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A novel oxidative free radical reaction between 2-hydroxy-1,4-naphthoquinone and β-enamino carbonyl compounds

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Abstract—The manganese(III) initiated oxidative free radical reaction between 2-hydroxy-1,4-naphthoquinone and β-enamino carbonyl compound **2** is described. Enamine radical **5** can be generated effectively from the oxidation of enamine **2** by manganese(III) acetate. Spirolactam **3** was prepared effectively from readily available 2-hydroxy-1,4-naphthoquinone and enamine **2**.

Free radical reactions have become increasingly important in organic synthesis in the last two decades.[1] Electrophilic radicals produced from the manganese(III) acetate oxidation of β-dicarbonyl compounds undergo efficient addition to a C–C double bond.[1d–f,2] These reactions can be performed intermolecularly and intramolecularly. The free radical addition of a carbon center radical to quinones has been reported.[2c–h,3] Enamine radical **5** can be generated effectively from the oxidation of enamine **2** by manganese(III) acetate.[4] This report describes our results on the reaction between 2-hydroxy-1,4-naphthoquinone and β-enamino carbonyl compounds via the manganese(III) acetate initiated oxidative free radical reaction.

We began our studies with the reaction shown in Scheme 1. When 2-hydroxy-1,4-naphthoquinone was treated with β-enamino ketone **2a** and manganese(III) acetate in acetic acid at room temperature, **3a** and **4a**[†] were obtained in 51 and 5% yields, respectively (Table 1, entry a). A possible mechanism for this reaction is outlined in Scheme 1. Initiation occurs with the manganese(III) acetate oxidation of **2a** to produce enamine radical **5a**. Enamine radical **5a** undergoes intermolecular addition followed by oxidation to give **7**, which undergoes either condensation to produce **4a** (path a) or oxidation to generate radical **8** (path b). This radical **8** undergoes 1,2-benzoyl group migration followed by oxidation and intramolecular nucleophilic addition to generate **3a**. The generalities of this reaction are illustrated in Table 1. In all cases, spirolactam **3** was prepared effectively from β-enamino ketone **2** (entries a–g). On the contrary, with β-enamino ester **2h**, the yield of **3h** is rather poor (entry h). With $R^3 = Me$, benzo[*f*]indole **4** was also formed as minor product (except entries g and h). In these two cases, enamine **2** has larger substituents (R^1, R^2). With $R^3 = n$-Bu, this reaction gave **3** as the only product. This is presumably due to the rate of condensation (path a) decreasing as the size of substituents increases.[‡]

A typical experimental procedure is given for the preparation of **3a**. A solution of 151 mg (0.86 mmol) of 2-hydroxy-1,4-naphthoquinone, 4-methylamino-3-penten-2-one [prepared from the reaction of 259 mg (2.59 mmol) of 2,4-pentanedione and 252 mg of 40% aqueous methylamine (3.25 mmol) in 4 ml of ethanol at room temperature for 24 h] and 924 mg (3.45 mmol) of manganese(III) acetate in 10 ml of acetic acid was stirred at room temperature for 24 h. The reaction mixture was then diluted with 100 ml of ethyl acetate, washed with 50 ml of saturated aqueous sodium bisulfite, 3×50 ml portions of water, 3×50 ml portions of aqueous saturated sodium bicarbonate, dried

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† A similar product has been prepared from the reaction between 2-ethylamino-1,4-naphthoquinone and 2,4-pentanedione, see Ref. 2h.

‡ Similar results have been reported, see Ref. 2h.

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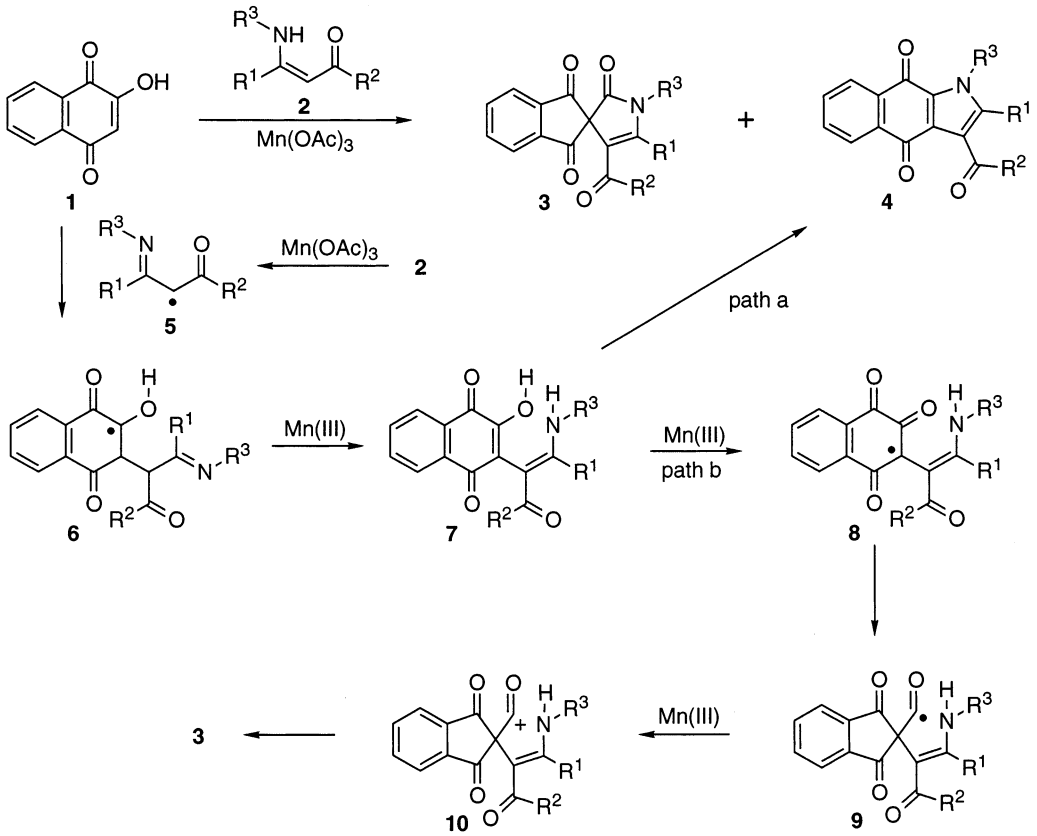

Scheme 1.

(Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with 4:1 dichloromethane–hexane and then 30:1 dichloromethane–ethyl acetate) followed by recrystallization (hexane–ethyl acetate) to give 12 mg (5%) of **4a** followed by 126 mg (51%) of **3a**. Compound **3a**: white crystals; mp 277–278°C; IR ($CHCl_3$) 1715, 1615 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 7.84–7.90 (m, 2H, ArH), 8.01–8.08 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 13.8(q), 27.2(q), 28.9(q), 71.0(s), 119.0(s), 124.4(d), 135.7(d), 143.3(s), 156.1(s), 170.0(s), 189.6(s), 193.2(s). Anal. calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.87; H, 4.70; N, 4.95. Compound **4a**: yellow needles; mp 179–180°C; IR ($CHCl_3$) 1655, 1595, 1500, 1465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.98 (s, 3H, CH_3), 7.60–7.66 (m, 2H, ArH), 8.01–8.07 (m, 2H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.7(q), 31.5(q), 32.7(q), 122.3(s), 124.6(s), 126.0(d), 126.4(d), 129.8(s), 133.0(d), 133.1(d), 133.3(s), 141.9(s), 176.0(s), 180.3(s), 198.8(s). Anal. calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.88; H, 4.91; N, 5.22.

In conclusion, enamine radical **5** can be generated from the reaction between enamine **2** and manganese(III) acetate and it undergoes efficient addition to the C–C double bond of 2-hydroxy-1,4-naphthoquinone. This free radical reaction provides a novel method for the synthesis of spirolactam **3** from readily available 2-hydroxy-1,4-naphthoquinone and β-enamino carbonyl compound. Further work on the oxidative free radical reaction of β-enamino carbonyl compounds is in progress.

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Table 1. Reaction between 2-hydroxy-1,4-naphthoquinone and β-enamino carbonyl compound **2**

Entry	Enamine **2**	Product (yield)	
a	**2a:** R^1=Me, R^2=Me, R^3=Me	**3a** (51%)	**4a** (5%)
b	**2b:** R^1=Me, R^2=Me, R^3=*n*-Bu	**3b** (48%)	**4b** (0%)
c	**2c:** R^1=Me, R^2=Ph, R^3=Me	**3c** (49%)	**4c** (10%)
d	**2d:** R^1=Me, R^2=Ph, R^3=*n*-Bu	**3d** (56%)	**4d** (0%)
e	**2e:** R^1=Me, R^2=*n*-Pr, R^3=Me	**3e** (45%)	**4e**[a]
f	**2f:** R^1=Et, R^2=Et, R^3=Me	**3f** (44%)	**4f**[a]
g	**2g:** R^1=*i*-Pr, R^2=*i*-Pr, R^3=Me	**3g** (52%)	**4g** (0%)
h	**2h:** R^1=*n*-Pr, R^2=OEt, R^3=Me	**3h** (27%)	**4h** (0%)

[a] **4e** and **4f** can not be isolated from the reaction mixture; however, they can be detected by thin-layer chromatography.

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