine system. We therefore carried out the reaction in the presence of a catalytic amount of $CuCl_2$. This resulted in a much higher yield (85%) of the product with a shorter reaction time (4 h) also. We therefore propose that the present reaction also proceeds through a radical chain process as shown in Scheme 2.[30]

Although, the spectral data were of help in establishing the structures of the products, considering the unusual course of the reaction a single crystal X-ray crystallographic analysis of **9** was performed for the unambiguous determination of its structure.[31] An ORTEP representation[32] of the molecule is given in Figure 1. It may be mentioned that the ethylene bridge in these tricyclic oxazino-2-quinolones remains unaffected on refluxing with 47% hydriodic acid for ~2 h as in the case of nybomycin[11] **1**. To the best of our knowledge this is the first report of a synthesis of tricyclic oxazino-2-quinolone analogues in a one-pot sequence.[33]

In conclusion, we have described a one-pot synthesis[34] of tricyclic oxazino-2-quinolones under phase-transfer catalyzed conditions from readily available starting materials. The preparative simplicity of this method, we feel, will find general applicability in the synthesis of other fused tricyclic antibiotics.

Acknowledgements

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References and notes

1. Gootz, T. D.; Brighty, K. E. *Med. Res. Rev.* **1996**, *16*, 43–62.
2. Llorente, B.; Leclerc, F.; Cedergren, R. *Bioorg. Med. Chem.* **1996**, *4*, 61–71.
3. Ferrero, L.; Cameron, L. B.; Manse, B.; Lagneaux, D.; Crouzet, J.; Famechon, A.; Blanche, F. *Mol. Microbiol.* **1994**, *13*, 641–653.
4. Wentland, M. P.; Lesher, G. Y.; Reuman, M.; Gruett, M. D.; Sing, B.; Aldous, S. C.; Dorff, P. H.; Rake, J. B.; Coughlin, S. A. *J. Med. Chem.* **1993**, *36*, 2801–2809.
5. Elsea, S. H.; Osheroff, N.; Nitiss, J. L. *J. Biol. Chem.* **1992**, *267*, 13150–13153.
6. Reddy, P. G.; Baskaran, S. *Tetrahedron Lett.* **2001**, *42*, 6775–6777.
7. Chu, D. T. W.; Plattner, J. J.; Katz, L. *J. Med. Chem.* **1996**, *39*, 3853–3874.
8. Strelitz, F.; Flon, H.; Asheshov, D. N. *Proc. Natl. Acad. Sci. U.S.A.* **1955**, *41*, 620.
9. Eble, T. E.; Boyack, G. A.; Large, C. M.; DeVries, W. H. *Antibiot. Chemother.* **1958**, *8*, 627.
10. Rinehart, K. L., Jr.; Leadbetter, G.; Larson, R. A.; Forbis, R. M. *J. Am. Chem. Soc.* **1970**, *92*, 6994–6996.
11. Forbis, R. M.; Kenneth, L.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 5003–5013.
12. Nadzan, A. M.; Kenneth, L.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 4647–4654.
13. Gerster, J. F.; Rohlfing, S. R.; Pecore, S. E.; Winandy, R. M.; Stern, R. M.; Landmesser, J. E.; Olsen, R. A.; Gleason, W. B. *Abstracts 25th Interscience Conference on Antimicrobial Agents and Chemotherapy*, Minneapolis, MN, 1985, *114*, Abstract 134.
14. Seiyaku, D. *Drugs Future* **1983**, *8*, 395.
15. Hayakawa, I.; Hiramitsu, T.; Tanaka, Y. *Chem. Pharm. Bull.* **1984**, *32*, 4907–4913.
16. Tanaka, Y.; Sujuki, N.; Hayakawa, I.; Sujuki, K. *Chem. Pharm. Bull.* **1984**, *32*, 4923–4928.
17. Mitscher, L. A.; Sharma, P. N.; Chu, D. T. W.; Shen, L. L.; Pernet, A. G. *J. Med. Chem.* **1987**, *30*, 2283–2286.
18. Arai, S.; Nakayama, K.; Hatano, K.; Shioiri, T. *J. Org. Chem.* **1998**, *63*, 9572–9575.
19. Farina, F.; Maestro, M. C.; Martin, M. V.; Soria, M. L. *Tetrahedron* **1987**, *43*, 4007–4014.
20. Halpern, M. E. *Phase-Transfer Catalysis. Mechanism and Syntheses*; American Chemical Society: Washington, DC, 1997.
21. Sasson, Y.; Neumann, R. *Handbook of Phase Transfer Catalysis*; Blackie A & M: London, 1997.
22. Mahato, S. B.; Mandal, N. B.; Chattopadhyay, S.; Nandi, G.; Luger, P.; Weber, M. *Tetrahedron* **1994**, *50*, 10803–10812.
23. Ray, S.; Sadhukhan, P. K.; Mahato, S. B.; Mandal, N. B.; Majumder, H. *Biochem. Biophys. Res. Commun.* **1997**, *230*, 171–175.
24. 2*H*,3*H*,5*H*-1,4-Oxazino[6,5,4-*i*,*j*]quinolin-5-one (**8**). Mp 97 °C; IR: ν_{max} cm^{-1} 3019, 1666, 1590, 1476, 1459, 1265, 1025, 835, and 734; MS: *m*/*z* 188 $[M+H]^+$, 187 $[M^+]$; ^1H NMR: δ 4.28 (2H, t, J = 4.5 Hz, H-2), 4.38 (2H, t, J = 4.5 Hz, H-3), 6.69 (1H, d, J = 9.6 Hz, H-6), 7.13 (3H, m, H-8, 9, 10), and 7.7 (1H, d, J = 9.6 Hz, H-7); ^{13}C NMR: δ 40.5 (t, C-3), 64.1 (t, C-2), 117.3 (d, C-10), 121.2 (d, C-8), 121.4 (s, C-7a), 122.0 (d, C-6), 123.1 (d, C-9), 127.2 (s, C-11a),

139.5 (d, C-7), 143.6 (s, C-11), and 160.6 (s, C-5) (Anal. Found: C, 70.54; H, 4.81; N, 7.51%; $C_{11}H_9NO_2$ requires C, 70.58; H, 4.85; N, 7.48%).

25. 8-Chloro-2*H*,3*H*,5*H*-1,4-oxazino[6,5,4-*i*,*j*]quinolin-5-one (**9**). Mp 156 °C; IR: ν_{max} cm^{-1} 3442, 2954, 1674, 1583, 1455, 1267, and 1211; MS: *m*/*z* 224 [$(M+H)^+$ for Cl^{37}, 27]; 222 [$(M+H)^+$, Cl^{35}, 86]; ^1H NMR: δ 4.26 (2H, t, $J = 4.5$ Hz, H-2), 4.37 (2H, t, $J = 4.5$ Hz, H-3), 6.78 (d, 1H, $J = 9.9$ Hz, H-6), 7.01 (d, 1H, $J = 8.7$ Hz, H-10), 7.16 (d, 1H, $J = 8.7$ Hz, H-9), and 8.10 (d, 1H, $J = 9.9$ Hz, H-7); ^{13}C NMR: δ 40.4 (t, C-3), 64.1 (t, C-2), 117.7 (d, C-10), 118.8 (s, C-7a), 121.4 (s, C-8), 122.8 (d, C-6), 123.4 (d, C-9), 124.8 (s, C-11a), 136.0 (d, C-7), 142.5 (s, C-11), and 160.1 (s, C-5) (Anal. Found: C, 59.58; H, 3.60; N, 6.29%; $C_{11}H_8ClNO_2$ requires C, 59.61; H, 3.64, N, 6.32%).
26. 8,10-Dibromo-2*H*,3*H*,5*H*-1,4-oxazino[6,5,4-*i*,*j*]quinolin-5-one (**10**). Mp 235 °C; IR: ν_{max} cm^{-1} 1669, 1570, 1450, 1360, 1323, 1259, 1132, 1028, and 832; MS: *m*/*z* 370, 368, 366 ($[M+Na]^+$ for Br isotopes); ^1H NMR: δ 4.29 (2H, m, H-2), 4.47 (2H, m, H-3), 6.78 (1H, d, $J = 9.9$ Hz, H-6), 7.62 (1H, s, H-9), and 8.03 (1H, d, $J = 9.9$ Hz, H-7); ^{13}C NMR: δ 40.3 (t, C-3), 64.7 (t, C-2), 112.0 (s, C-8), 114.2 (s, C-10), 119.3 (s, C-7a), 123.1 (d, C-6), 128.7 (s, C-1a), 129.8 (d, C-9), 138.4 (d, C-7), 140.4 (s, C-11), and 159.9 (s, C-5) (Anal. Found: C, 38.39; H, 2.16; N, 4.18%; $C_{11}H_7Br_2NO_2$ requires C, 38.30; H, 2.05; N, 4.06%).
27. Other 1,ω-dihalo derivatives of methane, propane, butane, and pentane did not produce the cyclized products, but yielded 1,ω-bis-(quinolyloxy) alkanes (unpublished work).
28. Arrault, A.; Guillaumet, G.; Léger, J.-M.; Jarry, C.; Mérour, J.-Y. *Synthesis* **2002**, 1–6.
29. Malhotra, S. K.; Hostynek, J. J.; Lundin, A. F. *J. Am. Chem. Soc.* **1968**, *90*, 6565–6566.
30. The authors thank the referees for suggestions regarding the mechanism.
31. The tricyclic molecule consists of two planar six membered rings (N1, C2, ... C13 and C5, C6, ... C13).The third ring is nonplanar (C9, O10, ... C13) and adopts an envelope form with C11 as the out-of-plane atom [Cremer–Pople puckering parameters (Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354): $Q = 0.455(5)$ Å, $\phi = 111.8(8)°$, $\theta = 127.4(6)°$]. If a least squares plane is calculated through all the ring atoms, except C11, the average deviation of contributing atoms is 0.03 Å. The double bond character of the C3–C4 bond is supported by its short length of 1.327(8) Å. The C–Cl bond length of 1.738(7) Å is comparable to corresponding bond lengths in other chlorinated benzene derivatives (Boese, R.; Kirchner, M. T.; Dunitz, J. D.; Filippini, G.; Gavezzotti, A. *Helv. Chim. Acta* **2001**, *94*, 1561). All further bond lengths and angles are as expected. CCDC 231307 (Deposition No.) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).
32. Johnson, C. K. ORTEP II, Report ORNL-5138, Oak Ridge National Laboratory, Tennessee, USA, 1976.
33. The scope of this reaction with more substrates will be the subject of future communications.
34. General procedure: Appropriate amounts (0.02, 0.025, or 0.03 mol) of 8-hydroxyquinoline **4**, and its 5-chloro- **5**, 5,7-dibromo- **6**, and 2-methyl- **7** derivatives were dissolved in ~10 mL of dichloroethane. Aq NaOH solution (10%, 50 mL) was added to the solution at ambient temperature followed by 1 mmol of tetrabutyl ammonium bromide. The mixture was stirred continuously for 24–48 h. After completion of the reaction (monitored by TLC), the contents were transferred to a separating funnel and the organic layer was separated, washed free from alkali with water, dried over anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel (E. Merck) using mixtures of petroleum ether (60–80°) and chloroform in different ratios.