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Nickel-promoted Reductive Cleavage of Nitrogen-nitrogen and Nitrogenoxygen Bonds Mediated by Lithium and a Catalytic Amount of an Arene or Polymer Supported Arene

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With one biographical summary

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Abstract: The NiCl₂·2H₂O/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). The reaction can be alternatively carried out in the presence of a polymer supported arene instead of DTBB as electron carrier.

Keywords: nickel, arene- and polymer supported arene, lithium, reduction, nitrogen containing compounds.

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 wellcome. 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 an arene [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 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.

On the other hand, in the last few years we have been using an arene-catalyzed lithiation reaction [3] as a potent methodology in order to prepare very unstable organolithium compounds under very mild reaction conditions. This procedure has been improved considerably using a catalytic amount of a polymer supported arene as the electron carrier catalyst [4], because its removal at the end of the reaction can be carried out easily by simple filtration and it can be reused. In this communication we also report the application of a polymer supported arene as electron carrier in the above mentioned reduction of nitrogen containing compounds.

Results and Discussion

1. 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).

Entry	Starting material (no.)	Product ^a	Yield (%) ^b
1	NHNH ₂ (1a)	NH ₂	68
2	NHNH ₂ (1b)	NH ₂	72
3	MeO NHNH ₂ (1c)	MeO NH2	73
4	Me N-NH ₂ (1d)	NHMe	78 (87) [¢]
5	NH ₂ N (1e)		88
6	$\mathbf{\mathbf{r}}^{\mathrm{T}} = \mathbf{\mathbf{r}}^{\mathrm{T}} $	NH ₂	65 ^d

Table 1. Reduction of Hydrazines 1

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: $1f \otimes 2PhNH_2$.

As an alternative for the activation of nickel in the reduction of hydrazines 1, it is also possible to use a polymer

supported arene as the catalytic electron transfer agent. The preparation of a polymer containing biphenyl was carried out following Itsuno's methodology [10] to give cross-coupling polymers. Thus, by refluxing a solution of 4-vinylbiphenyl and divinylbenzene in tetrahydrofuran, containing a catalytic amount of azobis(isobutyronitrile), the corresponding polymeric catalyst was obtained (Scheme 1). 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).



Scheme 1. Reagents and conditions: i, AIBN, THF, reflux

2. Reduction of Azo and Azoxy Compounds

The most important methods to reduce azo compounds lead to the corresponding hydrazo derivatives [11]. They include diimide, complex metal hydrides or cobalt boride in the presence of hydrazine [12], as well as metal mediated procedures [13, 14]. Concerning azoxy compounds, the corresponding deoxygenation is the most studied reaction [15]: well-established methods include catalytic hydrogenation [16] and metal-mediated procedures [17]. In addition, azoxy compounds are cleaved to amines by potassium borohydride an copper(I) chloride [18].

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. 1h), 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 eq. 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).

3. 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 [19] for that purpose include mainly catalytic hydrogenation [20] and metal promoted reductions [21]. The use of metal hydrides works only with borane [22] due to overreduction reactions [23, 24].

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

Entry	Starting material (no.)	Product ^a	Yield (%) ^b
1	(2a)	NH ₂	70 (71) ^c
2	ОН НО (2b)	UNH2 OH	88
3	(2c)	NH ₂ OMe	74
4	$MeO \longrightarrow N=N \longrightarrow OMe$ (2 d)	MeO NH2	78
5		N=N-	68 ^d (83) ^{d,e}
6		NH ₂	66 ^{f,g}
7	$MeO \longrightarrow N = \bigvee_{+}^{O^{-}} \longrightarrow OMe (3b)$		60 ^d (79) ^{d,e} (82) ^c
8	MeO - N=N+ OMe (3b)	MeO NH2	57 ^{f,g}

Table 2. Reduction of Azo (2) and Azoxy Compounds (3)

a All products were >95% pure (GLC); overnight reaction with 2.0 eq. of NiCl₂·2H₂O 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 1h 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 eq. of NiCl₂·2H₂O.

Entry	Starting material (no.)		Product ^a	Yield (%) ^b
1	+N-0-	(4a)		68
2	Ph +N O ⁻	(4b)	Ph	66°
3	OH	(4c)	OH N	55
4	CC+N-0-	(4d)		70 ^c (74) ^d
5		(4 e)		64 (75) ^c
6		(4f)		80

Table 3. Reduction of Amine N-Oxides 4

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.

Conclusion

From the results described herein we conclude that the NiCl₂·2H₂O/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. When a polymer supported arene is used as electron carrier instead of DTBB similar o better results are obtained making very easy the work-up step.

Experimental Part

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 [25]. Azoxy compounds **3** were prepared from the corresponding azo compounds by MCPBA oxidation [26]. Acridine *N*-oxide was obtained by MCPBA oxidation of acridine [27]. For the preparation of dihydrated nickel(II) chloride, see Ref. [5c]. Divinylbenzene (80% mixture of isomers), 4-vinylbiphenyl (Aldrich), and AIBN (Fluka) were commercially available and used without further purification, except in the case of divinylbenzene, which was successively washed twice with a 1% aqueous solution of sodium hydroxide and then with water, in order to remove the stabiliser.

Preparation of the polymeric catalyst

A solution of 4-vinylbiphenyl (720 mg, 4 mmol), divinylbenzene (71 ml, 0.4 mmol) and AIBN (75 mg, 0.45 mmol) in THF (5 ml) was refluxed for 6 h under an argon atmosphere. After cooling at room temperature, the resulting suspension was filtered and the solid obtained was successively washed with methanol, water, THF and ether (2x2 ml), and dried under vacuum (1 Torr) to give the expected polymer in quantitative yield as a pale yellow solid.

Found: C, 90.9; H, 6.7. (C₁₄H₁₂)₉·(C₁₀H₁₀) requires C, 93.2; H, 6.8.

Reduction of Hydrazines, Azo compounds, Azoxy compounds, and Amine N-oxides. General Procedure

To a mixture of NiCl₂·2H₂O (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 (3x20 ml), the organic phase was dried over anhydrous Na₂SO₄, 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), and separated from the reaction mixture in the work-up by simple filtration.

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