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On-Column Organic Reactions. III.[1] Catalysis by Phenol in the Nitration of *p*-Nitrophenol with Aqueous Nitric Acid on an Extrelut Column[2]

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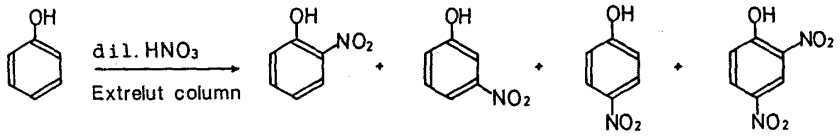
On prolongation of the reaction time in the on-column nitration of phenol (**1**) with 19% nitric acid at room temperature, the yield of 2,4-dinitrophenol (**5**) increased. The dinitro compound **5** was derived from *p*-nitrophenol (**4**) through catalysis by **1** and was not obtained from *o*-nitrophenol (**3**). The formation of **5** from **4** in the on-column nitration was also catalyzed by several kinds of phenol derivatives.

Keywords——on-column organic reaction; on-column nitration; Extrelut; nitration; phenol; 2,4-dinitrophenol; *p*-nitrophenol; catalysis

In our studies on the use of liquid–liquid partition chromatography for conducting organic experiments,[3] an Extrelut column was found capable of serving as a vessel in which reactions occur on the surface of a heterogeneous mixture, such as Schotten–Baumann reactions of phenols with benzoyl chloride.[4] A benzene solution of phenol (**1**) (mobile phase) was allowed to come into contact with 19% nitric acid solution (stationary phase) on an Extrelut column at room temperature for 10 min to afford *o*- and *p*-nitrophenols (**2** and **4**) as main products and very small amounts of *m*-nitrophenol (**3**) and 2,4-dinitrophenol (**5**) together with minimal formation of a reddish-brown tarry substance.[1]



1 **2** **3** **4** **5**

While conducting the above on-column nitration, the 2,4-dinitro product **5** was observed to be formed from the *p*-nitro intermediate **4**; this reaction was accelerated by the addition of a small amount of **1**. The present paper describes in detail the results obtained on this nitration.

Results and Discussion

Figure 1 shows the yields of **2**, **4** and **5** in the on-column nitration of **1** with 19% nitric acid at different reaction times at room temperature. The yields were determined by high performance liquid chromatography (HPLC) using a LiChrosorb SI-60 column and a mixture of *n*-hexane, ethyl acetate, water-saturated ethyl acetate and acetic acid (75 : 20 : 5 : 0.3) as the eluent.[5] As the reaction time was prolonged, the yield of **4** decreased while that of **5** increased at the same time. However, there was no appreciable change in the yield of **2**. Thus **5** is clearly formed from the *p*-nitro intermediate **4**.

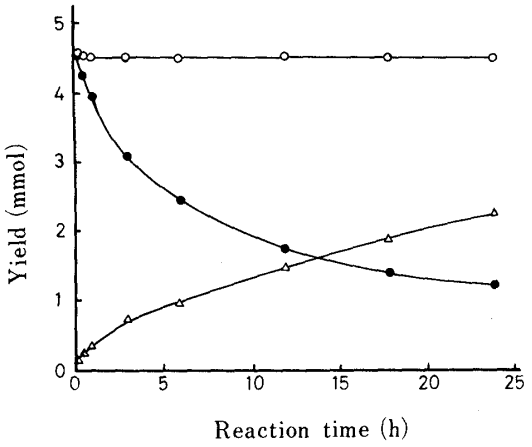


Fig. 1. Yields of **2**, **4** and **5** in the On-Column Nitration of Phenol at Various Reaction Times[a]

○—○, *o*-nitrophenol (**2**); ●—●, *p*-nitrophenol (**4**); △—△, 2,4-dinitrophenol (**5**). *a*) For details of the procedure, see Experimental.

TABLE I. On-Column Nitration of *o*- and *p*-Nitrophenols in the Presence of Various Phenols[a]

Entry	Catalyst[b]	Yield (mg) [%][c] of **5**
1	Phenol	226.7 [24.6]
2	*o*-Cresol	215.3 [23.4]
3	*m*-Cresol	194.6 [21.2]
4	*p*-Cresol	171.0 [18.6]
5	*o*-Chlorophenol	194.3 [21.1]
6	*m*-Chlorophenol	182.6 [19.8]
7	*p*-Methoxyphenol	211.9 [23.0]
8	BHT[d]	206.0 [22.4]
9	BHA[e]	233.9 [25.4]
10	TBHQ[f]	196.4 [21.4]
11	Hydroquinone	262.0 [28.4]
12	2,4,6-Trimethylphenol	215.3 [23.4]
13	*p*-Dimethoxybenzene	168.4 [18.3]
14	1-Naphthol	196.0 [21.3]
15	2-Naphthol	134.7 [14.6]

a) For details of the procedure, see Experimental. *b*) A catalyst (0.01 g) was added to the mobile phase. *c*) The yield was evaluated based on the amounts of **2** and **4**. *d*) 2,6-Di-*tert*-butyl-4-methylphenol. *e*) 2-*tert*-Butyl-4-methoxyphenol. *f*) 2-*tert*-Butylhydroquinone.

For confirmation of the above conclusion, benzene solutions of **2** and **4** were each brought into contact with 19% nitric acid on an Extrelut column at room temperature for 36 h and a small amount of **5** was confirmed to be formed in the reaction of **4** by HPLC.[6] However, no 2,4-dinitro product was produced from **2** under similar reaction conditions.

The question thus arises as to why the original on-column nitration of **1** gives **5** in fairly good yield. The results of the following experiments answered this question. When a small amount (0.01 g) of **1** was added to the mobile phase of the above on-column nitration of **4**, the yield of **5** was considerably improved (*ca.* 44%).[7] However, **5** was not formed from **2** even after the addition of **1**.

The above results clearly indicate the formation of the dinitro product **5** in the on-column nitration of **1** with aqueous nitric acid to be accelerated by unreacted **1** remaining in the reaction mixture.

This reaction was also accelerated by the addition of several kinds of phenolic and aromatic compounds but not by resorcinol, anisole, naphthalene or *N*,*N*-dimethylaniline. That is, a mixture of equal amounts of **2** and **4** and 0.01 g of a phenol derivative in benzene

TABLE II. Nitration of *o*- and *p*-Nitrophenols in a Suspension of Aqueous Nitric Acid and Benzene in the Presence of Phenol[a)]

Reaction time (h)	Contents (in benzene/in H_2O) (mmol)[b)]		
	2	**4**	**5**
1	2.42/0.07	0.70/1.74	0.01/0.01
2	2.43/0.05	0.66/1.74	0.04/0.02
4	2.37/0.07	0.66/1.69	0.07/0.01
7	2.39/0.05	0.55/1.56	0.19/0.02
15	2.35/0.06	0.47/0.83	0.96/0.07
24	2.33/0.05	0.39/0.66	1.26/0.07

a) The reaction was conducted in a flask in the usual manner at room temperature for 24 h. For details of the procedure, see Experimental. *b*) Products **2**, **4** and **5** derived from the additional **1** used as the catalyst are included, but their amounts are negligible.

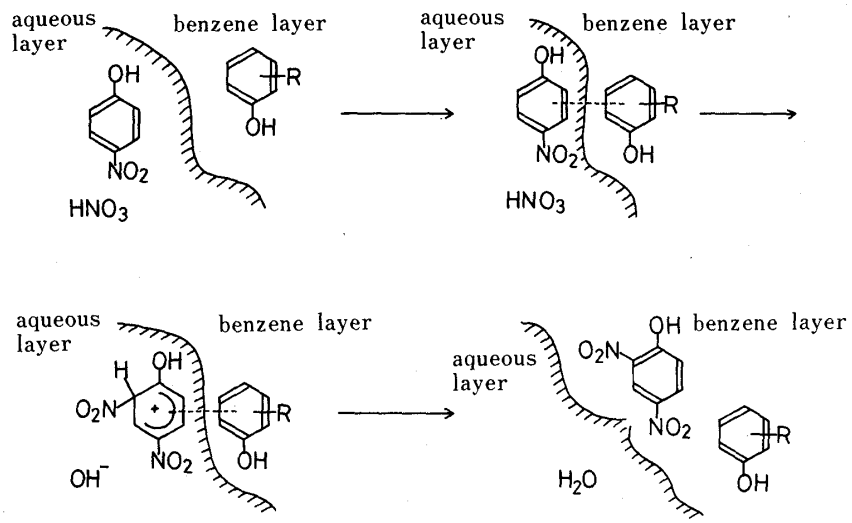


Chart 1

was subjected to the on-column nitration with 19% nitric acid following the general procedure. The yields of **5** in the above reactions are shown in Table I.

For clarification of the mechanism of formation of the 2,4-dinitro product from **4**, the distributions of **2**, **4** and **5** in both the stationary and mobile phases were examined. A mixture of **2** and **4** in benzene was shaken with 19% nitric acid in a flask at room temperature for 1, 2, 4, 7, 15 and 24 h. The contents of **2**, **4** and **5** in each phase were determined by HPLC, and the results are shown in Table II.

Compound **2** was clearly confirmed to be present in the organic layer and not to react with nitric acid. The *p*-nitro isomer **4**, however, was distributed in the aqueous and organic layers at a ratio of 2—2.5 : 1 and reacted gradually with nitric acid to form the 2,4-dinitro product **5** which dissolved mostly in the organic layer. Thus, the total content of **4** and **5** in both layers for each reaction time was essentially the same as that of **2** (about 2.5 mmol).

Although it is difficult to conclude only from the above results that phenols function as catalysts in the strict sense in the above on-column nitration of **4**, the following consideration appears to provide a possible reaction mechanism.

p-Nitrophenol (**4**) cannot react directly with nitric acid in an aqueous layer but interacts with a phenolic compound at the interface of the organic and aqueous layers to form an adduct which in turn reacts with nitric acid to afford 2,4-dinitrophenol (**5**). This product then dissolves in the organic layer. However, nearly all the *o*-nitro isomer **2** was distributed in the

organic layer, in which no reagent was present. A phenolic hydroxyl group in the catalyst may be neccessary for formation of an adduct.

Since the distribution ratio of **1** in the aqueous and benzene layers may be about 1 : 3 under the reaction conditions,[8] it is thus likely that the adduct is formed through the reaction of **4** with phenols in the aqueous layer, particularly when relatively water-soluble compounds such as phenol or hydroquinone are used.

Experimental

General Procedures for On-Column Nitration——The supporting matrix was prepared by dry-packing 15 g of Extrelut (E. Merck) into a glass tube (2 × 40 cm) equipped with a stop-cock and glass wool bed at its bottom. An aqueous solution of 19% nitric acid (15 ml, about 50 mmol) was applied onto the matrix and the system was allowed to stand for 10 min. After stabilization of the stationary phase, a benzene solution (10—15 ml) of 5 mmol of a phenol (**1**, **2** or **4**) was added to the column as the mobile phase and the stop-cock was closed after the mobile phase had penetrated the matrix. Both phases were allowed to contact each other for an appropriate period of time at room temperature (nitration) and the products thus formed were eluted with benzene. The eluate was collected in a 100 ml volumetric flask; 1.0 ml was transferred to a 100 ml volumetric flask, diluted to volume with ethyl acetate and mixed. Simultaneous determination of the products in 10 μl of this solution was carried out by HPLC under the conditions indicated below. The yields of **2**, **4** and **5** are shown in Fig. 1.

On-Column Nitration of *o*- and *p*-Nitrophenols with 19% Nitric Acid in the Presence of Various Phenols——The column was prepared as described above. A benzene solution (15 ml) of **2** (0.351 g, 2.5 mmol), **4** (0.351 g, 2.5 mmol) and 0.01 g of a catalyst was allowed to make intimate contact with aqueous nitric acid (19%, 15 ml) on the above column for 24 h at room temperature. The products were eluted with benzene and their yields were determined by HPLC following the above procedure. The results are shown in Table I.

Nitration of *o*- and *p*-Nitrophenols in a Suspension of Benzene and 19% Nitric Acid in the Presence of Phenol——A mixture of **2** (0.351 g, 2.5 mmol), **4** (0.351 g, 2.5 mmol) and **1** (0.01 g, 0.1 mmol) in benzene (15 ml) was stirred with 25 ml of 19% nitric acid in a 200 ml flask for 1, 2, 4, 7, 15 and 24 h at room temperature. Following separation of the organic and aqueous layers by the use of a separatory funnel, the former was applied to an Extrelut column containing 10 ml of water as the stationary phase. The products were eluted with benzene (100 ml) and their amounts determined. The aqueous layer was subjected to column extraction on an Extrelut column with benzene as the eluent, as described in the literature.[9] The eluate (100 ml) was also examined by HPLC as above. The yields of **2**, **4** and **5** thus obtained in both the aqueous and organic layers are shown in Table II.

Determination of Nitrophenols——HPLC determination was carried out at room temperature using a Kusano Kagaku KPW-14 equipped with a LiChrosorb SI-60 (5 μm) normal-phase column (4 × 250 mm, stainless steel) and a UVILOG-III UV photometer at 270 nm. Elution was conducted at a flow rate of 1.0 ml/min using a mixture of *n*-hexane, ethyl acetate, water-saturated ethyl acetate and acetic acid (75 : 20 : 5 : 0.3) as the eluent. The sample volume was 10 μl. Under these elution conditions, compounds **2** (capacity ratio; $k' = 0.39$), **1** ($k' = 0.97$), **5** ($k' = 1.76$), **3** ($k' = 2.00$) and **4** ($k' = 3.14$) were developed within 10 min in that order, and were well separated. A linear calibration curve was obtained for 10—100 μg/ml of each of these compounds.

References and Notes

1) Part II: A. Kunugi and K. Tabei, *Kagaku To Kyoiku*, **35**, 251 (1987).
2) This work was reported at the Congress of JUC Pharm Sci '87, Hawaii, Honolulu, Dec. 4, 1987 (M 04-Y-13).
3) A. Kunugi and K. Tabei, *Kagaku Kyoiku*, **33**, 152 (1985).
4) A. Kunugi and K. Tabei, *J. Chromatography*, **398**, 320 (1987).
5) A. Kunugi, C. Tsuji and K. Tabei, *J. High Resolution Chromatogr. & CC*, **10**, 624 (1987).
6) A peak of **5** was observed on the chromatogram, although it was too small to allow quantitative analysis.
7) The reaction period was 24 h and the yield was estimated based on the amount of **4**.
8) The distribution ratio of **1** in water (15 ml)–benzene (10 ml) at 20 °C was 1 : 2.5 and that in 11% hydrochloric acid (15 ml)–benzene (10 ml) was 1 : 3.6.
9) A. Kunugi, T. Inagaki and K. Tabei, *Kagaku Kyoiku*, **34**, 237 (1986).