

Selective reductions of nitroarenes to anilines using metallic zinc in near-critical water

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Received (in Cambridge) 16th February 1999, Accepted 14th April 1999

A new procedure for the preparation of anilines (**2**) in good yield by reduction of the corresponding nitroarenes (**1**) using Zn in H₂O at 250–300 °C is described. The procedure is powerful enough to reduce sterically hindered 2-nitro-*m*-xylene (**1c**) and is chemoselective for the NO₂ groups in 1-chloro-2-nitrobenzene (**1d**) and 1-nitro-3-vinylbenzene (**1h**). The process involves the reduction of H₂O by Zn to generate H₂ followed by hydrogenation of the NO₂ group catalysed by residual traces of Zn.

Introduction

Over the last decade water has been found increasingly attractive as a medium for organic reactions.^{1–5} Organic synthesis in water not only represents a new technology with minimum waste problems, but also a new methodology since the properties of water can be used to manipulate the reactivity of organic compounds. At the same time, the changes in the physical and chemical properties of water at high temperatures have encouraged research into chemistry in supercritical water.^{6–9} As water is heated towards its critical point ($T_c = 374$ °C, $p_c = 221$ bar), it changes from a polar liquid to an almost non-polar fluid. Its relative permittivity ϵ decreases favouring the solubility of organic compounds and gases,^{10,11} and its dissociation constant, K_w , increases,¹² resulting in enhanced acidity at high temperatures. These changes occur over a wide temperature range and the properties of H₂O can be tuned within wide limits by varying the temperature. Although much of supercritical water research has been focused on the total oxidation of toxic organic compounds^{13–15} and geochemical modelling,^{16,17} there are increasing numbers of papers which suggest that near-critical H₂O (250–325 °C) offers excellent opportunities for organic synthesis.^{18–20}

The selectivity of the metal reduction (e.g. Fe, Sn or Zn) of nitroarenes is highly dependent on the pH of the reaction medium.^{21,22} For instance, the reduction of nitrobenzene with Zn in acidic or alkaline solution has permitted the preparation of aniline and the corresponding intermediate reduction products, whilst in neutral water the system gives a mixture of products, which lacks any synthetic value.

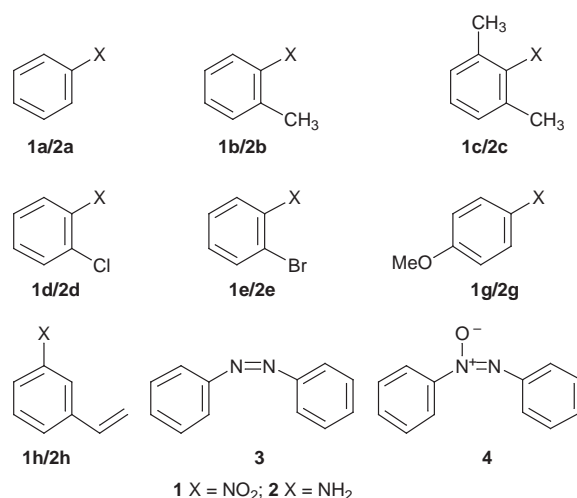
We have investigated the effect of the change of the H₂O acidity with temperature on the selectivity of this reduction. Furthermore, Zn reacts²³ quantitatively with water at high temperature producing H₂ and ZnO. Therefore, there is the possibility either of direct reduction of the NO₂ group by the metal or of hydrogenation by H₂. Up to now, the effect of high temperature on the selectivity of the reduction has not been investigated.

In this paper, we first report the scope and limitations of the Zn and H₂O system at 250 °C (Zn/H₂O) for the preparation of anilines **2** by reduction of substituted nitroarenes **1**. Then we describe the use of nitrobenzene as a model substrate to investigate the mechanism of the reduction by Zn/H₂O.

Results and discussion

i) Synthetic applications

Reactions were carried out in a high temperature/pressure batch



reactor system (see Experimental section). Even though individual reactions were not optimised, substituted nitroarenes (**1**) were reduced with Zn in H₂O at 250 °C to the corresponding anilines (**2**) in good yields (Table 1). Although nitrobenzene and aniline^{24,25} have been reported to be unstable in near-critical water, we have found that most **1** and **2** are stable under our reaction conditions.

Reactions can be performed either using the stoichiometric amount of Zn (3:1, Zn:1 molar ratio) for 2.5 h, or using an excess of Zn (>6:1) for 10–20 min. Thus, nitrobenzene (**1a**) was reduced to aniline (**2a**) in high yield following both procedures. Equally good results could be achieved even at 300 °C.

The reduction of the sterically hindered 2-nitro-*m*-xylene (**1c**) required rather more drastic conditions. Even so, only partial reduction (55%) was achieved with Zn excess (6:1) for 2.5 h, but the amine **2c** was produced with good selectivity. Usually its reduction requires the use of concentrated mineral acids, which generate unwanted by-products such as chloro- or hydroxy-anilines.

Chemoselectivity for the reduction of a NO₂ group *versus* reductive hydro dehalogenation could be achieved for 1-chloro-2-nitrobenzene (**1d**) either with Zn (3:1) in 1.5 h, or with Zn excess (9:1) in 12 min. However, 1-bromo-2-nitrobenzene (**1e**) or 1-iodo-4-nitrobenzene (**1f**) underwent reductive elimination of the Br- or I-atom in a competitive process, even for partial conversion of nitroarene **1e** or **1f**. Our results are consistent with the expected reactivity of halogen atoms in an aromatic ring, I > Br > Cl.

In the reaction of 1-methoxy-4-nitrobenzene (**1g**) it can be

Table 1 Reduction of nitroarenes (**1**) to anilines (**2**) with Zn/H₂O at high temperature^a

Entry no.	Nitroarene (1)	Zn:1	Time/h	Product(s) ^b	Yield (%) ^c	Conv. 1 (%)
1	1a	3:1	2.5	2a	98	90
2	1a	9:1	0.3	2a	97	96
3	1a	3:1 ^d	2.0	2a	93	100
4	1b	3:1	2.5	2b	85	85
5	1c	6:1	2.5	2c	90	55
6	1d	3:1	1.5	2d	88	93
7	1d	9:1	0.2	2d	86	89
8	1e	3:1	0.3	2e + 2a (1.7:1)	57	72 ^e
9	1f	3:1	0.1	2a	87	86
10	1g	6:1	2.0	2g	70	100
11	1h	6:1	0.2	2h	82	55
12	1h	6:1	1.0	2h	41	100 ^f
13	1h	10:1	0.2	2h	90	77

^a H₂O, **1** and Zn powder were reacted at 250 °C in a high *T/p* batch reactor system. ^b Products were identified by GC and NMR spectra, in comparison with authentic samples. ^c Gravimetric yield based on reacted **1**. ^d *T* = 300 °C. ^e Black solid from thermal decomposition. ^f Polymerisation.

Table 2 Reduction of nitrobenzene (**1a**) with metal in near-critical H₂O^a

Experiment no.	Metal ^b	<i>T</i> /°C	Time/h	Product distribution (%) ^{c,d}			
				1a	2a	3a	4a
1	Zn	300	2.5	—	100	—	—
2	Zn	250	2.5	10	90	—	—
3	Zn	200	2.5	34	52	11	3
4	Zn	150	2.5	54	23	8	15
5	Zn	100	2.5	66	23	1	10
6	Zn	250	0.1	78	20	2	—
7	Zn	250	0.3	64	34	2	—
8	Zn	250	1.5	30	70	—	—
9	Fe	250	2.5	90	10	—	—
10	Sn	250	2.5	95	5	—	—

^a H₂O, **1**, and Zn powder were reacted in a high *T/p* batch reactor system. ^b Metal: **1a** molar ratio: Zn, (3:1); Fe, (2:1); Sn, (3:1). ^c Determined by GC and NMR analysis of the reaction mixture. ^d Gravimetric yield >95%, based on starting **1a**.

seen that an electron-donating group in the *para* position renders the reduction more difficult. Thus, **1g** needed an excess of Zn (6:1) and 2 h to achieve quantitative conversion. Although it has been reported²⁶ that *o*-C₆H₄(OMe)₂ undergoes hydrolysis to *o*-C₆H₄(OH)₂ + MeOH in H₂O at 380 °C in 30 min, it has proved possible to reduce **1g** without significant hydrolysis of the OMe group under our reaction conditions.

The use of an excess of Zn for a short time permits the reduction of nitroarenes containing thermolabile substituents. For instance, 1-nitro-3-vinylbenzene (**1h**), which polymerises easily at high temperature, could be reduced to the aniline (**2h**). Longer reaction times gave poor product recovery. Although a large excess of Zn (10:1) was required to achieve high conversion, the nitro group could be reduced selectively in the presence of a C=C double bond.

Finally, the reducing system Zn/H₂O has significant advantages over classical procedures. One avoids the exothermic reaction of Zn with acid media by working in neutral H₂O. Therefore, Zn can be added at the start of the reaction without need to control the addition of reagents. Also, the milder reaction conditions avoid the formation of unwanted by-products such as hydroxy- and chloroanilines. The complete absence of organic solvents should lead to an easy work-up in larger scale preparations. ZnO, which is generated as a by-product, is a compound with many industrial applications.

ii) Mechanism of the reduction

We have used nitrobenzene (**1a**) as a model substrate to investigate the effect of temperature on the selectivity of the reduction with Zn/H₂O (Table 2). Reactions were performed with Zn (3:1) at five different temperatures for 2.5 h. Although temperature has a strong effect on the degree of conversion of

1a (from 34% at 100 °C to 90% at 250 °C), it has a more direct effect on the selectivity. Thus, significant amounts of azobenzene (**3**) and azoxybenzene (**4**) were only produced at *T* ≤ 200 °C. By contrast, aniline (**2a**) was the only detected product at *T* ≥ 250 °C. This selectivity at 250 °C was maintained even at short reaction times involving only partial conversion of **1a** (**3**, **4** < 3%). Furthermore, the reduction of **1a** with Zn (3:1) was a gradual process with conversion increasing from 20% (10 min) to 90% (2.5 h), and continued even after all of the Zn had reacted with H₂O (see later).

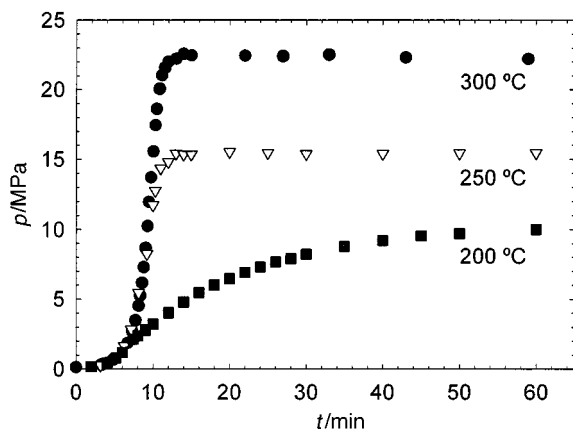
In contrast to Zn/H₂O, the systems Fe/H₂O or Sn/H₂O produced almost no reaction under the same conditions. Indeed, their different reactivity can be related to the generation of H₂. Thus, Zn reacted with H₂O at 250 °C generating H₂ and ZnO, whilst no reaction was observed for Fe or Sn even after 1 h at 250 °C. Monitoring the pressure in the batch reactor at different temperatures (Fig. 1) revealed that Zn reacts with H₂O within a few minutes at *T* ≥ 250 °C, and much more slowly at temperatures below (*e.g.* at 200 °C, constant pressure was reached after 90 min). Therefore, the reduction of **1a** with Zn at 250 °C requires a much longer time (2.5 h) than is required for the reaction of Zn with H₂O (few min), suggesting that the process taking place is hydrogenation of the NO₂ group by H₂ rather than direct reduction of the NO₂ group by Zn. This would also explain the lack of reactivity of Fe and Sn under the same conditions, since these metals do not generate H₂.

We have carried out a series of hydrogenation experiments as a comparison with Zn/H₂O (Table 3). The reaction of **1a** with H₂/H₂O gave only low conversion, suggesting that Zn/H₂O may also be acting as catalyst. Similarly, poor conversion was obtained when commercial ZnO was employed as a possible catalyst. However, the conversion increased to 34% when the

Table 3 Hydrogenation control experiments of nitrobenzene (**1a**)^a

Entry no.	Metal	Solvent	Product distribution (%) ^{b,c}	
			1a	2a
1	—	H ₂ O	82	18
2	ZnO ^d	H ₂ O	81	19
3	ZnO ^e	H ₂ O	66	34
4	Zn	Cyclohexane	60	40
5	—	Cyclohexane	95	5
6	ZnO ^{e,f}	H ₂ O	95	5

^a Solvent, **1a**, metal and H₂ (55 bar) were reacted at 250 °C for 2.5 h in a high *T/p* batch reactor system. ^b Determined by GC and NMR analysis of the reaction mixture. ^c Gravimetric yield >95%, based on starting **1a**. ^d Powder, commercial. ^e Freshly reacted Zn powder with H₂O at 250 °C for 20 min. ^f *T* = 200 °C.

**Fig. 1** Variation of the observed pressure within the reactor containing Zn/H₂O as a function of time at 200, 250 and 300 °C.

reaction was performed using ZnO, freshly prepared by reacting Zn with H₂O at 250 °C. This suggests that residual traces of Zn metal could be acting as a catalyst in the hydrogenation process. Indeed, it is known that Zn acts as a catalyst in the hydrogenation of acetylenic compounds to olefins.²⁷ The catalytic action of metallic Zn was confirmed by hydrogenation of **1a** in the non-protic solvent cyclohexane, which gave 40% conversion of **1a**. By contrast, reaction of **1a** in cyclohexane without Zn gave <5% conversion. Finally, less than 5% of **2a** was detected at 200 °C with H₂ and ZnO (from Zn/H₂O), suggesting that the hydrogenation process does not take place at temperatures <200 °C.

Therefore, the different selectivity in the reduction of nitroarenes with Zn/H₂O at different temperatures can be tentatively attributed to two processes: the direct reduction by metal at temperatures ≤200 °C, and catalytic hydrogenation by H₂ at temperatures ≥250 °C.

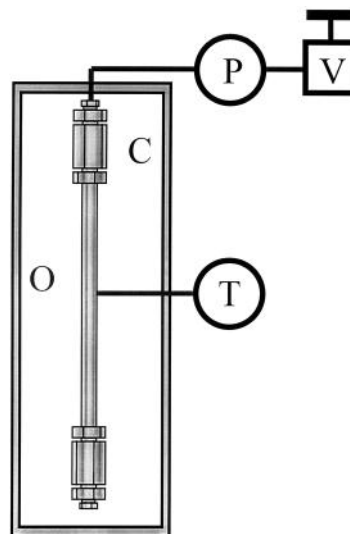
Conclusion

The reduction of nitroarenes to anilines with Zn/H₂O at 250 °C is a new and versatile procedure for the preparation of substituted anilines. It is powerful, chemoselective and has several advantages over more classical methods. The process involves the reaction of Zn with H₂O to generate H₂ followed by hydrogenation of the NO₂ group catalysed by residual traces of Zn.

Experimental

Materials

Nitroarenes (either Aldrich or Lancaster) were used as received. Zn powder (<10 μ), Fe powder (<10 μ), Sn granules (10–40

**Fig. 2** Schematic view of the high *T/p* batch reactor system. The components are labelled as follows: C, high pressure vessel; O, high temperature oven; P, pressure monitor; T, thermocouple; V, high pressure valve.

mesh) and ZnO powder (Aldrich) were used without previous activation. Water was purified by standard procedures. Hydrogen (99.999%) (BOC) was used without further purification.

Analysis

Reaction products were identified by GC and NMR spectra, in comparison with authentic samples. GC analyses were performed on a non-polar capillary column [EC-5 (SE-54), Alltech, 30 m, film thickness 0.25 μm, id 0.32 mm].

High pressure/temperature batch reactor system²⁸

Safety Warning: This procedure involves high pressures and temperatures and must only be carried out in an apparatus with the appropriate pressure rating at the reaction temperature. Reactions were carried out in a batch reactor system consisting of a reactor vessel connected to a shut-off valve via a pressure transducer (Fig. 2). The high temperature/pressure stainless steel 316 reactor vessel (0.9 cm od, 0.5 cm id, 5.2 ml internal volume, Keystone Scientific Inc.) had a maximum pressure rating of 690 bar at 400 °C. A Chromel/Alumel thermocouple monitored the temperature of the reactor wall. The pressure transducer (RDP electronics) had a pressure rating of 690 bar. The batch reactor was heated in an oven (PYE series 104). Overpressure could be avoided by releasing the pressure through the shut-off valve (HIP).

General procedure

The reaction vessel was leak-tested with N₂, charged with the appropriate amount of water and reagents, sealed, placed in the oven, and connected to the pressure transducer and thermocouple. The vessel was heated to the required temperature for a certain amount of time. Reaction time reported in this paper does not include the time required to heat or cool the system (10 min each). Reactions were performed at liquid densities of the fluid (0.6–0.8 g cm⁻³), depending on the temperature and amount of Zn (possible generation of H₂ in the reaction was considered when calculating the final pressures). Thus, the appropriate amount of water was calculated for each temperature considering the density of the liquid as follows: $\rho_w = \text{mass of water/vessel volume}$, being the densities given by the steam tables.²⁹ The working pressure at 250 °C was ca. 100–150 bar with correspondingly lower pressures at lower temperatures or less amount of Zn. The amount of organic compound in water was ca. 5–10 wt%. Thermal decomposition of the organic com-

pounds was observed when **1** was not in contact with Zn. Thus, the method of filling the vessel becomes important because it is not stirred. First the vessel was filled with half the required amount of water, then either the organic liquid and Zn or the organic solid previously mixed with Zn were added, and finally the remainder of the water was put in. No visible corrosion of the vessel was observed after experiments under these conditions.

Reduction of nitroarenes with Zn in near-critical H₂O

The reaction vessel was charged with H₂O (3.1–4.2 ml), Zn powder (0.3–0.6 g; 4.6–9.2 mmol) and nitroarene **1** (1.0–1.5 mmol). The amounts of reagents changed depending on temperature (100–300 °C) and Zn:nitroarene **1** ratio (3:1–10:1). In a typical experiment, the vessel was charged with H₂O (3.5 ml), Zn powder (0.29 g; 4.43 mmol) and nitrobenzene **1a** (0.15 ml, 1.46 mmol) (Zn:**1a** ratio of 3:1). The vessel was heated at 250 °C for 0.1–2.5 h reaching a final pressure of ca. 100 bar. The work-up of the reaction consisted of filtration of the inorganic solid (ZnO) followed by extraction with an organic solvent (methylene chloride or diethyl ether). In the experiments with nitrobenzene (**1a**), the product distribution was determined by GC and NMR analysis of the crude reaction products and recalculated considering the stoichiometry of the reaction (**3** and **4** are bimolecular compounds). This procedure gives a product distribution closer to a yield distribution. Anilines **2** were isolated by acid–base extraction and yields were determined gravimetrically.

Hydrogenation of nitrobenzene

The vessel was charged with H₂O (3.5 ml) or cyclohexane (3.0 ml), Zn powder (0.29 g; 4.43 mmol) or ZnO (0.36 g; 4.43 mmol) and nitrobenzene (**1a**) (0.15 ml; 1.46 mmol); it was sealed and pressurised with H₂ (55 bar). The system was heated for 2.5 h at 200 or 250 °C. The reaction work-up was the same as described above. The product distribution was determined by GC and NMR analysis of the crude reaction products. Yields were determined gravimetrically.

Reactivity of Zn in near-critical H₂O

The reaction vessel was charged with H₂O (3.5 ml), Zn powder (0.29 g; 4.43 mmol) and heated to the required temperature (200, 250 or 300 °C). The pressure increase was monitored as a function of temperature and time. Experiments were terminated 20 min after a constant pressure was reached. A residual pressure of 55 bar was measured after cooling the vessel to room temperature. This pressure was due to a flammable gas (H₂). Analysis of the inorganic solid by XRPD identified it as ZnO. The vapour pressure curve of H₂O (3.5 ml), and of the H₂O/H₂ system (3.5 ml of H₂O and 55 bar of H₂) were determined following the same procedure.

Acknowledgements

We are grateful for support from the EPSRC (Grant no. GR/K84929), the Royal Academy of Engineering, ICI Plc. and the European Union for Marie Curie TMR Fellowship (Contract no. ERBFMICT 972064). We thank Dr A. Kordikowski, Dr P. A. Hamley, Dr R. J. Pulham and Dr S. K. Ross for their help and advice. We thank Mr M. Guyler and Mr K. Stanley for their technical help.

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Paper 9/01271K