CONVENIENT ROUTE TO 2*H*-FURO[3,2-*c*]QUINOLIN-4-ONE FRAMEWORK USING Mn(III)-BASED OXIDATIVE RADICAL CYCLIZATION

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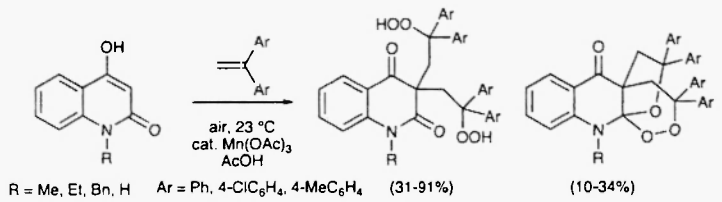
Abstract: The oxidation of a mixture of 1,1-disubstituted ethenes **1** with 4-hydroxy-2-quinolinone derivatives **2** with manganese(III) acetate in boiling glacial acetic acid was investigated. The reaction of 3-substituted quinolinones **2** gave 9b-hydroxy-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*]quinolin-4-ones **3** and 3-(2,2-diarylethenyl)quinoline-2,4-diones **4** in moderate to good yields. On the other hand, 3,5-dihydro-2*H*-furo[3,2-*c*]quinolin-4-ones **5** were mainly produced during the reaction of quinolinones **2** having no substituent at the 3-position. The reaction pathway and the application of the reaction were discussed.

Quinolinones are a very important class of heterocyclic compounds.[1] The quinolinone ring is present in many natural products, and a large number of quinolinone derivatives have displayed interesting biological activity.[2]

Recently, we have found a unique peroxide formation using the manganese(III)-catalyzed aerobic oxidation of 4-hydroxyquinolin-2-ones in the presence of alkenes.[3] The aerobic oxidation gave 3,3-bis(2-hydroperoxyethyl)quinolinediones together with [4.4.3]propellane-type cyclic peroxides. Both peroxides are quite interesting from the standpoint of their antimalarial activity.[4] In connection with our study using the 4-hydroxyquinolin-2-ones, we investigated the oxidation of the substituted 4-hydroxyquinolin-2-one derivatives with manganese(III) acetate in the presence of 1,1-disubstituted ethenes in order to develop a facial construction of the 2*H*-



furo[3,2-*c*]quinolin-4-one framework which was found as the basic skeleton of many natural alkaloids.[1,5] Although the manganese(III)-mediated radical addition of 4-hydroxy-1-methyl-1*H*-quinolin-2-one with some alkenes in the presence of potassium permanganate as a co-oxidant was recently reported,[6] the products were limited and the synthetic applications especially using the substituted 4-hydroxy-1*H*-quinolin-2-ones were not ascertained.

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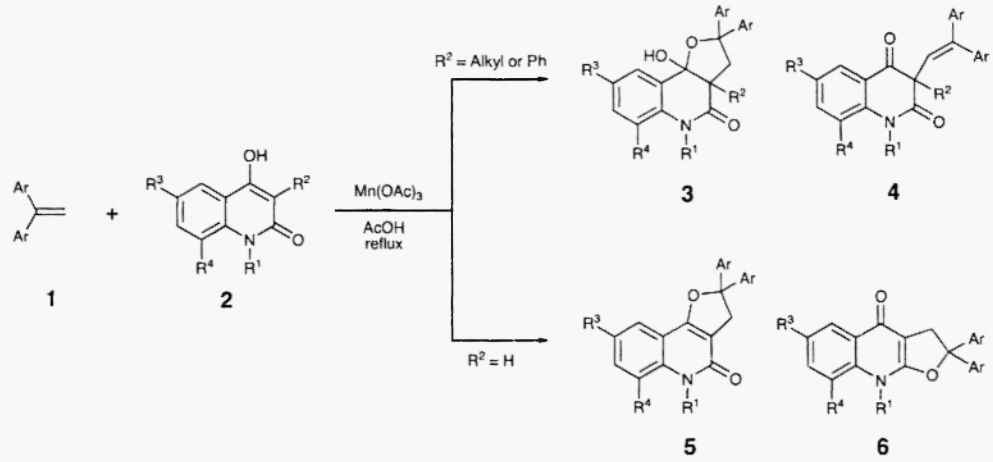
Table 1. Oxidation of Quinolinones **2** with Manganese(III) Acetate in the Presence of Alkenes **1**[a]

Entry	Alkene 1	Quinolinone 2	1:2: Mn(III)[b]	Temp (°C)	Time (min)	Product (Yield/%)[c]			
						3	4	5	6
1	Ar = Ph	$R^1 = R^3 = R^4 = H$, $R^2 = Me$	1:2:3	reflux	1.5	56	25		
2	Ar = Ph	$R^1 = R^3 = R^4 = H$, $R^2 = Me$	1:2:3	reflux	2.5	48	37		
3	Ar = Ph	$R^1 = R^3 = R^4 = H$, $R^2 = Me$	1:2:3	reflux	30		79		
4	Ar = Ph	$R^1 = R^3 = R^4 = H$, $R^2 = Me$	1:2:3	80	24 h		97		
5	Ar = Ph	$R^1 = R^3 = R^4 = H$, $R^2 = Me$	1:2:2:2[d]	23	3.5 h	72	trace		
6	Ar = Ph	$R^1 = R^3 = R^4 = H$, $R^2 = Pr$	1:2:3	reflux	2	51	32		
7	Ar = Ph	$R^1 = R^3 = R^4 = H$, $R^2 = Bu$	1:2:3	reflux	6	36	27		
8	Ar = Ph	$R^1 = R^3 = R^4 = H$, $R^2 = Bu$	1:2:3	reflux	30	trace	78		
9	Ar = Ph	$R^1 = R^3 = R^4 = H$, $R^2 = Ph$	1:2:3	reflux	2	31	20		
10	Ar = 4-ClC_6H_4	$R^1 = R^3 = R^4 = H$, $R^2 = Me$	1:2:3	reflux	2	35	37		
11	Ar = 4-MeC_6H_4	$R^1 = R^3 = R^4 = H$, $R^2 = Me$	1:2:3	reflux	0.5		55		
12	Ar = Ph	$R^1 = Me$, $R^2 = R^3 = R^4 = H$	1:2:3	reflux	3			87	7
13	Ar = Ph	$R^1 = Et$, $R^2 = R^3 = R^4 = H$	1:2:3	reflux	1.5			73	trace
14	Ar = Ph	$R^1 = Pr$, $R^2 = R^3 = R^4 = H$	1:2:3	reflux	1.5			76	
15	Ar = Ph	$R^1 = Bn$, $R^2 = R^3 = R^4 = H$	1:2:3	reflux	3			85	trace
16	Ar = Ph	$R^1 = R^2 = R^3 = R^4 = H$	1:2:3	reflux	2			73	
17	Ar = 4-ClC_6H_4	$R^1 = Me$, $R^2 = R^3 = R^4 = H$	1:2:3	reflux	3			87	12
18	Ar = 4-MeC_6H_4	$R^1 = Me$, $R^2 = R^3 = R^4 = H$	1:2:3	reflux	5			93	trace
19	Ar = Ph	$R^1 = R^2 = R^4 = H$, $R^3 = Me$	1:2:3	reflux	30			44	
20	Ar = Ph	$R^1 = R^2 = R^4 = H$, $R^3 = Cl$	1:2:3	reflux	4			58	
21	Ar = Ph	$R^1 = R^2 = R^4 = H$, $R^3 = F$	1:2:3	reflux	30			74	
22	Ar = Ph	$R^1 = R^2 = R^3 = H$, $R^4 = Me$	1:2:3	reflux	3			67	

[a] The reaction was carried out in acetic acid (25 mL). [b] Molar ratio of alkene **1** (1 mmol), quinolinone **2**, and manganese(III) acetate. [c] Isolated yield based on the alkene **1** used. [d] Copper(II) acetate (2 mmol) was added as a co-oxidant.

We first examined the reaction of 3-methyl substituted quinolinone **2** (R^2 = Me, $R^1 = R^3 = R^4$ = H) with 1,1-diphenylethene (**1**: Ar = Ph) (Table 1, Entries 1-5). The reaction was carried out in glacial acetic acid (25 mL) at reflux temperature using three equivalents of manganese(III) acetate. The oxidant was consumed within 1.5 min, and we obtained 9b-hydroxy-3a-methyl-2,2-diphenyl-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*]quinolin-4-one (**3**)[8] and 3-methyl-3-(2,2-diphenylethenyl)quinoline-2,4-dione (**4**)[9] in 56% and 25% yield, respectively (Entry 1). A similar reaction of the propyl, butyl, and phenyl substituted quinolinones **2** with **1** (Ar = Ph or 4-Cl_6H_4) also gave the corresponding **3** and **4**, respectively (Entries 6, 7, 9, 10). The use of an electron-rich alkene **1** (Ar = 4-MeC_6H_4) resulted in a complex mixture and only the corresponding **4** was isolated (Entry 11). When the reaction was carried out for longer reaction periods, only **4** was isolated (Entries 3, 4, 8). On the other hand, the addition of copper(II) acetate as a co-oxidant[10] to the same reaction mixture led to the predominant formation of **3** (72%) along with a trace amount of **4** without heating (Entry 5).

Quinolinones **2**, which have no substituent at the C-3 position, reacted with alkenes **1** under the manganese(III) oxidation conditions to give thermodynamically stable angular 3,5-dihydro-2*H*-furo[3,2-*c*]quinolin-4-ones **5** in good yields (Entries 12-22).[6] In some cases, trace amounts of the isomeric 3,9-dihydro-2*H*-furo[2,3-*b*]quinolin-4-ones were detected (Entries 13, 15, 17, 18).

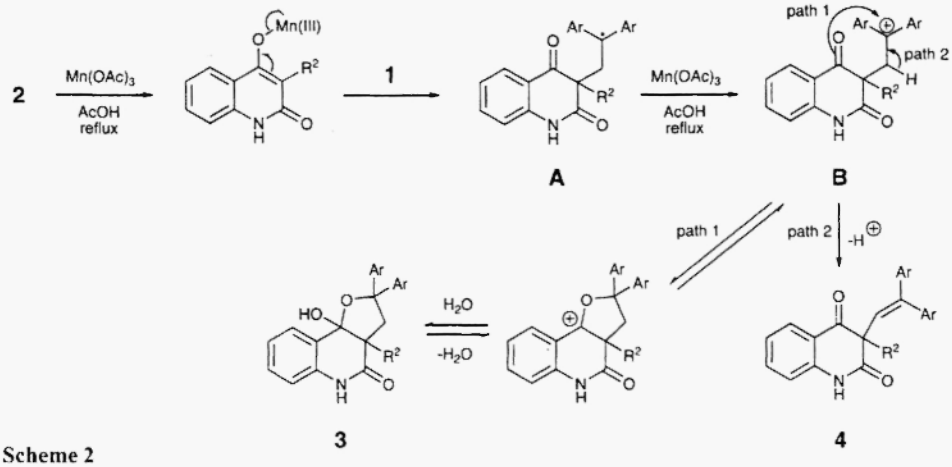


Scheme 1

In order to prove the reaction pathway, the 3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*]quinolin-4-one **3** (Ar = Ph, R^2 = Me, $R^1 = R^3 = R^4$ = H) was heated under reflux in glacial acetic acid for 30 min, giving the corresponding quinoline-2,4-dione **4** in 76% yield. Under reflux conditions, although the manganese(III) could oxidize tertiary carbon radicals **A** to afford the corresponding carbocations **B** which cyclized to give **3**, the deprotonation of the formed cations **B** would also be accelerated, affording **4**. On the other hand, the use of the co-oxidant, copper(II) acetate, which could easily oxidize the tertiary radicals **A** at room temperature,[10] favored the *O*-cyclization to produce only **3**. These results support the mechanism for the formation of **3** and **4** as depicted in Scheme 2.

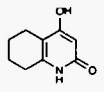
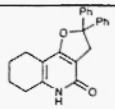
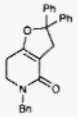
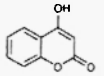
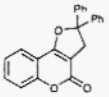
Since the facial construction of 2*H*-furo[3,2-*c*]quinolin-4-one framework using manganese(III)-based oxidation was demonstrated, we applied the same skill to the 4-hydroxypyridin-2-ones and 4-hydroxypyran-2-ones as the substrate. The reactions were conducted under similar reaction conditions to give the desired cyclic products as shown in Table 2.

In summary, it was proved that the use of a stoichiometric amount of manganese(III) acetate in the reaction of six-membered amide quinolinones **2** with 1,1-disubstituted alkenes **1** at reflux temperature resulted in the 2*H*-furo[3,2-*c*]quinolin-4-one derivatives, although the use of a catalytic amount of manganese(III) acetate in the same reaction at 23 °C gave molecular oxygen-included peroxide derivatives in high yields.[3] It was interesting that a similar manganese(III)-based oxidative addition-cyclization did not occur in the reaction of five-membered cyclic amides such as 2,3- and 2,4-pyrrolidinediones with alkenes at elevated temperature,[10] but the substitution products such as **4** were only obtained.



Scheme 2

Table 2. Mn(III)-Based Oxidation of 4-Hydroxydihydropyridin-2-ones and 4-Hydroxypyran-2-ones in the Presence of 1,1-Diphenylethene (**1**)[a]

Entry	Substrate	Time (min)	Product (Yield/%)[b]
1		1	 53
2		1	 47
3		5	 89
4		1	 56

[a] The reaction was carried out in boiling glacial acetic acid (25 mL) at the molar ratio of 1,1-diphenylethene:substrate:$Mn(OAc)_3$ = 1:2:3. [b] Isolated yield based on 1,1-diphenylethene (**1**) used.

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7. A typical procedure is as follows. A mixture of alkene **1** (1 mmol), 4-hydroxy-2-quinolinone **2** (2 mmol), and manganese(III) acetate dihydrate (3 mmol) in glacial acetic acid (25 mL) was heated under reflux until the brown color of manganese(III) disappeared (normally two or three minutes), and then water (25 mL) was added to the reaction mixture. The aqueous reaction mixture was extracted three times with dichloromethane (25 mL). The combined extract was washed with a saturated aqueous solution of sodium hydrogencarbonate, dried over anhydrous sodium sulfate, and then concentrated to dryness. The residue was separated by silica gel TLC, and developed with 4% methanol/dichloromethane. The obtained 2*H*-furo[3,2-*c*]quinolin-4-one derivatives **3** were further purified by recrystallization from methanol.
8. The characterization of **3** (Ar = Ph, $R^1 = R^3 = R^4 = H$, R^2 = Me): Colorless microcrystals (from MeOH); mp 217-225 °C (decompd.); IR (KBr) ν 3500-3400 (NH), 3400-3060 (OH), 1649 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.19 (1H, s, NH), 7.92-6.64 (14H, m, arom H), 3.73 (1H, d, J = 11.89 Hz, H_a-3), 3.42 (1H, s, OH), 2.96 (1H, d, J = 11.89 Hz, H_b-3), 2.07 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C=O), 149.6, 147.0, 135.7 (3C, arom C), 129.5 (5C), 127.8 (2C, arom C), 127.6 (2C, arom C), 126.8, 126.7 (2C, arom C), 126.1 (C-7), 125.9 (C-6), 125.5 (2C, arom C), 125.0, (2C, arom C), 123.5 (arom C), 121.9 (C-8), 102.7 (C-4), 85.9 (Ph-C-Ph), 53.6 (C-3), 46.7 (CH_2), 18.4 (CH_3). Anal. Calcd for $C_{34}H_{31}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.46; H, 5.52; N, 3.80.
9. The characterization of **4** (Ar = Ph, $R^1 = R^3 = R^4 = H$, R^2 = Me): Colorless microcrystals (from MeOH); mp 160-161 °C; IR (KBr) ν 3550-3400 (NH), 1701, 1655 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (1H, s, NH), 7.73-6.80 (14H, m, arom H), 6.42 (1H, s, HC=), 1.79 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 175.9 (C=O), 144.5, 140.8, 140.7, 138.7 (4C, arom C), 135.6 (C-7), 131.1 (C-5), 129.9 (2C, arom C), 128.1 (2C, arom C), 127.7 (C-6), 127.6 (2C, arom C), 127.5, (arom C), 127.4 (arom C), 127.2 (2C, arom C), 123.0 (C-8), 118.2 (CH=C), 116.2 (CH=C), 56.3 (C-3), 27.6 (CH_3). Anal. Calcd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.57; H, 5.31; N, 3.91.
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