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A new radical way to *N*,*N*-dimethylaniline hydroperoxide (DMAHP) and its application in organic synthesis

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Abstract

N,*N*-Dimethylaniline hydroperoxide was obtained when treating *N*,*N*-dimethylaniline with NHPI/$Co(OAc)_2$/O_2 *via* a radical reaction mechanism. This intermediate has potential application in the synthesis of some important chemical scaffolds.

Keywords: Aerobic oxidation; NHPI; *N*,*N*-Dimethylaniline

Recent studies showed that *N*-hydroxyphthalimide (NHPI) in combination with molecular oxygen and metal salt cocatalysts, such as $Co(OAc)_2$ or $Co(acac)_2$, was a valuable catalytic system for aerobic oxidation of various organic compounds under mild reaction conditions [1–6]. It is believed that the phthalimide *N*-oxyl (PINO) radical generated in situ from the reaction of O_2 and NHPI is able to abstract a hydrogen atom from the organic substrates. The newly formed carbon radical then rapidly reacts with O_2 to give hydroperoxide [7]. Normally, hydroperoxide will further convert into a variety of ultimately oxygenated products [7,8]. In this paper, we wish to report some useful results in the reaction of *N*,*N*-dimethylaniline (DMA) in NHPI/$Co(OAc)_2$/O_2 system.

The reaction was carried out in a two-neck flask equipped with a stopper and an oxygen balloon. DMA (10 mmol) was dissolved in acetonitrile (20 mL) followed by the addition of NHPI (10 mol%) and $Co(OAc)_2{\cdot}4H_2O$ (0.5 mol%). After stirring at rt for 30 min, a brown solution formed. TLC showed that DMA had disappeared and a product had formed. Although, this product underwent decomposition (the product on the TLC gradually became dark within 10 min), it could be purified with flash chromatography in 37% yield as a straw yellow semi-solid. From analysis data [9] of the product, we could deduce that the oxygenated products was *N*,*N*-dimethylaniline hydroperoxide (DMAHP). The proposed mechanism was shown in Scheme 1. Aleksandrov reported the formation of DMAHP *via* oxidation of DMA by molecular oxygen (AIBN as initiator). To our knowledge, DMAHP has not yet been fully investigated [10,11], so many experiments should be carried out to confirm its structure and also to demonstrate its application.

A surprising result was observed when an acetonitrile solution of DMAHP was exposed to an aqueous solution of sodium hydrosulfite. The reaction underwent rapidly and a new compound with great polarity was found in aqueous layer. We deduced the reaction occurring according to the equation as shown in Scheme 2. However, we had no direct

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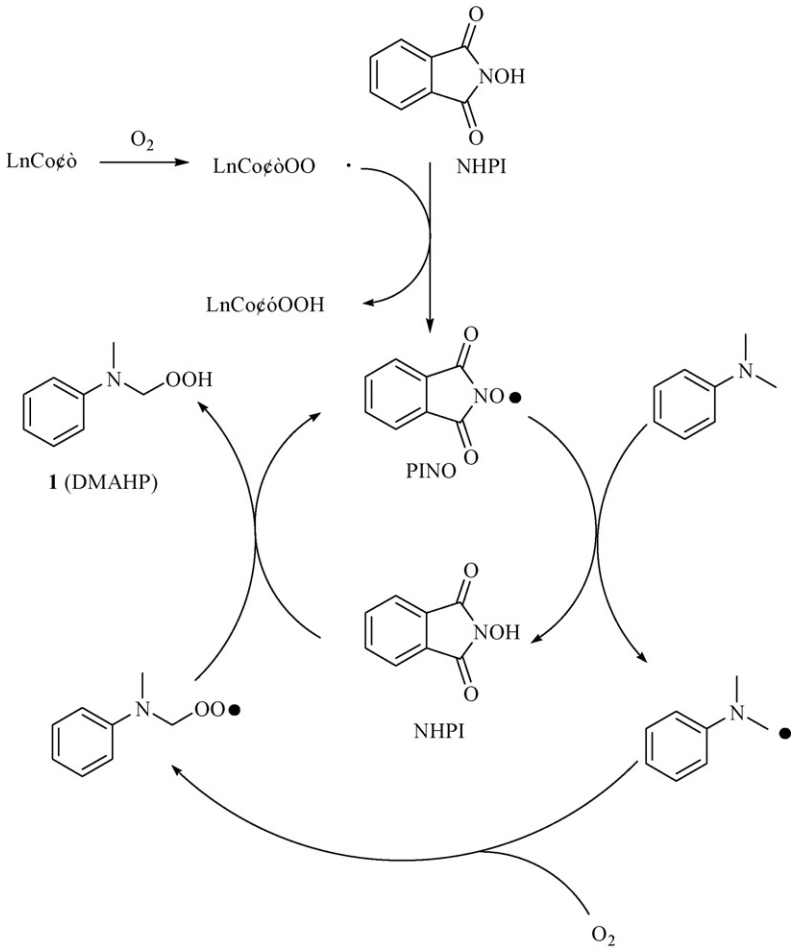
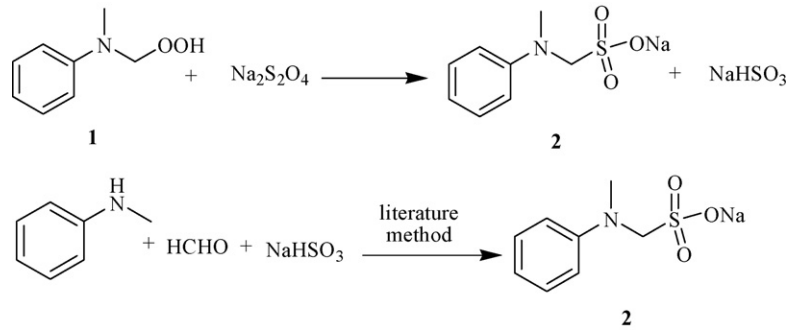


Scheme 1. The proposed mechanism for the synthesis of *N*,*N*-dimethylaniline hydroperoxide (DMAHP).

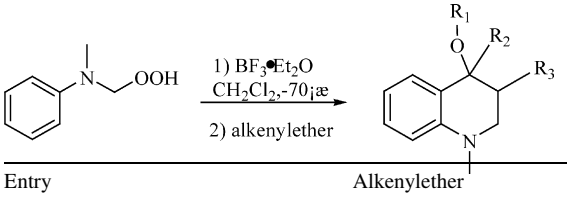
evidence towards this mechanism yet. So compound **2** was synthesized by a reported procedure [12] to corroborate our result. All the characters of compound **2** matched completely with those of the new compound formed by DMAHP with sodium hydrosulfite [13].

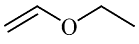
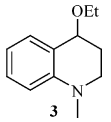
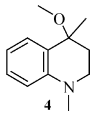
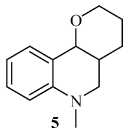
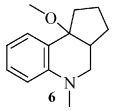
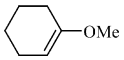
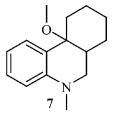
In 1982, Shono and coworkers reported the synthesis of tetrahydroquinolines from *N*-methoxylmethyl-*N*-methylaniline and olefins [14]. We envisioned that DMAHP could serve the same purpose for synthesis of congeners of tetrahydroquinolines. DMAHP was first treated with $BF_3{\cdot}Et_2O$ (1.5 eq) in CH_2Cl_2 at −70 °C for 10 min, then a methylene chloride solution of alkenylether (1.5 eq) was added. After stirred at −70 °C for 30 min, the resulting



Scheme 2.

Table 1
Synthesis of tetrahydroquinolines



Entry	Alkenylether	Product	Yield
1		 **3**	73%
2		 **4**	46%
3		 **5**	48%
4		 **6**	57%
5		 **7**	53%

solution was quenched with 2 eq Et_3N. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to furnish the desired product **3–7** (Table 1). All the compounds were characterized by ^1H NMR, ^{13}C NMR and EI-MS [15].

In conclusion, we have developed a new approach to DMAHP by oxidation of *N*,*N*-dimethylaniline in NHPI/$Co(OAc)_2/O_2$. The structure of DMAHP was confirmed by NMR analysis and a series of experiments. Further investigation of DMAHP is in progress.

Acknowledgment

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[9] Analysis data of DMAHP: ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.25 (m, 2H), 6.83 (m, 3H), 5.18 (s, 2H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 147.4 (C), 129.0 (CH), 118.4 (CH), 113.3 (CH), 87.1 (CH_2), 38.7 (CH_3)

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[13] ^{1}H NMR (300 MHz, D_2O, δ ppm): 7.20 (m, 2H), 6.86 (m, 2H), 6.72 (m, 1H), 4.48 (s, 2H), 2.97 (s, 3H).
[14] T. Shono, Y. Matsumura, K. Inoue, H. Ohmizu, S. Kashimura, J. Am. Chem. Soc. 104 (21) (1982) 5753.
[15] **3**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.20–7.13 (m, 2H), 6.66–6.62 (m, 2H), 4.33 (t, 1H, J = 3.6Hz), 3.59 (m, 2H), 3.42 (m, 1H), 3.11 (m, 1H), 2.92 (s, 3H), 2.17–2.08 (m, 1H), 1.97–1.85 (s, 1H), 1.23 (t, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 146.2 (C), 130.3 (CH), 129.2 (CH), 121.3 (C), 115.4 (CH), 111.2 (CH), 72.9 (CH), 62.9 (CH_2), 46.2 (CH_2), 38.9 (CH_3), 27.3 (CH_2), 15.6 (CH_3); IR (film, cm^{-1}): 3032, 2972, 2928, 2866, 1606, 1575, 1504, 1456, 1315, 1200, 1086, 1009, 972, 743; EI–MS (*m*/*z* %): 192(M^+ + 1, 8), 191 (M^+, 78), 146 (58), 144 (100), 131 (14), 118 (7), 103 (3), 91 (3). **4**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.29 (dd, 1H, J = 7.5, 1.8 Hz), 7.16 (td, 1H, J = 7.5, 1.5 Hz), 6.69 (td, 1H, J = 7.5, 1.2 Hz), 6.61 (d, 1H, J = 8.4 Hz), 3.35 (m, 1H), 3.21 (m, 1H), 3.10 (s, 3H), 2.90 (s, 3H), 2.27 (m, 1H), 1.80 (m, 1H), 1.53 (s, 3H); IR (film, cm^{-1}): 3032, 2933, 2821, 1605, 1572, 1502, 1452, 1333, 1211, 1103, 1076, 879, 746; EI–MS (*m*/*z* %): 192(M^+ + 1, 4), 191 (M^+, 40), 176 (7), 160 (100), 158 (80), 144 (60), 130 (12), 118 (17), 115 (9), 103 (3), 91 (8), 88 (6), 77 (10), 73 (3); HRMS (EI) *m*/*z* calcd. for $C_{12}H_{17}NO$ (M^+): 191.1310, found 191.1313. **5**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.22–7.14 (m, 2H), 6.70–6.62 (m, 2H), 4.42 (d, 1H, J = 3.0 Hz), 3.97 (m, 1H), 3.67 (td, 1H, J = 11.1, 2.4 Hz), 3.54 (t, 1H, J = 11.1 Hz), 2.96 (m, 1H), 2.90 (s, 3H), 2.15 (m, 1H), 1.98–1.70 (m, 3H), 1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 146.7 (C), 130.9 (CH), 129.6 (CH), 121.9 (C), 116.7 (CH), 111.6 (CH), 74.4 (CH), 67.7 (CH_2), 51.3 (CH_2), 39.3 (CH_3), 32.6 (CH), 25.8 (CH_2), 22.8 (CH_2); IR (film, cm^{-1}): 3032, 2930, 2833, 1608, 1574, 1506, 1454, 1360, 1294, 1207, 1092, 1065, 910, 746; EI-MS (*m*/*z* %): 204 (M^+ + 1, 5), 203 (M^+, 32), 174 (1), 158 (6), 146 (7), 144 (100), 132 (3), 117 (2), 103 (1), 91 (2), 77 (3), 65 (0.5), 51 (1). **6**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.34 (dd, 1H, J = 7.5, 1.5 Hz), 7.16 (td, 1H, J = 7.2, 1.5 Hz), 6.78 (td, 1H, J = 7.5, 1.2 Hz), 6.65 (d, 1H, J = 8.4 Hz), 3.03 (m, 1H), 2.98 (s, 3H), 2.84 (m, 1H), 2.84 (s, 3H), 2.65 (m, 1H),2.20–1.40(m, 6H); IR (film, cm^{-1}): 3027, 2953, 2868, 2820, 1605, 1576, 1498, 1450, 1331, 1209, 1074, 970, 752; EI–MS (*m*/*z* %): 217 (M^+, 52), 202 (4), 186 (100), 174 (26), 170 (5), 157 (11), 144 (17), 130 (15), 115 (5), 99 (4), 77 (4), 65 (1), 55 (2); HRMS (EI) *m*/*z* calcd. for $C_{14}H_{19}NO$ (M^+): 217.1467, found 217.1453. **7**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.27–7.14 (m, 2H), 6.67–6.59 (m, 2H), 3.53 (dd, 1H, J = 11.4, 3.6 Hz), 3.07 (m, 1H), 3.03 (s, 3H), 2.92 (s, 3H), 2.45 (m, 1H), 2.07 (m, 1H), 1.77–1.25 (m, 7H); IR (film, cm^{-1}): 2933, 2858, 2821, 1606, 1572, 1506, 1452, 1331, 1211, 1107, 1082, 918, 743; EI–MS (*m*/*z* %): 231 (M^+, 24), 200 (50), 184 (4), 174 (9), 170 (34), 157 (4), 144 (12), 132 (8), 120 (14), 113 (100), 97 (6), 81 (13), 77 (4), 69 (16), 55 (8); HRMS (EI) *m*/*z* calcd. for $C_{15}H_{21}NO$ (M^+): 231.1623, found 231.1615.