The selective reduction of nitroarenes to *N*-arylhydroxylamines using Zn in a CO_2/H_2O system†

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Nitroarenes are reduced to the corresponding *N*-arylhydroxylamines with high selectivity using Zn dust in a CO_2/H_2O system under mild conditions. The yield of *N*-phenylhydroxylamine from nitrobenzene is 88% when the reaction is carried out at 25 °C for 1.5 hours with a Zn to nitrobenzene molar ratio equal to 3 under 0.1 MPa CO_2. Other nitroarenes, which contain reducible functionality other than a nitro group, are also reduced to the corresponding *N*-arylhydroxylamines with yield from 88% to 99%. The process fully removes the need to use NH_4Cl and is environmentally benign.

Introduction

N-Arylhydroxylamines are useful intermediates in the synthesis of fine chemicals[1] and pharmaceuticals.[2] These amines are usually prepared by selective reduction of the corresponding nitroarenes. *N*-Phenylhydroxylamine (PHA) was first prepared by the zinc reduction of nitrobenzene (NB) more than a hundred years ago[3] and the method using Zn dust in aqueous NH_4Cl solution was modified into a conventional protocol.[4] Many other methods for the preparation of *N*-phenylhydroxylamine have been reported, which include catalytic hydrogenation,[5] catalytic hydrogen transfer,[6] reduction by sulfide[7] or by borohydride,[8] electrolytic reduction[9] and biocatalysis.[10] The catalytic hydrogenation is a clean method, but over reduction of nitroarenes to aromatic amines is a problem. The catalytic hydrogen transfer reduction consumes various reagents as a hydrogen source, such as formic acid or hydrazine, in the presence of metal catalysts (Pd, Rh and Raney Ni), many of which are very expensive. The reduction by sulfide produces much wastewater and the reduction by borohydride involves the use of poisonous elements Se, Te, Sb or Bi. Furthermore, the electrolytic reduction and biocatalyst methods are costly. The traditional method using Zn dust for the preparation of *N*-arylhydroxylamines shows the advantages of mild reaction conditions, good product selectivity and low cost. Nevertheless, it has the drawbacks that large amount of NH_4Cl is consumed and a lot of wastewater is formed. In view of environmental concerns, it is important to develop an efficient method, which avoids using NH_4Cl.

Recently, the CO_2/H_2O system has been regarded as an environmentally benign alternative to conventional acids. When water is pressurized by CO_2, pH values of the system can be as low as 3.1,[11] and the system will be self-neutralized on the release of CO_2. Several research works have been reported involving the application of this environmentally benign system.[12] In our previous work, the reductions of nitroarenes to aromatic amines using Fe in a CO_2/H_2O system have been developed,[13] and the same reaction using Zn dust as reducing agent has been also reported by Jiang *et al*.[14] The product formed in the zinc reduction of nitrobenzene is dependent on the pH value of the reaction medium. For example, azoxybenzene is obtained from nitrobenzene in basic solution, whereas *N*-phenylhydroxylamine is obtained using Zn in aqueous NH_4Cl, a weak acidic solution. It is noteworthy that the acidity of a CO_2/H_2O system is close to that of aqueous NH_4Cl solution, so the reduction of nitroarenes to *N*-arylhydroxylamines using Zn in a CO_2/H_2O system is very promising. In this manuscript the investigation results in this subject are presented.

Results and discussion

Firstly, the reduction of nitrobenzene to *N*-phenylhydroxylamine was tested in a 75 mL autoclave. The effects of different reaction conditions on the reduction were studied and the results were shown in Table 1. It should be pointed out that only trace reduction took place in the absence of CO_2 (entry 1), and the reaction could be accelerated dramatically with the charge of 0.1 MPa CO_2 (entry 2). Therefore, CO_2 plays a crucial role in the reaction. At a reaction temperature of 40 °C, the yield of *N*-phenylhydroxylamine reached 76% with a CO_2 pressure of 0.5 MPa (entry 3). With a further increase of CO_2 pressure, the amount of aniline (AN), the side product due to the full reduction of nitrobenzene, increased and the reaction selectivity to *N*-phenylhydroxylamine decreased (entries 4–6). When the reaction was run with a Zn to nitrobenzene molar ratio equal to 3 and 0.5 MPa CO_2 pressure for 3 hours, the yield of *N*-phenylhydroxylamine reached the maximum at 40 °C within the temperature range from 20 °C to 60 °C. Also, the conversion of nitrobenzene has the same trend. The main reason is the combined effect of the reaction temperature and the acidity of the system in this case. Some more results and discussion on this aspect are in the following content. A larger excess of Zn in the system resulted in an increase of the fraction of aniline

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Table 1 The effects of different reaction conditions on the selective reduction of nitrobenzene[a]

Entry	Zn/mmol	P_{CO_2}/MPa	T/°C	t/h	Conv.[b] (NB)/%	Yield[b] (PHA)/%	Yield[b] (AN)/%
1	30	0	40	3	3	trace	0
2	30	0.1	40	3	57	42	6
3	30	0.5	40	3	100	76	14
4	30	1	40	3	98	62	28
5	30	1.5	40	3	100	52	39
6	30	5	40	3	99	14	77
7	30	0.5	20	3	87	68	7
8	30	0.5	60	3	68	49	15
9	22	0.5	40	3	80	60	11
10	40	0.5	40	3	100	45	48
11	50	0.5	40	3	100	0	100
12	30	0.5	40	2	89	70	10
13	30	0.5	40	4	100	26	65

[a] Reaction condition: NB 10 mmol, H_2O 20 mL. [b] Determined by HPLC, small amount of azoxybenzene was also detected.

in the products (entries 3, 9–11). Under the reaction condition applied, nitrobenzene was reduced to aniline completely if the molar ratio of Zn to nitrobenzene was equal to 5 (entry 11). When the reaction time was prolonged (entries 3, 12, 13), the fraction of aniline in the products increased, too.

The above-mentioned results show that the introduction of CO_2 to the reaction system is essential to promote the reduction of nitrobenzene to *N*-phenylhydroxylamine. A very important matter is that the reaction can take place even at normal CO_2 pressure. Although the reaction result is not the best, the possibility to run the reaction under normal CO_2 pressure is very convenient. So a systematic study on the reaction parameters to optimize the yield of *N*-phenylhydroxylamine is carried out, and the reaction is run in a 100 mL three-necked glass bottle with CO_2 bubbling through the water phase for a better adsorption.

Fig. 1 shows the results of the influence of reaction temperature on the reaction.

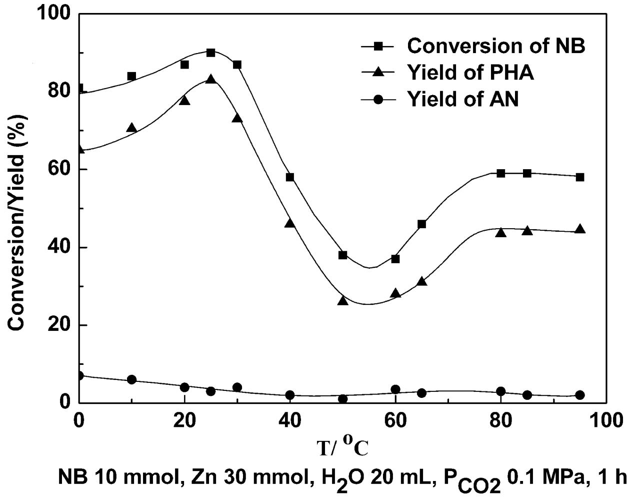


Fig. 1 The effect of temperature on the reaction.

It is interesting to see from Fig. 1 that in the temperature range from 0 °C to 60 °C, the conversion of nitrobenzene as well as the yield of *N*-phenylhydroxylamine reached to a maximum at 25 °C, and decreased again to a minimum at 55 °C. These results are similar to the results obtained in the pressurized reaction condition (see Table 1). When the reaction temperature is higher than 60 °C, the conversion of nitrobenzene is increased gradually with the increase of the reaction temperature. It seems that the reaction is affected to a greater extent by the acidity of the system in the temperature range from 0 °C to 60 °C. That is, the reaction is accelerated by both the increase of the acidity of the reaction system and the increase of reaction temperature. But the acidity of the system is decreased as the CO_2 solubility decreases with the increase of the reaction temperature. When the temperature is higher than 60 °C, the negative effect of the decrease of the acidity of the system on the reaction becomes not so serious. Over the range of the reaction temperature investigated, the reaction selectivity to *N*-phenylhydroxylamine in the reaction products does not change much.

The results of different amount of Zn dust on the reduction are illustrated in Fig. 2. With an increase of the molar ratio of Zn to nitrobenzene, the conversion of nitrobenzene increased. The yield of *N*-phenylhydroxylamine reached the maximum when the ratio of Zn to nitrobenzene was equal to 3 under the reaction conditions adopted. Further increase of the ratio of Zn to nitrobenzene leads to an increase of the amount of aniline, the complete reduction product.

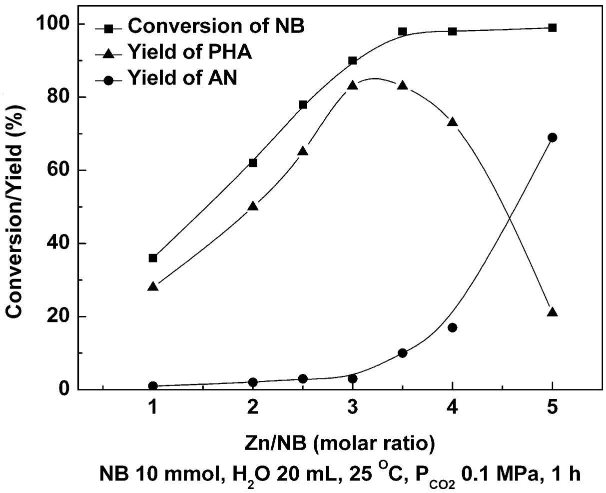
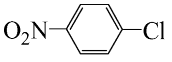
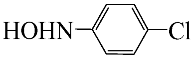
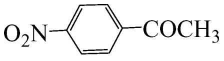
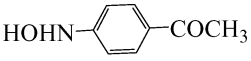
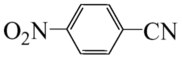
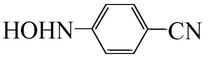
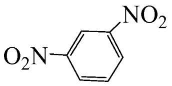
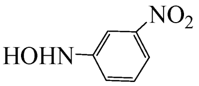
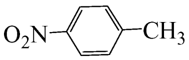
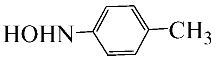


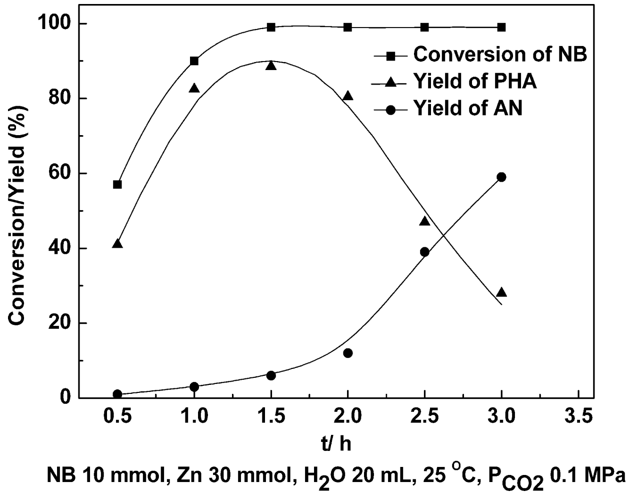
Fig. 2 The effect of molar ratio of Zn to NB on the reaction.

Table 2 The reduction of various substituted nitrobenzenes using Zn in CO_2/H_2O system[a]

Run	Substrate	Product	Substrate conv.[b]/%	Product Yield[b]/%
1			99	95
2			100	94
3			98	88
4			99	99
5			99	90

[a] Reaction conditions: substrate 5 mmol, Zn 15 mmol, H_2O 20 mL, P_{CO_2} 0.1 MPa, 25 °C, 1.0 h. [b] Calculated by ^1H NMR data.

The reaction results with different reaction times are shown in Fig. 3. It could be seen that the yield of *N*-phenylhydroxylamine reached up to 88% when the reaction time was 1.5 hours. Further increase of the reaction time results in increasing the content of aniline in the reaction products. So to monitor the reaction product during the reaction progress is very important to optimize the yield of *N*-phenylhydroxylamine.



NB 10 mmol, Zn 30 mmol, H_2O 20 mL, 25 °C, P_{CO_2} 0.1 MPa

Fig. 3 The effect of reaction time on the reaction.

This new method is also applicable for the selective reduction of nitrobenzenes substituted with other reducible functional groups, such as $-COCH_3$ and –CN. The scope and generality of this method is illustrated with several examples and the results are summarized in Table 2.

Conclusion

In conclusion, the selective reduction of nitroarenes to *N*-arylhydroxylamines is realized using Zn dust in a CO_2/H_2O system. Nitrobenzene can be reduced to *N*-phenylhydroxylamine with a yield of 88% when the reaction was carried out at 25 °C for 1.5 hours with a Zn to nitrobenzene molar ratio equal to 3 under 0.1 MPa CO_2. Nitroarenes having other reducible functional groups can also be selectively transformed to the corresponding *N*-arylhydroxylamines. The method provides an environmentally benign way for the preparation of *N*-arylhydroxylamines.

Experimental

Materials and reaction procedure

Nitroarenes and Zn dust are commercial products and used without further purification. An appropriate amount of nitroarene, Zn dust and water were placed in a reactor. The reactor was put in a preheated oil bath with magnetic stirring and then CO_2 was charged to the reactor for a fixed time. After completing the reaction, the suspension was filtered, the solid was washed with CH_2Cl_2, and the filtrate was extracted by CH_2Cl_2. The combined organic phase was dried over anhydrous $MgSO_4$. The crude product was obtained from the organic phase by evaporation and the product analysis was performed by HPLC or by ^1H NMR. The solid was further purified by recrystallisation from the solvent mixture of CH_2Cl_2 and petroleum ether (bp 60–90 °C).

Product analysis and characterization. Melting points of the products were measured on a X-6 (Beijing Tech. instrument Co. Ltd) melting-point apparatus. ^1H NMR spectra were recorded on Inova 400 (Varian, USA). The data of melting points and ^1H NMR spectra of these *N*-arylhydroxylamines were consistent with those reported in the literature. The analyses of the products from the reduction of nitrobenzene were performed by HPLC on Agilent 1100 series (column: Agilent TC-C18, 4.6 mm × 250 mm, 5 μm; UV detector: 254 nm; eluent: water–methanol).

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