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Reduction of Hydrazines, Azo and Azoxy Compounds, and Amine *N*-Oxides with the $NiCl_2{\cdot}2H_2O$–Li–DTBB (cat.) Combination[☆]

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This paper is dedicated to Professor Günter Wilke on the occasion of his 75th birthday in recognition to his pivotal contributions to nickel chemistry

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Abstract—The $NiCl_2{\cdot}2H_2O$/Li/DTBB (10 mol%) combination allows the reduction of aromatic hydrazines **1** (to amines), azo compounds **2** (to primary amines), azoxy compounds **3** (to azo compounds or to primary amines, depending on the reaction conditions) or amine *N*-oxides **4** (to tertiary amines), under mild reaction conditions (THF, room temperature). © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Although there are many methodologies reported in the literature concerning the reduction of nitrogen-containing functional groups, most of them involve metal-catalysed hydrogenations, complex hydrides or metals in solution,[1] so any new and general procedures to carry out these conversions are welcome. In our laboratory, we have been using in the last recent years a new combination consisting of a mixture of dihydrated nickel(II) chloride and lithium in the presence of a catalytic amount of naphthalene[2–4] for the reduction of alkenes,[5a] alkynes,[5b] carbonyl compounds and their imines,[5c] alkyl halides,[5d] and sulfonates or aromatic systems.[5e] We think that an advantage of this *hydrogenation without using external hydrogen* is that the source of the hydrogenation agent is the water included in the metallic salt. In this paper we describe the use of the mentioned combination for the reduction of different nitrogenated functionalities, such as hydrazines, azo and azoxy compounds, and amine *N*-oxides.

Results and Discussion

Reduction of hydrazines

There are few general methods to reduce the nitrogen–nitrogen bond in hydrazines, and the conditions required to cleave this bond depend markedly on the substituents attached to it.[6] However, substituted hydrazines can be reduced to the corresponding amines by catalytic hydrogenation[7] or using metals in a protic solvent.[8,9] In the first case, usually it is necessary to work under pressure and acidic medium, and in the second case, liquid ammonia is the most common solvent.

The reaction of monosubstituted, *N*,*N*- or *N*,*N′*-disubstituted hydrazines **1** with an equimolar amount of dihydrated nickel chloride, an excess of lithium powder [8:1 molar ratio, referred to the nickel(II) salt] and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) [0.1:1 molar ratio, referred to the nickel(II) salt] in THF at room temperature overnight, led to the formation of the corresponding primary or secondary amines (Table 1). In order to get good results, the starting hydrazine has to bear at least one aryl group in one of the nitrogen atoms: when the same protocol was applied to *N*-butyl-*N′*,*N′*-dimethyl-*N*-nonylhydrazine, no conversion was observed even heating the reaction mixture under reflux for 4 h. The reaction applied to tetrasubstituted hydrazines (*N*,*N*,*N′*-trimethyl-*N′*-phenylhydrazine or *N*-butyl-*N′*-methyl-*N*-nonyl-*N′*-phenylhydrazine) gave less than 15% conversion. However, this behaviour is in agreement with the dependence on the substitution pattern of the starting hydrazine observed in the literature.[6]

As an alternative for the activation of nickel in the reduction of hydrazines **1**, it is also possible to use an arene-supported polymer as the catalytic electron transfer agent. Thus, using 4-vinylbiphenyl-divinylbenzene copolymer,[4] a slightly better yield was obtained for the reduction of *N*-methyl-*N*-phenylhydrazine (**1d**) (Table 1, entry 4 and footnote c).

[☆] Part 6 in the series 'The $NiCl_2{\cdot}2H_2O$–Li-Arene (cat.) Combination as Reducing System'. For Part 5 see Ref. 5e.

Keywords: hydrazines; azo compounds; azoxy compounds; amine *N*-oxides; reduction.

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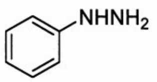
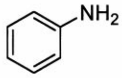
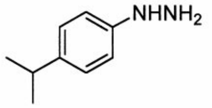
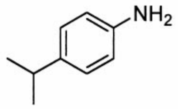
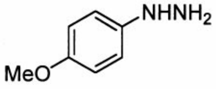
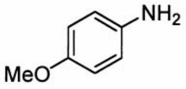
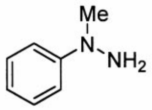
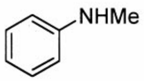
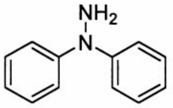
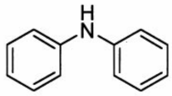
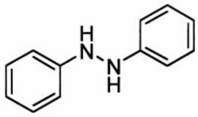
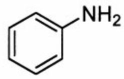
Table 1. Reduction of hydrazines **1**

Entry	Starting material (no.)		Product[a]	Yield (%)[b]
1		(**1a**)		68
2		(**1b**)		72
3		(**1c**)		73
4		(**1d**)		78 (87)[c]
5		(**1e**)		88
6		(**1f**)		65[d]

[a] All products were >95% pure (GLC).
[b] Isolated yield after acid–base extraction.
[c] Reaction performed in the presence of a vinylbiphenyl-divinylbenzene copolymer as electron carrier.
[d] Yield corresponding to the reaction: **1f**→2PhNH$_2$.

Reduction of azo and azoxy compounds

The most important methods to reduce azo compounds lead to the corresponding hydrazo derivatives.[10] They include diimide, complex metal hydrides or cobalt boride in the presence of hydrazine,[11] as well as metal mediated procedures.[12,13] Concerning azoxy compounds, the corresponding deoxygenation is the most studied reaction:[14] well-established methods include catalytic hydrogenation[15] and metal-mediated procedures.[16] In addition, azoxy compounds are cleaved to amines by potassium borohydride an copper(I) chloride.[17]

The application of the procedure described above for hydrazines **1** was also applied to azo compounds **2**, leading to the corresponding primary aromatic amines (Table 2, entries 1–4). In the case of azoxy derivatives **3**, the final products depend on the reaction conditions used: for short reactions times (ca. 1 h), the corresponding azo compounds were isolated (Table 2, entries 5 and 7, and footnote d), whereas either longer reaction time (10 h) or 2.5 equiv. of dihydrated nickel(II) chloride led to full reduction to the corresponding primary amines (Table 2, entries 6 and 8, and footnotes f and g). Also here, the use of an arene-supported polymer as electron carrier catalyst[4] in the reaction showed to be as effective as the use of DTBB (Table 2, entries 1 and 7, and footnote c).

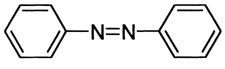
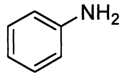
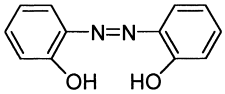
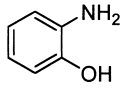
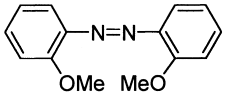
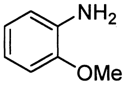
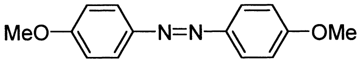
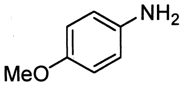
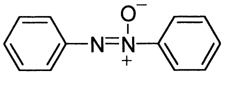
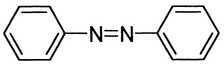
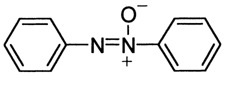
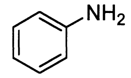
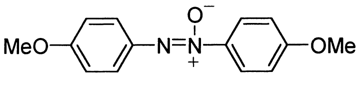
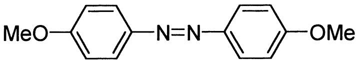
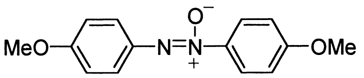
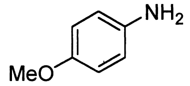
Reduction of amine *N*-oxides

The deoxygenation of amine *N*-oxides to the corresponding tertiary amines is an interesting reaction, especially in aromatic nitrogen-containing heterocycles because their conversion into amine oxides makes possible electrophilic substitution of the aromatic ring in different positions in comparison with the parent heterocyclic compounds. General methods[18] for that purpose include mainly catalytic hydrogenation[19] and metal promoted reductions.[20] The use of metal hydrides works only with borane[21] due to over-reduction reactions.[22,23]

We report in this section the application of the combination of dihydrated nickel(II) chloride, lithium and a catalytic amount of DTBB for the deoxygenation of amine *N*-oxides **3**. Thus, Table 3 shows the results obtained for aromatic (Table 3, entries 1–5) or aliphatic (Table 3, entry 6) systems. The reduction can also be carried out using the same supported polymer version[4] as described above, working the process with similar yield (Table 3, entry 4 and footnote d).

As we proposed in previous papers of this series,[5] a reasonable mechanism pathway would involve both (a) the activation of nickel(0) by reduction of the nickel(II) salt used, and (b) the generation of hydrogen from the salt crystallisation

Table 2. Reduction of azo (**2**) and azoxy compounds (**3**)

Entry	Starting material (no.)		Product[a]	Yield (%)[b]
1		(**2a**)		70 (71)[c]
2		(**2b**)		88
3		(**2c**)		74
4		(**2d**)		78
5		(**3a**)		68[d] (83)[d,e]
6		(**3a**)		66[f,g]
7		(**3b**)		60[d] (79)[d,e] (82)[c]
8		(**3b**)		57[f,g]

[a] All products were >95% pure (GLC); overnight reaction with 2.0 equiv. of $NiCl_2 \cdot 2H_2O$ unless otherwise is stated.
[b] Isolated yield after acid–base extraction unless otherwise is stated.
[c] Reaction performed in the presence of a vinylbiphenyl-divinylbenzene copolymer as electron carrier.
[d] 1 h reaction time.
[e] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate).
[f] 10 h reaction time.
[g] The reaction time was reduced to 2 h by using 2.5 equiv. of $NiCl_2 \cdot 2H_2O$.

water and the excess of lithium. Since we never observed any gas evolution, the molecular hydrogen is probably adsorbed on the nickel(0) surface.

Conclusion

From the results described herein we conclude that the $NiCl_2 \cdot 2H_2O$/Li/DTBB (cat.) combination is an useful mixture to carry out the reduction (hydrogenation without hydrogen) of nitrogen-containing functionalities such us hydrazines, azo and azoxy compounds, and amine *N*-oxides, this methodology being a reasonable alternative to the procedures described in the literature.

Experimental

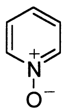
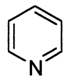
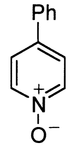
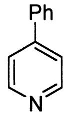
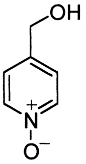
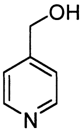
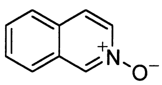
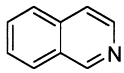
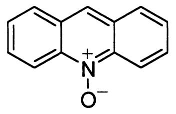
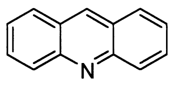
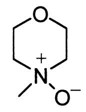
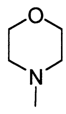
General

For general information see Ref. 5d. All starting hydrazines **1**, azo compounds **2a**, **2b**, and *N*-oxides **4a–d**, **f**, were commercially available (Aldrich, Fluka) of the best grade and were used without further purification. Azo compounds **2c** and **2d** were prepared by MnO_2 oxidation of the corresponding aromatic amines.[24] Azoxy compounds **3** were prepared from the corresponding azo compounds by MCPBA oxidation.[25] Acridine *N*-oxide was obtained by MCPBA oxidation of acridine.[26] For the preparation of dihydrated nickel(II) chloride, see Ref. 5c.

Preparation of starting materials

Preparation of azo compounds 2c and 2d. *General procedure.*[24] A mixture of the corresponding anisidine (10 mmol) and activated MnO_2 (80 mmol) in toluene was placed in a Dean–Stark apparatus and heated under reflux for 20 h, at which time water evolution had virtually ceased. The cold reaction mixture was filtered through a Büchner and washed with toluene to afford the corresponding azo compound as a red solid, which was pure enough to be used without further purification. Their physical and spectroscopic data were in agreement with those reported in the

Table 3. Reduction of amine *N*-oxides **4**

Entry	Starting material (no.)	Product^{a}	Yield (%)^{b}
1	 **(4a)**		68
2	 **(4b)**		66^{c}
3	 **(4c)**		55
4	 **(4d)**		70^{c} (74)^{d}
5	 **(4e)**		64 (75)^{c}
6	 **(4f)**		80

^{a}All products were >95% pure (GLC).
^{b}Isolated yield after acid–base extraction unless otherwise is stated.
^{c}Isolated yield after column chromatography (silica gel, hexane/ethyl acetate).
^{d}Reaction performed in the presence of a vinylbiphenyl-divinylbenzene copolymer as electron carrier.

literature.[27,28] 2,2′-Dimethoxyazobenzene (**2c**): 50% yield, mp 153°C. 4,4′-Dimethoxyazobenzene (**2d**): 48% yield, mp 165°C.

Preparation of azoxy compounds 3. *General procedure.*[25] To a solution of the corresponding azo compound (5 mmol) in chloroform (5 ml) was added *m*-chloroperbenzoic acid (12.5 mmol) in chloroform (25 ml). The reaction mixture was allowed to react for 1 h at 60°C. Then, the crude reaction mixture was cooled to room temperature, washed with 2 M Na_2SO_3, dried over anhydrous Na_2SO_4 and concentrated under vacuum (15 Torr). The oily residue was recrystallized from ethanol to yield the corresponding azoxy compound **3**. Their physical and spectroscopic data were in agreement with those reported in the literature.[29,25] Azoxybenzene (**3a**): 55% yield, mp 36–38°C. 4,4′-Dimethoxyazoxybenzene (**3b**): 60% yield, mp 115–116°C.

Preparation of acridine *N*-oxide (4e).[26] *m*-Chloroperbenzoic acid (1.47 g, 5.5 mmol) was added to a solution of acridine (0.90 g, 5.0 mmol) in chloroform (20 ml) at room temperature. The reaction mixture was heated at 50°C for 12 h. Then, it was quenched with water (2 ml) and the solvents removed in vacuo (15 and 1 Torr). Flash column chromatography (silica gel, hexane/ethyl acetate 1:1) provided acridine *N*-oxide (0.58 g, 60% yield) as yellow needles (mp 168–170°C). Its physical and spectroscopic data were in agreement with those reported in the literature.[30]

Reduction of hydrazines, azo compounds, azoxy compounds, and amine *N*-oxides

General procedure. To a mixture of $NiCl_2{\cdot}2H_2O$ (166 mg, 1.0 mmol), lithium powder (56 mg, 8 mmol) and DTBB (27 mg, 0.1 mmol), was added a solution of the starting material (1.0 mmol) in THF (10 ml) at room temperature. The reaction mixture, which was initially dark green, changed to black, indicating the formation of Ni(0). After stirring overnight, the resulting black suspension was diluted with diethyl ether (20 ml). 2N HCl (20 ml) was added and the mixture stirred until transparency. The aqueous phase was treated with NaOH up to alcaline pH, and extracted with diethyl ether (3×20 ml), the organic phase was dried over anhydrous Na_2SO_4, and evaporated (15 Torr) to furnish the expected reduced products. All isolated products gave satisfactory physical and spectroscopic analyses by comparison with commercially available samples.

4-Vinylbiphenyl-divinylbenzene copolymer (20 mg, 0.1 mmol) was used as an alternative electron transfer agent instead of DTBB to perform the reactions in Table 1 (entry 4 and footnote c), Table 2 (entries 1 and 7, and footnote c), and Table 3 (entry 4 and footnote d).

Acknowledgements

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