Pursuit of Reaction Process of 4-Nitrotoluene with Potassium *t*-Butoxide in *N*, *N*-Dimethylformamide in the Presence of Air by High-Performance Liquid Chromatographic Methods with UV and Three-Dimensional Photodiode Array-UV Detections

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In the presence of air at room temperature, a reaction of 4-nitrotoluene with potassium *t*-butoxide in *N*,*N*-dimethylformamide gave interestingly bis(3-hydroxy-4-nitrophenyl)-acetylene *via* 1,2-bis(4-nitrophenyl)ethane, 4,4'-dinitrostilbene and bis(4-nitrophenyl)-acetylene, and the reaction progress was pursued by high-performance liquid chromatographic (HPLC) methods with both a UV and a three-dimensional photodiode array-UV detections. The reaction process could be successfully shown on profiles by the above UV-HPLC methods.

Potassium *t*-butoxide (*t*-BuOK) is a quite well known and convenient reagent for organic syntheses. In the previous papers,[1] we reported that the new formation of a carbon-carbon triple bond (-C≡C-) from a carbon-carbon double bond (-CH=CH-) and the direct hydroxylation into the *ortho*-position of a nitro group on the benzene nucleus were observed when 4-substituted 4'-nitrostilbenes were treated with *t*-BuOK in *N*,*N*-dimethylformamide (DMF) in the presence of air at room temperature. Further, a radical anion species was detected in the step of dehydrogenation of 4-diethylamino-4'-nitrostilbene, and thus the mechanism *via* the radical anion was proposed. In this study, the method above was applied to 4-nitrotoluene (NT). The oxidative coupling of NT has been so far reported by several authors. The preparation of 1,2-bis(4-nitrophenyl)ethane (NE) and/or 4,4'-dinitrostilbene (NS) from NT was carried out by the treatment as follows: passing air or oxygen through the mixture of NT with a methanolic KOH solution of NT[2] or *t*-BuOK/*t*-BuOH.[3] The conversion of NE into NS was reported by Stunbury, Jr. and Proops under the conditions of ethylenediamine/methanolic KOH/oxygen.[4] However, the direct conversion of NT to bis(4-nitrophenyl)acetylene (NA) and bis(3-
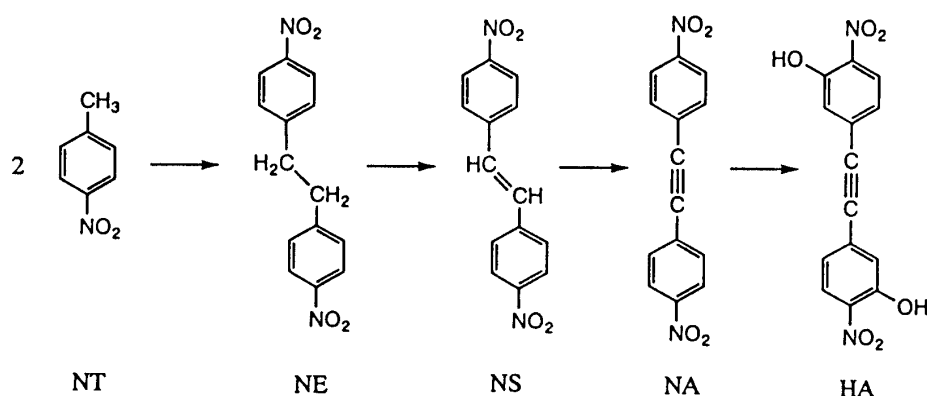
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hydroxy-4-nitrophenyl)acetylene (HA) has not reported so far. Under the conditions developed in our laboratory, we have carried out the reaction of NT stated in ref. 1 (a) and (c) and got interesting results, namely, we found that NA and HA are produced in succession of the formation of NE and NS (Scheme 1). The reaction aspect was investigated by using high-performance liquid chromatographic (HPLC) methods with a UV and a three-dimensional photodiode array-UV detections. In this paper, we tried to clarify these reaction processes from NT to NA and HA via NE and NS by the above HPLC-UV methods.

Scheme 1

NT → NE → NS → NA → HA

Results and Discussion

As shown in Scheme 1, three reactions originated from NT, $i.e.$, a) deprotonation from a methyl group, b) dehydrogenation from NE or/and NS, and c) direct hydroxylation against the o-position of a nitro group on the benzene ring, seem to occur one after another by t-BuOK (5-15 molar excess to the substrate) under the reaction conditions ($cf.$ Experimental). Even if, the treatment by the base was applied to NE, NS or NA, the final product was HA (Scheme 1). The reaction products obtained were purified by a flash column chromatography with silica gel and have been assigned to the compounds NE, NS, NA and HA by elemental analyses and their spectral data (UV, IR, ^{1}H NMR and EI-MS). Then, we have pursued steps of the above reactions by employing an HPLC method. The separation of five standard substances (NT, NE, NS, NA and HA) was accomplished with a reversed phase silica-gel column by using an acetonitrile-10 mM (1 M = 1 mol dm^{-3}) phosphate buffer (pH 5.3-7.5) (70:30, v/v) solution. A typical chromatogram of these compounds is shown in Fig. 1. In order to confirm each reaction step in Scheme 1, the substances resulted from NT, NE, NS or NA employed as a starting material were analyzed at regular intervals. Time course experiments for the formation of reaction products by the procedure described in Experimental are shown in Fig. 2(a) - (d) in which peak areas
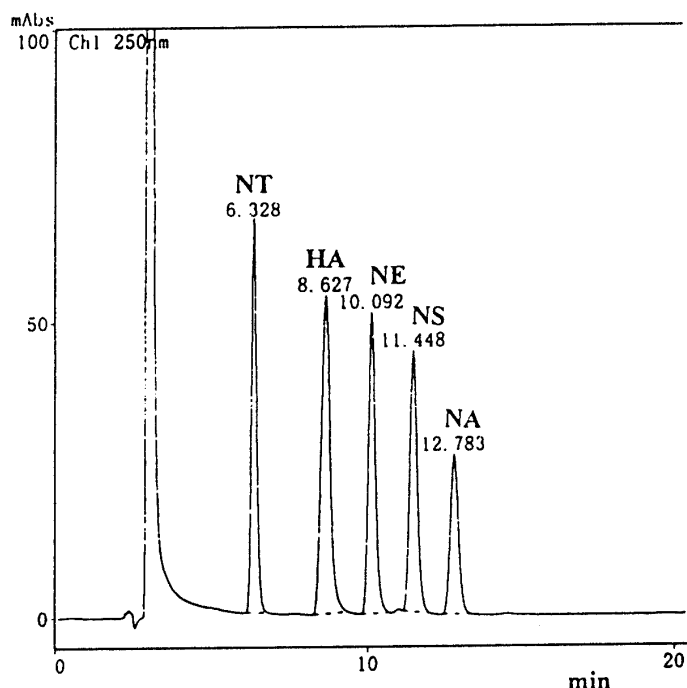
Fig. 1. Chromatogram of the standard substances.

HPLC conditions: pump, Shimadzu LC-10AS; detector, Shimadzu SPD-M6A (250 nm); column, Daisopak-SP-120-4-ODS (250 x 4.6 mm, i.d.); eluent, MeCN-10 mM phosphate buffer (pH 5.5, 70:30, v/v); flow rate, 1.0 ml/min; injector, Rheodyne 7125 with a 20 μl sample loop.

are expressed by an arbitrary unit and are not directly related to concentration. In the all cases, we could observe the increase of HA with the decrease of the starting compound. A very dramatic result was characteristically obtained in the case of NT. As illustrated in Fig. 2(a), we could catch the reaction profiles as follows: (1) the quite rapid decrease of the starting material, (2) the intense increase within ca. 2 min and the linear decrease of NE, (3) the gradual ups and downs of both NS and NA (cf inset), (4) the steady increase of HA. Conclusively, characteristic ups and downs observed in Fig. 2(a)-(d) could clarify that a sequence of the reactions from NT to HA goes stepwise by way of NE, NS and NA as shown in Scheme 1. Being quantitatively recovered after the treatment with the base even until 5 h, HA was defined as the final product in these reactions. For the measurement of three-dimensional chromatograms, an HPLC system equipped with a photodiode array UV-detector was employed to examine whether each single peak consists of a pure component or not. We could show very excellent profiles of a three-dimensional analysis in the reactions of NT under the conditions in Fig. 3, from which it was observed that the peak due to NT decreased rapidly and the bands corresponding to NE and NS grew within 1 min; after elapse of 1h, the disappearance of NT, the decrease of NE, the increase of NS and the formation of both NA and HA were subsequently occurred;

the largest peak being invariable from the beginning to the end was assigned to DMF. These absorption spectra agreed completely with those of the corresponding authentic compounds. Yields of
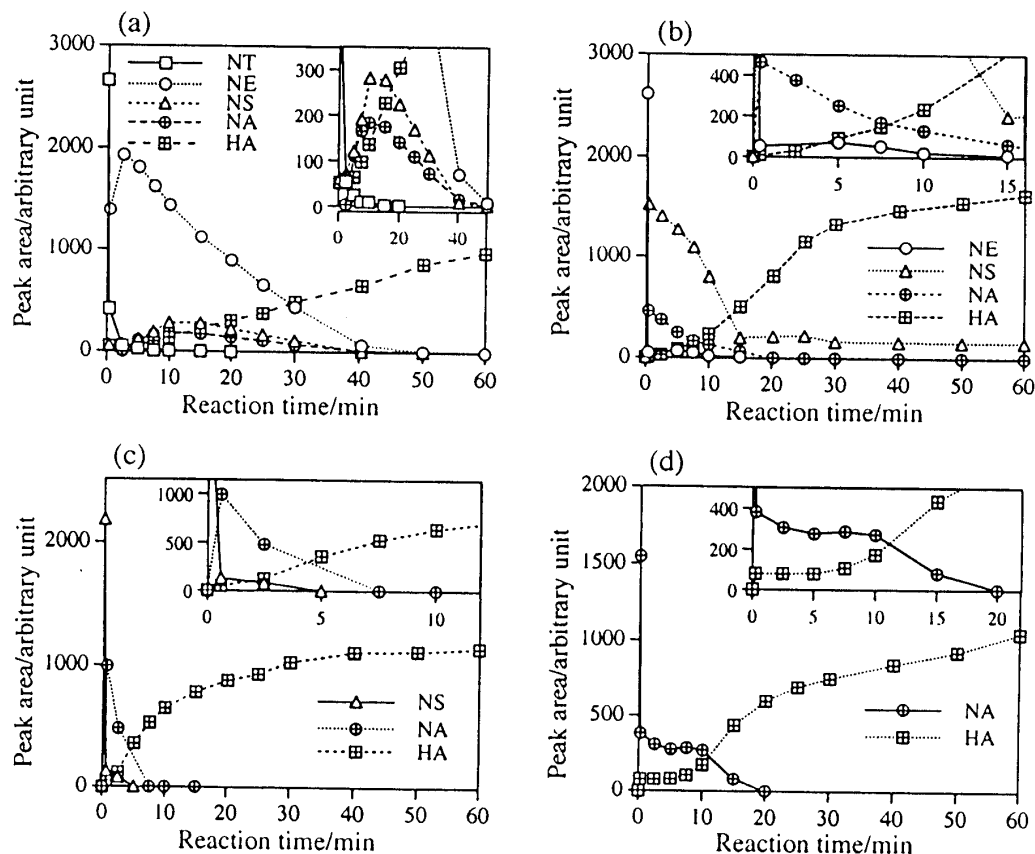

Fig. 2. Time course for the formation of reaction products of a starting material [NT (a), NE (b), NS (c) or NA (d)] with t-BuOK in DMF.

HPLC conditions: pump, Tosoh CCPD; detector, Hitachi variable wavelength UV monitor (250 nm); column, Daisopak-SP-120-4-ODS (250 x 4.6 mm, i.d.); eluent, MeCN-10 mM phosphate buffer (pH 7.5, 70:30, v/v); flow rate, 1.0 ml/min; injector, Rheodyne 7125 with a 20 μ l sample loop.

each step were obtained from HPLC as follows: NT to NE, 70; NE to NS, 68; NS to NA, 71; NA to HA, 30%. Total yield of HA from NT was ca. 10% and the yield agreed approximately with that of HA estimated by a calibration method.

In conclusion, we propose a simple synthetic method for HA starting from NT, NE, NS or NA and have shown that these reaction processes were thoroughly explained by a UV and a three dimensional UV-HPLC techniques which might be convenient and powereful tools for microanalyses of the process of various organic reactions.
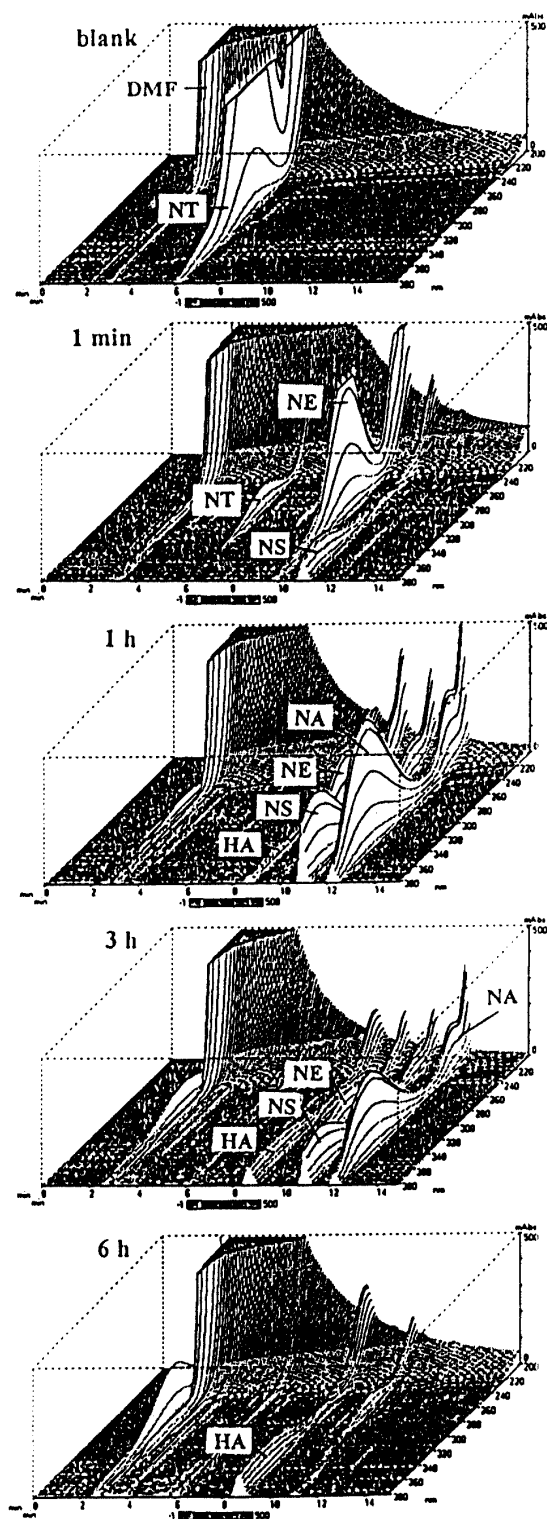
Fig. 3. Chromatograms with a three-dimensional photodiode array UV detection.

HPLC conditions: Shimadzu LC-10AS; detector, Shimadzu SPD-M6A photodiode array; column, Daisopak-SP-120-4-ODS (250 x 4.6 mm, i.d.); eluent, MeCN-10 mM phosphate buffer (pH 5.5, 70:30, v/v); flow rate, 1.0 ml/min; injector, Rheodyne 7125 with a 20 μ l sample loop.

Experimental

Apparatus

Melting points were measured on a Yanagimoto MP-35 melting point apparatus and are uncorrected. The other apparatuses used were a UV-250F and a Hitachi UV-250 spectrometers, IR spectra on a JASCO 810 spectrophotometer, ^{1}H NMR spectra in CDCl$_3$ solution on a Varian unity plus 500 (500 MHz) and a JEOL LNMGX-400 (400 MHz) spectrometer with Me$_4$Si as the internal standard (*J* values are given in Hz).

HPLC instrumentation

The HPLC system consisted of a Tosoh CCPD pump, a Rheodyne Model 7125 injector with a 20 μl sample loop, a Daisopak-SP-120-4-ODS (250 x 4.6 mm, i.d.), a Hitachi variable wavelength UV monitor and a Sic chromatocorder 12. For the measurement of three-dimensional chromatograms, a Shimadzu LC-10AS HPLC system equipped with an SPD-M6A photodiode array UV-VIS detector was used.

Preparation of an HPLC sample solution and measurement of time course

The HPLC sample solution for the time course experiments of NT with *t*-BuOK was prepared as follows: A solution of *t*-BuOK in DMF (0.36 M, 1 ml) was added to a solution of NT in DMF (2.4 mM, 1 ml); after stirring, the mixture (50 μl) was taken and merged with the eluent (900 μl) as described in Fig. 2; 0.2 M HCl (50 □l) was added to stop the reaction; the resultant solution (20 □l) was injected onto HPLC at regular intervals.

Reaction of NT with t-BuOK in DMF

A typical procedure example for the reaction of NT is as follows: a mixture of NT (0.27 g, 2 mmol) and *t*-BuOK (3.32 g, 30 mmol) was stirred in DMF (20 ml) at room temperature for 3 h. The reaction was stopped by adding water (100 ml). The resulting mixture was adjusted to pH 3 with 2 M HCl and the organic layer was extracted with benzene (200 ml). The extract was washed with water and then with 10% aqueous NaOH (10 ml) to transfer acidic compounds into the aqueous layer, which was adjusted to pH 2 with 2 M HCl and extracted with benzene. Evaporation of the extract under reduced pressure afforded HA (0.09 g) as yellow crystals. Neutral mixtures (0.17 g) were obtained as yellow crystals from the organic extract after alkali washing by evaporating under reduced pressure. Condensation of the organic extract under reduced pressure gave neutral compounds as yellow crystals, which were separated by a column chromatography (SiO$_2$, benzene) into pure NS (0.02 g), NE (0.01 g) and NA (0.01 g). All the compounds obtained were identified with the corresponding authentic samples.[c]

Reaction of NE with t-BuOK in DMF

A mixture of NE (0.20 g, 0.7 mmol) and *t*-BuOK (1.19 g, 11 mmol) was stirred in DMF (20 ml) at room temperature for 3h. A post-treatment of the reaction was followed as the same as the case of DNT described above. Neutral (0.13 g) and acidic compounds (0.06 g) were obtained as yellow crystals. These compounds were separated by a column chromatography (SiO$_2$, benzene) and then purified by recrystallization from benzene.

NE: mp 180-182°C (lit.,[2] 179-180°C) (Found: C, 61.67; H, 4.42; N, 10.30%. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29%); δ_H (CDCl$_3$) 3.08 (4H, s, CH$_2$), 7.28 (4H, d, J8.79, ArH), 8.14 (4H, d, J8.79, ArH); EI-MS (*m/z*) 272 (M$^+$).

NS: mp 294-296°C (lit.,[4] 293-295°C) (Found: C, 62.22; H, 3.76; N, 10.30%. Calcd for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.74; N, 10.37%); δ_H (CDCl$_3$) 7.31 (2H, s, CH=CH), 7.70 (4H, d, J8.79, ArH), 8.27 (4H, d, J8.79, ArH); EI-MS (*m/z*) 270 (M$^+$).

NA: mp 204-207°C (lit.,[1c] 205-207°) (Found: C, 62.83; H, 3.26; N, 10.39%. Calcd for $C_{14}H_8N_2O_4$: C, 62.68; H, 3.01; N, 10.45%); δ_H (CDCl$_3$) 7.72 (4H, d, J8.79, ArH), 8.27 (4H, d, J8.79, ArH); EI-MS (*m/z*) 268 (M$^+$).

HA: mp 249-252°C (lit.,[1c] 250-252°C) (Found: C, 56.09; H, 2.86; N, 9.23%. Calcd for $C_{14}H_{10}N_2O_6$: C, 56.00; H, 2.69; N, 9.33%); δ_H (CDCl$_3$) 7.14 (2H, dd, J1.46/8.79, ArH), 7.34 (2H, d, J1.46, ArH), 8.13 (2H, d, J8.79, ArH), 10.62 (2H, s, OH); EI-MS (*m/z*) 300 (M$^+$).

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