Chemoselective Reduction of Nitroarenes and Nitroalkanes by Sodium Dithionite Using Octylviologen as an Electron Transfer Catalyst

Kwanghee Koh Park,* Chang Hun Oh, and Woo-Jeon Sim

Department of Chemistry, Chungnam National University, Taejon 305-764, Korea

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Viologens (1,1'-dialkyl-4,4'-bipyridinium, V^{2+}) have been utilized as electron-transfer catalysts (ETC) for the reduction of various organic compounds.[1-9] We have shown that various aromatic nitro compounds are reduced conveniently to the corresponding aniline derivatives with sodium dithionite using octylviologen (OcV^{2+}) as an ETC in a dichloromethane–water two-phase system, while aliphatic nitro compounds remain intact under the same reaction conditions.[9]

The reduction of nitro compounds may give a range of possible products as shown in eq 1, and numerous

$$RNO_2 \xrightarrow[-H_2O]{2e,\,2H^+} RNO \xrightarrow{2e,\,2H^+} RNHOH \xrightarrow[-H_2O]{2e,\,2H^+} RNH_2 \quad (1)$$

procedures have been developed to obtain the reduction product at a desired stage.[10] In this paper, we report chemoselective reduction of nitroarenes and nitroalkanes with sodium dithionite using OcV^{2+} as an ETC in 1:3 (v/v) acetonitrile–water.

Various tertiary aliphatic nitro compounds were reduced conveniently to the corresponding hydroxylamines in very high yields, whereas aromatic nitro compounds were reduced to the corresponding aniline derivatives under the same conditions (Table 1). Exceptions to this were reduction of 1-nitro-1-phenylcyclohexane (entry 8) and 1-nitroadamantane (entry 9), where mixtures of the hydroxylamine (major) and the amine (minor) were obtained at shorter reaction time and prolonged reaction yielded the amine exclusively. When the viologen was excluded from the reaction system, no reduction was observed. These results clearly indicate that the viologen mediates the reduction. Since the molar ratio of the viologen to the substrate was much less than the stoichiometric value, the active reductant is recycled in the process.

The chemoselectivity of the reduction is manifested clearly in the reaction of 2-methyl-2-nitropropyl *p*-nitrobenzoate (entry 4a), of which aliphatic and aromatic nitro groups present in the same molecule are reduced to hydroxylamine and amine groups, respectively. The same substrate yields different reduction product in dichloromethane–water (entry 4b): an aromatic nitro group is transformed into an amino group, while an aliphatic nitro group remains unreacted. Aliphatic nitro groups in entries 8 and 9, which are reduced to hydroxylamines and then to amines in acetonitrile–water, also remain intact in a dichloromethane–water two-phase system. This result agrees with our previous report.[9] Entry 10 shows that the reduction of an aromatic nitro group to an amino group proceeds at a faster rate in acetonitrile–water than in dichloromethane–water. Clarification of the difference in reactivity of nitro compounds depending on the reaction medium (entries 4, 8, 9, and 10) is beyond the scope of this work.

We also attempted to reduce a secondary aliphatic nitro compound, 1-nitro-1-phenylethane, by the same procedure in an acetonitrile–water medium. Acetophenone oxime was obtained as the major product (see Experimental Section). It can be assumed that the nitro compound is first reduced to the nitroso compound, and the fast nitroso-to-oxime prototropy may prevent the reduction of –NO to –NHOH.[11]

A few methods have been reported for the reduction of aliphatic nitro compounds to hydroxylamines.[12] One is the use of diborane:[13,14] reduction of α,β-unsaturated nitro compounds with diborane in the presence of catalytic amount of $NaBH_4$ or reduction of the salts of primary and secondary nitro compounds with diborane produces hydroxylamines. However, the method cannot be applied for reduction of tertiary nitro compounds to hydroxylamines. Bartra *et al.* demonstrated that tin(II) complexes, $Sn(SR)_3^-$, reduce aromatic and tertiary aliphatic nitro compound to the corresponding hydroxylamines.[11] However, reduction of only one tertiary aliphatic nitro compound, $PhCMe_2NO_2$, was illustrated.

In conclusion, this work demonstrates a mild, convenient, and efficient route for chemoselective reduction of nitroarenes and tertiary aliphatic nitro compounds to the corresponding anilines and hydroxylamines, respectively, *via* viologen-mediated sodium dithionite reduction in acetonitrile–water medium. The mildness of the present method is clearly seen from the fact that cyano (entry 2), carbonyl (entry 5 and 10), and ester groups (entry 3, 4, and 6) remain unaffected in the reaction processes.

Experimental Section

Melting points are uncorrected. ^{1}H-NMR spectra were obtained at 500 MHz, and chemical shifts are reported in δ (ppm) relative to residual solvent ($CHCl_3$ or DMSO) as internal standards. Elemental analyses data were determined by Korea Research Institute of Chemical Technology, Taejon. Octylviologen was prepared from 4,4'-bipyridine and 1-bromooctane.[6]

Substrates. 2-Nitro-2-phenylpropane (**1**) and 1-nitro-1-phenylcyclohexane (**8**) were made by the phenylation of 2-nitropropane and nitrocyclohexane, respectively, with diphenyliodonium

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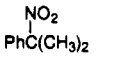
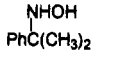
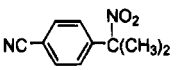
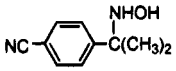
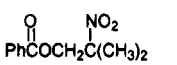
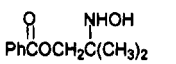
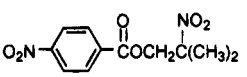
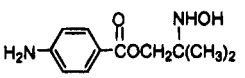
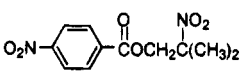
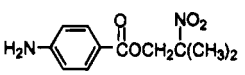
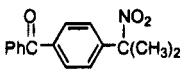
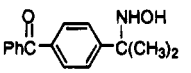
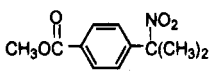
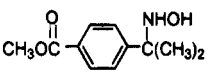
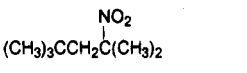
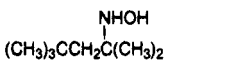
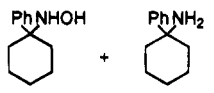
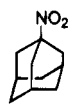
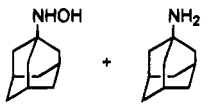
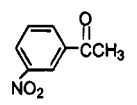
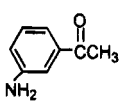
Table 1. Reduction of Nitroarenes to Anilines and Tertiary Nitroalkanes to Hydroxylamines by Sodium Dithionite Using Octyl Viologen as an Electron-Transfer Catalyst[a]

Entry	Substrate	Medium[b]	Time,h	Product[c]	Yield,[d] %
1		A	4		91
2		A	2		93
3		A	4		95
4a		A	7		91
4b		B	4		92
5		A	6		92
6		A	1		91
7		A	2		89
8		A	2		78+16[e,f]
		B	10	No Reaction[g]	
9		A	2		63+34[e,f]
		B	10	No Reaction[g]	
10		A	<0.5		92
		B	1.5		91

[a] The molar ratio of the viologen to the substrate was 1:10. [b] A: 1:3 (v/v) CH_3CN-H_2O. B: 2:1 (v/v)$CH_2Cl_2-H_2O$. [c] The hydroxylamines were isolated and characterized as their HCl salts. [d] Isolated yields. [e] Yields of the amines. [f] After 24 h reaction time, the amine was obtained as the only product. [g] Starting materials were recovered in >90% yields.

tosylate.[15] *p*-Cyano-α-nitrocumene (**2**), *p*-benzoyl-α-nitrocumene (**5**), and *p*-carbomethoxy-α-nitrocumene (**6**) were prepared *via* nucleophilic displacement of the nitro group of the corresponding substituted nitrobenzenes by the lithium salt of 2-nitropropane.[16] 2,2,4-Trimethyl-4-nitropentane (**7**) and 1-nitroadamantane (**9**) were obtained by the oxidation of the corresponding amines with $KMnO_4$.[17] 2-Methyl-2-nitropropyl benzoate (**3**) and *p*-nitrobenzoate (**4**) were prepared by reacting 2-methyl-2-nitropropanol with benzoyl chloride and *p*-nitrobenzoyl chloride, respectively, in diethyl ether using *N,N*-dimethylaniline as a base. 1-Nitro-1-phenylethane was available from our previous study.[8] 3′-Nitroacetophenone (**10**) was purchased from Aldrich.

General Procedure for the Reduction. An aqueous solution (16 mL) containing K_2CO_3 (1.66 g) and $Na_2S_2O_4$ (2.76 g) was added dropwise to a mixture of a substrate (2 mmol) and octylviologen (0.2 mmol, 0.11 g) in acetonitrile (6 mL)–water (2 mL), and the reaction mixture was stirred at 35 °C under a nitrogen atmosphere. A blue color, which is due to the one-electron reduction product of viologen, $OcV^{\bullet+}$, persisted until the end of the reaction. The reaction mixture was made alkaline (pH 12–13) and then extracted with ethyl acetate (30 mL × 4). The combined organic layers were dried with anhydrous Na_2SO_4 and treated with silica gel to remove any remaining viologen species, after which TLC showed a single spot of the corresponding hydroxylamine for all the substrates shown in Table 1 except for entry 8. Since some of the hydroxylamines are labile, they were converted to HCl salts: after removal of solvent by flash evaporation, the residue was dissolved in ether or ethanol and then treated with a saturated ethereal solution of HCl. The salts were recrystallized from ethanol/ethyl acetate unless otherwise noted. Control experiments were carried out in the same manner, but without viologen. Reactions in CH_2Cl_2–water medium were carried out similarly.[9]

2-(Hydroxylamino)-2-phenylpropane hydrochloride (entry 1): mp 169 °C (mp of the free base, 82–85 °C);[11] ^1H NMR (DMSO-d_6) δ 11.79 (2 H, s), 10.80 (1 H, s), 7.62 (2 H, d, J = 8.0 Hz), 7.40 (2 H, t, J = 7.5 Hz), 7.34 (1 H, t, J = 7.2 Hz), 1.65 (6 H, s). Anal. Calcd for $C_9H_{14}ClNO$: C, 57.60; H, 7.52; N, 7.46. Found: C, 57.72; H, 7.43; N, 7.21.

2-(Hydroxylamino)-2-(*p*-cyanophenyl)propane hydrochloride (entry 2): mp 168–169 °C; ^1H NMR (DMSO-d_6) δ 12.04 (2 H, s), 10.94 (1 H, s), 7.88 (2 H, d, J = 8.4 Hz), 7.83 (2 H, d, J = 8.4 Hz), 1.67 (6 H, s). Anal. Calcd for $C_{10}H_{13}ClN_2O$: C, 56.47; H, 6.16; N, 13.17. Found: C, 56.23; H, 6.20; N, 13.25.

2-(Hydroxylamino)-2-methylpropyl benzoate hydrochloride (entry 3): mp 162–163 °C; ^1H NMR (DMSO-d_6) δ 11.70 (2 H, s), 11.03 (1 H, s), 8.15 (2 H, d, J = 7.2 Hz), 7.66 (1 H, t, J = 6.6 Hz), 7.52 (2 H, t, J = 6.8 Hz), 4.33 (2 H, s), 1.37 (6 H, s).

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Anal. Calcd for $C_{11}H_{16}ClNO_3$: C, 53.77; H, 6.56; N, 5.70. Found: C, 53.61; H, 6.66; N, 5.72.

2-(Hydroxylamino)-2-methylpropyl *p*-aminobenzoate dihydrochloride (entry 4a): mp 132–133 °C; ^{1}H NMR (DMSO-d_6) δ 11.61 (2 H, s), 11.0 (1 H, broad s), 7.96 (2 H, d, J = 8.0 Hz), 6.88 (2 H, d, J = 8.0 Hz), 5.76 (3 H, broad, s), 4.24 (2 H, s), 1.34 (6 H, s). Anal. Calcd for $C_{11}H_{18}Cl_2N_2O_3$: C, 44.46; H, 6.11; N, 9.43. Found: C, 44.22; H, 6.38; N, 9.23.

2-Methyl-2-nitropropyl *p*-aminobenzoate (entry 4b): mp 75 °C; ^{1}H NMR ($CDCl_3$) δ 7.78 (2 H, d, J = 8.4 Hz), 6.62 (2 H, d, J = 8.4 Hz), 4.58 (2 H, s), 4.13 (2 H, broad s), 1.68 (6 H, s). Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.57; H, 5.89; N, 11.72.

2-(Hydroxylamino)-2-(*p*-benzoylphenyl)propane hydrochloride (entry 5): mp 166–167 °C; ^{1}H NMR (DMSO-d_6) δ 11.97 (2 H, s), 10.94 (1 H, s), 7.82 (2 H, d, J = 8.2 Hz), 7.74 (4 H, t, J = 9.0 Hz), 7.68 (1 H, t, J = 7.3 Hz), 7.56 (2 H, t, J = 7.5 Hz), 1.71 (6 H, s). Anal. Calcd for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; N, 4.80. Found: C, 65.74; H, 6.29; N, 4.75.

2-(Hydroxylamino)-2-(*p*-carbomethoxyphenyl)propane hydrochloride (entry 6): mp 159–160 °C; ^{1}H NMR (DMSO-d_6) δ 11.93 (2 H, s), 10.92 (1 H, s), 7.96 (2 H, d, J = 8.4 Hz), 7.77 (2 H, d, J = 8.4 Hz), 3.85 (3 H, s), 1.68 (6 H, s). Anal. Calcd for $C_{11}H_{16}ClNO_3$: C, 53.77; H, 6.56; N, 5.70. Found: C, 54.04; H, 6.52; N, 5.50.

2-(Hydroxylamino)-2,4,4-trimethylpentane hydrochloride (entry 7): mp 106–107 °C (recrystallized from ethyl acetate/hexane); ^{1}H NMR (DMSO-d_6) δ 11.12 (2 H, s), 10.70 (1 H, s), 1.62 (2 H, s), 1.31 (6 H, s), 0.97 (9 H, s). Anal. Calcd for $C_8H_{20}ClNO$: C, 52.88; H, 11.09; N, 7.71. Found: C, 52.83; H, 11.12; N, 7.78.

1-(Hydroxylamino)-1-phenylcyclohexane Hydrochloride (entry 8). 1-Nitro-1-phenylcyclohexane was reacted as described. The concentrated ethyl acetate extract was subjected to column chromatography on silica gel eluted with ethyl acetate to separate the hydroxylamine and the amine. Each component was dissolved in ether and treated with saturated solution of HCl to give the corresponding salt. Hydroxylamine hydrochloride (78% yield): mp 215–216 °C; ^{1}H NMR (DMSO-d_6) δ 11.47 (2 H, s), 10.61 (1 H, s), 7.60 (2 H, d, J = 7.5 Hz), 7.44 (2 H, t, J = 7.5 Hz), 7.39 (1 H, t, J = 7.1 Hz), 2.55 (2 H, d, J = 12.8 Hz), 1.95 (2 H, t, J = 12.0 Hz), 1.68 (2 H, m), 1.50 (1 H, m), 1.26–1.17 (1 H, m), 1.15–1.04 (2 H, m). Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15. Found: C, 63.40; H, 8.16; N, 5.91. Amine hydrochloride (16% yield): mp 246–247 °C (lit.[18] 247–248 °C); ^{1}H NMR (DMSO-d_6) δ 8.5 (3 H, s), 7.63 (2 H, d, J = 8.0 Hz), 7.44 (2 H, t, J = 7.6 Hz), 7.36 (1 H, s, J = 7.2 Hz), 2.29 (2 H, m), 1.96 (2 H, m), 1.71 (2 H, m), 1.48–1.20 (4 H, m).

When the reaction was continued for 24 h, the amine was obtained as the only product in 90% yield.

1-(Hydroxylamino)adamantane Hydrochloride (entry 9). 1-Nitroadamantane was reacted as described. A solid was formed as the reaction proceeded. When the starting material was not present, the solid was filtered from the reaction mixture and washed with water and then ethyl acetate to give 1-aminoadamantane in 34% yield. The filtrate was extracted with ethyl acetate, and the combined organic layers were worked up as described to afford 1-(hydroxylamino)adamantane hydrochloride in 63% yield: mp 290 °C dec; ^{1}H NMR (DMSO-d_6)δ 11.23 (2 H, s), 10.60 (1 H, s), 2.10 (3 H, s), 1.81 (6 H, s), 1.65 (3 H, d, J = 12.0 Hz), 1.56 (3 H, d, J = 12.0 Hz). Anal. Calcd for $C_{10}H_{18}ClNO$: C, 58.96; H, 8.91; N, 6.88. Found: C, 59.09; H, 9.10; N, 6.63.

When the reaction was continued for 24 h, the amine was obtained as the only product in 98 % yield.

Reduction of 1-Nitro-1-phenylethane. Reacted as described for 13 h. After separation by column chromatography [silica gel; hexane–ethyl acetate (9:1)], acetophenone (*E*)-oxime[19] (74% yield) and acetophenone (13% yield) were obtained.

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(19) Melting point and spectroscopic data were identical with the reported ones (Smith, J. H.; Kaiser, E. T. *J. Org. Chem.* **1974**, *39*, 728).