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Oxidative Access to Quinolinone Derivatives with Simultaneous Rearrangement of Functional Groups

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Received 27 September 2007

Abstract: Hypervalent iodine-mediated oxidation of aromatic compounds carrying methoxyamide side chains provided the corresponding quinolinones. The reactive point was at the *para* position to electron-donating groups (such as a MeO group) in the aromatic ring. Introduction of AcO or halogen groups to this position resulted in a cyclization, concomitant with rearrangement of the functional group.

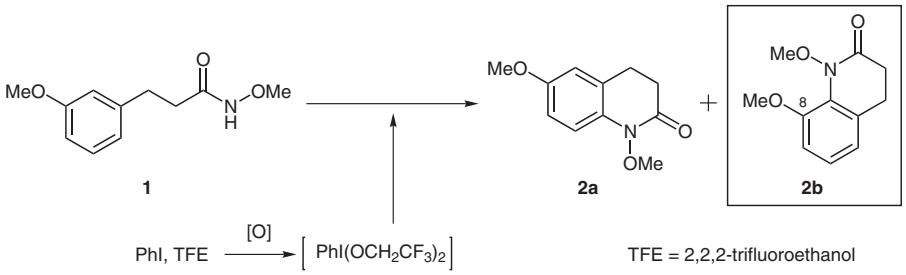
Key words: quinolinone synthesis, oxidations, cyclizations, rearrangements, hypervalent iodine

Quinoline alkaloids, widely distributed in nature, possess diverse biological activities. As part of major efforts to acquire valuable chemotherapeutic agents, a safe and effective synthetic methodology for quinoline derivatives has been elaborated as an alternative conventional approach.[1] We recently attained oxidative construction of quinolinones with a hypervalent iodine reagent electrochemically generated from iodobenzene in 2,2,2-trifluoroethanol (TFE) (Scheme 1), during synthetic investigation of bioactive natural products.[2] Quinoline moieties, possessing an oxygen function at the C-8 position, have been found in several biologically important molecules.[3] During elaboration to construct the C-8 substituted quinolinones, interesting rearrangement properties of aromatic substituents were observed. We disclose herein our investigation progress.

Previously, we reported oxidative cyclization of **1** using a hypervalent iodine species generated by anodic oxidation, leading to the quinolinones **2a** and **2b** in 66% and 10% yields, respectively.[2] Electrophilic attack of the methoxyamide moiety at the *para* position to the MeO group provided the major product **2a**, whereas the desired **2b**, carrying oxygen function at C-8, was produced as a minor product by cyclization at the corresponding *ortho* position. To improve yields of the **2b**-type product by introduction of a functional group *para* to the MeO group, **3** was submitted to cyclization conditions.[4] We expected that **3** carrying the only reactive point at the *ortho* position might produce predominantly **4b** due to blocking of the *para* position with an electron-withdrawing AcO group. However, against expectations, the oxidation exclusively provided **4a** by *para* cyclization, concomitant with rearrangement of the AcO group (Scheme 2).

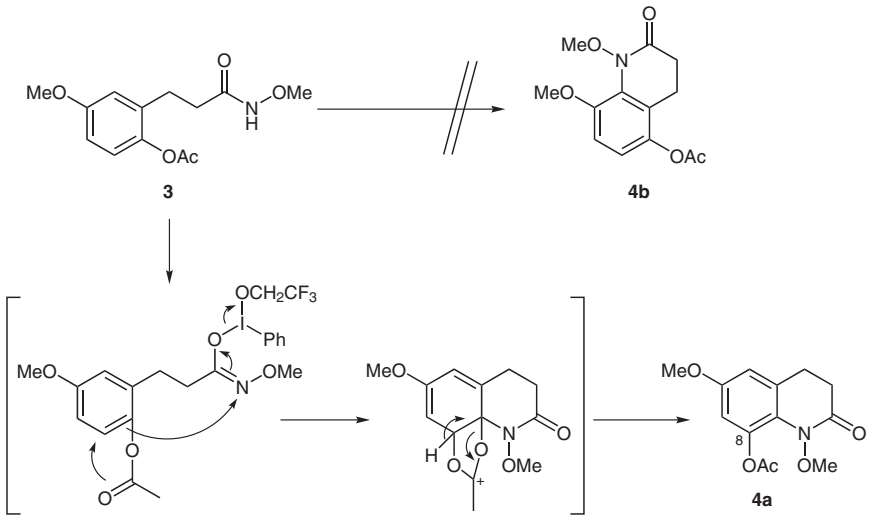
Despite the unexpected result, this methodology might be applicable for construction of the quinoline skeletons with C-8 oxygen functions. Therefore, details of this rearrangement were further examined. Oxidation of **5** carrying a Cl group at the *para* position to the MeO group provided **6** in 68% yield through a reaction pathway similar to that of **4a**. In contrast to **5**, the bromine derivative **7** afforded a mixture of **8a** and **8c**, the latter might have been produced through an attack of Br^+ generated in situ. Whereas derivatives having AcO or halogen groups at the *para* position effected *para* cyclization with rearrangement of the functional groups, oxidation of **9** carrying a CN group with relatively strong electron-withdrawing properties, resulted in the desired cyclization at the *ortho* position to the MeO group to give **10b** in low yield.[5] From these findings, electron-withdrawing properties of the AcO group may be accordant with this cyclization reaction to efficiently produce C-8 oxygenated quinolinones.

Additionally, we inspected the roles of functional groups located at the *meta* position to the alkyl chain. In contrast to the methoxy derivative **1** leading to a mixture of **2a** and **2b**, oxidation of the benzyl derivative **11** smoothly pro-



Scheme 1 Conversion of the methoxyamide **1** into the quinolinones

SYNLETT 2008, No. 1, pp 0134–0136
Advanced online publication: 11.12.2007
DOI: 10.1055/s-2007-1000829; Art ID: U09107ST



Scheme 2 Synthesis of **4a** with the functional group rearrangement

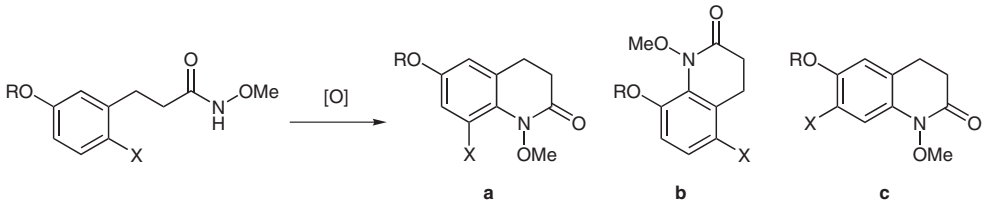
ceeded to give **12a** in 82% yield. Introduction of an AcO group at the *para* position in **13** effected rearrangement of the acyloxy group under the oxidation conditions to furnish **14a** in 84% yield.

Dominant regioselectivity to cyclize at the *para* position to the BnO group might be evoked by steric hindrance of the bulky benzyl substituent, whereas in the case of **1**, carrying the rather small MeO group, a complex mixture was obtained. On the other hand, upon use of AcO groups at the *meta* position, **15** and **16** provided complex mixtures. Accordingly, the aromatic substituents featuring electron-donating properties significantly contribute to the cyclization reaction, particularly the benzyl group as a functional group of choice, not only for high regioselectivity, but also for ready handling in practical synthesis.

As mentioned above, we employed our own hypervalent iodine reagent electrochemically generated from iodobenzene. In addition to being safe, inexpensive, and stable, its reactivity can stand comparison with phenyliodine(III) bis(trifluoroacetate) (PIFA), a representative hypervalent iodine oxidant (Table 1).

In conclusion, oxidation of aromatic derivatives carrying electron-donating groups at the *meta* position to the methoxyamide side chain and electron-withdrawing groups such as AcO, Br, and Cl, effected cyclization to provide the corresponding quinolinone derivatives. The cyclization reaction by our electrochemically generated hypervalent iodine reagent provided the quinolinones **2a**, **4a**, **6a**, **8a**,**c**, **10b**, **12a**, and **14a** in good yields with rearrangement of the functional groups. The hypervalent iodine oxidant

Table 1 Oxidation of the Methoxyamides Leading to the Corresponding Quinolinones



Entry	Substrate[5]	Product [yields (%)][5]	
		Preoxidized iodobenzene	PIFA
1	**3** (R = Me, X = OAc)	**4a** (83)	**4a** (76)
2	**5** (R = Me, X = Cl)	**6a** (68)	**6a** (43) + **6c** (15)[6]
3	**7** (R = Me, X = Br)	**8a** (32) + **8c** (26)	**8a** (26) + **8c** (32)
4	**9** (R = Me, X = CN)	**10b** (17)	**10b** (44)
5	**11** (R = Bn, X = H)	**12a** (82)	–
6	**13** (R = Bn, X = OAc)	**14a** (84)	**14a** (75)
7	**15** (R = Ac, X = OAc)	complex mixture	
8	**16** (R = Ac, X = Cl)	complex mixture	

in fact showed comparable results to PIFA. Synthetic investigation of several bioactive molecules using this oxidation protocol is now in progress.

Acknowledgment

Part of this work was supported by Scientific Research C from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References and Notes

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(4) **General Procedure for Oxidation with Preoxidized Iodobenzene**: A solution of iodobenzene (0.5 mmol, 2 equiv mol) in TFE (25 mL) containing $LiClO_4$ was electrolyzed (CCE at 0.3 mA/cm^2, 2.5 F/mol, a glassy carbon beaker as an anode and a platinum wire as a cathode). After electrolysis, the substrate (0.25 mmol) was added to the mixture. After stirring for 30 min, the reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on preparative TLC to give products.

(5) Selected spectroscopic data of new compounds **3**–**16**. Compound **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (br s, 1 H), 6.92 (d, *J* = 8.8 Hz, 1 H), 6.74–6.77 (m, 2 H), 3.75 (s, 3 H), 3.62 (s, 3 H), 2.84 (t, *J* = 7.6 Hz, 2 H), 2.27–2.31 (m, 5 H). **4a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (d, *J* = 2.8 Hz, 1 H), 6.49 (d, *J* = 2.8 Hz, 1 H), 3.78 (s, 3 H), 3.73 (s, 3 H), 2.87 (t, *J* = 7.2 Hz, 2 H), 2.66 (t, *J* = 7.2 Hz, 2 H), 2.27 (s, 3 H). Compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (br s, 1 H), 7.22 (d, *J* = 8.8 Hz, 1 H), 6.80 (d, *J* = 3.0 Hz, 1 H), 6.70 (dd, *J* = 3.0, 8.8 Hz, 1 H), 3.75 (s, 3 H), 3.69 (s, 3 H), 3.04 (t, *J* = 7.8 Hz, 2 H), 2.40–2.75 (m, 2 H). HRMS: *m*/*z* [M – MeO] calcd for $C_{10}H_{11}{}^{35}ClNO_2$: 212.0473; found: 212.0454. Compound **6a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (d, *J* = 3.0 Hz, 1 H), 6.64 (d, *J* = 3.0 Hz, 1 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 2.88 (t, *J* = 7.0 Hz, 2 H), 2.67 (t, *J* = 7.0 Hz, 2 H). HRMS: *m*/*z* [M] calcd for $C_{11}H_{12}{}^{35}ClNO_3$: 241.0505; found: 241.0521. Compound **6c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87 (s, 1 H), 6.68 (s, 1 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 2.83 (t, *J* = 7.6 Hz, 2 H), 2.68 (t, *J* = 7.6 Hz, 2 H). Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (br s, 1 H), 7.41 (d, *J* = 8.8 Hz, 1 H), 6.83 (d, *J* = 2.6 Hz, 1 H), 6.66 (dd, *J* = 2.6, 8.8 Hz, 1 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.06 (t, *J* = 7.8 Hz, 2 H), 2.39–2.75 (m, 2 H). HRMS: *m*/*z* [M] calcd for $C_{11}H_{14}{}^{81}BrNO_3$: 289.0136; found: 289.0110. Compound **8a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 2.6 Hz, 1 H), 6.69 (d, *J* = 2.6 Hz, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 2.88 (t, *J* = 7.0 Hz, 2 H), 2.67 (d, *J* = 7.0 Hz, 2 H). HRMS: *m*/*z* [M + H] calcd for $C_{11}H_{13}{}^{79}BrNO_3$: 286.0078; found: 286.0085. Compound **8c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (s, 1 H), 6.73 (s, 1 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 2.88 (t, *J* = 7.0 Hz, 2 H), 2.69 (t, *J* = 7.0 Hz, 2 H). HRMS: *m*/*z* [M + H] calcd for $C_{11}H_{13}{}^{79}BrNO_3$: 286.0079; found: 286.0113. Compound **9**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 6.90 (d, *J* = 2.4 Hz, 1 H), 6.81 (dd, *J* = 2.4, 8.0 Hz, 1 H), 3.84 (s, 3 H), 3.72 (s, 3 H), 3.16 (t, *J* = 7.6 Hz, 2 H), 2.46–2.80 (m, 2 H). HRMS: *m*/*z* [M + H – MeO] calcd for $C_{11}H_{12}N_2O_2$: 204.0897; found: 204.0879. Compound **10b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.4 Hz, 1 H), 6.94 (d, *J* = 8.4 Hz, 1 H), 4.01 (s, 3 H), 3.98 (s, 3 H), 3.14 (t, *J* = 7.6 Hz, 2 H), 2.74 (t, *J* = 7.6 Hz, 2 H). HRMS: *m*/*z* [M + H – MeO] calcd for $C_{11}H_{10}N_2O_2$: 202.0742; found: 202.0769. Compound **11**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.84 (br s, 1 H), 7.29–7.41 (m, 5 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 6.77–6.82 (m, 3 H), 5.02 (s, 2 H), 3.63 (s, 3 H), 2.92 (t, *J* = 7.6 Hz, 2 H), 2.34–2.75 (m, 2 H). Compound **12a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.41 (m, 5 H), 7.11 (d, *J* = 8.8 Hz, 1 H), 6.85 (dd, *J* = 2.4, 8.8 Hz, 1 H), 6.79 (d, *J* = 2.4 Hz, 1 H), 5.02 (s, 2 H), 3.88 (s, 3 H), 2.85 (d, *J* = 7.4 Hz, 2 H), 2.65 (d, *J* = 7.4 Hz, 2 H). Compound **13**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (br s, 1 H), 7.21–7.29 (m, 5 H), 6.70–6.83 (m, 3 H), 4.90 (s, 2 H), 3.50 (s, 3 H), 2.74 (t, *J* = 7.4 Hz, 2 H), 2.14–2.60 (m, 5 H). Compound **14a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.34 (m, 5 H), 6.64 (d, *J* = 2.6 Hz, 1 H), 6.51 (d, *J* = 2.6 Hz, 1 H), 4.94 (s, 2 H), 3.66 (s, 3 H), 2.80 (t, *J* = 7.0 Hz, 2 H), 2.59 (t, *J* = 7.0 Hz, 2 H), 2.20 (s, 3 H). Compound **15**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (br s, 1 H), 7.24 (d, *J* = 8.1 Hz, 1 H), 6.85–6.93 (m, 2 H), 3.59 (s, 3 H), 2.87 (t, *J* = 7.6 Hz, 2 H), 2.24–2.70 (m, 8 H). Compound **16**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (br s, 1 H), 7.31 (d, *J* = 8.4 Hz, 1 H), 6.99 (d, *J* = 2.7 Hz, 1 H), 6.89 (dd, *J* = 2.7, 8.4 Hz, 1 H), 3.64 (s, 3 H), 3.04 (t, *J* = 7.4 Hz, 2 H), 2.25–2.75 (m, 5 H). HRMS: *m*/*z* [M + H] calcd for $C_{12}H_{15}{}^{35}ClNO_4$: 272.0688; found: 272.0690.

(6) This compound was slightly contaminated with **6a**.