Manganese(III) Acetate Initiated Oxidative Free Radical Reaction Between 2-Anilino-1,4-naphthoquinones And Diethyl Malonate

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Abstract: A free radical reaction between 2-anilino-1,4-naphthoquinones and diethyl malonate initiated by manganese (III) acetate is described. This reaction provides a novel method for the synthesis of naphtho[2,3-b]quinoline-5,12-diones.

Introduction

Recently, there has been a growing interest in the application of free radical cyclization reactions to the formation of ring systems.[1] The manganese(III) - based oxidative free radical reaction have been studied by several groups.[2,3] These reactions can be performed intermolecularly and intramolecularly. The free radical addition of a carbon center radical to quinones has been reported.[4] This report described our recent result on manganese(III) initiated oxidative free radical reaction between 2-anilino-1,4-naptthoquinones and diethyl malonate.

Results and Discussion

We began our studies with the reaction shown in Scheme I. Thus, treatment of 1,4-naphthoquinone **1a** and diethyl malonate with manganese(III) acetate in glacial acetic acid at 80°C for 2 h gave **2a** in 30% yield. The generality of this reaction is illustrated in Table I. (Method A) This reaction could be proceeded in fair to good yieds expect **2j**. (entry j, R_2=OCH_3) In this case, no desire product could be found. It presumably be ascribed to the oxidation of much electron rich anisidine ring. The yield is increased by adding an electron withdrowing group to decrease the electron density of aniline ring. (entry h, R_1=OCH_3, R_3=Cl) The results for **1a**, **1b** and **1c** are rather poor. (entries a,b,c, Method A) To improve the reaction yield, we also performed this reaction with **1a** in different solvents. The yield is increased by using acetonitrile (method B) or DMSO (Method C) as solvent, however, it proceeds in a much slower reaction rate (24h) than that performed in acetic acid. In DMF, the reaction rate is even slower. After heated for 48h, the yield is 60% based on 58% conversion. In HMPA, no reaction occurred after heated for 24h.Other examples are shown in Table I.

A possible mechanism for this free radical annulation reaction is shown in Scheme I. Initiation occurs with the manganese(III) acetate oxidation of diethyl malonate followed by intermolecular addition and oxidation to produce malonate **4**. Malonyl radical **5** produced by the manganese(III) oxidation of malonate **4** undergoes intramolecular cyclization and oxidation to give 2.

Scheme I

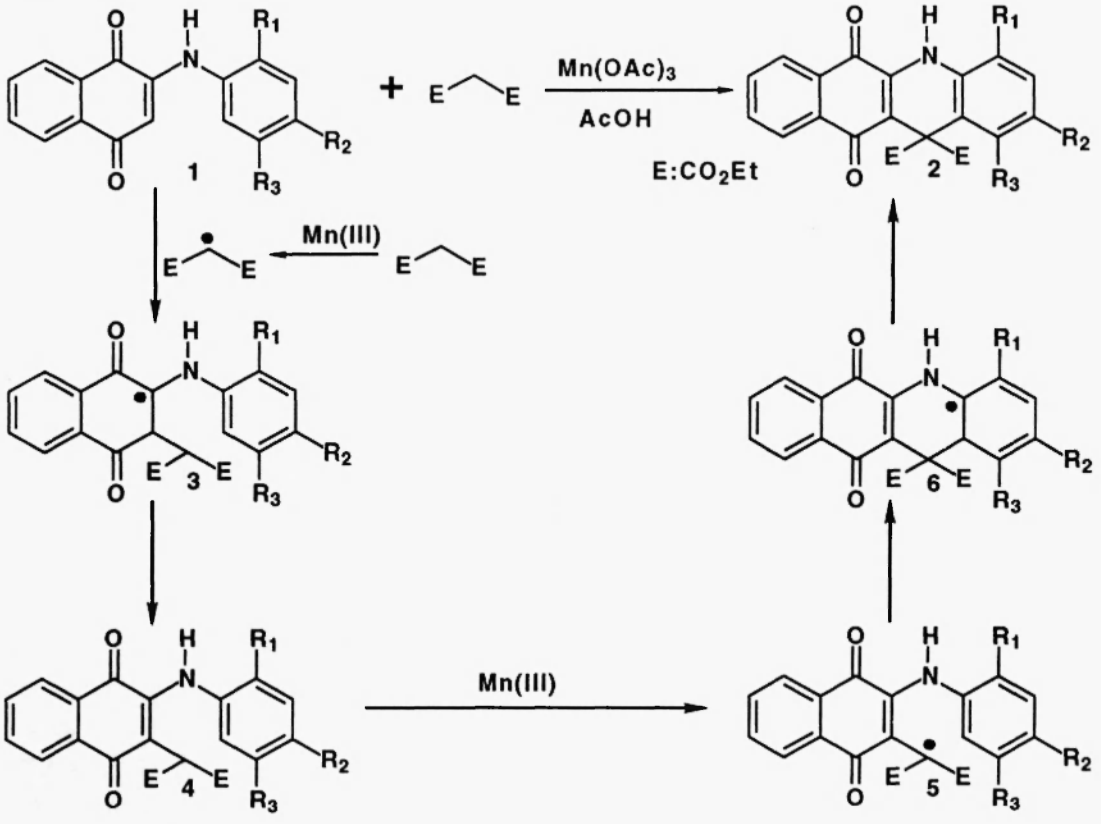

Table I: The Free Radical Reaction Between 2-Anilino-1,4-naphthoquinones And Diethyl Malonate

Entry	Substrate 1			Method	Yield
	R_1	R_2	R_3		
a	H	CH_3	H	A	30%
				B	48%
				C	65%
b	CH_3	H	H	A	33%
				B	52%
				C	52%
				D	36%
c	H	H	H	A	38%
				B	57%
				C	46%
				D	31%
d	Cl	H	H	A	63%
				B	63%
				D	62%

e	Br	H	H	A	66%
				B	57%
				D	63%
f	I	H	H	A	65%
				D	72%
g	Cl	Cl	H	A	58%
				D	52%
h	OCH_3	H	Cl	A	32%
				B	42%
i	CN	H	H	A	53%
				B	40%
j	H	OCH3	H	A	0%
				C	0%

Sonochemically-induced radical reaction has been used in organic synthesis.[5] We also performed the reaction shown in Scheme I by sonication method. Under sonication, **1c** and diethyl malonate (4 eq) was treated with manganese(III) acetate (5 eq), **2c** was obtained in 31% yield. Other examples for this sonication method are also shown in Table I (Method D) and the results are similar to those by thermal method. (method A)

In conclusion, this oxidative free radical reaction provides a novel method for the synthesis of naphtho[2,3-b]quinoline-5,12-diones from readily available 2-anilino-1,4-naphthoquinones and diethyl malonate.

Experimental

Melting points were taken with a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were taken with Hitachi 260-30 spectrometer. Nuclear magnetic resonance spectra were recorded on Bruker AMX 400 or Bruker Ac-200 spectrometer. Mass spectra were recorded with Jeol JMS-SX/SX 102A mass spectrometer. Sonochemical reactions were carried out in a Vibracell 400 Watt probe transducer, operating at 160w/cm^2 equipped with a titanium microtip (Φ 6.5 mm), directly connected to the horn. All reactions were carried out under an atmosphere of nitrogen. Analytical thin-layer chromatography was performed by precoated silica gel 60 F-254 plates (0.25 mm thick) of EM Laboratories. The reaction mixture was purified by column chromatography over EM Laboratories silica gel (230-400 Mesh).

General procedure for thermal method: A solution of 156 mg (0.59 mmol) of **1a**, 380 mg (2.38 mmol) of diethyl malonate and 798 mg (2.98 mmol) of manganese(III) acetate in 10 ml of glacial acetic acid was heated in an 80°C oil bath for 2h. The reaction mixture was diluted with 100 ml of dichloromethane, washed with 50 ml of saturated aqueous sodium bisulfite, three 50-mL portions of aqueous saturated sodium bicarbonate, three 25-mL portions of water, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with dichloromethane-hexane, 3:1) followed by recrystallization to give 74 mg (30%) of **2a** .

General procedure for sonication method: A solution of 157 mg (0.63 mmol) of **1c**, 385 mg (2.41 mmol) of diethyl malonate and 810 mg (3.02 mmol) of manganese(III) acetate in 10 ml of glacial acetic acid was sonicated in a 5°C water bath for 2h. The reaction mixture was diluted with 100 ml of dichloromethane, washed with 50 ml of aqueous

saturated sodium bisulfite, three 50-mL portions of aqueous saturated sodium bicarbonate, three 25-mL portions of water, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with dichloromethane-hexane, 3:1) followed by recrystallization to give 78 mg (31%) of **2c**.

2a: mp 254°C; IR ($CHCl_3$) 3395, 3010, 1740, 1675, 1635, 1505, 1340, 1300, 1215 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 (t, J=7.2 Hz, 6H, CH_3), 2.32 (s, 3H, CH_3), 4.23 (q, J=7.2 Hz, 4H, OCH_2), 6.88 (d, J=8.1 Hz, 1H, ArH), 7.04 (dm, J=8.1 Hz, 1H, ArH), 7.37 (s, 1H, ArH), 7.61-7.82 (m, 3H, ArH, NH), 8.06-8.20 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9(q), 21.0(q), 56.4(s), 62.2(t), 111.0(s), 116.3(d), 119.0(s), 126.1(d), 126.8(d), 130.0(d), 130.1(d), 130.2(s), 131.2(s), 132.4(d), 133.2(s), 134.2(s), 135.0(d), 138.0(s), 169.1(s), 180.2(s), 180.9(s); Anal. Calcd for $C_{24}H_{21}NO_6$: C, 68.73; H, 5.05; N, 3.34. Found: C, 68.81; H, 4.91; N, 3.37.

2b: mp 184°C; IR ($CHCl_3$) 3410, 2990, 1740, 1680, 1635, 1475, 1350, 1340, 1300 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, J=7.1 Hz, 6H, CH_3), 4.20 (q, J=7.1 Hz, 4H, OCH_2), 7.01 (t, J=7.6 Hz, 1H, ArH), 7.11 (d, J=7.6 Hz, 1H, ArH), 7.40 (d, J=7.6 Hz, 1H, ArH), 7.63 (t, J=7.6 Hz , 1H, ArH), 7.67-7.78 (m, 3H, ArH, NH), 8.06 (d, J=7.6 Hz, 1H, ArH), 8.13 (d, J=7.6 Hz, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8(q), 16.7(q), 56.7(s), 62.1(t), 112.0(s), 118.8(s), 123.6(s), 123.7(d), 126.1(d), 126.7(d), 127.6(d), 130.0(s), 130.4(d), 131.8(s), 132.5(d), 133.0(s), 135.0(d), 137.6(s), 169.0(s), 180.1(s), 180.9(s); Anal. Calcd for $C_{24}H_{21}NO_6$: C, 68.73; H, 5.05; N, 3.34. Found: C, 68.75; H, 5.10; N, 3.38.

2c: mp 234°C; IR ($CHCl_3$) 3395, 3010, 1740, 1680, 1635, 1495, 1340, 1305, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J=7.0 Hz, 6H, CH_3), 4.23 (q, J=7.0 Hz, 4H, OCH_2), 6.98 (dd, J=8.0, 1.1 Hz, 1H, ArH), 7.11 (tm, J=7.8 Hz, 1H, ArH), 7.24 (tm, J=7.8 Hz, 1H, ArH), 7.56 (dm, J=8.0 Hz, 1H, ArH), 7.67 (td, J=7.5, 1.3 Hz, 1H, ArH), 7.77 (td, J=7.5, 1.3 Hz, 1H, ArH), 7.81 (s, 1H, NH), 8.09 (dd, J=7.5, 1.3 Hz, 1H, ArH), 8.16 (dd, J=7.5, 1.3 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9(q), 62.3(t), 70.4(s), 111.4(s), 116.4(d), 119.1(s), 124.3(d), 126.2(d), 126.8(d), 129.2(d), 129.9(d), 130.1(s), 132.5(d), 133.1(s), 133.5(s), 135.0(s), 138.0(s), 169.0(s), 180.2(s), 181.0(s); Anal. Calcd for $C_{23}H_{19}NO_6$: C, 68.14; H, 4.72; N, 3.45. Found: C, 68.05; H, 4.61; N, 3.24.

2d: mp 194°C; IR ($CHCl_3$) 3380, 2990, 1740, 1680, 1640, 1500, 1350, 1335, 1300 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, J=7.0 Hz, 6H, CH_3), 4.24 (q, J=7.0 Hz, 4H, OCH_2), 7.07 (t, J=8.0 Hz, 1H, ArH), 7.37 (d, J=8.0 Hz, 1H, ArH), 7.48 (d, J=8.0 Hz, 1H, ArH), 7.69 (t, J=7.5 Hz, 1H, ArH), 7.78 (t, J=7.5 Hz, 1H, ArH), 8.10-8.20 (m, 2H, ArH), 8.26 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7(q), 56.8(s), 62.3(t), 112.1(s), 120.6(s), 121.1(s), 124.0(d), 126.2(d), 126.7(d), 128.3(d), 129.2(d), 130.0(s), 130.7(s), 132.7(d), 135.0(d), 137.5(s), 168.4(s), 179.5(s), 180.9(s); Anal. Calcd for $C_{23}H_{18}ClNO_6$: C, 62.81; H, 4.12; N, 3.18. Found: C, 62.83; H, 3.89; N, 3.27.

2e: mp 194°C; IR ($CHCl_3$) 3360, 2980, 1740, 1680, 1640, 1500, 1465, 1350, 1335, 1295, 1230 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 (t, J=7.1 Hz, 6H, CH_3), 4.23 (q, J=7.1 Hz, 4H, OCH_2), 7.01 (t, J=8.0 Hz, 1H, ArH), 7.52 (tm, J=7.1 Hz, 2H, ArH), 7.62-7.82 (m, 2H, ArH), 8.10-8.20 (m, 2H, ArH), 8.32 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8(q), 57.0(s), 62.4(t), 111.2(s), 112.3(s), 120.8(s), 124.6(d), 126.3(d), 126.8(d), 129.1(d), 130.1(s), 131.8(s), 132.6(d), 132.8(d), 135.1(d), 137.8(s), 168.6(s), 179.6(s), 181.0(s); Anal. Calcd for $C_{23}H_{18}BrNO_6$: C, 57.04; H, 3.75; N, 2.89. Found: C, 56.94; H, 3.77; N, 2.82.

2f: mp 201°C; IR ($CHCl_3$) 3345, 2990, 1740, 1680, 1640, 1500, 1460, 1350, 1290, 1230 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.19 (t, J=7.1 Hz, 6H, CH_3), 4.21 (q, J=7.1 Hz, 4H, OCH_2), 6.85 (t, J=7.7 Hz, 1H, ArH), 7.49 (d, J=7.7 Hz, 1H, ArH), 7.60-7.83 (m, 3H, ArH), 8.09 (dd, J=7.4, 1.3 Hz, 1H, ArH), 8.13 (dd, J=7.6, 1.2 Hz, 1H, ArH), 8.23 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7(q), 57.0(s), 62.3(t), 112.3(s), 120.0(s), 125.2(d), 126.2(d), 126.7(d), 129.8(s), 130.0(d), 132.7(d), 133.8(s), 135.0(d), 138.1(s), 139.0(d), 168.4(s), 179.3(s), 180.8(s); Anal. Calcd for $C_{23}H_{18}INO_6$: C, 52.00; H, 3.41; N, 2.64. Found: C, 51.93; H, 3.29; N, 2.73.

2g: mp 224°C; IR ($CHCl_3$) 3380, 3020, 2990, 1740, 1680, 1640, 1500, 1335, 1295 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J=7.2 Hz, 6H, CH_3), 4.25 (q, J=7.2 Hz, 4H, OCH_2), 7.38-7.40 (m, 1H, ArH), 7.45-7.47 (m, 1H, ArH), 7.71 (t, J=7.5 Hz, 1H, ArH), 7.79 (t, J=7.5 Hz, 1H, ArH), 8.14 (d, J=7.4 Hz, 1H, ArH), 8.16 (d, J=7.4 Hz, 1H, ArH), 8.22 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8(q), 56.8(s), 62.7(t), 112.1(s), 121.6(s), 121.7(s), 126.4(d), 126.9(d), 128.5(d), 128.8(s), 129.2(d), 129.7(s), 130.0(s), 132.7(s), 132.9(d), 135.2(d), 137.4(s), 168.1(s), 179.4(s), 180.9(s); Anal. Calcd for $C_{23}H_{17}Cl_2NO_6$: C, 58.24; H, 3.61; N, 2.95. Found: C, 58.30; H, 3.54; N, 2.97.

2h: mp 226°C; IR ($CHCl_3$) 3390, 2985, 1730, 1680, 1635, 1575, 1505, 1470, 1335, 1305, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J=7.2 Hz, 6H, CH_3), 3.95 (s, 3H, OCH_3), 4.18-4.37 (m, 4H, OCH_2), 6.81 (d, J=8.8 Hz, 1H, ArH), 7.13 (d, J=8.8 Hz, 1H, ArH), 7.67 (t, J=7.6 Hz, 1H, ArH), 7.76 (t, J=7.6 Hz, 1H, ArH), 8.10 (d, J=7.6 Hz, 1H, ArH), 8.18 (d, J=7.6 Hz, 1H, ArH), 8.47 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7(q), 56.1(q), 57.5(s), 62.3(t), 110.3(d), 118.1(s), 125.9(d), 126.1(d), 127.1(d), 129.7(s), 132.4(d), 133.3(s), 135.1(d), 137.5(s), 145.7(s), 169.1(s), 179.6(s), 180.7(s); Anal. Calcd for $C_{24}H_{20}ClNO_7$: C, 61.35; H, 4.29; N, 2.98. Found: C, 61.30; H, 4.35; N, 2.95.

2i: mp 176°C; IR ($CHCl_3$) 3365, 3030, 2990, 2225, 1740, 1680, 1500, 1470, 1340, 1290, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J=7.0 Hz, 6H, CH_3), 4.25 (q, J=7.0 Hz, 4H, OCH_2), 7.23 (t, J=7.8 Hz, 1H, ArH), 7.63 (d, J=7.8 Hz, 1H, ArH), 7.70-7.86 (m, 3H, ArH), 8.17 (d, J=7.6 Hz, 2H, ArH), 8.23 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7(q), 56.2(s), 62.5(t), 99.4(s), 113.0(s), 115.1(s), 120.1(s), 123.6(d), 126.4(d), 126.7(d), 129.7(s), 132.3(s), 132.8(d), 133.0(d), 134.7(d), 135.1(d), 135.9(s), 136.9(s), 168.0(s), 178.8(s), 180.9(s); Anal. Calcd for $C_{24}H_{18}N_2O_6$: C, 66.97; H, 4.22; N, 6.51. Found: C, 66.95; H, 4.33; N, 6.63.

Acknowledgements: The authors wish to thank the National Science Council, R.O.C. for financial support. (NSC-85-2113-M-006-006)

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Received November 17, 1995