Preparation of quinolines by reduction of *ortho*-nitroarenes with zinc in near-critical water

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We report a preparation of quinoline **2** and indole **4** derivatives by reduction of suitably functionalised *o*-nitroarenes with Zn powder in H_2O at 250 °C. The process involves the reduction of the nitro group to an amino group followed by *in situ* cyclisation with a carbonyl or alcohol moiety in an aqueous medium. The amount of hydroquinoline **3** produced depends on the nature of the carbonyl moiety of the nitroarene.

Introduction

Water as a solvent in organic chemistry offers many advantages in terms of pollution prevention. Although the use of water is limited by the low solubility of most organic compounds in aqueous media, the change of the physical properties of water from room temperature to supercritical (374 °C) has encouraged research into supercritical water.[1,2] The decrease[3,4] of its permittivity constant (ε) with increasing temperature implies an increasing solubility of the organic compounds; and the increase[5] of its dissociation constant (K_w) can promote acid–base catalysed reactions which do not take place at lower temperature. Furthermore, these changes occur over a wide temperature range and the properties of water can be tuned within wide limits by varying the temperature. Therefore, near-critical (200–325 °C) or supercritical water are unique solvents with high potential for organic chemistry. The main research in supercritical water has been focused on the total oxidation of organic compounds[6–8] and geochemical modelling[9,10] and the study of the reactivity of simple molecules in near-critical water has led to the development of several solvent-free synthetic procedures[11–16] in organic chemistry. In this area, we reported recently the reduction of nitroarenes by zinc[17] in water at 250 °C as a selective and efficient procedure for the preparation of substituted anilines. The reaction of Zn with near-critical H_2O produces H_2, which then reacts with the substrate. Therefore, the process involves hydrogenation of the nitroarene rather than direct reduction by Zn.

In this paper we report the application of Zn–H_2O to the synthesis of quinoline and indole derivatives from suitable nitroarenes in a single step process. One of the first syntheses of a quinoline derivative involved the reduction of *o*-nitrocinnamic acid to 2-hydroxyquinoline with ammonium sulfide.[18] Later investigations involved the use of several reducing agents and different cinnamyl derivatives, *e.g.* aldehydes, acids or esters. Usually, the synthesis involves a reduction step to the amino acid intermediate followed by its further treatment in acid medium to achieve the cyclisation.[19,20]

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Results and discussion

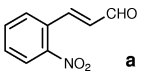
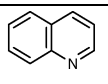
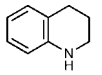
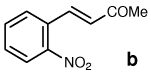
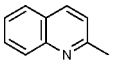
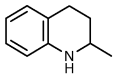
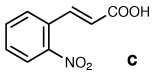
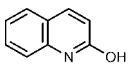
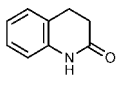
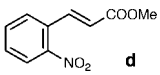
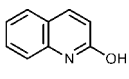
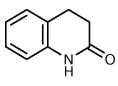
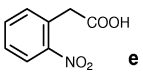
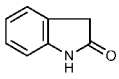
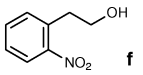
Reactions were carried out in a high temperature/pressure batch reactor system (see Experimental section) using Zn (1.3 equivalents) in H_2O at 250 °C. For most substrates the reaction took place in only 10 min. Quinolines **2** and tetrahydroquinolines **3** were obtained in good yield from the reduction of the nitroarenes **1a**, **1b**, **1c** and **1d**, and indoles **4** obtained from **1e** and **1f** (Table 1). The treatment of 2-nitrocinnamaldehyde **1a** with Zn (4 : 1, Zn : **1a** molar ratio) in H_2O at 250 °C for 10 min led to quinoline **2a** in 85% yield, containing a small amount (< 5%) of the corresponding tetrahydroquinoline **3a**. The quinoline results from the reduction of the NO_2 group in **1a** to NH_2, followed by *E*,*Z* isomerisation of the α,β-C=C double bond and subsequent imine formation. The *E*,*Z* isomerisation of the C=C bond is an example of how the higher concentration of hydronium ions in water at 250 °C can promote an acid catalysed reaction that does not take place at ordinary temperatures.

The reduction of quinoline **2a** to tetrahydroquinoline **3a** requires remarkably harsh conditions. Thus, reaction of **2a** with excess Zn (8 : 1) for 2 h gave only 10% of **3a**. Therefore, we assume that tetrahydroquinoline **3a** is formed from 2-nitrocinnamaldehyde **1a** by reduction of the α,β-C=C bond followed by imine formation and further reduction, as shown in Scheme 1. Then, the formation of tetrahydroquinolines should be closely related to the ease of condensation between the amino group and the carbonyl group, as shown in the following examples.

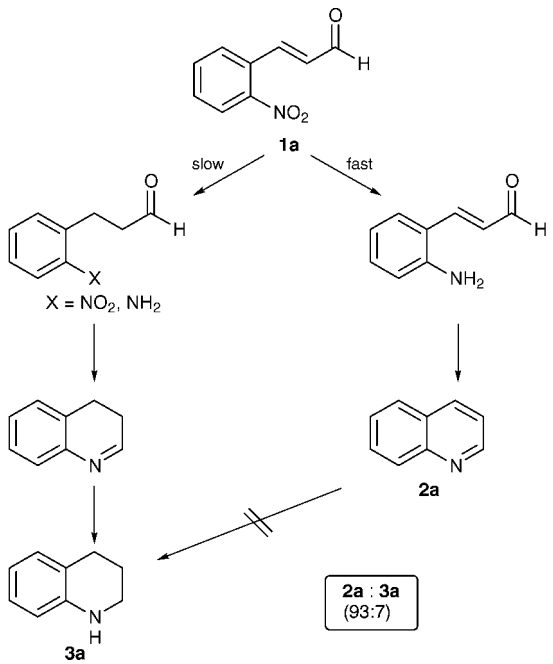
In contrast to the selectivity observed for **1a**, the nitro ketone **1b** gave a (65 : 35) mixture of 2-methylquinoline **2b** and 2-methyl-1,2,3,4-tetrahydroquinoline **3b**. Also, the reduction of *o*-nitrocinnamic acid **1c** and its methyl ester **1d** gave a different mixture of 2-hydroxyquinoline **2c** and dihydroquinolone **3c**. Whilst **3c** was the main product from **1c**, hydroxyquinoline **2c** was the primary product from **1d**. Therefore, the differences can be attributed to the faster cyclisation of the amino aldehyde and amino ester compared to the amino acid or amino ketone, thus preventing the reduction of the α,β-C=C bond on the linear nitroaromatic.

As a corollary, we also evaluated this procedure in the synthesis of dihydroindoles. Thus, the reduction of *o*-nitrophenylacetic acid **1e** gave 1,3-dihydroindol-2-one **4e** in excellent yield, with a different selectivity than in the reduction with Zn in dilute H_2SO_4, which leads to the *N*-oxide[21] of **4e**.

Table 1 Reduction of nitroarenes **1** with Zn in H_2O at 250 °C[a]

Entry	Nitroarene **1**	Time/h	Product(s)[b]	Yield[c] (%) (**2** : **3**)
1	 **a**	0.2	 **2a**  **3a**	85 (93 : 7)
2	 **b**	2.0	 **2b**  **3b**	83 (65 : 35)
3	 **c**	0.2	 **2c**  **3c**	69 (40 : 60)
4	 **d**	0.2	 **2c**  **3c**	62 (80 : 20)
5	 **e**	0.5	 **4e**	80
6	 **f**	2.0	 **4f**	91

[a] Water, **1**, and Zn (4 : 1, Zn : **1** molar ratio) were reacted at 250 °C in a high T/P batch reactor. [b] Determined by GC and NMR analysis. [c] Isolated.



Scheme 1

Finally, the reduction of 2-(*o*-nitrophenyl)ethanol **1f** gave 2,3-dihydroindole **4f** cleanly, in excellent yield, thus providing a new and efficient route to **4f**.

Conclusion

In summary, quinoline and indole derivatives are easily prepared in good yield by reduction of suitable substituted *o*-nitroarenes by Zn in H_2O at 250 °C. The procedure is efficient, avoids the use of solvents or acid medium (facilitating the work up of the reaction) and requires short reaction times (usually some minutes). Therefore, it has considerable potential for use in heterocyclic preparations.

Experimental

Materials

Nitroarenes **1a**, **1c**, **1e** and **1f** (Aldrich or Lancaster) were used as received. Zn dust (<10 μ) (Aldrich) was used without previous activation. Water was purified by standard procedures. 4-(*o*-Nitrophenyl)-3-buten-2-one **1b** was prepared by an aldol-condensation[22] of *o*-nitrobenzaldehyde with acetone in alkaline solution. Methyl *o*-nitrocinnamate **1d** was prepared by acid-catalysed esterification[23] of *o*-nitrocinnamic acid with methanol.

General procedure

Safety warning: this procedure involves high temperatures and pressures. Reactions were performed in a high pressure/temperature batch reactor system consisting of a stainless steel 316 reactor vessel (5.2 ml, P_{max} rating of 690 bar at 400 °C), connected to the pressure transducer and thermocouple (for a complete description, see ref. 16 and 17). Reaction times reported do not include the time required to heat or cool the system (10 min each). Reactions were performed at the liquid densities of the fluid (0.6–0.8 g cm^{-3}) and the appropriate amounts of water to reach these densities were calculated from the steam tables.[24]

Reduction of nitroarenes with Zn. The reaction vessel was charged with H_2O (3.0 ml), Zn dust (10 mmol), nitroarene **1** (2.5 mmol), and heated in an oven to 250 °C for 10 min to 2 h. The work-up of the reaction consisted of filtration of the inorganic solid (ZnO), followed by extraction with methylene chloride or diethyl ether. Reaction products were identified by GC and NMR spectroscopy, in comparison with authentic samples and yields were determined gravimetrically. GC analyses were performed on a non-polar capillary column [EC-5 (SE-S4), Alltech, 30 m, film thickness 0.25 μm, internal diameter 0.32 mm].

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