Alumina-Catalyzed Ipso Attack in Electrophilic Aromatic Substitution: Methylation of 2,6-Xylenol to 2,3,6-Trimethylphenol

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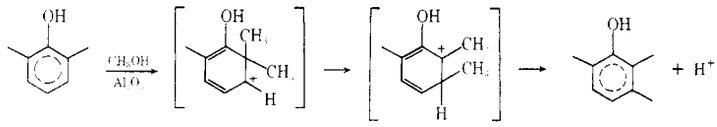
Received July 26, 1977

We have observed a highly unexpected meta-methylation in the reaction of 2,6-xylenol with methanol over an alumina catalyst to yield 2,3,6-trimethylphenol (2,3,6-TMP) rather than the expected 2,4,6-TMP. An ipso (Latin:



itself) mechanism is proposed to explain the high selectivity to 2,3,6-TMP. In a continuous reactor isomerization and disproportionation do not occur at 350 °C, 450 psig, due to the water formed in the reaction. Selectivity to 2,3,6-TMP is highest at low temperatures. Substantial evidence for the ipso mechanism was obtained by the reaction of 2,6-xylenol with CD_3OD to give a product with nearly equal amounts of CD_3 in the meta and ortho positions, in agreement with a proposed ipso transition state. The high-purity γ-alumina is strongly ortho-directing and lowers the activation energy for the ipso reaction pathway.

Methylation of 2,6-xylenol to produce 2,3,6-trimethylphenol (2,3,6-TMP) in high selectivity under mild conditions has been reported.[1] The unexpected meta-methylation suggested experiments to determine a mechanism which would explain why 2,3,6-TMP rather than 2,4,6-TMP is the major product. Evidence for an ipso electrophilic aromatic substitution mechanism[2] is presented.

Results and Discussion

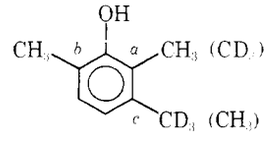
Methylation of gaseous 2,6-xylenol over alumina catalyst yields 2,3,6-TMP in low selectivity with the formation of 2,4,6-TMP as a major component (Table I). A change from vapor phase feed to trickle bed reaction conditions,[3] where most of the 2,6-xylenol and methanol enter the reactor as a liquid, results in a much higher selectivity to 2,3,6-TMP. Uniform reaction temperatures at pressures in the range 400–700 psig, where most of the phenols are in the liquid phase, allowed the determination that the selectivity to 2,3,6-TMP increases at higher pressures (Table II) and lower reactor temperatures (Table III).

In the trickle bed reactor a liquid phase and a gas phase flow concurrently downward through a fixed bed of catalyst while the reaction takes place. The catalyst particles are bathed in liquid which slowly trickles down the reactor. The reactor is in the subcritical region under normal operation. The vapor pressure of the reaction mixture at 360 °C using 0.5 mol of methanol per mole of 2,6-xylenol is about 650 psia. Since the reactor pressure is 490 psia, both gas and liquid phases will be present throughout the reactor. The predicted vapor pressure in the reactor from Raoult's or Henry's Law is much greater than that observed. Therefore, some chemical interaction is occurring in the liquid phase which complexes the light components methanol and dimethyl ether, preventing high vapor pressures. Similar vapor pressure curves were observed for water as for methanol. A complex between 2 molecules of 2,6-xylenol and a molecule of water, methanol, or dimethyl ether was hypothesized to explain the low vapor pressure observed.[4]

Isomerization and disproportionation, which would lead to meta substitution, albeit unselectively, are higher-temperature reactions which do not occur in a continuous reactor at 350 °C, 450 psig, and a contact time of 10 min due to the water formed in the reaction. This is important because the high ratios of 2,3,6-TMP/2,4,6-TMP in the reaction product (Table III) would not be predicted from the effects of the groups in 2,6-xylenol on electrophilic aromatic substitution, and thus meta-alkylation has been previously postulated to involve isomerization or disproportionation.

These reactions do occur with gaseous[5] feed to the reactor and at higher temperatures when the reactor is under pressure. However, at the lower temperatures where the 2,3,6-TMP/2,4,6-TMP ratio is largest, the 2,5-xylenol intermediate expected from isomerization is absent. High selectivity for *m*-alkylphenols is usually realized when the reaction is carried out at high temperatures and/or on catalysts having high acid strength.[6] Application of these principles to 2,6-xylenol methylation results in decreased selectivity to 2,3,6-TMP such that 2,4,6-TMP becomes the major product at higher temperatures and with silica–alumina catalyst. Indeed the highest selectivity to 2,3,6-TMP is observed under mild reaction conditions where 2,6-dimethylanisole[7] is found in increasing quantities.

Substantial evidence for the ipso mechanism was obtained from the reaction of 0.3 mol of CD_3OD per mole of 2,6-xylenol at 350 °C and 475 psig. A sample of the 2,3,6-TMP product was collected after separation on a GLC column and analyzed by Fourier transform NMR spectroscopy. The three methyl groups in 2,3,6-TMP can be distinguished,[8] and the integration of protons due to the methyl groups is reduced by the presence of the CD_3 group in one position. The aromatic protons serve as a standard in the integration and a check on the substitution pattern. No exchange of CD_3 for CH_3 groups occurred in 2,6-xylenol in the reactor. The intensity of the mass 125 peak was <0.1% that of the mass 122 parent peak in the mass spectrum of the 2,6-xylenol fraction. The relative amount of CD_3 at the ortho and meta positions can be determined by assigning the largest integration value to the one unchanged methyl group. If a high percentage of CD_3 was in the meta position, direct attack at that position or the undistinguishable rearrangement of the 2,6-dimethylanisole[9,10] would be implied. An ipso transition state would result in nearly equal migration of CH_3 and CD_3, and experimentally one should see the following.



a = 1.5, *b* = 3, and *c* = 1.5 protons by integration

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Table I. Comparison of Liquid and Vapor Phase 2,6-Xylenol Methylation[a,b]

Product	Feed,[c] % wt	Product composition, % wt			
		Product period, 0–4 h		Product period, 4–8 h	
		Liquid phase	Vapor phase	Liquid phase	Vapor phase
Anisole–MeOH		1.3	0.7	1.1	0.5
o-Methylanisole					
o-Cresol	0.5	1.2	5.0	1.3	3.6
m,p-Cresol	9.9	3.7	0.9	3.7	0.7
2,6-Dimethylanisole					
2,6-Xylenol	89.6	67.9	55.8	68.4	63.3
2,4/2,5-Xylenol		2.2	5.3	2.2	3.3
2,3/3,5-Xylenol		0.3	1.2	0.3	0.5
2,4,6-Trimethylphenol		3.0	8.0	2.9	7.2
2,3,6-Trimethylphenol		12.2	9.1	12.3	9.2
2,3,5/2,4,5-Trimethylphenol		0.6	3.5	0.4	1.9
Pentamethylbenzene		0.6	0.6	0.6	0.4
3,4,5/2,3,4-Trimethylphenol		0.4	0.3	0.3	0.2
2,3,5,6/2,3,4,6-Tetramethylphenol		3.8	6.0	3.8	4.8
2,3,4,5-Tetramethylphenol		0.1	1.1	0.1	1.0
Hexamethylbenzene		Trace	0.2	0.1	0.2
Pentamethylphenol		1.7	1.9	1.8	2.8

[a] Vapor phase refers to vaporized feed entering the reactor. Liquid phase refers to predominantly liquid feed entering the reactor. [b] Liquid hourly space velocity (LHSV) = 4.7 (volume of feed/volume of catalyst per hour); CATAPAL SB alumina $\frac{1}{16}$-in extrudate, 15 cm^3 of catalyst; reactor temperature set at 355 °C, which defines the operating temperature in the liquid phase, but hot spots occur in the vapor phase which change with time. Maximum temperature in vapor phase during 0–4 h is ~420 °C; 4–8 h, 400 °C. Pressure for liquid phase is 450 psig; vapor phase, 1 atm. [c] Note: the feed contains *m,p*-cresol which adversely affects the selectivity to 2,3,6-TMP.

The spectrum observed is shown in Figure 1, and the integration values are $a \cong 1.5$, $b \cong 3.0$, and $c \cong 1.5$, consistent with the ipso mechanism. Rapid exchange occurs between methyl groups on the alumina surface and the ether methyl in 2,6-dimethylanisole. Direct methyl attack at the occupied ortho position and anisole rearrangement to the same transition state can not be kinetically distinguished.

Benzylation of 2,6-xylenol in the liquid phase at 190 °C with alumina catalyst produced 84% of 3-benzyl-2,6-dimethylphenol and 16% of 4-benzyl-2,6-dimethylphenol, in agreement with the greater migrating tendency of the benzyl group. 2,6-Dibenzylphenol at 220–250 °C formed the benzyl ether but did not yield a tribenzylphenol. Steric hindrance of the two benzyl groups at the ortho positions may have prevented formation of the ipso transition state.

The relative rates of methylation of 2,3- and 2,5-xylenol where the ortho substituent is hydrogen, k_H, can be compared to 2,6-xylenol where the ortho substituent is methyl, k_{CH_3}. The values of k_H/k_{CH_3}, the reactivity ratio of the xylenols, were found to be 6.5 and 3.5 for 2,3- and 2,5-xylenol, respectively, by a competitive reaction with 2,6-xylenol for methanol at 360 °C, 475 psig, and LHSV = 6 (liquid hourly space velocity). If entropy changes are unimportant, the $\Delta H^{\ddagger}$ difference, $\delta(\Delta H^{\ddagger})$, between methyl attack at an ortho position occupied by a methyl group would be 1.6–2.4 kcal/mol greater than attack at the same position occupied by hydrogen. A similar value of k_H/k_{CH_3} of 3.7 was found in the bromination of 2,6-di-*tert*-butylphenols, where the bromination occurred at the para position.[11]

The data in Table III indicate a relatively small $\delta(\Delta H^{\ddagger})$ value for competing exothermic reactions, which requires close temperature control in the reactor to observe the selective rearrangement of the ipso intermediate to 2,3,6-TMP.

The alumina catalyst plays a critical role in the methylation of 2,6-xylenol. Phenol on alumina forms a phenoxide which is located perpendicular to the surface of the catalyst.[12] The ortho positions are closer to the catalyst surface than the meta and para positions, and this argument has been used to explain the ortho-directing effect of alumina.[6]

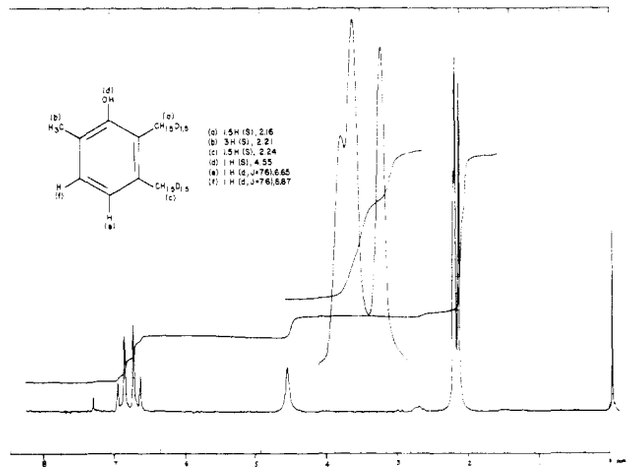

Figure 1. NMR spectrum of 2,3,6-trimethylphenol obtained by the reaction of methanol-d_4 with 2,6-xylenol.

In the past few years, ipso attack has been demonstrated to be significant in some electrophilic nitrations of disubstituted benzenes[13,14] and in photobromination of dihalobenzenes.[15] Ipso mechanisms may operate to a greater extent in electrophilic aromatic substitution reactions than has been realized and may contribute significantly to the reaction products.[16–18]

Wheland intermediates can be written for ortho, meta, and para attachment of methyl to the ring, and repetitive 1,2 shifts can lead to isomerized products. The transition state leading to a Wheland intermediate could be a π complex.[19] Stabilization of the charged Wheland intermediate and π complex in the 2,6-xylenol methylation would be predicted because of the interaction of reactant with alumina catalyst, the liquid vs. vapor phase reactions conditions, and the presence of a −I methyl group in the ortho position.[20] This should particularly stabilize the Wheland intermediate, leading to 2,3,6-TMP as the final product.

Table II. Pressure Effects in the Methylation of Pure 2,6-Xylenol[a]

	Pressure, psig				
	400	450	500	600	700
Product composition, % wt					
2,6 Dimethylanisole	1.22	1.94	3.14	4.95	6.16
2,6-Xylenol	64.55	67.95	70.68	71.04	73.82
2,4/2,5-Xylenol	0.13	0.00	0.00	0.00	0.00
2,3-Xylenol	0.16	0.00	0.04	0.03	0.03
2,4,6-Trimethylphenol	4.24	2.57	1.89	1.77	1.63
2,3,6-Trimethylphenol	16.30	16.19	14.85	14.02	12.40
2,3,5/2,4,5-Trimethylphenol	0.13	0.14	0.18	0.22	0.17
2,3,4/3,4,5-Trimethylphenol	0.79	0.56	0.40	0.22	0.17
2,3,4,6/2,3,5,6-Tetramethylphenol	7.34	6.16	5.01	4.50	3.38
2,3,4,5-Tetramethylphenol	0.41	0.15	0.25	0.21	0.29
Pentamethylphenol	4.72	4.33	3.56	3.04	1.96
Product distribution, % wt					
Methanol	1.37	2.07	4.10	5.25	6.85
Water	6.88	6.49	5.34	4.70	3.80
Total phenols, % wt	91.75	91.45	90.55	90.05	89.36

[a] Reaction conditions: continuous reactor; CATAPAL SB alumina catalyst, 15 cm^3 ($1/16$-in extrudate); LHSV (liquid hourly space velocity, i.e., volume of feed/volume of catalyst per hour) = 4.7; 0.60 mol of methanol per mole of 2,6-xylenol; 355 °C set point on reactor. This defines the temperature under >400 psig pressure, but hot spots are inherent in the vapor phase flow into reactor. The 400-psig run represents a transition between the two regimes.

Table III. Effect of Increasing Reaction Temperature on Liquid Phase Methylation of Pure 2,6-Xylenol

	345 °C	350 °C	355 °C	360 °C	378 °C
Product distribution, % wt					
Methanol–dimethyl ether	3.5	3.2	2.6	1.4	0.6
Product composition, % wt					
o-Methylanisole	0.94	0.03	0.02	0.00	0.02
m,p-Cresol	0.00	0.00	0.00	0.00	0.77
2,6-Dimethylanisole	4.13	4.28	3.49	2.18	0.44
2,6-Xylenol	76.92	77.37	75.90	71.02	66.35
2,4/2,5-Xylenol	0.00	0.00	0.00	0.00	0.56
2,3/3,5-Xylenol	0.43	0.46	0.37	0.13	0.29
2,4,6-Trimethylphenol	0.71	0.71	0.91	2.00	6.53
2,3,6-Trimethylphenol	12.22	12.33	13.29	15.55	14.05
2,3,5/2,4,5-Trimethylphenol	0.06	0.06	0.12	0.43	0.38
2,3,4/3,4,5-Trimethylphenol	0.09	0.11	0.11	0.14	0.39
2,3,4,6/2,3,5,6-Tetramethylphenol	2.94	3.05	3.60	5.17	6.45
2,3,4,5-Tetramethylphenol	0.00	0.00	0.00	0.00	0.21
Hexamethylbenzene	0.05	0.06	0.10	0.30	0.34
Pentamethylphenol	1.51	1.53	2.07	3.07	2.88
High boilers	0.00	Trace	Trace	Trace	0.35
2,3,6-/2,4,6-Trimethylphenol ratio	17.2	17.4	14.6	7.8	2.2

[a] Reaction conditions: continuous reactor; 450 psig; LHSV = 5.0; 0.5 mol of methanol per mole of 2,6-xylenol; 15 cm^3 of CATAPAL SB alumina $1/16$-in extrudate catalyst.

Only highly active γ-alumina of high purity reduces the activation energy for attack at the ortho position sufficiently to bring the ipso pathway involving attack of a methyl group at an ortho position occupied by a methyl group to a lower activation energy than the expected attack at the para position which would yield 2,4,6-TMP. Less active catalysts result in lower selectivity to 2,3,6-TMP at similar conversion levels. In the case of 2,6-xylenol, where ortho hydrogens are replaced by the $-I$ methyl groups, the ipso reaction pathway appears to predominate under mild reaction conditions.

Experimental Section

Reactor. The data were generated using an electrically heated 0.5 × 14 in stainless steel (SS) tube filled with catalyst as the reactor. A $1/8$ in thin-wall SS tube welded at one end served as the thermowell. Temperatures were measured in the center of the reactor with an adjustable thermocouple. The skin temperature of the reactor was controlled to ±1 °C by a Thermo Electric 400 Model 32422 proportional temperature controller. The reactor was well insulated, but heat loss from the large fittings on the ends was unavoidable. The extremities of the reactor were packed with inert glass beads, and the catalyst was confined to the central portion of the reactor (15 cm^3).

The xylenol and methanol were premixed and pumped with a Milton Roy Mini-Pump at a constant rate through a Nupro check valve into a preheater segment of stainless steel tubing to the top of the reactor where the feed enters at 320 °C in a typical run. The reaction products exit at the bottom of the reactor through a water-cooled condensor and a pressure control valve which maintains a set pressure between the check valve and the diaphragm in the control valve. The product was collected for GLC analysis after the reactor ran for 1 h at constant conditions.

Catalyst. The catalyst was a $1/16$-in extrudate of γ-alumina. Typical surface area and pore volume values were 200 m^2/g and 0.45 cm^3/g, respectively. The extrudate was formed from CATAPAL SB alumina which is derived from hydrolysis of aluminum alkoxides. It was calcined for 2 h at 538 °C prior to use.

GLC Analysis. Toluene was added to the reactor product as an internal standard, and actual percentages were calculated by a com-

puterized program which measured the area under the GLC curves. A 10 ft, 10% SE-30 column, 70–300 °C, with a program rate of 6 °C/min using a thermal conductivity detector was used to analyze the phenols. A flame detector was used to determine methanol, dimethyl ether, and the anisoles with a 11 ft, 20% UCON 50 HB 5100 on 80–100 mesh HMDS-treated Chromosorb P column at 70 °C.

Reagents. The phenols were obtained from CONOCO Chemicals and were analyzed by GLC. Methanol and benzenemethanol were of analytical grade. CD_3OD was 99.5% isotopically pure. The $CDCl_3$ used as a solvent for NMR analysis was 99.96% isotopically pure.

3-Benzyl-2,6-dimethylphenol. Benzenemethanol was added dropwise to a stirred flask containing 2,6-xylenol at 190 °C. The water formed in the reaction was removed in a Dean-Stark trap. Analysis by NMR spectroscopy of the product indicated 84% of 3-benzyl-2,6-dimethylphenol and 16% of 4-benzyl-2,6-dimethylphenol.

Methanol-d_4 Experiment. CD_3OD (10 g) was added to 127 g of 2,6-xylenol, and the feed was pumped through the reactor at 350 °C, LHSV = 3, and 475 psig pressure. The product was collected after a 1-h run time and distilled to give a 2,6-xylenol cut and an enriched 2,3,6-TMP cut. A 2,6-xylenol sample was introduced via the direct inlet probe of a Consolidated Electrodynamics Corp. Model 21-110B mass spectrometer. A parent peak at mass 122 was observed at 100 °C, and the intensity of the mass 125 peak (CD_3 incorporation in 2,6-xylenol or ^{13}C contribution) was <0.1% that of the 122 mass parent peak intensity for $C_8H_{10}O$ (2,6-xylenol).

A 10 μL sample of the crude 2,3,6-TMP cut was injected onto the GLC column used to analyze the phenols. The component corresponding to 2,3,6-TMP was collected in a 2.0 × 125 mm tube at the exit port, and the capillary tube was sealed at one end and used as the NMR sample tube. $CDCl_3$ was added, and the NMR spectrum was obtained on a Bruker WP-80 Fourier transform NMR spectrometer with $CDCl_3$ as the lock solvent and Me_4Si as an internal standard. A total of 347 scans were used to generate the spectrum in Figure 1.

Acknowledgment. The author wishes to thank C. M. Starks and K. Yang for helpful discussions and F. M. McEnroe for obtaining the NMR spectrum.

Registry No.—2,6-Xylenol, 576-26-1; 2,3,6-TMP, 2416-94-6; 2,4,6-TMP, 527-60-6.

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Chemistry of the Sulfur–Nitrogen Bond. 13. A New Synthesis of *N*-Alkylidenearenesulfenamides (Sulfenimines): Alkylation of Sulfenamide Enolate Equivalents

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Received August 23, 1977

The alkylation of sulfenamide enolate equivalents (**2**), derived by treatment of **1** with LDA, represents a new and important source of sulfenimine derivatives. Not only does this procedure afford **1**, not available by other methods, but it avoids the limitation of the metal-assisted sulfenamide synthesis. These enolate equivalents are formed in excellent yield, with high stability and good regioselectivity. They are, however, highly reactive toward electrophiles such as halides, carbonyl compounds, and aryl disulfides without detectable polyalkylation or self-condensation. Elimination to form phenylthiolate ion and nitrile occurs on treatment of **1**, derived from aldehydes, with LDA.

N-Alkylidenearenesulfenamides (sulfenimines) (**1**) are an important class of reactive sulfur–nitrogen compounds[2] which have recently been shown to be useful intermediates in organic synthesis. These compounds are precursors of 2-arenesulfonyl-3-phenyloxaziridines,[3] a new class of stable oxaziridine derivative. The synthetic utility of **1** as "masked" imine derivatives of ammonia has recently been demonstrated in a convenient, one-step synthesis of secondary and tertiary carbinamines.[4]

Although **1** can generally be prepared in good yield from the corresponding aldehyde or ketone, disulfide, and ammonia using the metal-assisted procedure (eq 1),[1,5] this method has certain limitations.

$$\mathrm{ArSSAr} + \mathrm{MX} + \mathrm{R_1CR_2}\overset{\mathrm{NH_3}}{\longrightarrow} \underset{\mathbf{1}}{\mathrm{ArS}\!-\!\mathrm{N{=}CR_1R_2}} + \mathrm{ArSM} \quad (1)$$

$$\mathrm{MX} = \mathrm{AgNO_3},\ \mathrm{HgCl_2}$$

First is the inability to prepare **1** from aldehydes or ketones containing bulky and/or reactive functional groups.[1,5] Second, the excess of ammonia required by this method necessitates a correspondingly large excess of the carbonyl compound. From a synthetic point of view this becomes undesirable if the aldehyde or ketone is difficult to prepare.

Enolate equivalents of imines have received relatively little study and have generally not been used to prepare new imine derivatives.[6] They are primarily used as protecting functionalities to avoid self-condensation and polyalkylation reactions observed for the corresponding carbonyl enolates.[7] Corey and Enders have recently reported high regioselectivity for the alkylation of enolate equivalents derived from *N,N*-dimethylhydrazones.[8]

Alkylation of sulfenamide enolate equivalents, **2**, would provide an alternative source of sulfenimine derivatives (eq 2) which would avoid the limitations of the metal-assisted synthesis.[1,5] These enolate equivalents, **2**, are conveniently

0022-3263/78/1943-1797$01.00/0