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One-pot Synthesis of Phenols by Hydroxylation of Aromatics with Hydroxylamine

Dongsheng Zhang,* Liya Gao, Wei Xue, Xinqiang Zhao, Shufang Wang, and Yanji Wang*
Key Laboratory of Green Chemical Technology and High Efficient Energy Saving of Hebei Province,
Hebei University of Technology, Tianjin 300130, P. R. China

(Received December 28, 2011; CL-111242; E-mail: zds1301@hebut.edu.cn, yjwang@hebut.edu.cn)

In this study, a new approach for one-pot synthesis of phenols is presented, i.e., benzene, ethylbenzene, and xylene were hydroxylated with hydroxylamine to give the corresponding phenols in good yield using molybdenum as a key catalyst.

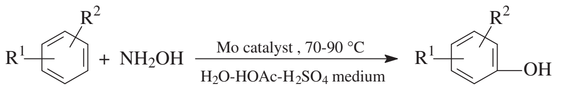
Hydroxyaromatics including phenol, cresol, ethylphenol, and xylenol are valuable intermediates for the production of phenolic resins, plastics, pharmaceuticals, etc. These phenols were originally extracted from coal tar and other natural sources. To this day, several synthetic routes have been developed, such as sulfonation or chlorination of the benzene ring, and the well-known cumene/cymene process.[1] However, these processes suffer from some drawbacks such as multistep procedures and harsh reaction conditions. Vapor-phase alkylation of phenol is another way to produce cresols, ethylphenol, or xylenol.[2] Additionally, synthesis of xylenol has been achieved by reaction of methanol and cyclohexanone.[3] The processes, however, use relatively expensive starting materials and require high capital costs for separation of products.

Fortunately, direct hydroxylation of aromatics has been realized in recent years. It has attracted considerable attention for its potential economic advantage and eco-efficiency.[4] Currently there are several approaches, involving catalytic oxidation of aromatics employing N_2O,[5] O_2,[6] and H_2O_2[7] as oxidant. Recently, it was reported that cresols can be formed as by-products in the reaction of direct amination of toluene with hydroxylamine.[8] In our previous work,[9] cresols were successfully synthesized as the main product from toluene and hydroxylamine catalyzed by $(NH_4)_6[Mo_7O_{24}]\cdot 4H_2O$.

Here, a question came to our mind. Could other aromatics be hydroxylated with hydroxylamine to give the corresponding phenols? Therefore, a variety of aromatics including benzene, ethylbenzene and xylene, were examined by using molybdenum (Mo) catalyst in this work. A schematic representation of the one-pot reaction is given in Scheme 1.

Analytical grade $(NH_4)_6[Mo_7O_{24}]\cdot 4H_2O$ and $Na_2[MoO_4]\cdot 2H_2O$ were obtained commercially and tested as homogeneous catalysts. Supported Mo oxide catalyst was prepared by impregnation,[10] and the reactions were carried out separately in open air and in closed systems.[11]

Initially, the reaction between ethylbenzene and hydroxylamine sulfate was selected as a model reaction for optimizing the reaction conditions in an open air system. First, several acidic solvents were tried for hydroxylation of ethylbenzene. As shown in Table 1, incorporation of water into $HOAc–H_2SO_4$ acidic medium is favorable to the hydroxylation. And $H_2O–HOAc–H_2SO_4$ medium with a volume ratio of 4:10:1 provides high yield of ethylphenol.



(R^1 = H, CH_3, C_2H_5; R^2 = H, CH_3)

Scheme 1. Schematic representation of the one-pot reaction.

Table 2 shows the influence of reaction temperatures and time on the hydroxylation. The yield of ethylphenol increases first, passing through a maximum at 80 °C, and then decreases. Among the reaction times, ethylphenol yield can be improved by having longer reaction times. However, ethylphenol yield increases slightly as the time exceeded 4 h. Hence, the ideal reaction temperature and time are 80 °C and 4 h, respectively.

Next, various amounts of $(NH_4)_6[Mo_7O_{24}]\cdot 4H_2O$ catalyst and hydroxylamine were screened, and the results are summa-

Table 1. Effect of reaction medium on ethylbenzene hydroxylation[a]

Solvent (mL:mL:mL)	X_E /%[b]	Product selectivity/%	
		Ethylphenols[c]	Others[d]
$HOAc–H_2SO_4$ (12:3)	36	4 (2:1:1) [1]	96
$H_2O–HOAc–H_2SO_4$ (2:10:3)	14	34 (4:21:9) [5]	66
$H_2O–HOAc–H_2SO_4$ (3:10:2)	12	60 (12:29:19) [7]	40
$H_2O–HOAc–H_2SO_4$ (4:10:1)	13	68 (19:35:14) [9]	32
$H_2O–HOAc–H_3PO_4$ (4:10:1)	10	69 (16:40:13) [7]	31
$H_2O–HCOOH–H_2SO_4$ (4:10:1)	10	77 (18:37:22) [8]	23

[a]Reaction conditions: 0.25 g $(NH_4)_6[Mo_7O_{24}]\cdot 4H_2O$ catalyst, 10 mmol $(NH_2OH)_2\cdot H_2SO_4$, 20 mmol ethylbenzene, 15 mL medium, 85 °C, 4 h. [b]Ethylbenzene conversion. [c]Numbers in parenthesis and blanket show the ratio of *o*-, *p*-, and *m*-ethylphenol and the yield of ethylphenol, respectively. [d]Ethylanilines.

Table 2. Effect of temperature and time on ethylbenzene hydroxylation[a]

Temperature /°C	Time /h	X_E /%	Product selectivity/%	
			Ethylphenols	Ethylanilines
70	4	8	54 (18:21:15) [4]	46
80	4	13	74 (20:35:19) [10]	26
85	4	13	68 (19:35:14) [9]	32
90	4	13	60 (22:23:15) [8]	40
80	1	10	50 (14:25:11) [5]	50
80	2	11	68 (18:33:17) [7]	32
80	3	12	70 (20:34:16) [8]	30
80	6	14	77 (21:35:21) [11]	23

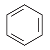
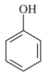
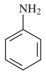
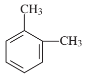
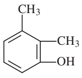
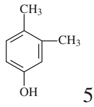
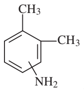
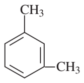
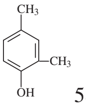
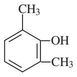
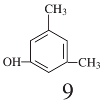
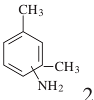
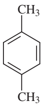
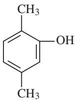
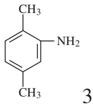
[a]Reaction conditions: 0.25 g $(NH_4)_6[Mo_7O_{24}]\cdot 4H_2O$ catalyst, 10 mmol $(NH_2OH)_2\cdot H_2SO_4$, 20 mmol ethylbenzene, 15 mL $H_2O–HOAc–H_2SO_4$ medium (volume ratio is 4:10:1).

Table 3. Effect of the amount of hydroxylamine and catalyst on ethylbenzene hydroxylation[a]

Hydroxylamine sulfate/g	Catalyst /g	X_E /%	Product selectivity/%	
			Ethylphenols	Ethylaniline
1.64	0.10	10	59 (11:37:11) [6]	41
1.64	0.25	13	74 (20:35:19) [10]	26
1.64	0.55	14	83 (24:34:25) [12]	17
1.64	1.00	9	91 (24:33:34) [8]	9
0.88	0.25	4	76 (20:28:28) [3]	24
3.25	0.25	31	75 (20:38:17) [23]	25
4.89	0.25	40	80 (24:36:20) [32]	20
1.40[b]	0.25	6	68 (16:39:13) [4]	32
1.64	0.50[c]	15	83 (22:35:26) [13]	17
1.64	0.20[d]	8	59 (11:38:10) [5]	41
1.64	0.25	19[e]	71 (21:34:16) [14]	29

[a]Reaction conditions: $(NH_4)_6[Mo_7O_{24}]\cdot4H_2O$ catalyst, 15 mL H_2O–HOAc–H_2SO_4 medium (volume ratio is 4:10:1), 80 °C, 4 h. [b]$NH_2OH\cdot HCl$. [c]$Na_2[MoO_4]\cdot2H_2O$ catalyst. [d]15% MoO_3/Al_2O_3 catalyst. [e]In closed system.

Table 4. Hydroxylation of various aromatic compounds[a]

Aromatics	X_i /%[b]	Product selectivity/%	
		Phenol derivatives	Anilines[c]
	51	 55	 45
	16	 23  59	 18[d]
	18	 58  10  9	 23[d]
	17	 70	 30[d]

[a]Reaction conditions: In closed system, 0.25 g $(NH_4)_6[Mo_7O_{24}]\cdot4H_2O$ catalyst, 10 mmol $(NH_2OH)_2\cdot H_2SO_4$, 20 mmol aromatic compounds, 15 mL H_2O–HOAc–H_2SO_4 medium (volume ratio is 4:10:1), 80 °C (70 °C for benzene hydroxylation), 4 h. [b]The conversion of aromatics. [c]Aniline derivatives. [d]Besides dimethylaniline, trace amounts of tetramethylbiphenyl was also produced as by-products.

rized in Table 3. With increasing catalyst dosage, the selectivity for ethylphenol increases steadily, whereas the conversion of ethylbenzene increases first and then decreases. Better results can be achieved at 0.25–0.55 g of catalyst. For the influence of hydroxylamine, ethylphenol yield can be strongly improved by increasing hydroxylamine dose. When 4.89 g of hydroxylamine sulfate is added, ethylphenol yield increases up to 32% with ethylbenzene conversion of 40%. In addition, hydroxylamine hydrochloride was being substituted for hydroxylamine sulfate in the present hydroxylation, and ethylphenol was also synthesized with good selectivity. However, the conversion of ethylbenzene was only 6%. Hence hydroxylamine sulfate was chosen for the rest of the experiments.

Furthermore, $Na_2[MoO_4]\cdot2H_2O$ and supported catalysts 15% MoO_3/Al_2O_3 were tested for the hydroxylation. As shown in Table 3, these Mo catalysts also exhibit good activity. It means that the supported Mo oxide catalyst and dissolved Mo species are equally effective, and the real active component may be Mo species in the hydroxylation. To see the effect of the absence of air, ethylbenzene hydroxylation was carried out in a closed autoclave. Interestingly, ethylphenol yield was 14%, which is higher than those (10%) in open air under the same reaction conditions.

On the basis of the above results, benzene and xylene isomers were examined in a closed system. Table 4 gives the results. Benzene can also be hydroxylated with hydroxylamine to give phenol, with the selectivity to phenol around 55%. In the hydroxylation of xylene isomers, altogether six dimethylphenols were obtained with good selectivity, corresponding to 2,3-dimethylphenol, 2,4-dimethylphenol, 2,5-dimethylphenol, 2,6-dimethylphenol, 3,4-dimethylphenol, and 3,5-dimethylphenol. For *o*-xylene or *m*-xylene hydroxylation, the total selectivity of dimethylphenols is around 80%.

It is not clear but we believe the reaction mechanisms of the hydroxylations may be related to a radical mechanism. Take ethylbenzene hydroxylation for example, the hydroxylation gives a non-regiospecific mixture of *o*-, *p*-, and *m*-ethylphenols as shown in Tables 1–3. This result is similar to former studies of toluene hydroxylation.[9] If ethylbenzene hydroxylation progressed by an electrophilic mechanism, then *o*- and *p*-ethylphenols would be predominant in the products. The unselective product formation indicates the present hydroxylation may occur through a radical mechanism. Further studies are now in progress.

In conclusion, a new approach for one-pot synthesis of phenol derivatives was described in this work. Benzene, ethylbenzene, and xylene were hydroxylated with hydroxylamine to give the corresponding phenols by using molybdenum as a key catalyst.

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10 The supported 15%MoO_3/Al_2O_3 catalyst was prepared by wet impregnation as follows: 5 g of activated Al_2O_3 carrier was calcined in air at 400 °C for 4 h. Then 1.08 g of $(NH_4)_6[Mo_7O_{24}]\cdot 4H_2O$ was dissolved in 5 mL of distilled water to form a solution. The solution was added to the above Al_2O_3 carrier while being stirred. Afterwards, it was dried at 25 °C for 12 h and 100 °C for 2 h, and finally calcined at 400 °C for 3 h in air.

11 For the reaction in open air: a certain amount of catalyst, hydroxylamine salts, and acid solvents were loaded into a three-necked flask. After stirring for about 20 min at 30 °C, aromatics were poured into the reactor, and the reaction mixture was heated to 80 °C under intensive agitation and reflux in air. After about 4 h, the reaction was stopped. The resulting mixture was cooled, neutralized with a solution of 30% NaOH, and the obtained organic phase was extracted with ether. The products were analyzed with a SP-3420 gas chromatography using a PEG-20M capillary column. For reaction in closed systems, the reaction was carried out in a Teflon-lined stainless steel autoclave. The same procedure was used as mentioned above.