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The Selective Liquid-Phase Oxidation of 3,4,5-Trimethoxytoluene to 3,4,5-Trimethoxybenzaldehyde

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Synopsis. The selective liquid-phase oxidation of 3,4,5-trimethoxytoluene to 3,4,5-trimethoxybenzaldehyde, an important chemical intermediate for medicine production, was developed; when 2.0 mmol of the reactant was heated at 110 °C for 2 h in an autoclave under 3 atm O_2 with 10 ml of acetic acid in the presence of 0.75 mmol of $Co(OAc)_2$–$Mn(OAc)_2$ (3:1 mole ratio), a 92% yield of the aldehyde was obtained.

3,4,5-Trimethoxybenzaldehyde, an important chemical intermediate for medicine production, is produced by a stoichiometric synthesis from vanillin or an electrochemical oxidation of 3,4,5-trimethoxytoluene in the current manufacturing processes.[1] These procedures, however, still have several disadvantages which need to be improved. For example, a recent improvement in the electrochemical process has resulted in excessive electricity consumption. The liquid-phase oxidation of 3,4,5-trimethoxytoluene to 3,4,5-trimethoxybenzaldehyde is another attractive procedure from an industrial point of view. In a previous paper,[2] we demonstrated the potential effectiveness of the liquid-phase oxidation of substituted toluenes to the corresponding aldehydes; *p*-anisaldehyde could be obtained in a relatively high yield from *p*-methoxytoluene using multi-component metal salts. Through continuous efforts, we have developed a very selective method for the liquid-phase oxidation of 3,4,5-trimethoxytoluene to the aldehyde using a $Co(OAc)_2$–$Mn(OAc)_2$ mixture as the catalyst.

Experimental

Materials. The acetic acid, $Co(OAc)_2 \cdot 4H_2O$ (purchased from Wako), $Mn(OAc)_2 \cdot 4H_2O$ and all other reagents were used without further purification. 3,4,5-Trimethoxytoluene was obtained from Otsuka Chem. Co Ltd. 3,4,5-Trimethoxybenzyl alcohol and 3,4,5-trimethoxybenzyl acetate used as authentic standards for GC analysis were synthesized by an LAH reduction of 3,4,5-trimethoxybenzaldehyde and an esterification of 3,4,5-trimethoxybenzyl alcohol with acetic acid.

Procedure and Analysis. In a 50-ml autoclave, the substrate, catalysts, acetic acid, and the additives were mixed with a magnetic stirring bar. The autoclave was pressurized under 3.0 atm of O_2 and placed in an oil bath pre-warmed to the reaction temperature. After vigorous stirring for the prescribed time, the reaction was quenched by immersing the autoclave in an ice bath. After the reaction, naphthalene was added into the reaction mixture as an internal standard; the products were analyzed by GC on a Thermon 3000 on Chromosorb W.

Results and Discussion

Oxidation with $Co(OAc)_2$. The catalytic activities of various metal salts for the liquid-phase oxidation of 3,4,5-trimethoxytoluene were investigated. The results are summarized in Table 1. The reaction was carried out at 110 °C under 3 atm of O_2 in AcOH. With most of the metal salts, the reaction did not proceed. However, several cobalt salts, CoO, $Co(OAc)_2 \cdot 4H_2O$, and $Co_3(PO_4)_2 \cdot 8H_2O$, were found to be effective for the production of 3,4,5-trimethoxybenzaldehyde. The other products include 3,4,5-trimethoxybenzyl acetate and 3,4,5-trimethoxybenzyl alcohol. No detectable amount of 3,4,5-trimethoxybenzoic acid was yielded. The time course of the reaction of the oxidation of 3,4,5-trimethoxytoluene

Table 1. Liquid-Phase Oxidations of 3,4,5-Trimethoxytoluene with Various Metal Salts

Metal salt	Conv.	Ph′CHO	$Ph'CH_2OAc$	$Ph'CH_2OH$	Ph′COOH
	%	%	%	%	%
NiO	17.0	4.6	3.0	0	0
MnO_2	42.9	8.1	3.9	0	0
$Pd(NO_3)_2 \cdot 2H_2O$	64.7	0.6	12.5	0	0
$Ce(NO_3) \cdot 6H_2O$	84.9	6.4	36.1	0	0
CuCl	33.7	0	0	0	0
$FeCl_2 \cdot 4H_2O$	38.0	0	0	0	0
CoO	100.0	72.9	1.2	21.4	0
$CoF_2 \cdot 3H_2O$	31.4	5.6	6.8	0	0
$CoCl_2 \cdot 6H_2O$	16.0	0	0	0	0
$CoBr_2 \cdot 6H_2O$	19.8	0	0	0	0
$Co(OAc)_2 \cdot 4H_2O$	100.0	73.6	2.4	0	0
$Co_3(PO_4)_2 \cdot 8H_2O$	100.0	63.7	1.3	0	0

Ph′ denotes 3,4,5-trimethoxyphenyl; O_2, 3 atm; temp, 110 °C; time, 2 h; $Ph'CH_3$, 2.0 mmol; cat. amount, 0.5 mmol.

Table 2. Liquid-Phase Oxidations of 3,4,5-Trimethoxytoluene with $Co(OAc)_2 \cdot 4H_2O$ in the Presence of an Additive

$Co(OAc)_2 \cdot 4H_2O$ mmol	Additive mmol	Conv. %	Ph'CHO %	$Ph'CH_2OAc$ %	$Ph'CH_2OH$ %	Ph'COOH %
0.50	NaBr, 1.0	4.6	3.4	Trace	0	Trace
0.50	$MgBr_2$, 1.0	11.3	4.7	0	0	0
0.50	H_2O, 27.8	80.5	29.5	19.0	4.3	3.6
0.50	Ac_2O, 52.6	100.0	49.5	0	0	0
0.56	$Ni(OAc)_2 \cdot 4H_2O$, 0.19	100.0	76.4	2.2	0	0
0.56	$Cr(OAc)_3 \cdot H_2O$, 0.19	100.0	76.8	0	0	0
0.56	$Cu(OAc)_2 \cdot H_2O$, 0.19	65.2	45.1	22.6	0	0
0.56	$Ce(OAc)_3 \cdot H_2O$, 0.19	100.0	80.2	7.9	0	0
0.56	$Mn(OAc)_2 \cdot 4H_2O$, 0.19	100.0	91.2	4.2	0	0

O_2, 3 atm; temp, 110 °C; time, 2 h; $Ph'CH_3$, 2.0 mmol.

catalyzed by $Co(OAc)_2 \cdot 4H_2O$ was examined under the same reaction conditions employed for the experiments outlined in Table 1. The conversion of 3,4,5-trimethoxytoluene initially increased with the reaction time and reached 100% at 1.5 h, when a 70% yield of 3,4,5-trimethoxybenzaldehyde was obtained. A further reaction did not increase the yield of 3,4,5-trimethoxybenzaldehyde (the yields were almost constant). The by-products, mainly 3,4,5-trimethoxybenzyl acetate, were formed during the initial 1.5 h; however, they were only detectable in trace amounts for longer reaction times. The total material balance decreased significantly, implying the formation of undetermined polymeric products. The effects of the reaction temperature and O_2 pressure were investigated in order to optimize the reaction conditions to obtain higher yields of the aldehyde; however, with $Co(OAc)_2 \cdot 4H_2O$, the maximum yield did not exceed 70%.

Synergism of $Co(OAc)_2$ and $Mn(OAc)_2$. The effects of several additives for the present reaction were examined (summarized in Table 2). The addition of metal bromides[3] critically lowered the catalytic activity; the yield of 3,4,5-trimethoxybenzaldehyde was very low. The addition of water[4] also retarded the catalytic activity. Ac_2O addition evidently enhances the activity; however, it causes an unpreferable further oxidation of the aldehyde.

The addition of several metal acetate salts were also attempted. Neither $Cr(OAc)_3$, $Ni(OAc)_2$ nor $Cu(OAc)_2$ resulted in a favorable improvement of the 3,4,5-trimethoxybenzaldehyde yield. However, upon the addition of $Ce(OAc)_3$ or $Mn(OAc)_2$ a considerable improvement was found. Especially, a $Co(OAc)_2$–$Mn(OAc)_2$ (3:1) mixture gave a very high yield of the aldehyde (91%). The synergistic effect of $Co(OAc)_2$ and $Mn(OAc)_2$ is evident from Fig. 1, in which the yield of 3,4,5-trimethoxybenzaldehyde is plotted against the ratio of $Mn(OAc)_2$ to $Mn(OA)_2+Co(OAc)_2$. $Mn(OAc)_2$, itself, shows only a low activity regarding oxidation. However, when it was combined with $Co(OAc)_2$, the mixture showed a higher activity for the production of 3,4,5-trimethoxybenzaldehyde than $Co(OAc)_2$ alone. The yield of the aldehyde strongly depends on the mixing ratio; the highest yield was obtained for a Co:Mn ratio of 3:1. The yield of the aldehyde also depended upon the total amount of the catalyst. In the range of the catalyst amount up to 0.75 mmol (with the fixed Co:Mn ratio, 3:1), the yield was almost proportional to the amount of catalyst, and reached the highest yield. The use of more catalyst, however, did not affect the yield very much.

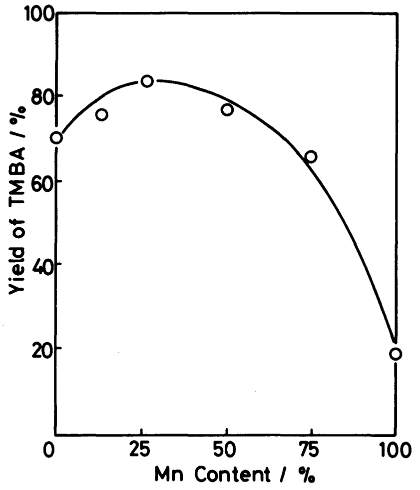

Fig. 1. The dependence of 3,4,5-trimethoxybenzaldehyde (TMBA) yield on Mn content in the oxidation of 3,4,5-trimethoxytoluene with $Co(OAc)_2$–$Mn(OAc)_2$ catalyst. O_2, 3 atm; 3,4,5-trimethoxytoluene, 2.0 mmol; solvent(AcOH), 10 ml; $Co(OAc)_2 \cdot 4H_2O + Mn(OAc)_2 \cdot 4H_2O$ 0.5 mmol; at 110 °C for 2 h.

Since a relatively high concentration of the catalyst was required to obtain a high yield of 3,4,5-trimethoxybenzaldehyde, recycling uses of the catalyst are desirable for industrial applications. Hence, the repeated oxidations of 3,4,5-trimethoxytoluene with the recovered catalyst from the resulting reaction mixture by extraction were attempted. Almost no decline in the catalytic activity and selectivity was observed, even after repeating 25 times. These results indicate the high utility of the present catalytic system for industrial use.

References

1) T. Hirashima and I. Nishiguchi, *J. Synth. Org. Chem.*

Jpn., **43**, 634 (1985); K. Shimizu, K. Kizawa, T. Yoshimoto, and J. Imamura, *J. Japan Petrol. Inst.*, **25**, 7 (1982).

2) N. Kitajima, S. Sunaga, Y. Moro-oka, T. Yoshikuni, M. Akada, Y. Tomotaki, and M. Taniguchi, *Bull. Chem. Soc. Jpn.*, **61**, 967 (1988).

3) C. E. H. Bawn and T. K. Wright, *Discuss. Faraday Soc.*, **46**, 164, (1969).

4) Y. Kamiya, "Yuki Sanka Hannou," Gihōdō (1973); T. Taguchi, N. Okabayashi, S. Futamura, and Y. Kamiya, Preprints, 20th Ann. Symp. Oxi. React., p. 7 (1986).