Studies on the Nitration of *m*-Cresol. A New Selective Method for the Preparation of 3-Methyl-6-nitrophenol

Mitsuru SASAKI, Katsuji NODERA, Kunio MUKAI, and Hirosuke YOSHIOKA

Research Department, Pesticides Division, Institute for Biological Science, Sumitomo Chemical Co., Ltd., Takatsukasa, Takarazuka, Hyogo 665

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A new selective method for the nitration of *m*-cresol has been established. 3-Methyl-6-nitrophenol was most efficiently prepared by nitration of 3-methyl-4-sulfophenyl carbonate or phosphate and subsequent hydrolysis and desulfonation. Steric effects on the attacks of sulfonium or nitronium ion to the phosphate are discussed.

Certain mononitro derivatives of *m*-cresol are important intermediates for the preparation of organophosphorus pesticides such as Fenitrothion (*O,O*-dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate)[1] and herbicide Metacrephos (*O*-ethyl *N*-*s*-butyl *O*-(3-methyl-6-nitrophenyl) phosphoramidothioate).[2] The preparative value of direct nitration of *m*-cresol is limited due to a number of side reactions, *i.e.*, non-selective isomer formation together with oxidation with nitric acid and poor yield.[3] Various modifications were studied in order to overcome the defects of direct nitration.[4-7] Nitration after the introduction of a suitable protecting functional group to the hydroxyl group was the most common procedure. As an example, tri-*m*-tolyl phosphate was nitrated with a mixed acid, followed by hydrolysis, to yield 3-methyl-4-nitrophenol selectively.[6] 4-Hydroxy-6-methyl-1,3-benzenedisulfonic acid was nitrated and the subsequent desulfonation gave 3-methyl-2-nitrophenol in a good yield.[7] However, no report seems to have been given on an efficient method for selective preparation of 3-methyl-6-nitrophenol in a high yield.

This paper describes the formation of the three isomers of mononitro-3-methylphenols under various conditions, establishing a new selective method for the preparation of 3-methyl-6-nitrophenol. The mechanism of the formation of the product is also discussed.

Results

Syntheses of the Three Isomers of Mononitro-3-methylphenol. The results are given in Table 1. When *m*-cresol was sulfonated at 120 °C for 2 h with a slight excess of sulfuric acid, nitrated with a mixed acid and then desulfonated with diluted sulfuric acid, 3-methyl-6-nitrophenol(6-nitro isomer) was obtained as the major product and 3-methyl-2-nitrophenol (2-nitro isomer) as

TABLE 1. DISTRIBUTION OF ISOMERS OF NITRO-3-METHYLPHENOLS OBTAINED FROM SEVERAL STARTING MATERIALS BY SULFONATION AND NITRATION UNDER VARIOUS CONDITIONS

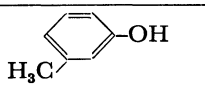
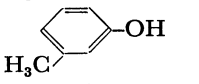
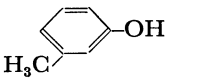
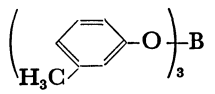
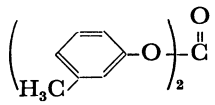
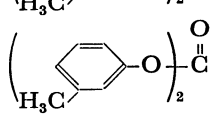
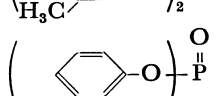
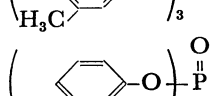
No.	Substrate	Sulfonation conditions: 96% H_2SO_4	Temp (°C)	Time (h)	Yield (%): Total	2-Isomer	4-Isomer	6-Isomer	Dinitro isomer
1		1.10	120	2	62.0	14.6	4.4	33.0	8.7
2		6.80	20—30	24	86.7	72.8	4.8	4.0	5.7
3		6.80	Direct nitration		50.7	8.7	18.2	9.1	12.0
4		6.80	20—30	24	76.8	59.4	1.5	11.2	3.0
5		6.80	Direct nitration		80.0	3.2	66.4	10.4	—
6		6.80	20—30	24	92.5	6.7	1.8	67.2	6.4
7		6.80	Direct nitration		95.0	1.9	86.5	6.6	—
8		6.80	20—30	24	89.6	7.6	3.7	76.7	1.0

Table 2. Nitro isomer distribution undre different sulfonation conditions

No.	Sulfonating reagent (molar ratio)[a]	Temp (°C)	Time (h)	Yield (%)			
				Total	2-Isomer	4-Isomer	6-Isomer
1	90% H_2SO_4 (6.8)	70	4	81.3	11.8	4.7	61.8
2	96% H_2SO_4 (6.8)	70	5	86.5	8.6	2.7	72.2
3	100% H_2SO_4 (6.8)	70	1	87.3	7.5	3.3	71.6
4	110% H_2SO_4 (6.8)	25	0.5	85.6	8.1	3.0	69.8
5	96% H_2SO_4 (3.0)	30	20	60.7	6.8	5.4	43.9
6	96% H_2SO_4 (4.0)	30	20	81.3	8.7	4.1	65.4
7	96% H_2SO_4 (5.0)	30	20	84.3	9.7	3.7	68.3
8	96% H_2SO_4 (6.8)	30	20	89.5	8.7	3.6	74.4
9	96% H_2SO_4 (10.0)	30	20	90.0	9.1	2.5	74.4
10	96% H_2SO_4 (6.8)	80	0.5	81.7	8.5	2.5	66.9
11	96% H_2SO_4 (6.8)	100	0.5	86.9	9.7	4.2	69.8
12	96% H_2SO_4 (6.8)	120	0.5	72.1	16.9	1.6	52.3

a) Molar ratio; sulfuric acid/tri-*m*-tolyl phosphate.

Table 3. Nitro isomer distribution in sulfonation followed by nitration of tri-*m*-tolyl phosphate under different ratio of nitric acid[a]

No.	Molar ratio[b]	Yield (%)					
		Total	2-Isomer	4-Isomer	6-Isomer	2,6-Isomer	4,6-Isomer
1	3.00	81.7	9.2	2.0	67.7	0.1	0.2
2	3.15	87.3	8.9	3.3	71.8	0.4	1.1
3	3.30	90.1	7.4	2.8	73.9	2.0	2.1
4	3.60	87.1	2.5	2.3	73.1	5.0	3.6

a) A mixture of tri-*m*-tolyl phosphate (0,5 mol) and 96% H_2SO_4 (10 mol) was kept at 20—30 °C for 24 h. The resulting solution was divided into 4 portions. Mixed acid (70% HNO_3, calculated amount plus 96% H_2SO_4, 2 equiv. weight) was added dropwise to each portion at −5—0 °C. b) Molar ratio; 70% HNO_3/tri-*m*-tolyl phosphate.

a minor one. The ratio of formation of the 2- to the 6-nitro isomer was about 1: 2. When a large excess of sulfuric acid was used, the 2-nitro isomer was obtained as the major product. Direct nitration of *m*-cresol with a mixed acid at −5—0 °C yielded about 50% of nitro-3-methylphenols and dinitro isomers accounted for 12%. Although tri-*m*-tolyl borate appeared to be a poor substrate owing to its rapid hydrolytic nature, the yield of the nitro isomers was 76.8%, the 2-nitro isomer being a main product.[8] Direct nitration of di-*m*-tolyl carbonate or tri-*m*-tolyl phosphate gave 3-methyl-4-nitrophenol (4-nitro isomer) as the major product (Nos. 5 and 7). In contrast, when both compounds were sulfonated, nitrated and followed by hydrolysis and desulfonation, the 6-nitro isomer was a predominant product (Nos. 6 and 8). The yield of the 6-nitro isomer from tri-*m*-tolyl phosphate was higher in comparison with that of the carbonate.

Selective Synthesis of the 6-Nitro Isomer. We see from Table 1 that tri-*m*-tolyl phosphate is the most favorable substrate for the preparation of the 6-nitro isomer. The following optimum conditions for selective preparation of the 6-nitro isomer were selected (Table 2). 96% Sulfuric acid was a better sulfonating reagent than 90% sulfuric acid or 10% oleum. We see from Table 3 that a small excess of nitric acid to the tolyl phosphate was effective for the most selective formation of the 6-nitro isomer (for No. 4, the ratio of the mono-nitro isomer was 1: 1: 28). Pure 6-nitro isomer was obtained from the crude mixture by dissociation extraction with a dilute alkaline solution.[9]

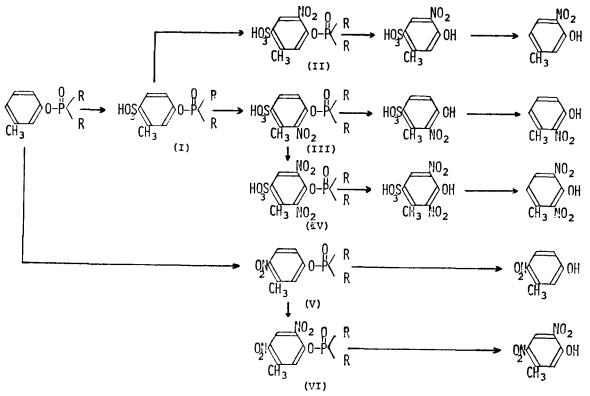
Identification of the Sulfonated Intermediates. All attempts to isolate the intermediates such as sulfo-*m*-tolyl phosphate or nitro-sulfo-*m*-tolyl phosphate after sulfonation or nitration were unsuccessful since they hydrolyze too easily. After nitration, the reaction mixture was poured onto ice and allowed to stand at room temperature for 48 h to give a yellow solid product. The product was extremely soluble in water and identical (mp and NMR) with an authentic specimen of 4-hydroxy-2-methyl-5-nitrobenzenesulfonic acid.[10] Desulfonation of the sulfonated nitrophenol with 60% sulfuric acid gave the 6-nitro isomer. 4-Hydroxy-2-methyl-5-nitrobenzenesulfonic acid (87.2%) and 4-hydroxy-2-methyl-3-nitrobenzenesulfonic acid (10.7%) were also detected by HLC analysis. 3-Methyl-4-nitrophenol was detected in the dephosphorylated solution by TLC on silica gel and quantitatively determined by GLC.

Discussion

The 4-nitro isomer was a dominant product of direct nitration of di-*m*-tolyl carbonate and tri-*m*-tolyl phosphate.[4,6] Haworth and Lapworth reported that the 4-position of *m*-cresol was predominantly sulfonated at 120 °C.[11] This was confirmed by the fact that the *o*-nitro isomers, *viz.*, 2- and 6-nitro isomers, occurred after subsequent nitration in a 1: 2 ratio.

The use of a large excess of sulfuric acid at low temperature resulted in the selective formation of the 2-nitro isomer. This seems to be due to the formation of 4-hydroxy-6-methyl-1,3-benzenedisulfonic acid as an intermediate.

On the other hand, when the carbonate or the phosphate was monosulfonated, nitrated and followed by hydrolysis and desulfonation, the 6-nitro isomer was selectively obtained.



R: *m*-tolyl, nitro-*m*-tolyl, or nitro-sulfo-*m*-tolyl group

Fig. 1.

Selective formation of the 6-nitro isomer from tri-*m*-tolyl phosphate can be illustrated by the reaction sequence shown in Fig. 1. Tri-*m*-tolyl phosphate is sulfonated to give the 4-sulfo derivative (I), which is nitrated to yield the corresponding 6-nitro derivative (II) and 2-nitro derivative (III). It appears that attack of a nitronium ion takes place predominantly at the 6-position of I, since the 2-position of I is apparently hindered by the bulky ditolyloxyphosphinyl group and the 3-methyl group which may be inclined toward the 2-position by a buttressing effect from the 4-sulfonyl group. The higher selectivity of the nitration at the 6-position in the 4-sulfonated intermediates may be due to the peculiar geometry. A small excess of nitronium ion predominantly attacks the 6-position of the intermediate (III) to give the dinitro derivative (IV). IV is hydrolyzed, followed by desulfonation, to yield 2,6-dinitro-3-methylphenol. The unaffected *m*-tolyl group of the phosphate is directly nitrated to give the 4-nitro derivative (V), which undergoes nitration to give the 4,6-dinitro derivative (VI). Hydrolysis of VI produces 4,6-dinitro-3-methylphenol.

In conclusion, the present method of nitration after the specifically controlled sulfonation to the phosphate or the carbonate of *m*-cresol can provide the respective *o*-nitro derivatives in high yields in a convenient "one-pot-procedure." 3-Methyl-6-nitrophenol in particular can be efficiently prepared.

Experimental

Materials. Di-*m*-tolyl carbonate and tri-*m*-tolyl borate were prepared according to the procedures previously reported.[4,8] Tri-*m*-tolyl phosphate (99% pure) and *m*-cresol (98% pure) were prepared at Sumitomo Chemical Co. Ltd., Oita Works and used without further purification. Authentic specimens of 3-methyl-2-nitrophenol, 3-methyl-4-nitrophenol, 3-methyl-6-nitrophenol, 4,6-dinitro-3-methylphenol, 2,6-dinitro-3-methylphenol and 2,4,6-trinitro-3-methylphenol were prepared by the method given in the respective references.[3,10] 2,4-Dinitro-3-methylphenol was prepared by nitration of 3-methyl-2-nitrophenol in acetic acid, whose melting point was quite different from that in the literature.[10] Mp 130 °C (lit, 74 °C). Found: C, 42.56; H, 3.25; N, 14.20%. Calcd for $C_7H_6N_2O_5$: C, 42.43; H, 3.06; N, 14.14%. Physical and spectral data of these nitrophenols are given in Table 4. The following sulfonated nitro-3-methylphenols were prepared.[10] 4-Hydroxy-2-methyl-5-nitrobenzenesulfonic acid, mp 131—132 °C, NMR (D_2O): 2.60 (3H, s, CH_3), 7.10 (1H, S, H-5), and 8.50 (1H, s, H-2). 4-Hydroxy-2-methyl-3-nitrobenzenesulfonic acid, mp 78—79 °C, NMR (D_2O): 2.50 (3H, s, CH_3), 7.00 (1H, d, H-6, J=9.0 Hz), and 7.90 (1H, d, H-5, J=9.0 Hz).

TABLE 4. PHYSICAL AND SPECTRAL DATA OF NITRO-3-METHYLPHENOLS

Compound	Mp[a] (°C)	pK_a	UV in EtOH λ max (nm)	log ε
3-Methyl-2-nitrophenol	41 (39)	7.20	212 235 270	4.08 3.29 3.25
3-Methyl-4-nitrophenol	129 (129)	7.08	208 232 308	4.02 3.93 3.96
3-Methyl-6-nitrophenol	55 (54)	7.63	213 283 351	4.17 3.83 3.55
2,4-Dinitro-3-methylphenol	130 (74)[b]	4.81	207 291 370	4.16 3.84 3.55
4,6-Dinitro-3-methylphenol	65 (64)	4.60	212 260 310	4.13 4.12 3.71
2,6-Dinitro-3-methylphenol	100 (101)	4.00	211 278 337	4.22 3.80 3.52
2,4,6-Trinitro-3-methylphenol	110 (110)[c]	3.73[c]	212 254 348	4.22 3.98 4.02

a) ( ) value cited from Ref. 10. b) See Experimental.
c) Determined in 5% EtOH.

Analysis. Identification and quantitative analysis of the nitro isomers were carried out on a GLC(Yanagimoto G-80 or Yanagimoto GCG-550 F, FID detecter) and a GC-Mass spectrometer (Shimadzu LKB-9000). Products were identified with authentic samples by GC retention time on at least two different columns (2% XE-60 on chromosorb W, 3 mm × 1.5 m, glass column programmed at 110—220 °C; 10% PEG-20M on Chromosorb W, 3 mm × 1.0 m, glass column programmed at 150—200 °C; 2% FFAP on Shimalite TPA, 3 mm × 1.0 m, glass column programmed at 170—200 °C). Neither 2,4-dinitro-3-methylphenol nor 2,4,6-trinitro-3-methylphenol were detected under the conditions described above. Mass spectra of peaks obtained from GLC were determined at 70 eV as follows; 3-methyl-6-nitrophenol (*m/e* 153 M^+), 3-methyl-2-nitrophenol (*m/e* 153 M^+), 3-methyl-4-nitrophenol (*m/e* 153 M^+), 2,6-dinitro-3-methylphenol (*m/e* 198 M^+) and 4,6-dinitro-3-methyl-phenol (*m/e* 198 M^+). 4-Methyl-3-nitrophenol (*m/e* 153 M^+) was obtained among other minor products by the nitration of *p*-cresol, a major impurity in the starting material. The sulfonated nitro-3-methylphenols formed as intermediates were analyzed as follows. The

reaction mixture occurring after nitration was poured onto ice and then neutralized with aqueous sodium hydroxide to pH 7.40. One μl of the solution was subjected to HLC. Operating conditions are follows; instrument, Shimadzu Du Pont 830 liquid chromatograph; column SAX 2 mm × 1.0 m; column temp, 40 °C; column pressure, 70 kg/cm²; mobile phase, distilled water at pH 7.40 with 0.2 M $NaNO_3$; detector, UV photometer at 254 nm; flow rate, 1 ml/min; retention time 4-hydroxy-2-methyl-5-nitrobenzenesulfonic acid (4.0 min', 4-hydroxy-2-methyl-3-nitrobenzenesulfonic acid (6.0 min). Concentrations of sulfuric acid and nitric acid were determined by alkaline titration or specific gravity. pK_a values of the nitro isomers were measured by alkaline titration on a pH meter. UV was recorded with a Shimazu double beam spectrophotometer UV-200. NMR was recorded on a Hitachi NMR spectrometer R-20B (60 Mz).

Preparation of the Mononitro-3-methylphenols. A typical procedure for preparation of the mononitro-3-methylphenols is as follows (see No. 8, Table 1). A mixture of 96% sulfuric acid (200 g, 2.0 mol) and tri-*m*-tolyl phosphate (36.8 g, 0.1 mol) was kept under stirring at 20—30 °C for 24 h. A mixed acid consisting of 70% nitric acid (28.0 g, 0.315 mol) and 96% sulfuric acid (50.0 g 0.5 mol) was added to the solution at −5—0 °C. After 2 h, the reaction mixture was poured onto ice (150 g). The resulting solution was heated and distilled with steam at 140—170 °C until no oily distillate was detected in the steam condensate. The distillate was extracted 3 times with 50 ml portions of chloroform. The combined chloroform extract dried over anhydrous sodium sulfate, chloroform was evaporated *in vacuo*. The yellow residue (41.0 g) was subjected to GLC for analysis. The crude mixture was again distilled with steam at 100 °C. The distillate dissolved in 100 ml of toluene was washed 3 times with 100 ml portions of 0.8% aqueous sodium hydroxide. Removal of toluene gave pure 3-methyl-6-nitrophenol (26.0 g). In experiments Nos. 3, 5, and 7 in Table 1 the mixed acid was added to the reaction mixture immediately after the starting material had been mixed with 96% sulfuric acid. The reaction conditions are summarized in Tables 1, 2, and 3.

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