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Selective reduction of nitroarenes to *N*-arylhydroxylamines by use of Zn in a CO_2–H_2O system, promoted by ultrasound

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Abstract The promoting effect of ultrasound on the selective reduction of nitroarenes to *N*-arylhydroxylamines by use of Zn in an environmentally benign CO_2–H_2O system has been demonstrated. The yield of *N*-phenylhydroxylamine reaches 95 % when the reaction is carried out with a Zn-to-nitrobenzene molar ratio of 2.2 under ultrasound (40 kHz) at 25 °C and normal pressure of CO_2 for 60 min. Application of ultrasound to the reaction has the advantages of higher yield of *N*-arylhydroxylamines, shorter reaction time, and consumption of less Zn.

Keywords Nitroarenes · Reduction · Zn · CO_2–H_2O · Ultrasound · *N*-Arylhydroxylamines

Introduction

N-Arylhydroxylamines, useful intermediates in the synthesis of fine chemicals [1–3] and pharmaceuticals [4–6], are usually prepared by the selective reduction of the corresponding nitroarenes. Methods for preparation of *N*-arylhydroxylamines include catalytic hydrogenation [7–9], catalytic transfer hydrogenation [10, 11], metal-mediated reduction [12], and others [13–16]. Zn-mediated reduction of nitroarenes, a widely used conventional method, is performed in aqueous NH_4Cl solution. The method has the advantages of mild reaction conditions and good product selectivity, but a large amount of NH_4Cl is consumed and much waste is produced.

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The accelerating effect of ultrasound on chemical reactions was first reported in 1927 [17]; since then ultrasound has been extensively applied in organic reactions. Recently Ferround's group [18] reported the promoting effect of ultrasound on Zn mediated reduction of nitroarenes using NH_4Cl. The reaction was complete in 5 min, and yields of the corresponding *N*-arylhydroxylamines were 75–95 %. Later Shi [19] described the preparation of *N*-arylhydroxylamines by use of Zn–$HCOONH_4$-MeCN-ultrasound; selectivity for *N*-arylhydroxylamines was 90–98 %, but their procedure still consumed ammonium salt and they did not report any results on selective reduction of nitrobenzene.

Very recently, we developed a novel procedure using Zn in CO_2–H_2O for selective reduction of nitroarenes to *N*-arylhydroxylamines [20, 21]. This environmentally benign system is fully free from NH_4Cl and the yield of *N*-phenylhydroxylamine reaches 88 % under the optimum conditions. Nitroarenes with reducible functionality in addition to nitro groups were also reduced selectively to the corresponding *N*-arylhydroxylamines. In this manuscript we report the promoting effect of ultrasound (40 kHz) on the selective reduction of nitroarenes to *N*-arylhydroxylamines using Zn in CO_2–H_2O.

Experimental

Apparatus and analysis

Nitroarenes and Zn dust were commercial reagents and were used without further purification. Ultrasound was produced by a KQ5200B ultrasonic cleaner (200 W, 40 kHz; Kunshanshi Chaosheng Instrument, China). Melting points of the products were measured on a X-6 (Beijing Tech. Instrument) melting-point apparatus. ^{1}H NMR spectra were recorded on Inova 400 (Varian, USA) and chemical shifts were recorded in ppm from TMS as internal standard. Melting points and ^{1}H NMR spectra of the *N*-arylhydroxylamines obtained were consistent with those reported in the literature [22–26]. Analysis of products from reduction of nitrobenzene was performed by HPLC on an Agilent 1100 series (column: Agilent TC-C18, 4.6 mm × 250 mm, 5 μm; UV detection: 254 nm; mobile phase: water–methanol).

Typical procedure for preparation of *N*-arylhydroxylamines

Appropriate amounts of nitroarene, Zn dust, and water were placed in a 100-mL three-necked flask which was equipped with mechanic stirrer and condenser. The flask was immersed in the water bath of the ultrasonic cleaner, then CO_2 was bubbled through the reaction mixture which was sonicated under mechanical stirring at the designed temperature for a fixed time. After completion of the reaction, the suspension was isolated by filtration, the solid was washed with CH_2Cl_2, and the filtrate was extracted with 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 product analysis was performed by HPLC or by ^{1}H NMR.

The product was purified by recrystallization from a mixture of CH_2Cl_2 and petroleum ether (bp 60–90 °C).

Characterization data for the products

N-(4-acetophenyl) hydroxylamine mp 116–117 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.45 (s, 3 H, CH_3), 6.83 (pseudo-q, 2 H, $J_{AX} + J_{AX'} = 8.4$ Hz, A–H and A′–H), 7.80 (pseudo-q, 2 H, $J_{AX} + J_{AX'} = 8.4$ Hz, X–H and X′–H), 8.69 (s, 1 H, OH), 9.01 (s, 1 H, NH).

N-(4-cyanophenyl) hydroxylamine mp 85–86 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.86 (pseudo-q, 2 H, $J_{AX} + J_{AX'} = 8.8$ Hz, A–H and A′–H), 7.55 (pseudo-q, 2 H, $J_{AX} + J_{AX'} = 8.8$ Hz, X–H and X′–H), 8.76 (s, 1 H, OH), 9.10 (s, 1 H, NH).

N-(3-nitrophenyl) hydroxylamine mp 118 - 119 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.20 (br d, 1 H, $J = 8.0$ Hz, 6-H), 7.44 (t, 1 H, $J = 8.0$ Hz, 5-H), 7.59 (br d, 1 H, $J = 8.0$ Hz, 4-H), 7.63 (br s, 1 H, 2-H), 8.76 (s, 1 H, OH), 8.88 (s, 1 H, NH).

N-(p-tolyl) hydroxylamine mp 82–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.29 (s, 3 H, CH_3), 6.47 (br s, 2 H, NH and OH), 6.90 (pseudo-q, 2 H, $J_{AX} + J_{AX'} = 8.0$ Hz, A–H and A′–H), 7.08 (pseudo-q, 2 H, $J_{AX} + J_{AX'} = 8.0$ Hz, X–H and X′–H).

N-(4-bromophenyl) hydroxylamine mp 92–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.79 (br s, 2 H, NH and OH), 6.87 (pseudo-q, 2 H, $J_{AX} + J_{AX'} = 8.0$ Hz, A–H and A′–H), 7.37 (pseudo-q, 2 H, $J_{AX} + J_{AX'} = 8.0$ Hz, X–H and X′–H).

N-(2-chlorophenyl) hydroxylamine mp 53–54 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.77 (t, 1 H, $J = 7.6$ Hz, ArH), 7.17–7.25 (m, 3 H, ArH), 8.19 (s, 1 H, OH), 8.56 (s, 1 H, NH).

N-(3-chlorophenyl) hydroxylamine mp 49–50 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.75 (br d, 2 H, $J = 8.0$ Hz, 4-H and 6-H), 6.84 (br s, 1 H, 2-H), 7.16 (t, 1 H, $J = 8.0$ Hz, 5-H), 8.51 (s, 1 H, OH), 8.53 (s, 1 H, NH).

N-(4-chlorophenyl) hydroxylamine mp 83–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.09 (br s, 2 H, NH and OH), 6.99 (pseudo-q, 2 H, $J_{AX} + J_{AX'} = 8.8$ Hz, A–H and A′–H), 7.30 (pseudo-q, 2 H, $J_{AX} + J_{AX'} = 8.8$ Hz, X–H and X′–H).

Results and discussion

Selective reduction of nitrobenzene (NB) to *N*-phenylhydroxylamine (PHA) was examined under different conditions; the results were listed in Table 1. From Table 1 it is apparent that the reaction did not occur without bubbling CO_2, even though both mechanical stirring and ultrasound were applied (entries 1 and 2). In contrast, 5 % conversion of nitrobenzene was achieved if CO_2 was bubbled into the reaction mixture with no other treatment (entry 3). With the combination of CO_2 bubbling and mechanical stirring, conversion of nitrobenzene and yield of *N*-phenylhydroxylamine were 50 % and 47 % respectively (entry 5) for a reaction time of 60 min, and the latter was only 76 % when the reaction period was four times longer (entry 7). Higher yield of *N*-phenylhydroxylamine could be achieved at the expense of use of an excessive amount of Zn (entries 8 and 9). The results given

Table 1 Selective reduction of nitrobenzene to *N*-phenylhydroxylamine under different conditions[a]

Entry	P_{CO_2} (MPa)	Stirring	U.[b]	Zn (mmol)	*t* (min)	NB Conv.[c] (%)	PHA Yield[c] (%)	Selec.[c] to PHA (%)
1	0	Without	Yes	22	60	0	0	0
2	0	With	Yes	22	60	0	0	0
3	0.1	Without	No	22	60	5	4	80
4	0.1	Without	Yes	22	60	8	7	87
5	0.1	With	No	22	60	50	47	94
6	0.1	With	Yes	22	60	98	93	95
7	0.1	With	No	22	240	86	76	89
8	0.1	With	No	30	90	99	88	89
9	0.1	With	No	40	60	98	91	93
10	0.1	With	Yes	30	30	98	92	94
11	0.1	With	Yes	30	60	99	11	11
12	0.1	With	No	30	30	57	51	89
13	0.1	With	No	30	60	90	83	92

[a] Reaction conditions: NB 10 mmol, H_2O 30 mL, 25 °C

[b] Under ultrasound

[c] Determined by HPLC

for entries 4–6 revealed that selective reduction of nitrobenzene with the combination of CO_2 bubbling, mechanical stirring, and ultrasound irradiation was the best. 98 % conversion of nitrobenzene and 93 % yield of *N*-phenylhydroxylamine were obtained (entry 6). It was found that when more Zn was used (Zn:NB = 3), a good yield of *N*-phenylhydroxylamine (92 %) was obtained in shorter time (30 min) (entry 10) and a further increase in the reaction time resulted in reduced yield of *N*-phenylhydroxylamine because of its further reduction to aniline (AN) (entry 11). However, without ultrasound the reaction was less efficient, and the yield of *N*-phenylhydroxylamine was 51 % and 83 % for reaction time of 30 and 60 min, respectively (entries 12 and 13).

In summary, higher yield of *N*-phenylhydroxylamine was obtained with smaller Zn-to-nitrobenzene molar ratio and shorter reaction time when ultrasound was applied.

Selective reduction of nitrobenzene to *N*-phenylhydroxylamine using Zn in CO_2–H_2O is more efficient under the action of ultrasound. This phenomenon may be attributed to the cavitation effect caused by ultrasound in the solid–liquid heterogeneous reaction medium. The formation of *N*-phenylhydroxylamine from nitrobenzene involves the following steps:

1 transfer of nitrobenzene to the Zn^0 surface from the solution;
2 adsorption of nitrobenzene on the Zn^0 surface;
3 chemical reaction on the Zn^0 surface, which involves formation of *N*-phenylhydroxylamine and its successive reduction to aniline;
4 desorption of the products from the solid surface; and
5 transfer of the products into the solution.

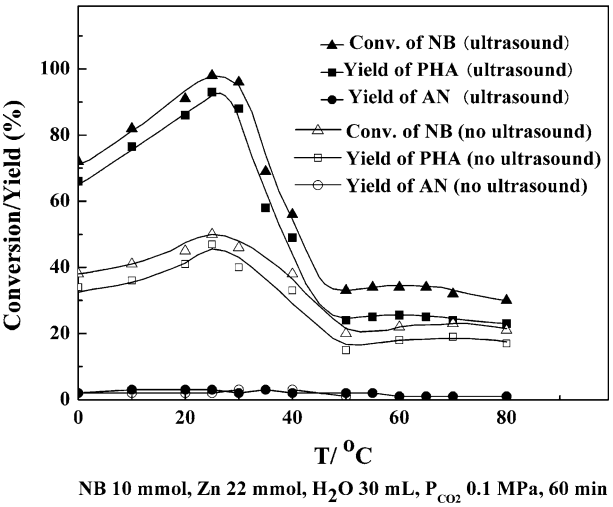


Fig. 1 The effect of reaction temperature on the reaction

So desorption of *N*-phenylhydroxylamine from the metal surface would preclude the further reduction. Although mechanical stirring would enhance mass transfer between the solution and the metal surface to some extent, its main effect is to make the whole system turbulent, a long-range effect. On the metal surface there is a near static thin liquid layer (short range) and mass transfer through this layer is less affected by mechanical stirring. When ultrasound is applied in a solid–liquid heterogeneous system, ultrasonic activation occurs, i.e. as a consequence of the mechanical effects of cavitation a liquid jet propagates toward the solid–liquid phase boundary with high velocity, and hits the solid surface violently [27]. As a result, the metal surface may be continuously cleaned by the shock wave and microjets formed during cavitation bubble collapse. Thus application of ultrasound compensated for the deficiency of mechanical stirring. In addition, the Zn^0 surface would be increased, because of rupture of particles by the highspeed microjet when the cavity implodes asymmetrically [28, 29]. Hence, higher reaction efficiency is achieved under the action of ultrasound, and the selectivity and the yield of *N*-phenylhydroxylamine are higher under these conditions.

To optimize the yield of *N*-phenylhydroxylamine, the effects of different reaction conditions were studied.

The results of the reaction with and without ultrasound at different temperature are shown in Fig. 1. From Fig. 1, it can be seen that conversion of nitrobenzene and yield of *N*-phenylhydroxylamine in the reaction under the action of ultrasound were higher than those in the reaction without ultrasound. In the temperature range from 0 to 50 °C, conversion of nitrobenzene and yield of *N*-phenylhydroxylamine reached a maximum at 25 °C. The reason is that the reaction is accelerated by both increasing acidity of the reaction system and an increase in the reaction temperature. But the acidity of the reaction system is reduced as the solubility of CO_2 in H_2O decreases with increasing reaction temperature.

In the range of reaction temperature examined, the yield of aniline, the by-product from further reduction of *N*-phenylhydroxylamine, is low (less than 5 %).

The reaction results with different reaction time and different amounts of water used in the system under the action of ultrasound are listed in Table 2.

It is apparent the optimum yield of *N*-phenylhydroxylamine (95 %) was obtained under the reaction conditions used for the entry 7 in Table 2.

Table 2 Selective reduction of nitrobenzene to *N*-phenylhydroxylamine using Zn in CO_2–H_2O under different reaction conditions[a]

Entry	*t* (min)	H_2O (mL)	NB Conv.[b] (%)	PHA Yield[b] (%)	Selec.[b] to PHA (%)
1	30	30	73	70	96
2	40	30	88	84	95
3	50	30	92	87	95
4	60	30	98	93	95
5	80	30	98	91	93
6	60	20	89	82	92
7	60	40	98	95	97
8	60	50	95	92	97

[a] Reaction conditions: NB 10 mmol, Zn 22 mmol, 25 °C, P_{CO2} 0.1 MPa, ultrasound 40 kHz

[b] Determined by HPLC

Table 3 Selective reduction of different nitroarenes by use of Zn in CO_2–H_2O[a]

Entry	R	Zn (mmol)	H_2O (mL)	*t* (min)	**a** Conv.[b] (%)	**b** Yield[b] (%)	Selec.[b] to **b** (%)
1	*p*-$COCH_3$	11	40	40	98	92	94
2	*p*-CN	11	40	40	99	98	99
3	*m*-NO_2	11	40	40	96	95	99
4	*p*-CH_3	11	40	40	97	94	97
5	*p*-Br	11	40	40	99	94	95
6	*o*-Cl	11	40	40	98	97	99
7	*m*-Cl	11	40	40	99	98	99
8	*p*-Cl	11	40	40	99	97	98
9[c]	*p*-$COCH_3$	15	20	60	100	94	94
10[c]	*p*-CN	15	20	60	98	88	90
11[c]	*m*-NO_2	15	20	60	99	99	100
12[c]	*p*-CH_3	15	20	60	99	90	91
13[c]	*p*-Cl	15	20	60	99	95	96

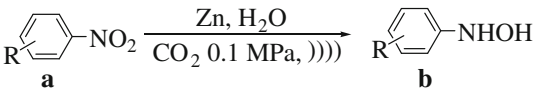
Bold "a" represents nitroarene substrate, bold "b"represents *N*-arylhydroxylamine product, which are described in Scheme1 as "a" and "b" .

[a] Reaction conditions: substrate 5 mmol, P_{CO_2} 0.1 MPa, 25 °C, ultrasound 40 kHz

[b] Calculated from ^{1}H NMR data

[c] These data were taken from Ref. [20]

Scheme 1 The selective reduction of various nitroarenes



a **b**

Nitroarenes with other functional groups, for example –Cl, –Br, $-COCH_3$, and –CN, were also tested in the reaction under the action of ultrasound (Scheme 1); the corresponding yields of *N*-arylhydroxylamines were also high (92–98 %), as shown in Table 3.

Compared with our previous results [20], high yields of *N*-arylhydroxylamines were obtained with smaller Zn-to-nitrobenzene molar ratio (from 3 to 2.2) and shorter reaction time (from 60 to 40 min). Ultrasound substantially enhanced the efficiency of the reaction.

Conclusion

In summary, the promoting effect of ultrasound on the selective reduction of nitroarenes to *N*-arylhydroxylamines using Zn in an environmentally benign CO_2–H_2O system was demonstrated. Higher yield of *N*-arylhydroxylamines could be obtained with less Zn consumption and shorter reaction times under the action of ultrasound. Use of ultrasound makes the reaction more efficient.

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