

OXIDATIVE COUPLING OF 4-SUBSTITUTED N,N-DIMETHYLANILINES
WITH N-SUBSTITUTED MALEIMIDES IN THE PRESENCE OF
MANGANESE(II) NITRATE UNDER OXYGEN

Satoru Murata, Koji Teramoto, Masahiro Miura,* and Masakatsu Nomura
Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita,
Osaka 565, Japan

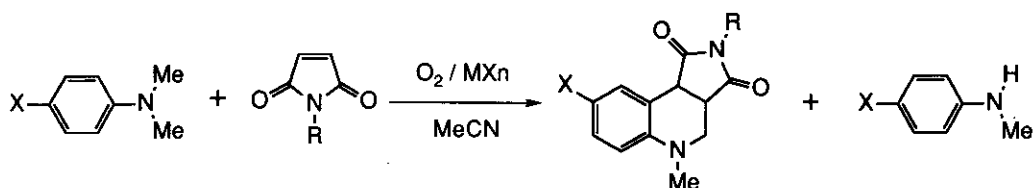
Abstract - The reaction of 4-substituted N,N-dimethylanilines with N-substituted maleimides proceeds in the presence of a catalytic amount of manganese(II) nitrate under oxygen to give the corresponding N-substituted 1,2,3,4-tetrahydro-1-methylquinoline-3,4-dicarboximides along with N-methylanilines.

The synthesis of polycyclic compounds involving a quinoline ring is of current interest, since they are expected to exhibit pharmacological effects.¹⁻³

Swan *et al.* described that N-alkyl-N-methylanilines react with electron deficient alkenes such as N-substituted maleimides in the presence of benzoyl peroxide⁴ or by γ -radiation⁵ to give the corresponding 1,2,3,4-tetrahydroquinoline-3,4-dicarboximides which were also transformed into 2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,4-*c*]quinoline derivatives by treatment with lithium aluminum hydride. They proposed a mechanism involving (N-alkyl-N-phenylamino)methyl radical for the formation of the former tricyclic compounds.

We have recently reported that 4-substituted N,N-dimethylanilines (**1**) are readily oxidized by molecular oxygen in the presence of various transition metal salts and complexes to give the corresponding N-methylformanilides and N-methylanilines.⁶ In the presence of electron-rich alkenes, acyclic and cyclic vinyl ethers,^{6,7} N-methyl-1,2,3,4-tetrahydroquinoline derivatives are produced as the predominant products.

We thought that electron deficient alkenes could also react with **1** as well as vinyl ethers, since the oxidation reaction is considered to involve both aminomethyl radical and iminium cation intermediates. Indeed, the anilines **1** were found to react with N-substituted maleimides **2** under our oxidation conditions to afford 1,2,3,4-



1a; X=Me
1b; X=OMe
1c; X=Cl
1d; X=H

2a; R=Me
2b; R=Ph

3a; X=Me, R=Me
3b; X=OMe, R=Me
3c; X=Cl, R=Me
3d; X=H, R=Me
3e; X=Me, R=Ph
3f; X=OMe, R=Ph
3g; X=Cl, R=Ph

4a; X=Me
4b; X=OMe
4c; X=Cl
4d; X=H

tetrahydroquinoline-3,4-dicarboximides (3).

Table 1 summarizes the results for the reaction of *N,N*-dimethyl-*p*-toluidine (**1a**) (2 mmol) and *N*-methylmaleimide (**2a**) (2 mmol) in acetonitrile under oxygen (1 atm) at 50 °C for 20 h in the presence of a number of metal salts (0.2 mmol) as the catalysts. From each run, the coupling product **3a** was obtained along with *N*,4-dimethylaniline (**4a**) as a single detectable by-product. Among the catalysts tested, manganese(II) or cobalt(II) species gave satisfactory results, as for the reaction with cyclic vinyl ethers in place of **2a**.⁷

The results for the reactions of the anilines **1a-d** with **2a** or *N*-phenylmaleimide (**2b**) using manganese(II) nitrate

Table 1. Oxidative coupling of *N,N*-dimethyl-*p*-toluidine (**1a**) with *N*-methylmaleimide (**2a**) in the presence of a number of metal salts.^(a)

MXn	Conv. of 1a / %	Yield / % ^(b)	
		3a	4a
MnCl ₂	89	45	7
Mn(NO ₃) ₂ · 6H ₂ O	89	45	11
FeCl ₃	27	11	2
CoCl ₂	80	41	4
Co(NO ₃) ₂ · 6H ₂ O	72	35	6
NiCl ₂	25	12	(c)
CuCl	89	35	7

(a) Reaction conditions; [**1a**]:[**2a**]:[MXn]=2:2:0.2, in acetonitrile at 50 °C under O₂ for 20 h. (b) Yield based on **1a** charged was determined by GC analysis. (c) Not detected.

Table 2. Oxidative coupling of 4-substituted *N,N*-dimethylanilines (**1**) with *N*-substituted maleimides (**2**) in the presence of manganese nitrate(II).^(a)

Aniline	Maleimide	Conv. of 1 / %	Yield / % ^(b)	
			3	4
1 a	2 a	89	45(40) ^(c)	11
1 b	2 a	80	(20)	_(d)
1 c	2 a	60	(33)	8
1 d	2 a	23	6	_(d)
1 a	2 b	93	(54)	6
1 b	2 b	77	(48)	4
1 c	2 b	77	(45)	7

(a) Reaction conditions; [1]:[2]:[Mn(NO₃)₂]=2:2:0.2, in acetonitrile at 50 °C under O₂ for 20 h. (b) Yield based on **1** charged was determined by GC analysis. (c) The value in the parentheses is isolated yield. (d) Not detected.

are also recorded in Table 2. Tricyclic coupling products **3** were obtained in modest to good yields along with *N*-methylanilines (**4**), while the conversion of **1** depended markedly on the 4-substituent. The reaction of **1 a** with maleic anhydride in place of **2** was also examined. While analysis of the reaction mixture suggested formation of a coupling product, it could not be isolated (see Experimental). With dimethyl maleate and ethyl acrylate, no coupling product was detected.

To obtain an insight into the reaction mechanism, the early stage of the reaction of **1 a-c** with **2 a** in the presence of Mn(NO₃)₂ was followed by GC (Figure 1). The aniline **1 a** reacted quickly after an induction period of ca. 1 h. The rate of the reaction of **1 b** in the steady state was slower than that of **1 a**, although the reaction started smoothly. The reaction of **1 c** began after a longer induction period.

The above results seem to be rationalized by the reaction sequence illustrated in Scheme 1 which is similar to that proposed for the oxygenation of **1**, previously.⁶ The first step of the reaction may involve one electron oxidation of **1** under the influence of the catalyst and oxygen to give amine cation radical (**5**) and the successive proton loss affords aminomethyl radical (**6**). Thus, the reaction of **1 b** having a good electron-donating substituent may start smoothly. However, the proton loss in the radical cation **5** (X=OMe) is considered to be slower than in that from **1 a**, which could be one of the major reasons for the different reaction pattern between **1 a** and **1 b**.

The observation of a considerable length of the induction period in the reaction **1 a** and **1 c** suggests participation of a free radical chain process involving hydrogen abstraction from **1** by radicals derived from peroxidic species

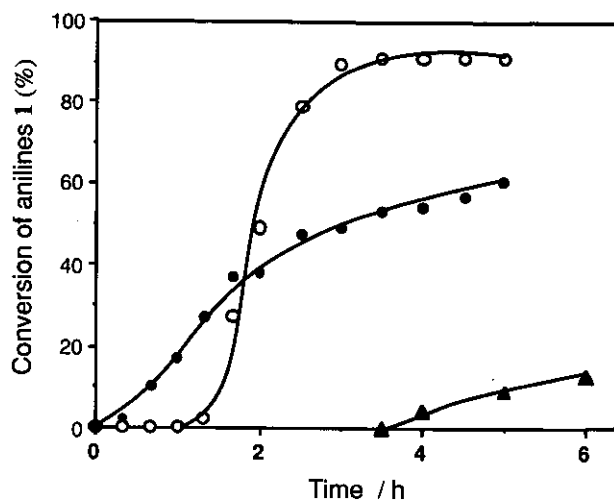
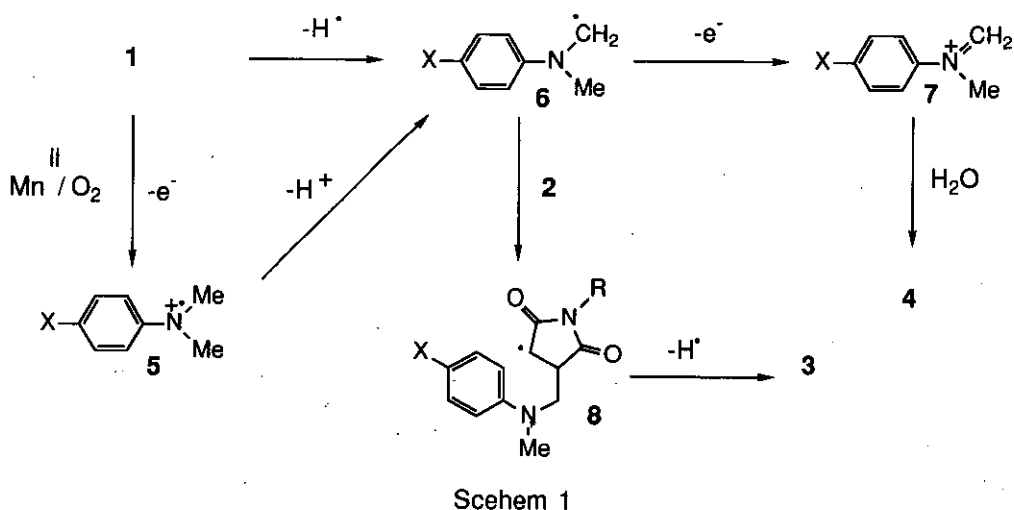


Figure 1. Time course of oxygen uptake in the reaction of 4-substituted *N,N*-anilines (**1**) with *N*-methylmaleimide (**2a**) in the presence of $\text{Mn}(\text{NO}_3)_2$ in acetonitrile under O_2 at 50 °C; **1a** (○), **1b** (●), and **1c** (▲)

generated in the reaction medium. One of the possible species may be the hydroperoxy radical from the reaction of radical intermediate **8** and oxygen.

The reaction of the radical **6** with **2** may lead to the tricyclic product **3**. The radical **6** may also react with oxygen to give *N*-methylformanilides.⁶ The fact that no evidence for the formation of the formanilides could be obtained would imply that the reaction of **6** with **2** is much faster than that with oxygen. Another possible fate of the



intermediate **6** may be the transformation to iminium cation (**7**) by a further one electron oxidation. While **7** may react with electron rich alkenes such as vinyl ethers as reported previously,^{6,7} it is unlikely to react with the electron deficient alkenes **2**. Thus, the iminium cation **7** appears to be prone to react with adventitious or *in situ* generated water to give **4**.

EXPERIMENTAL

¹H-Nmr spectra were obtained with a JEOL JNM-GSX-400 spectrometer for CDCl₃ solutions. Ms spectra were obtained with a Shimadzu GCMS-QP2000 spectrometer. Gc analysis was carried out on a Shimadzu GC-8APF gas chromatograph.

The anilines **1b**,⁸ and maleimide **2b**⁹ were prepared by the method reported previously. Other starting materials were commercially available.

General procedure for coupling reaction of N,N-dimethylanilines (**1**) with N-substituted maleimides (**2**): To a flask containing an appropriate metal salt (0.2 mmol) was added a solution of **1** (2 mmol) and **2** (2 mmol) in acetonitrile (10 ml). The mixture was stirred for 20 h at 50 °C under oxygen (with a balloon). The resulting mixture was poured into water (50 ml) and extracted with ether (50 ml x 2). The organic layer was dried over sodium sulfate and evaporated. The product was isolated by column chromatography on silica gel using ethyl acetate-hexane as eluant and purified by recrystallization.

Coupling reaction of N,N-dimethyl-p-toluidine (**1a**) with maleic anhydride: An acetonitrile solution containing the aniline (**1a**) (2 mmol), maleic anhydride (2 mmol), and manganese(II) nitrate (0.2 mmol) was stirred for 20 h at 50 °C under oxygen. Analysis of the reaction mixture by GC-MS suggested formation of a coupling product ($m/z=231, M^+$). However, it could not be isolated by column chromatography because of its decomposition.

1,2,3,4-Tetrahydro-1,6-dimethylquinoline-N-methyl-3,4-dicarboximide (**3a**): Mp 180 °C (from methanol) (lit.⁴ 183-184 °C). ¹H-Nmr δ: 2.29 (s, 3H), 2.76 (s, 3H), 2.96 (dd, J=11.7, 4.4 Hz, 1H), 2.98 (s, 3H), 3.33 (ddd, J=9.3, 4.4, 2.4 Hz, 1H), 3.50 (dd, J=11.7, 2.4 Hz, 1H), 3.95 (d, J=9.3 Hz, 1H), 6.60 (d, J=8.3 Hz, 1H), 7.01 (dd, J=8.3, 1.7 Hz, 1H), 7.27 (d, J=1.7 Hz, 1H). Ms m/z : 244 (M^+).

6-Methoxy-1,2,3,4-tetrahydro-1-methylquinoline-N-methyl-3,4-dicarboximide (**3b**): Mp 122-123 °C (from methanol). ¹H-Nmr δ: 2.74 (s, 3H), 2.94 (dd, J=11.2, 4.4 Hz, 1H), 2.99 (s, 3H), 3.34 (ddd, J=9.3, 4.4, 2.4 Hz, 1H), 3.48 (dd, J=11.2, 2.4 Hz, 1H), 3.79 (s, 3H), 3.96 (d, J=9.3 Hz, 1H), 6.63 (d, J=2.9 Hz, 1H), 6.78 (dd, J=9.0, 2.9 Hz, 1H), 7.08 (d, J=9.0 Hz, 1H). Ms m/z : 260 (M^+). Anal. Calcd for C₁₄H₁₆N₂O₃: C 64.60, H 6.20, N 10.77. Found: C 64.47, H 6.19, N 10.79.

6-Chloro-1,2,3,4-tetrahydro-1-methylquinoline-N-methyl-3,4-dicarboximide (3c): Mp 188-190 °C (from methanol). $^1\text{H-Nmr}$ δ : 2.78 (s, 3H), 2.99 (s, 3H), 3.02 (dd, $J=11.7, 4.4$ Hz, 1H), 3.36 (ddd, $J=9.8, 4.4, 2.4$ Hz, 1H), 3.52 (dd, $J=11.7, 2.4$ Hz, 1H), 3.95 (d, 9.8 Hz, 1H), 6.61 (d, $J=8.8$ Hz, 1H), 7.15 (dd, $J=8.8, 2.4$ Hz, 1H), 7.46 (d, $J=2.4$ Hz, 1H). Ms m/z : 264, 266 (M^+). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2\text{Cl}$: C 58.98, H 4.95, N 10.59, Cl 13.39. Found: C 58.86, H 4.82, N 10.56, Cl 13.26.

1,2,3,4-Tetrahydro-1-methylquinoline-N-methyl-3,4-dicarboximide (3d): Mp 178-179 °C (from methanol) (lit.⁴ 175 °C) $^1\text{H-Nmr}$ δ : 2.79 (s, 3H), 2.98 (s, 3H), 3.03 (dd, $J=11.7, 4.5$ Hz, 1H), 3.31 (ddd, $J=9.3, 4.5, 2.4$ Hz, 1H), 3.51 (dd, $J=11.7, 2.4$ Hz, 1H), 4.00 (d, $J=9.3$ Hz, 1H), 6.69 (d, $J=8.3$ Hz, 1H), 6.87-6.91 (m, 1H), 7.19-7.23 (m, 1H), 7.47 (d, $J=7.3$ Hz, 1H). Ms m/z : 230 (M^+).

1,2,3,4-Tetrahydro-1,6-dimethylquinoline-N-phenyl-3,4-dicarboximide (3e): Mp 196-198 °C (from methanol) (lit.⁴ 199 °C). $^1\text{H-Nmr}$ δ : 2.30 (s, 3H), 2.80 (s, 3H), 3.05 (dd, $J=11.2, 4.4$ Hz, 1H), 3.51 (ddd, $J=9.8, 4.4, 2.9$ Hz, 1H), 3.58 (dd, $J=11.2, 2.9$ Hz, 1H), 4.11 (d, $J=9.8$ Hz, 1H), 6.65 (d, $J=8.3$ Hz, 1H), 7.03 (dd, $J=8.3, 2.0$ Hz, 1H), 7.25-7.28 (m, 2H), 7.32-7.37 (m, 2H), 7.40-7.44 (m, 2H). Ms m/z : 306 (M^+).

6-Methoxy-1,2,3,4-tetrahydro-1-methylquinoline-N-phenyl-3,4-dicarboximide (3f): Mp 156-157 °C (from methanol). $^1\text{H-Nmr}$ δ : 2.79 (s, 3H), 3.03 (dd, $J=11.2, 4.4$ Hz, 1H), 3.51 (ddd, $J=9.7, 4.4, 2.9$ Hz, 1H), 3.56 (dd, $J=11.2, 2.9$ Hz, 1H), 3.79 (s, 3H), 4.12 (d, $J=9.7$ Hz, 1H), 6.68 (d, $J=8.8$ Hz, 1H), 6.81 (dd, $J=8.8, 2.9$ Hz, 1H), 7.13 (d, $J=2.9$ Hz, 1H), 7.25-7.28 (m, 2H), 7.33-7.37 (m, 1H), 7.41-7.44 (m, 2H). Ms m/z : 322 (M^+). Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2$: C 70.79, H 5.63, N 8.69. Found: C 70.50, H 5.61, N 8.62.

6-Chloro-1,2,3,4-Tetrahydro-1-methylquinoline-N-phenyl-3,4-dicarboximide (3g): Mp 158-159 °C (from methanol). $^1\text{H-Nmr}$ δ : 2.82 (s, 3H), 3.10 (dd, $J=11.7, 4.4$ Hz, 1H), 3.52 (ddd, $J=9.7, 4.4, 2.4$ Hz, 1H), 3.60 (dd, $J=11.7, 2.4$ Hz, 1H), 4.10 (d, $J=9.7$ Hz, 1H), 6.65 (d, $J=8.8$ Hz, 1H), 7.17 (dd, $J=8.8, 2.4$ Hz, 1H), 7.24-7.30 (m, 2H), 7.34-7.38 (m, 1H), 7.41-7.45 (m, 2H), 7.51 (d, $J=2.4$ Hz, 1H). Ms m/z : 326, 328 (M^+). Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_2\text{Cl}$: C 66.16, H 4.63, N 8.57, Cl 10.85. Found: C 66.02, H 4.51, N 8.57, Cl 10.89.

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