Studies on catalytic side-chain oxidation of nitroaromatics to aldehydes with oxygen

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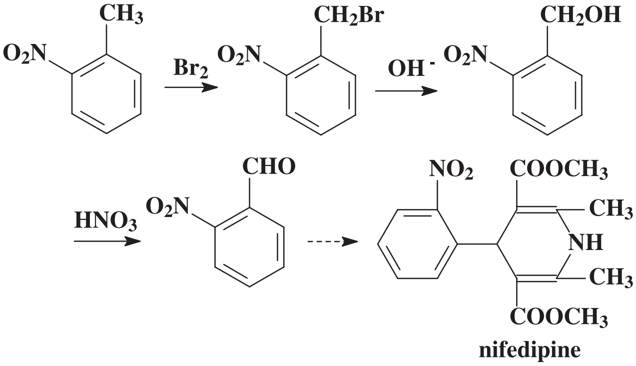
The side-chain oxidation of 2-nitrotoluene in liquid phase in the presence of catalytic amount of manganese sulfate and stoichiometric amount of potassium hydroxide with oxygen was studied. In the most favorable conditions, over 80% of conversion of 2-nitrotoluene and 50% of selectivity to 2-nitrobenzaldehyde was achieved. Effects of the reaction parameters on the conversion of the reactant and the selectivity of the product were examined. These results, together with EPR spectroscopic study, show that a benzyl anion was formed in the early stage of the reaction, which was then converted to the final product via a free radical mechanism.

KEY WORDS: oxidation; substituted benzyl anion; free radical; reaction mechanism; active intermediate.

1. Introduction

Aromatic aldehydes, important intermediates for the manufacture of pharmaceuticals and fine chemicals, are prepared on industrial scale via oxidation of aromatic alcohols with chemical oxidizers such as potassium permanganate, sodium bichromate or nitric acid. For example, 2-nitrobenzaldehyde, an important intermediate for the manufacture of nifedipine, is prepared in China via the following route:



Problems associated with the route are that multiple steps are needed and the overall yield is low. Moreover, the oxidation step caused severe environmental pollution. In order to solve these problems, several catalytic side-chain oxidation methods are developed in the literature recently. We used the copper-catalyzed air oxidation method developed by Marko and coworkers [1] to oxidize 2-nitrobenzyl alcohol to 2-nitrobenzaldehyde in toluene in the presence of 1,10-phenanthroline and hydrazine dicarboxylic acid diethyl ester. The reaction was successful and the yield of recrystallized product was over 70% [2]. But the copper-catalyzed oxidation method still needs multiple steps for the preparation of aromatic aldehydes starting from substituted toluenes.

The simplest and ideal way to prepare aromatic aldehydes would be the direct side-chain oxidation of substituted toluenes to aldehydes with air or oxygen. Most of the reactions are carried out in gas phase, and vanadium pentoxide is usually used as the catalyst [3–6]. The reactions are carried out at high temperatures (usually 300–500 °C). Because aldehydes are easier to oxidize than an alkyl group, it is difficult to stop the oxidation at the aldehyde stage. Thus, at a reasonable conversion, selectivity to aldehydes is low, and the main product is usually a substituted benzoic acid. This situation is slightly changed by the use of liquid-phase catalytic side-chain oxidation of substituted toluenes [7,8]. Liquid-phase oxidation, which uses Co or Mn as a catalyst, can be carried out at much lower temperatures and the selectivity to aldehydes can be improved. Sodium bromide or a strong base such as potassium hydroxide is usually used as a catalyst promoter.

In this paper, side-chain oxidation of 2-nitrotoluene in liquid phase in the presence of a catalytic amount of manganese sulfate and a stoichiometric amount of potassium hydroxide with oxygen was studied. In the most favorable conditions, over 80% of conversion of 2-nitrotoluene and 50% of selectivity to 2-nitrobenzaldehyde was achieved. Effects of the reaction parameters on the conversion of the reactant and the selectivity of the product were examined. These results together with electron paramagnetic resonance (EPR) spectroscopic study show that a benzyl anion was formed in the early

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stage of the reaction, which was then converted to the final product via a free radical mechanism.

2. Experimental

2.1. *Oxidation procedure*

To a mixture of 2-nitrotoluene (6.86 g, 50 mmol) and $MnSO_4 \cdot H_2O$ (0.05 g, 0.3 mmol) in 50 mL of solvent, oxygen (30 mL/min) at 0–5 °C was introduced. A solution of KOH (3.3 g, 59 mmol) in 7 mL of methanol was then added to the reaction mixture dropwise. The resultant mixture was stirred at 0–5 °C for 4.5 h. KOH was then neutralized with 80% sulfuric acid and the solvent was removed *in vacuo*. The residue was dissolved in water and acidified with sulfuric acid to pH 2–3. The aqueous solution was then extracted with methylene chloride three times. Removal of methylene chloride gives the oxidation product containing 2-nitrobenzaldehyde and the unconverted 2-nitrotoluene, which was weighed and analyzed qualitatively by GC-MS (Saturn 2000) and quantitatively by high performance liquid chromatography (HPLC) (Waters 600E chromatograph, 2487 detector).

2.2. *Detection of reactive free radical intermediate by EPR*

The reactants and the spin-trapping agent N-tert-butyl-α-phenylnitrone were added to the sample cell of the EPR spectrometer at 0 °C, and the absorption peak was recorded every few minutes. The microwave frequency and power was controlled at 9.4910 GHz and 20 to 64 mW respectively. Resonance occurred at 3380.75 G. $MnSO_4$ shows a strong EPR absorption peak under the reaction conditions. In order to eliminate the interference of Mn on the detection of organic free radicals, $MnSO_4$ was not added in these experiments.

3. Results and discussion

3.1. *Effects of KOH concentration on the oxidation*

The dependence of reactant conversion (C) and product selectivity (S) on the amount of KOH used ($R_{KOH/o\text{-}MNT}$, the molar ratio of KOH over 2-nitrotoluene) was determined, and results obtained at 0–5 °C for 4.5 h is illustrated in figure 1.

Figure 1 shows that both the conversion of 2-nitrotoluene and the selectivity of product increase with the increasing of $R_{KOH/o\text{-}MNT}$ until $R_{KOH/o\text{-}MNT}$ reaches 1.5. If $R_{KOH/o\text{-}MNT}$ is larger than 1.5, the two curves tend to change in different directions, the conversion curve going upward and the selectivity curve going downward. But the upward change of the conversion curve is much slower than the downward change of the selectivity curve.

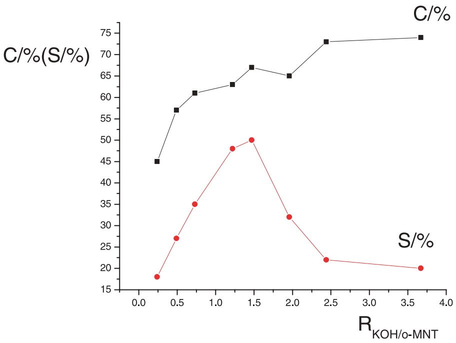
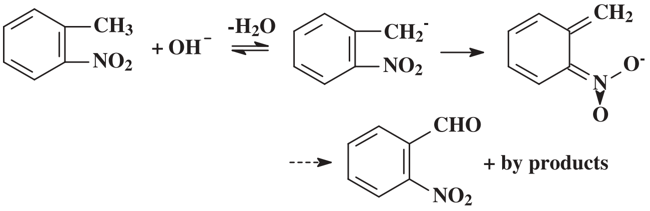


Figure 1. Dependence of reactant conversion (C) and product selectivity (S) on the amount of KOH used ($R_{KOH/o\text{-}MNT}$, the molar ratio of KOH over 2-nitrotoluene).

When $R_{KOH/o\text{-}MNT} = 1$ and the initial concentration of *o*-MNT(A_0) and KOH(B_0) is 1.0 mol L^{-1}, the oxidation shows second-order kinetics until 6 h of reaction in morpholine according to the observed linear relationship between $1/(A_0\text{–}C)$ and reaction time *t*. The second-order constants, the turnover frequencies and the activation energy in the temperature range −5 to 10 °C are listed in table 1.

The above results can be explained by a nitro-stabilized benzyl anion mechanism, i.e. the first and rate-determining step of the reaction is deprotonation of 2-nitrotoluene to form 2-nitrobenzyl anion. The anion was then converted into a more stable form and was finally transferred to the product via further reactions. If excess amount of KOH is used, side reactions may occur because of which conversion increases and selectivity decreases.



The above hypothesis was further strengthened by the oxidation of 3-nitrotoluene (m-MNT) under the same conditions. The dependence of conversion of m-MNT on the amount of KOH used at 0–5 °C for 4.5 h is illustrated in figure 2 together with the conversion of o-MNT under the same conditions for convenience of comparison.

Table 1
Kinetic data for the oxidation of o-MNT in morpholine

T (°C)	$k_2 \times 10^5$ (L mol^{-1} s^{-1})	Catalyst turnover (h^{-1})	Ea (kJ mol^{-1})
−5	3.56	8	52 kJ mol^{-1}
5	9.26	19	
10	12.9	25	

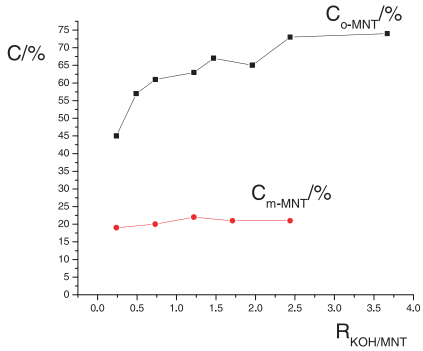


Figure 2. The dependence of reactant conversion (C) on the amount of KOH used.

Table 2
Conversion and selectivity of the reaction in different solvent

Solvent	C (%)	S (%)
Methanol	21	0
Methanol/benzene (v/v = 1/5)	33	0
2-methoxyethanol	35	3
Morpholine	63	50
Propylamine	72	52
2-methoxyethylamine	81	50

The curves in figure 2 indicate that the conversion of m-MNT is much lower than the conversion of *o*-MNT under the same conditions and is almost independent of the amount of KOH used. This evidence supports the hypothesis of benzyl anion formation given above, because a nitro group attached to the meta-position could not stabilize a benzyl anion effectively.

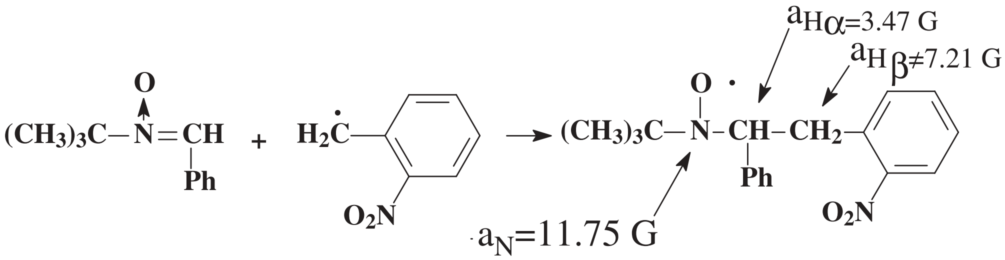
3.2. *Effects of solvent on the oxidation*

Solvent dependence of the reactant conversion (C) and aldehyde selectivity (S) was also examined and the results are listed in table 2.

It can be seen from table 2 that organic amines with an additional functional group are favorable solvents for the reaction. In protic solvents such as alcohols, the reaction could not take place. These results can again be explained by the hypothesis of benzyl anion formation. Obviously in protic solvents such as alcohols, it is difficult to form a carbanion with metal hydroxides. The basicity of an amine is much stronger, and the formation of a carbanion in an amine solvent would be much easier than in alcohols. Moreover, amines with an additional functional group are good ligands to form complexes with transition metals, which may play a key role in the catalytic cycle.

3.3. *Formation of reactive free radical intermediate*

Although the mechanism of catalytic side-chain oxidation of aromatics in gas phase has been studied extensively and free radical mechanism is widely accepted, reports about the mechanism of liquid-phase oxidation, especially the direct detection of reactive intermediates is scarce in the literature. The evidence given above confirms the formation of benzyl anion as a reactive intermediate in catalytic side-chain oxidation of aromatics in the presence of a strong base. Interesting phenomena were observed in further studies of the reaction by EPR. In methanol, no free radical signal was observed (figure 3) until 25 min of the reaction. In morpholine, a remarkable free radical signal appears



Scheme 3.

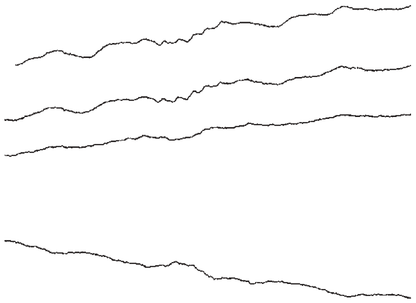


Figure 3. EPR spectrum in methanol.

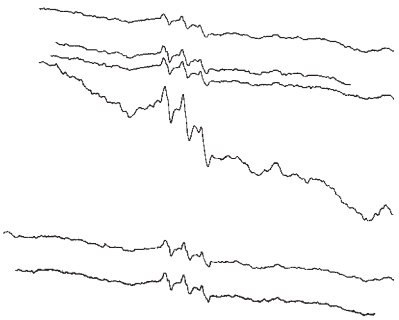


Figure 4. EPR spectrum in morpholine.

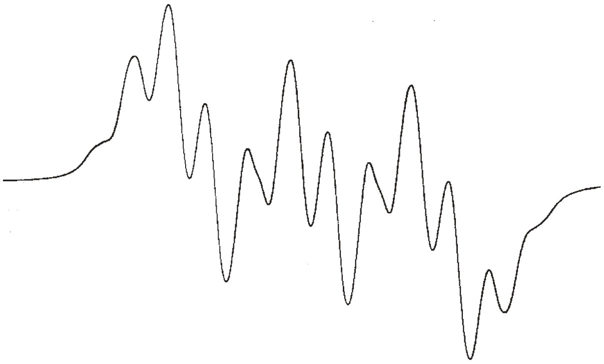


Figure 5. EPR spectrum in 2-methoxyethylamine.

within a few minutes of the reaction (figure 4). In 2-methoxyethylamine, a strong free radical signal appeared after a few minutes of the reaction and the splitting is clear (figure 5). These results are in accordance with the experimental data of conversion and selectivity of the reaction in corresponding solvents. Spectrum analysis shows that the free radical is a spin-trapping species of 2-nitrobenzyl radical by the spin-trapping agent N-tert-butyl-α-phenylnitrone.

The g value for the spin-trapping species was calculated to be 2.0057, which is in good accordance with the g_e value of 2.0023 for free radicals. The electron–nuclear hyperfine interaction constants are 11.75 G for a_N, 3.47 G for $a_{H\alpha}$ and 7.21 G for $a_{H\beta}$ respectively. A large $a_{H\beta}$ is reasonable, considering the electron withdrawing effect of the nitro group.

All the results given above support a conclusion that benzyl anion was the initially formed intermediate in liquid-phase catalytic side-chain oxidation of aromatics in the presence of a strong base, which was then converted to the final product via a free radical mechanism.

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