CONVENIENT SYNTHESIS OF 3,4-DIHYDRO-2(1*H*)-QUINOLINONES FROM MALONATE DERIVATIVES

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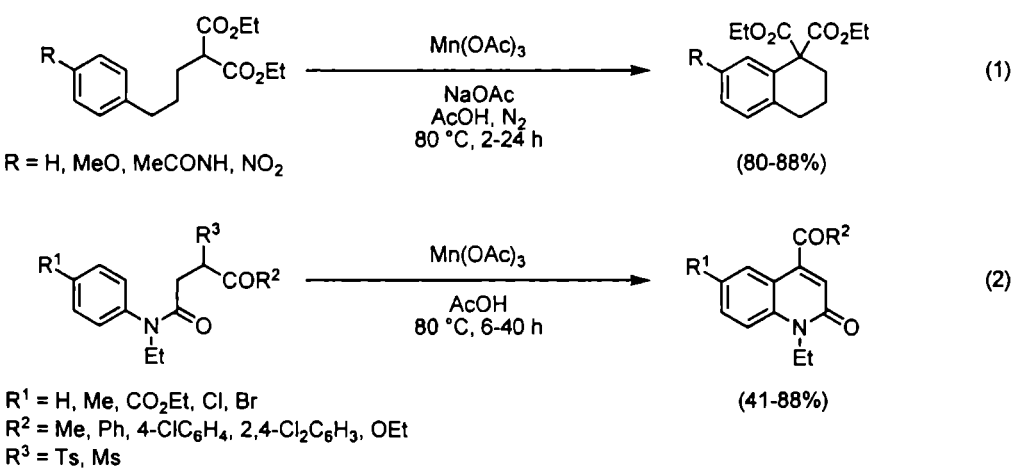
Dedicated to the Memory of Distinguished Professor R. R. Gupta, Editor-in-Chief of *Heterocyclic Communications*.

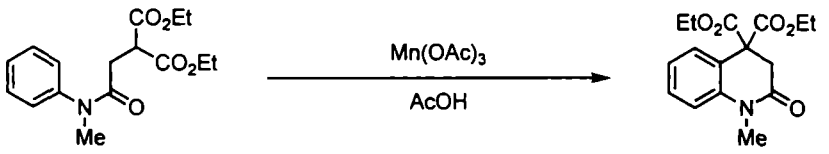
Abstract: The diethyl 2-[2-(*N*-arylamino)-2-oxoethyl]malonates underwent manganese(III)-mediated oxidative 6-*endo-trig* cyclization to produce the 4,4-bis(ethoxycarbonyl)-3,4-dihydro-2(1*H*)-quinolinones in excellent yields.

The manganese(III) acetate-mediated oxidative intramolecular cylization reaction is one of the most useful and efficient techniques to obtain cyclization products.[1] The reaction has also been used to synthesize heterocyclic compounds.[2,3] Since amide derivatives are easily prepared by the condensation of anilines with acid halides, we planned to examine the oxidative intramolecular cyclization of the 2-[2-(*N*-arylamino)-2-oxoethyl]malonates using manganese(III) acetate in order to synthesize dihydroquinolinones. The dihydroquinolinones are a kind of biologically very important quinoline alkaloid.[4] Although Citterio et al. reported the manganese(III)-mediated intramolecular cyclization of malonates (eq. 1 in Scheme 1)[5] and Chuang et al. also showed a similar reaction using alkylsulfonylanilides, producing 2(1*H*)-quinolinones (eq. 2 in Scheme 1),[2a] to the best of our knowledge, the reaction using the 2-[2-(*N*-arylamino)-2-oxoethyl]malonates has never been examined.



Scheme 1

Diethyl 2-[2-(*N*-methyl-*N*-phenylamino)-2-oxoethyl]malonate (**1**) was prepared by the reaction of *N*-methylaniline with 2-chloroacetyl chloride followed by the condensation with diethyl malonate (2 steps, 90%).[6] With the malonate **1** in hand, we examined the reaction of **1** with manganese(III) acetate under various conditions. When the reaction was carried out in glacial acetic acid at 80 °C, we fortunately obtained only one product **2** (Scheme 2 and Table 1, Entry 1). When comparing the ^{1}H NMR spectrum of the malonate **1** with that of the product **2**, the characteristic triplet methine



1 2

Scheme 2

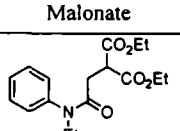
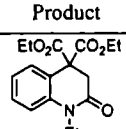
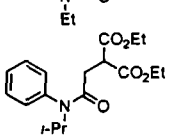
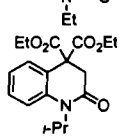
Table 1. Oxidation of Diethyl 2-[2-(*N*-Methyl-*N*-phenylamino)-2-oxoethyl]malonate (**1**) with Manganese(III) Acetate[a]

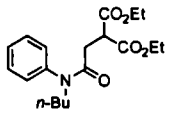
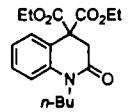
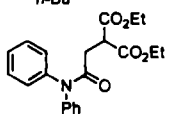
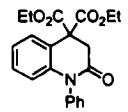
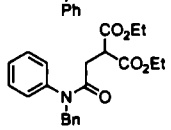
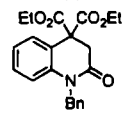
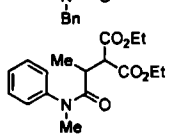
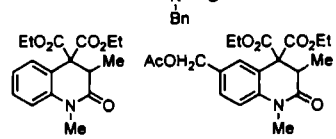
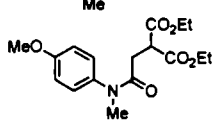
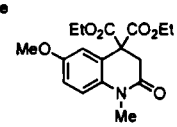
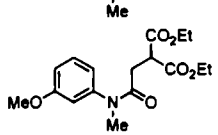
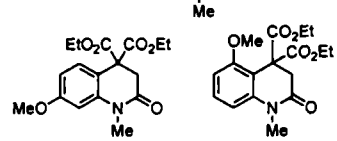
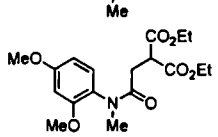
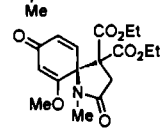
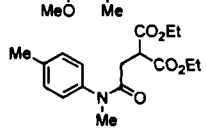
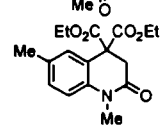
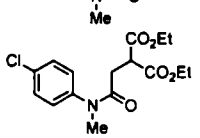
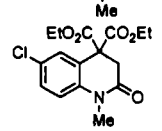
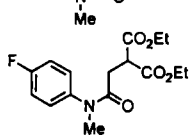
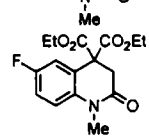
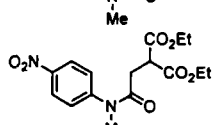
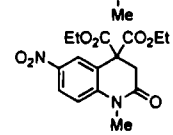
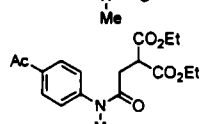
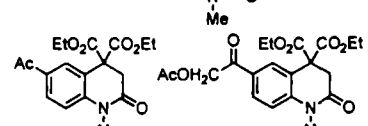
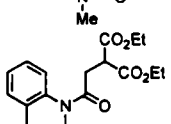
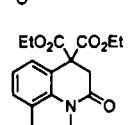
Entry	1:Mn(OAc)$_3$[b]	AcOH mL	Temperature °C	Time min	2 %[c]
1	1:2.5	15	80	240	60
2	1:2.5	15	100	60	78[d]
3	1:2.5	15	reflux	18	85[d]
4	1:3	15	reflux	30	90
5	1:3	15	reflux	30	90
6	1:3	30	reflux	30	97
7	1:3	50	reflux	30	91

[a] The reaction of 1 (0 5 mmol) was carried out in glacial acetic acid under ambient conditions except for entry 5 under an argon atmosphere
[b] Molar ratio.
[c] Isolated yield based on 1 used.
[d] The malonate 1 was recovered in 3% based on the ^{1}H NMR spectrum

proton (□ = 3.96 ppm, J = 7.3 Hz) of the malonate **1** disappeared and a doublet of the methylene protons (□ = 2.66 ppm, J = 7.3 Hz) of **1** collapsed into a sharp singlet (□ = 3.23 ppm) in the ^{1}H NMR spectrum of **2**. In addition, the aromatic protons of **2** showed an ABCD splitting pattern. The corresponding methine carbon of **1** changed into a quaternary carbon in the ^{13}C NMR spectrum of **2**. Furthermore, the sp^2 carbon attached to no proton appeared at □ = 122 ppm assigned to one of the aromatic carbons *ortho* to the amino group. These spectroscopic data supported the fact that the structure of the product **2** must be 4,4-bis(ethoxycarbonyl)-3,4-dihydro-2(1*H*)-quinolinone and the combustion analysis was also identical to the structural formula $C_{16}H_{19}NO_5$.[7] The reaction was optimized and the yield of **2** was improved to 97% (Entry 6).[8] We next applied the oxidative cyclization to other diethyl 2-[2-(*N*-arylamino)-2-oxoethyl]malonates under the optimized oxidation conditions as shown in Table 2, and the desired 3,4-dihydro-2(1*H*)-quinolinones were obtained in excellent yields except for the reaction of the 2,4-dimethoxyphenyl-substituted malonate[9] (Table 2, Entry 9), giving the 5-*exo-trig* cyclization product.[10] The electronic effect probably caused the 5-*exo-trig* cyclization. As a result, it was found that the diethyl 2-[2-(*N*-arylamino)-2-oxoethyl]malonates underwent the 6-*endo-trig* cyclization reaction under the current manganese(III) acetate oxidation conditions to produce the desired dihydroquinolinones, though the corresponding oxidation products were also isolated in a small amount (Table 2, Entries 6 and 14).

Table 2. Oxidation of Other Diethyl 2-[2-(*N*-Arylamino)-2-oxoethyl]malonates with Manganese(III) Acetate[a]

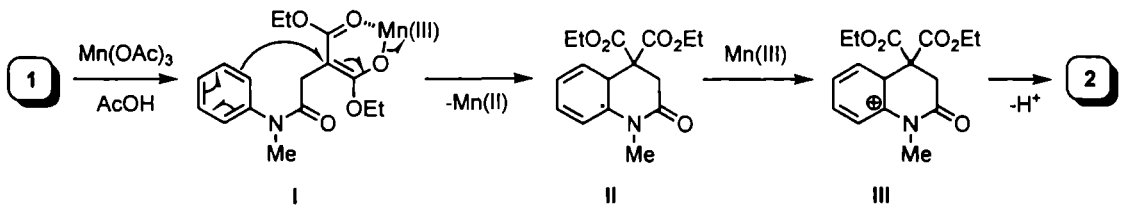
Entry	Malonate	Product	Yield/%[b]
1			98
2			93

3			92
4			100
5			93
6			61 + 28[c]
7			97
8			46 + 51
9			85
10			97
11			88
12			95
13			92
14			80 + 17
15			99

[a] The oxidation of the malonate (0 5 mmol) with manganese(III) acetate dihydrate (1.5 mmol for entries 1-9, 12-15; 2 0 mmol for entries 10,11,14) was carried out in glacial acetic acid (30 mL) at reflux temperature for 30 min in air.

[b] Isolated yield based on the malonate used

[c] The oxidation of the malonate (0.5 mmol) with manganese(III) acetate dihydrate (5 mmol) was conducted in glacial acetic acid (30 mL) at reflux temperature for 5 h in air



Scheme 3

The mechanism for the formation of the dihydroquinolinole **2** could be explained by a well-known oxidation mechanism (Scheme 3).[3] That is, the enolate complex **I** would be formed *in situ* by the ligand-exchange reaction of the malonate **1** with manganese(III) acetate in acetic acid, followed by the oxidative 6-*endo-trig* cyclization to give the dihydroquinolinone intermediate radical **II**. This intermediate **II** could be oxidized by manganese(III) species under the current reaction conditions, which was then deprotonated to finally produce the dihydroquinolinone **2**.

In summary, we have demonstrated the convenient and useful synthesis of 4,4-bis(ethoxycarbonyl)-3,4-dihydro-2(1*H*)-quinolinones from the corresponding 2-[2-(*N*-arylamino)-2-oxoethyl]malonates in excellent yields. The reaction is very simple and the product is easily isolated and purified. The dihydroquinolonones **2** could then be converted into the corresponding quinoline derivatives, which is currently underway.

Acknowledgments

This research was supported by a Grant-in-Aid for Scientific Research (C), No.19550046, from the Japan Society for the Promotion of Science.

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6. Diethyl 2-[2-(*N*-methyl-*N*-phenylamino)-2-oxoethyl]malonate (**1**): R_f = 0.45 (diethyl ether-hexane, 8:2 v/v); colorless oil; IR ($CHCl_3$) □ 1744, 1724, 1651 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.48-7.22 (5H, m, arom. H), 4.26-4.08 (4H, m, O-C$\underline{H_2}$CH$_3$), 3.96 (1H, t, J = 7.3 Hz, H-2), 3.26 (3H, s, N-C$\underline{H_3}$), 2.66 (2H, d, J = 7.3 Hz, C$\underline{H_2}$), 1.24 (6H, t, J = 7.3 Hz, O-CH$_2$C$\underline{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 169.6 (C=O), 169.0 (2C, C=O), 143.2 (arom. C), 129.8, 127.9, 127.2 (5C, arom. C$\underline{H}$), 61.4 (2C, O-C$\underline{H_2}$CH$_3$), 48.1 (N-C$\underline{H_3}$), 37.3 (C-2), 33.3 (C$\underline{H_2}$), 13.8 (2C, O-CH$_2$C$\underline{H_3}$). FAB HRMS (acetone-NBA) calcd for $C_{16}H_{22}NO_5$ 308.1498 (M+1). Found 308.1499.
7. 4,4-Bis(ethoxycarbonyl)-3,4-dihydro-2(1*H*)-quinolinone (**2**): R_f = 0.47 (diethyl ether-hexane, 8:2 v/v); colorless prisms (from chlorofrom-hexane); mp 86-87 °C; IR (KBr) □ 1757, 1734, 1688 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.40-7.29 (2H, m, arom. H), 7.13-7.02 (2H, m, arom. H), 4.35-4.19 (4H, m, O-C$\underline{H_2}$CH$_3$), 3.33 (3H, s, N-C$\underline{H_3}$), 3.23 (2H, s, C$\underline{H_2}$), 1.27 (6H, t, J = 7.3 Hz, O-CH$_2$C$\underline{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 168.8 (2C, C=O), 166.5 (C=O), 139.6 (arom. C), 129.2, 127.6, 122.9 (arom. C$\underline{H}$), 122.4 (arom. C), 115.1 (arom. C$\underline{H}$), 62.2 (2C, O-C$\underline{H_2}$CH$_3$), 56.7 (C-4), 37.8 (C$\underline{H_2}$), 29.4 (N-C$\underline{H_3}$), 13.7 (2C, O-CH$_2$C$\underline{H_3}$). Anal. calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.90; H, 6.35; N, 4.62.
8. The typical oxidation was as follows. To a mixture of malonate **1** (0.5 mmol) and glacial acetic acid (30 mL) was added manganese(III) acetate dihydrate (1.5 mmol). The mixture was heated under reflux for 30 min in air. The solvent was removed *in vacuo*, and the residue was triturated with water followed by extraction with dichloromethane (10 mL x 3). The combined extract was dried over anhydrous magnesium sulfate, and then concentrated to dryness. The obtained product **2** was purified by silicagel TLC while eluting with diethyl ether-hexane (80:20 v/v).
9. Diethyl 2-[2-{*N*-(2,4-dimethoxyphenyl)-*N*-methylamino}-2-oxoethyl]malonate: R_f = 0.41 (ethyl acetate-hexane, 5:5 v/v); yellow oil; IR ($CHCl_3$) □ 1744, 1728, 1651 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.17-7.08 (1H, m, arom. H), 6.58-6.46 (2H, m, arom. H), 4.28-4.06 (4H, m, O-C$\underline{H_2}$CH$_3$), 3.92 (1H, t, J = 7.3 Hz, H-2), 3.83 (6H, s, O-C$\underline{H_3}$), 3.13 (3H, s, N-C$\underline{H_3}$), 2.75 (1H, dd, J = 17.2, 8.4 Hz, C$\underline{H_2}$), 2.48 (1H, dd, J = 17.2, 6.2 Hz, C$\underline{H_2}$), 1.32-1.19 (6H, m, O-CH$_2$C$\underline{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 170.6 (C=O), 169.1 (2C, C=O), 160.4, 155.7 (arom. C), 129.3 (arom. C$\underline{H}$), 124.6 (arom. C), 104.5, 99.4 (arom. C$\underline{H}$), 61.2 (2C, O-C$\underline{H_2}$CH$_3$), 55.3 (2C, O-C$\underline{H_3}$), 48.0 (N-C$\underline{H_3}$), 36.1 (C-2), 32.6 (C$\underline{H_2}$), 13.8 (2C, O-CH$_2$C$\underline{H_3}$). FAB HRMS (acetone-NBA) calcd for $C_{18}H_{26}NO_7$ 368.1709 (M+1). Found 368.1707.
10. 4,4-Bis(ethoxycarbonyl)-6-methoxy-1-methyl-1-azaspiro[4,5]deca-6,9-diene-2,8-dione: R_f = 0.18 (diethyl ether); colorless prisms (from chloroform-hexane); mp 119 °C; IR (KBr) □ 1740, 1719, 1670, 1603 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) □ 6.66 (1H, d, J = 10.3 Hz, H-10), 6.43 (1H, dd, J = 10.3, 1.5 Hz, H-9), 5.71 (1H, d, J = 1.5 Hz, H-7), 4.36-4.05 (4H, m, O-C$\underline{H_2}$CH$_3$), 3.70 (3H, s, O-C$\underline{H_3}$), 3.31 (1H, d, J = 17.2 Hz, C$\underline{H_2}$), 2.84 (1H, d, J = 17.2 Hz, C$\underline{H_2}$), 2.62 (3H, s, N-C$\underline{H_3}$), 1.29 (3H, t, J = 7.3 Hz, O-CH$_2$C$\underline{H_3}$), 1.20 (3H, t, J = 7.3 Hz, O-CH$_2$C$\underline{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 185.6 (C=O), 173.0, 170.9, 168.5, 166.8 (C=O, C-6), 140.3, 132.8, 104.8 (C-7, C-9, C-10), 66.4 (C-5), 62.9, 62.3 (O-C$\underline{H_2}$CH$_3$), 61.3 (C-4), 56.3 (O-C$\underline{H_3}$), 38.5 (C$\underline{H_2}$), 26.2 (N-C$\underline{H_3}$), 13.9, 13.7 (O-CH$_2$C$\underline{H_3}$). Anal. calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99. Found: C, 58.12; H, 5.94; N, 4.09.

Recevied on October 15, 2008