Side-Chain Nitration of Styrene and *Para*-Substituted Derivatives with a Combination of Nitrogen Dioxide and Ozone

Hitomi Suzuki* and Tadashi Mori

Department of Chemistry, Graduate School of Science, Kyoto University, Kitashirakawa, Sakyo-ku, Kyoto 606-01, Japan

The side-chain nitration of styrene and four *para*-substituted derivatives **1** with a combination of nitrogen dioxide and ozone has been investigated as part of our continued effort to define the scope of applicability of this new nitration methodology (*kyodai* nitration). Styrene and derivatives underwent a smooth addition reaction across the olefinic bond in dichloromethane at −20 °C, affording the corresponding isomeric nitro-nitrato adducts **2** and **3** in excellent combined yield. ^{1}H-NMR data were collected for all possible nitro-nitrato adducts of styrene and derivatives. The mechanism of the formation of these addition products is discussed in terms of the reversible addition of nitrogen dioxide to form unstable nitroso-nitrates **9** and **10** followed by rapid oxidation of these to the corresponding nitro-nitrates **2** and **3**.

Introduction

β-Nitrostyrenes and derivatives are useful as intermediates for the synthesis of aryl-substituted nitroalkanes, hydroxylamines, aldoximes, ketoximes, amines, and ketones.[1] However, it is quite difficult to achieve direct transformation of styrenes to β-nitrostyrenes due to the highly sensitive nature of the vinylic hydrocarbons concerned; the action of nitration agents commonly used for aromatic nitration results in the formation of an intractable mixture of products. Thus, the literature to date contains only a few scattered reports, which include the treatment of styrene with sodium or potassium nitrate in polyphosphoric acid,[2] nitration of a deactivated styrene with 98% HNO_3 in concentrated H_2SO_4,[3] nitrohalogenation with nitryl halide (NO_2X) followed by dehydrohalogenation with triethylamine,[4] and reaction with tetranitromethane (TNM) in the presence of pyridine.[5] The photochemical charge transfer activation of the electron donor−acceptor (EDA) complex derived from TNM and styrenes in acetonitrile has been reported to give different products depending on the structures of styrenes:isoxazolidines from styrene and *p*-methylstyrene, a β-nitrostyrene from *p*-methoxystyrene, and an α-nitroacetophenone from *p*-chlorostyrene.[6] The action of $HgCl_2$−$NaNO_2$ on styrene results in a varying degree of ring nitration in parallel with the expected addition across the olefinic bond,[4,7] while sonic treatment of styrenes in the presence of $NaNO_2$−$Ce(NH_4)_2(NO_3)_6$−AcOH in a sealed tube gives a high yield of β-nitrostyrenes.[8] Other reagents used for the conversion of styrenes to the β-nitro derivatives include $AgNO_2$−PhSeBr−$HgCl_2$[9] and $AgNO_2$−I_2−ethylene glycol.[10] A recent report of interest describes the action of nitrogen monoxide on styrenes in 1,2-dichloroethane followed by treatment with activated acidic alumina. The reaction is clean and smooth, but it consumes 4 equiv of nitrogen monoxide per one nitro group to be introduced.[11] In order to explore further the possibility of obtaining β-nitrostyrenes directly from styrenes, we have investigated the reaction of styrene and derivatives **1** with nitrogen dioxide in the presence of ozone. The combination of nitrogen dioxide and ozone has recently been shown to be highly efficient as a nitrating agent for a wide variety of arenes (*kyodai* nitration).[12]

Results

In the present work, the reaction of styrenes with nitrogen dioxide and ozone has been investigated using mainly *p*-chlorostyrene as the substrate in dichloromethane at −20 to 0 °C owing to the ease of product analysis and stability of the substrate as well as cleanness of the reaction. Under these conditions, *p*-chlorostyrene gave the best combined yield of nitro-nitrates **2** and **3**. Above this temperature range, the concurrent ring nitration began to be detectable, although its extent was not so significant even at 0 °C, while the reaction carried out below −40 °C began to afford the dinitro adduct **6** at

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* Corresponding author. Tel: +81-75-753-4041. Fax: +81-75-751-2085. E-mail: suzuki@kuchem.kyoto-u.ac.jp.
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Table 1. Reaction of *Para*-Substituted Styrenes 1 with Nitrogen Dioxide and Ozone in Dichloromethane under Various Conditions[a]

R	temp (°C)	yield of nitro-nitrates 2 and 3 (%)	2:3	yield of β-nitroolefin 4 (%)
NO$_2$[b]	−20	95	54:46	49
CF$_3$[b]	−20	99	52:48	50
Cl	0	96	51:49	
	−20	99	47:53	51
	−20	98[c]	41:59	
	−20	100[d]	62:38	
	−20	89[e]	57:43	
	−20	97[f]	54:46	
	−40	62 (29[g])	37:63	
	−78	0 (46[h])		
H	−20	94	40:60	58
Me	−20	94	53:47	43
MeO	−20	0 (21[i])		

[a] Unless otherwise indicated, all reactions were carried out as follows: A dichloromethane solution of substrate (0.4 M, 25 mL) was mixed with nitrogen dioxide (1.0 mL) and kept for 1 h at an indicated temperature; then ozone was introduced at a rate of 10 mmol/h for 1 h. [b] Scale was reduced to one-half (substrate, 0.2 M, 25 mL; nitrogen dioxide, 0.5 mL; reaction time, 0.5 + 0.5 h). [c] Nitrogen dioxide in dichloromethane (10 mL) was slowly added to a solution of substrate (15 mL) over 2 h followed by introduction of ozone. [d] The reaction was carried out with nitrogen dioxide (0.1 mL) in dichloromethane (0.04 M, 25 mL) for 6 min. [e] A dichloromethane solution (10 mL) of methanesulfonic acid (10 mol %) and nitrogen dioxide (1.0 mL) was added dropwise to a solution of substrate (15 mL) over 1 h. [f] Lithium nitrate (5 equiv) was added. [g] Yield of 1,2-dinitro-1-(4-chlorophenyl)ethane. [h] Yield of *p*-chlorobenzaldehyde. Polymeric by-products were also formed.[i] Yield of *p*-anisaldehyde. Small amounts of unidentified products were also detected by ¹H-NMR.

Table 2. ¹H-NMR Chemical Shifts of Aliphatic Protons of Nitro-nitrates 2 and 3 Derived from *Para*-Substituted Styrenes 1

R	product	chemical shift (δ, ppm)[a]	coupling constant (*J*, Hz)
NO$_2$	2	6.77, 4.88, 4.69	9.5, 4.0, 15
	3	6.35, 5.62, 4.82	10.3, 3.3, 16
CF$_3$	2	6.63, 4.86, 4.65	9.8, 3.7, 14
	3	6.28, 5.60, 4.78	10.6, 3.1, 16
Cl	2	6.54, 4.83, 4.61	9.8, 3.7, 14
	3	6.17, 5.55, 4.74	10.6, 3.1, 16
H	2	6.56, 4.83, 4.62	10.0, 3.6, 15
	3	6.19, 5.55, 4.73	10.7, 2.8, 16
Me	2	6.54, 4.84, 4.59 (2.38[b])	10.0, 3.7, 14
	3	6.14, 5.57, 4.70 (2.38[b])	10.7, 3.0, 16

[a] All but methyl protons appear in a double doublet form. [b] Methyl protons.

the expense of nitro-nitrates **2** and **3**. At −78 °C, *p*-chlorobenzaldehyde (46%) was the major product obtained along with some polymeric byproducts, and no further nitro-nitrates could be obtained. A control experiment carried out in the absence of nitrogen dioxide under similar conditions gave the same aldehyde in 41% yield, when no reductive treatment was undertaken. Other styrenes, excepting the *p*-methoxy compound, reacted with nitrogen dioxide with similar ease and cleanness at −20 °C, giving the corresponding addition products **2** and **3** in nearly quantitative combined yield (Table 1). For the convenience of interested researchers, ¹H-NMR chemical shifts and coupling constants of aliphatic protons of all nitro-nitrato adducts obtained are collected in Table 2, thus providing a useful means for identification of these types of compounds.

Treatment of the crude product mixture over a short alumina column using a mixture of *n*-hexane and ethyl acetate (5−20:1) as the eluent provided a simple way to obtain (*E*)-β-nitrostyrenes **4**, the isolated yields of which

Table 3. Reaction of *p*-Chlorostyrene 1 (R = Cl) with Nitrogen Dioxide in the Presence of Ozone in Various Solvents[a]

solvent	yields (%)			material balance (%)
	2	**3**	**6**	
CH$_2$Cl$_2$	47	52	0	99
Cl(CH$_2$)$_2$Cl	52	45	0	97
CHCl$_3$	50	45	0	95
CCl$_4$	37	43	0	80[b]
n-C$_6$H$_{14}$	11	47	33	91[b]
MeCN	36	40	12	88
MeNO$_2$	21	37	36	94

[a] All reactions were carried out in a given solvent (0.4 M, 25 mL) at −20 °C as shown in footnote a in Table 1. [b] Unidentified products were also detected by ¹H-NMR.
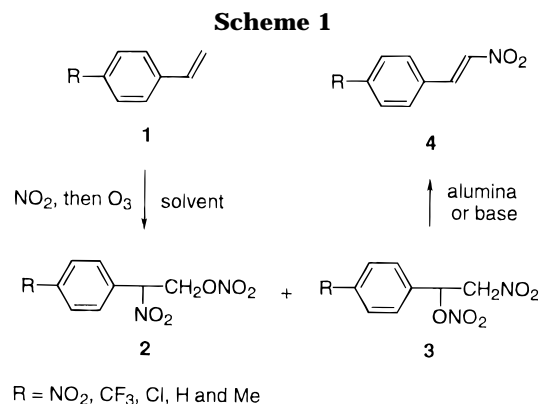
are also included in Table 1. These β-nitrostyrenes **4** were no doubt derived from β-nitro-α-nitrato compounds **3**, whereas the counterpart adducts, α-nitro-β-nitrato compounds **2**, were retained on the column (probably as α-nitro alcohol and/or its descendants) and could not be eluted under the conditions employed. The transformation of adducts **3** into β-nitrostyrenes **4** was also feasible by treating the crude product mixture with a weak base such as aqueous sodium hydrogen carbonate followed by chromatographic separation on a silica gel column. Using the latter method, the α-nitro-β-nitrato adducts **2** were also obtained in acceptable isolated yields (∼40%).

The reaction of *p*-chlorostyrene with nitrogen dioxide and ozone was also examined in several different solvent systems (Table 3). In chlorinated hydrocarbons such as dichloromethane, chloroform, and 1,2-dichloroethane, the reaction was very clean and the addition of NO$_2$ and ONO$_2$ moieties across the olefinic bond was the only reaction that took place. The reaction in carbon tetrachloride was somewhat sluggish, and the expected addition products were accompanied by small amounts of unidentified products. As expected, the reaction in *n*-hexane led to the dinitro adduct **6** in 33% yield in addition to the β-nitro-α-nitrato compound **3** (47%). Interestingly, the reaction in polar solvents such as nitromethane and acetonitrile also produced an appreciable amount of dinitro compound **6** (12−36%) in addition to nitro-nitrates **2** and **3** (21−36% and 37−40%, respectively). A possible explanation for the unexpected results may be that N$_2$O$_4$ might have added partly in the form of nitronium nitrite (NO$_2^+$NO$_2^-$) to the olefinic bond, leading to the adducts **6** and **7** in these polar solvents. This aspect of the *kyodai* nitration of styrenes remains to be clarified.

Discussion

The reaction of alkenes with nitrogen dioxide has not so often been used for the synthesis of nitroalkenes, probably because of the complicated nature of the reaction product arising from competing addition, substitution, oxidation, and C−C bond cleavage. Accordingly, the reported results are often confusing in the literature.[13] The reaction usually affords a complex mixture of dinitro, nitro-nitrito, and nitro-nitrato compounds, often accompanied by further degradation products of these.

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Scheme 1

R—⟨benzene⟩—CH=CH₂   R—⟨benzene⟩—CH=CH—NO₂

1   **4**

NO₂, then O₃ | solvent   ↑ alumina or base

R—⟨benzene⟩—C(NO₂)(CH₂ONO₂)H + R—⟨benzene⟩—C(ONO₂)(CH₂NO₂)H

2   **3**

R = NO₂, CF₃, Cl, H and Me

Scheme 2

Addition products **2** and **3** are known to release the elements of nitrous or nitric acid by the action of a base to give nitroalkenes. However, the product yields are low to modest at best.

As for the styrenes, the yields of nitroolefins are quite poor, and the nitro alcohols (ArCH(OH)CH₂NO₂) obtained are usually accompanied by a complex mixture of products arising from addition, substitution, and oxidative degradation.[14] In the presence of ozone, however, the initially formed unstable nitroso-nitrates **9** and **10** are rapidly converted to nitro-nitrates **2** and **3**, which are stable enough to show little tendency to revert to the original olefin **1** (Scheme 1). This would probably be the reason why the nitro-nitrates **2** and **3** were obtained in good combined yield in the *kyodai* nitration of styrenes and derivatives. The aliphatic nitroso compounds are known to form oximes, which may undergo either hydrolysis to carbonyl compounds, cyclization with a neighboring nitro group to form furoxans, or oxidation to reactive *gem*-nitro-nitroso compounds. The nitroso compounds may also be transformed to diazonium compounds in the presence of excess nitrogen oxides and go into further complicated modes of degradation.[15] Ozone can convert the unstable nitroso-nitrates **9** and **10** rapidly to the stable nitro-nitrates **2** and **3**, thus removing all complexities arising otherwise from the reactions.

Recently, the reaction of nitrogen dioxide with various hexenes has been intensively investigated in *n*-hexane and several other solvent systems, and the major products were fully identified.[16] The heterolytic reaction of nitrogen dioxide *via* nitrosonium nitrate (NO⁺NO₃⁻)[17] was effectively depressed by using *n*-hexane as the solvent, where the dinitro adducts resulted as the major products.[16] The reversible nature of this addition reaction has been confirmed by ¹H-NMR monitoring using 2,3-dimethyl-2-butene as a substrate and benzene, ether, or *n*-hexane as the solvent.[16] The mechanism of the addition of nitrogen dioxide to alkenes has been studied extensively by kinetic[18,19] and spectroscopic means.[20] The
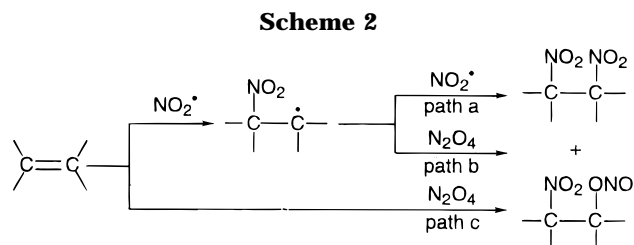
¹⁵N nuclear polarization has revealed that the addition of two molecules of nitrogen dioxide to alkene in *n*-hexane occurs stepwise and gives rise to both dinitro and nitro-nitrito compounds (Scheme 2, path *a*).[20] However, different modes of addition may also be operative under certain conditions, since the kinetic order of the reaction becomes higher in [NO₂]. Thus, at high nitrogen dioxide concentration, the initial attack by dimeric molecule N₂O₄ may partly contribute to the addition (path c),[18] while the reaction between an intermediate carbon radical and N₂O₄ may also be competitive (path b).[19] In chloroform solution, however, the reaction of alkenes with nitrogen dioxide has been reported to give only the corresponding nitroso-nitrates.[21] A recent paper[22] reported the quantitative formation of β-nitro-α-nitrato adducts from the nitration of *p*-nitro- and *p*-(trifluoromethyl)styrenes with dinitrogen pentoxide at low temperatures in dichloromethane.[23] However, for more activated substrates such as the parent styrene as well as the 4-chloro and 4-methyl derivatives, the reaction proceeded quickly and gave a complex mixture of products composed of nitro-nitrates, dinitrates, dinitro compounds, and ring nitration products, among which the nitro-nitrato adducts were prominent.[24–26]

Based on our experimental results, a tentative pathway from styrene **1** to the side-chain nitration products **2** and **3** in the *kyodai* nitration is depicted in Scheme 3. In dichloromethane, 1,2-dichloroethane, and chloroform, the addition of nitrogen dioxide to the olefinic double bond may occur *via* a heterolytic mode, where the NO⁺ and ONO₂⁻ moieties add successively to yield the corresponding nitroso-nitrato adducts **9** and **10**. This addition process is considered to be reversible, since the initially formed nitroso-nitrato adducts were found to be gradually transformed into the dinitro products **6** when the reaction mixture stood in the absence of ozone. As far as can be judged from the ¹H-NMR spectra, the major compounds present in the reaction mixture were the addition products, especially so at higher temperatures. In order to estimate the relative stability of these two unstable nitroso-nitrato adducts **9** and **10**, PM3 calculations were carried out to obtain the heats of formation of the relevant adducts. The results disclosed that the dinitro

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(23) Addition of N₂O₅ to the olefinic bond is known to occur in a *cis*-mode at low concentration.[24] Thus, the electrogenerated N₂O₅ has been reported to add to *trans*-stilbene to yield a *threo* product,[25] and the nitration of styrene with acetyl nitrate has been reported to give the β-nitroacetate *via cis*-addition.[26]

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Scheme 3
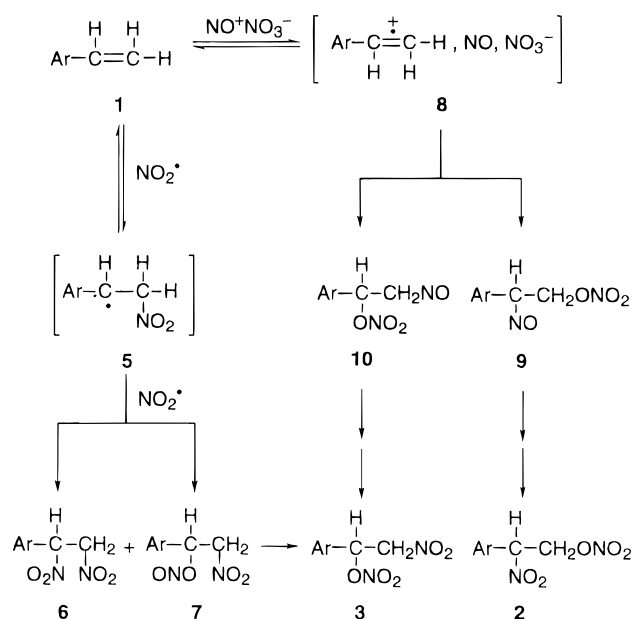
Table 4. PM3-Calculated Heats of Formation of Nitroso-nitrates 9 and 10 and Dinitro Compounds 6 and Ionization Potential of *Para*-Substituted Styrenes 1

		H_f (kJ/mol)			
R	IP (eV)	**9**	**10**	**6**	ΔH_f (kJ/mol)[a]
NO2	10.00	26.99	27.70	11.95	15.4
CF3	9.72	−600.50	−599.74	−613.27	13.2
Cl	9.01	30.81	31.42	9.16	22.0
H	8.94	57.65	55.28	34.51	22.0
Me	9.13	17.90	15.44	−6.01	22.7
MeO	8.73	−102.26	−105.02	−126.79	23.2

[a] ΔH_f values are obtained as the difference of a heat of formation of dinitro compound and a mean heat of formation of two isomeric nitroso-nitrates.

compounds **6** are generally preferred in energetic terms by 13−23 kJ/mol as compared to the mean values of the isomeric nitroso-nitrates **9** and **10**, in accordance with the above observation (Table 4). Thus, this would probably be the major reason why the relative contribution of nitrosonium nitrate (NO⁺NO3⁻) is lowered and the radical addition of nitrogen dioxide becomes preferred in nonpolar solvents. In *n*-hexane as the solvent, the ratio of β-nitro-α-nitrato *versus* α-nitro-β-nitrato adducts was quite large, and the initial addition of nitrogen dioxide to the β-carbon was apparently favored. Although the GLC and ¹H-NMR monitorings of the reaction process confirmed the complete disappearance of styrenes **1** about 1 h after the addition of nitrogen dioxide, the reaction profiles obtained at −78 °C were found to be almost identical with those of simple ozonolysis of styrenes examined under similar conditions, clearly showing the reversible nature of the addition of nitrosonium nitrate to the olefinic bond even at such a low temperature.

The reversible addition of nitrosonium nitrate to the styrenes may be initiated *via* the electron transfer between the olefin donor **1** and nitrosonium ion. Although the calculated ionization potentials of the styrene derivatives vary considerably (Table 4), the charge transfer bands of the EDA complexes of [olefin, NO⁺]NO3⁻ have been observed and the olefinic radical cations have also been spectrally identified as the first observable intermediate upon irradiation.[17] In our case, therefore, the first intermediate would be a styrene radical cation,

which subsequently couples with either the nitrate anion or nitrogen monoxide, eventually leading to the isomeric nitro-nitrates **2** and **3** *via* intermediates like **9/10**. PM3 calculation of the frontier electron densities for the styrene radical reaction (*fd*-R, *f*R)[27,28] showed that the initial addition of nitrogen dioxide occurs at the terminal β-carbon (see Table 5 in Supporting Information). The calculated LUMO densities or frontier densities (*fd*-R) of the relevant radical cations also showed higher values at the β-carbon than at the α-carbon, indicating that the coupling of the nitrate anion or nitrogen monoxide with the styrene radical cation in an intermediate pair (**8**) occurs preferentially at the β-carbon in accord with the prediction of the Pross−Shaik CM model.[29] Thus, the present reaction of styrenes with nitrogen dioxide and ozone may well be characterized such that the initial addition of N2O4 to the olefinic bond occurs reversibly *via* the electron transfer mechanism to form the nitroso-nitrates **9** and **10**, which undergo rapid oxidation of the nitroso group to the nitro group in the presence of ozone to yield the nitro-nitrates **2** and **3** as the final products.

Summary

Successive treatment of styrene and derivatives **1** with nitrogen dioxide and ozone in dichloromethane at 0 to −20 °C afforded the corresponding isomeric nitro-nitrato adducts **2** and **3** in excellent combined yield. The β-nitro-α-nitrato adducts **3** easily released the elements of nitric acid by the action of a weak base such as sodium hydrogen carbonate or alumina, giving the corresponding β-nitrostyrenes **4** in good yield. The reaction most likely starts with a reversible addition of N2O4 (=NO⁺NO3⁻) to form the labile nitroso-nitrato adducts **9** and **10** followed by rapid oxidation of these nitroso-nitrates to the nitro-nitrates **2** and **3** in the presence of ozone. Semiempirical PM3 calculations carried out on styrenes **1** and their radical cations also support the initial electron transfer between the styrene donor and nitrosonium nitrate, although more detailed studies are needed to reach a conclusion.

Experimental Section

Nitration of Styrene and Derivatives with a Combination of Nitrogen Dioxide and Ozone. Typical Procedure. To a solution of styrene in freshly distilled CH2Cl2 (10 mmol, 0.4 M, 25 mL) was added nitrogen dioxide (1 mL) in one portion with a glass syringe in the dark at a given temperature externally controlled by a cooling bath. After 1 h, ozonized oxygen was bubbled in continuously from the glass inlet tube for 1 h (10 mmol of ozone in a flow of 10 L of oxygen). The reaction was quenched with ice-cooled water, and the organic phase was separated, extracted, washed with brine and water, dried with anhydrous sodium sulfate, and evaporated, leaving a mixture of two isomeric nitro-nitrates as an oily residue. The progress of the reaction was monitored by GLC at a low

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injection-port temperature (typically 100 °C), and the final product composition was determined by ^{1}H-NMR analysis.

Supporting Information Available: Results of semiempirical calculations and one ^{1}H-NMR chart of a typical product mixture (**2** and **3** for R = Cl) (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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