ORGANIC
LETTERS

2003
Vol. 5, No. 10
1773−1776

Indium-Mediated Reduction of Hydroxylamines to Amines

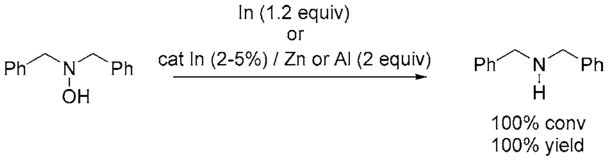
Stefano Cicchi, Marco Bonanni, Francesca Cardona, Julia Revuelta, and Andrea Goti*

Dipartimento di Chimica Organica “Ugo Schiff”, Università di Firenze,
via della Lastruccia 13, I-50019 Sesto Fiorentino (FI), Italy

andrea.goti@unifi.it

Received March 12, 2003

ABSTRACT



A novel and simple procedure for reduction of hydroxylamines to the corresponding amines by means of indium powder in aqueous media is reported. Applicability to one-pot reactions and isoxazolidine N–O bond reduction is also demonstrated. A catalytic version of the process using 2–5% In in the presence of other metals (Zn, Al) has been successfully developed.

In the past decade, indium metal has emerged as a suitable and valuable reagent for accomplishing organometal additions to carbonyl and related compounds under Barbier conditions in aqueous media.[1] More recently, the huge potential of indium powder as a broad scope reducing agent for organic compounds has also been disclosed by Moody, Ranu, and others.[2] Many functional groups have served as appropriate substrates for reductions with indium. Notable examples are the reductions of nitroaromatics,[2a,b,l] azines,[2a,c] oximes,[2a,e] 1,2-dibromides,[2f] α-halocarbonyl compounds,[2g] benzyl halides,[2g] azides,[2l,p] *N*-oxides,[2n,s,w] nitrostyrenes,[2o] 1,1-dibromoalkenes,[2h] and propargyl ethers, amines and esters.[2i] The efficiency of In(0) as a reducing agent has been related to its uncommonly low first ionization potential (5.8 eV), which makes, in this respect, indium closer to alkaline metals than to metals of groups 12−14. However, indium metal is inert toward water and acid solutions, allowing its use in aqueous media and making this metal an optimal “green chemistry” reagent for reduction and allylation reactions.

In this Letter we report our results in the reduction of hydroxylamines by indium metal. Being involved in the chemistry of nitrones,[3] we were interested in developing new methods for reduction of N−O bonds of *N*,*N*-disubstituted hydroxylamines and isoxazolidines, which are key intermediates deriving, respectively, from nucleophilic additions[4] and 1,3-dipolar cycloadditions[5] to nitrones. Conversion of isox-

---

(1) Reviews: (a) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149−11176. (b) Paquette, L. A. In *Green Chemistry−Frontiers in Benign Chemical Syntheses and Processes*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: Oxford, 1998; pp 250−264. (c) Cintas, P. *Synlett* **1995**, 1087−1096.

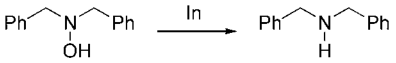
(2) (a) Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 955−977. (b) Moody, C. J.; Pitts, M. R. *Synlett* **1998**, 1028. (c) Moody, C. J.; Pitts, M. R. *Synlett* **1998**, 1029−1030. (d) Moody, C. J.; Pitts, M. R. *Synlett* **1999**, 1575−1576. (e) Harrison, J. R.; Moody, C. J.; Pitts, M. R. *Synlett* **2000**, 1601−1602. (f) Ranu, B. C.; Guchhait, S. K.; Sarkar, A. *Chem. Commun.* **1998**, 2113-2114. (g) Ranu, B. C.; Dutta, P.; Sarkar, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1139−1140. (h) Ranu, B. C.; Samanta, S.; Guchhait, S. K. *J. Org. Chem.* **2001**, *66*, 4102−4103. (i) Ranu, B. C.; Dutta, J.; Guchhait, S. K. *J. Org. Chem.* **2001**, *66*, 5624−5626. (j) Ranu, B. C.; Samanta, S.; Das, A. *Tetrahedron Lett.* **2002**, *43*, 5993−5995. (k) Lim, H. J.; Keum, G.; Kang, S. B.; Chung, B. Y.; Kim, Y. *Tetrahedron Lett.* **1998**, *39*, 4367−4368. (l) Lee, J. G.; Choi, K. I.; Koh, H. Y.; Kim, Y.; Kang, Y.; Cho, Y. S. *Synthesis* **2001**, 81−84. (m) Chae, H.; Cho, S.; Keum, G.; Kang, S. B.; Pae, A. N.; Kim, Y. *Tetrahedron Lett.* **2000**, *41*, 3899−3901. (n) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. M. *Tetrahedron Lett.* **2000**, *41*, 2663−2665. (o) Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Ramalingam, T. *Synlett* **2000**, 1447−1449. (p) Reddy, G. V.; Rao, G. V.; Iyengar, D. S. *Tetrahedron Lett.* **1999**, *40*, 3937−3938. (q) Miyai, T.; Ueba, M.; Baba, A. *Synlett* **1999**, 182−184. (r) Baek, H. S.; Lee, S. J.; Yoo, B. W.; Ko, J. J.; Kim, S. H.; Kim, J. H. *Tetrahedron Lett.* **2000**, *41*, 8097−8099. (s) Jeevanandam, A.; Cartwright, C.; Ling, Y. C. *Synth. Commun.* **2000**, *30*, 3153−3160. (t) Banik, B. K.; Suhendra, M.; Banik, I.; Becker, F. F. *Synth. Commun.* **2000**, *30*, 3745−3754. (u) Kim, B. H.; Jin, Y.; Jun, Y. M.; Han, R.; Baik, W.; Lee, B. M. *Tetrahedron Lett.* **2000**, *41*, 2137−2140. (v) Hutchinson, I.; Stevens, M. F. G.; Westwell, A. D. *Tetrahedron Lett.* **2000**, *41*, 425−428. (w) Ilias, M.; Barman, D. C.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **2002**, *43*, 1877−1879.

10.1021/ol034434l CCC: $25.00

azolidines into the corresponding amino alcohols can be accomplished by a variety of methods, including hydrogenation over Raney Ni,[6,7] Pd/C,[6,8] or $Pd(OH)_2$,[9] reaction with Zn/H^+,[6] Ni boride,[10] $Mo(CO)_6/H_2O$,[11] $Zn/Cu(OAc)_2/AcOH$,[12] and SmI_2.[13] Reduction of *N*,*N*-disubstituted hydroxylamines to the corresponding amines can also be performed by several reagents, among which Zn/HCl,[14] H_2/Pd or Raney Ni,[15] aqueous $TiCl_3$,[16] $Zn/Cu(OAc)_2/AcOH$,[17] and Ni boride[18] are the most used. However, none of these reagents display broad substrate generality, particularly for the latter transformation, and their choice has to be evaluated on an individual basis. Moreover, some of these methods, such as hydrogenations and Zn/HCl, which are otherwise quite reliable and of considerable scope, do not tolerate the presence of several functional groups, such as unsaturated and acid-sensitive ones. Therefore, new methods able to perform N−O bond reductive cleavage, which may show greater generality and chemoselectivity, are still desired.

The reduction with In(0) was first tested on *N*,*N*-dibenzylhydroxylamine (**1**) in order to prove its feasibility and to find the optimal reaction conditions (Table 1).

Table 1. Reduction of *N*,*N*-Dibenzylhydroxylamine (**1**) with Indium Metal

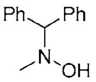
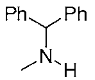
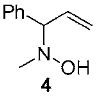
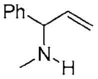
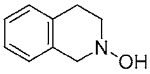
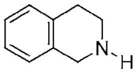
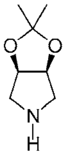
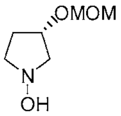
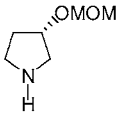
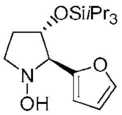
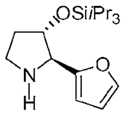
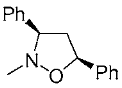
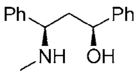

1 **2**

entry	In[a] (mol equiv)	conditions	*t* (h)	conv (%)[b]	yield (%)[c]
1	1.25	EtOH/sat. aq NH_4Cl 2:1, reflux	3.5	100	100
2	0.5	EtOH/sat. aq NH_4Cl 2:1, reflux	7	35	nd
3	1.25	H_2O, reflux	13	60	57
4	1.25	EtOH/H_2O 2:1, reflux	8	100	100
5	1.25	sat. aq NH_4Cl, reflux	13	54	nd

[a] In(0) powder purchased from Aldrich (2640322) was used. [b] Based on integration of ^1H NMR spectra of the crude reaction mixtures. [c] Isolated yields of products (nd = not determined).

The fact that less than 2 mol equiv is able to convert the hydroxylamine completely into amine suggests that In(0) is oxidized, at least partially, to In(III) rather than to In(I). However, more than a stoichiometric amount of In (considering its conversion to In(III)) is required for maintaining an acceptable rate of reaction (see also entry 2). Comparison of results in entry 1 and entries 3−5 establishes that a mixed ethanol/saturated aqueous NH_4Cl solution is the best medium for the reaction. Indeed, the presence of EtOH allows the substrate to be more soluble and to reach complete conversions, and the acidity furnished by the ammonium salt significantly shortens the reaction times. Therefore, the conditions of entry 1 (Table 1) have been selected in order to study the scope of the reduction.[19]

Table 2. Reduction of Hydroxylamines **3**−**8** and Isoxazolidine **9** with Indium Metal

entry	substrate	In (mol equiv)	product	*t* (h)	yield (%)
1	 **3**	1.25	 **10**	4	100
2	 **4**	1.8	 **11**	5	94
3	 **5**	2	 **12**	6	100
4	 **6**	2.2	 **13**	10	58
5	 **7**	2	 **14**	5.5	51
6	 **8**	1.2	 **15**	4	75
7	 **9**	3.2	 **16**	8	63

Hydroxylamines **3**−**8** (Table 2) have been subjected to reduction by In under these conditions, with the only variation consisting in the equivalent amounts of In powder used, which has been increased in some cases in order to

---

(3) See for example: (a) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315−2318. (b) Merino, P. Tejero, T.; Revuelta, J.; Romero, P.; Cicchi, S.; Mannucci, V.; Brandi, A.; Goti, A. *Tetrahedron: Asymmetry* **2003**, *14*, 367−379. (c) Cicchi, S.; Corsi, M.; Marradi, M.; Goti, A. *Tetrahedron Lett.* **2002**, *43*, 2741−2743. (d) Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Fedi, V.; Brandi, A. *Eur. J. Org. Chem.* **2000**, 3633−3645 and references therein.

(4) (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (b) Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946. (c) Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759−774. (d) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442−454. (e) Lombardo, M.; Trombini, C. *Curr. Org. Chem.* **2002**, *6*, 695−713.

(5) (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A.; Ed.; John Wiley & Sons: New York, 1984. (b) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1−173. (c) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; Feuer, H., Ed.; VCH Publishers: New York, 1988. (d) Frederickson, M. *Tetrahedron* **1997**, *53*, 403−425.

(6) (a) Huisgen, R.; Grashey, R.; Hauck, H.; Seidl, H. *Chem. Ber.* **1968**, *101*, 2548−2558. (b) Huisgen, R.; Grashey, R.; Seidl, H.; Hauck, H. *Chem. Ber.* **1968**, *101*, 2559−2567. (c) Huisgen, R.; Hauck, H.; Grashey, R.; Seidl, H. *Chem. Ber.* **1968**, *101*, 2568−2584. (d) Huisgen, R.; Hauck, H.; Grashey, R.; Seidl, H. *Chem. Ber.* **1969**, *102*, 736−745.

(7) LeBel, N. A.; Post, M. E.; Whang, J. J. *J. Am. Chem. Soc.* **1964**, *86*, 3759−3767.

(8) Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5048−5050.

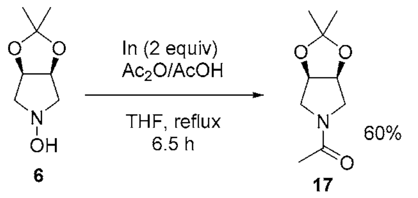
(9) DeShong, P.; Leginus, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1686−1688.

(10) Tufariello, J. J.; Meckler, H.; Pushpananda, K.; Senaratne, A. *Tetrahedron* **1985**, *41*, 3447−3453.

keep the reaction times below practical values (<10 h). All of the hydroxylamines **3**−**8** have been converted completely into the corresponding amines **10**−**15** under the conditions reported in Table 2. The recovered yields of amine vary from excellent (entries 1−3) to moderate (entries 4−5). The lower yields obtained of amines **13** and **14** are presumably connected with their higher hydrosolubility and volatility. This reduction protocol can also be applied successfully to trisubstituted hydroxylamines and particularly to isoxazolidines, as demonstrated by reductive ring opening of **9** to the corresponding β-amino alcohol **16** (entry 7). The N−O bond cleavage of isoxazolidines to amino alcohols is one of the most important transformations of these heterocycles and is largely applied in organic synthesis.[3,5]

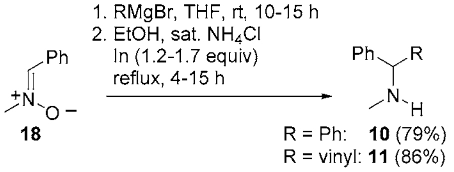
The present reduction method is mild and selective enough to tolerate the presence of C═C double bonds (entry 2) and of acid-labile hydroxyl protecting groups, such as a methoxymethyl (entry 5) and a ketal (entry 4). A particularly challenging substrate concerning the chemoselectivity of this method was provided by the *N*-hydroxypyrrolidine **8**, which was reluctant to undergo reduction to the corresponding pyrrolidine. Indeed, the methods commonly used for reduction of hydroxylamines failed to give the desired pyrrolidine **15**, required as an intermediate in the synthesis of a proline-type amino acid, satisfactorily. Apart from hydrogenation methods, which would give simultaneous saturation of the furan ring, $Zn/Cu(OAc)_2$[17] was not able to accomplish the reduction at all. $TiCl_3$[16] afforded a complex reaction mixture containing the corresponding imine as the main product. Only in situ generated Ni boride[18] allowed recovery of pyrrolidine **15**, but with a poor 15% yield, again from a mixture of byproducts. In contrast, we were delighted to find that reduction with In powder worked properly, affording cleanly and with complete conversion the pyrrolidine **15**, which was isolated in 75% yield (Table 2, entry 6).

The possibility of introducing this new reduction protocol for N−O bonds in sequential reaction procedures has also been exploited. First, a domino reduction/acetylation sequence was pursued. To accomplish this goal, a shift to the use of acetic anhydride/acetic acid as the reaction medium was envisaged, since a similar procedure has been previously successful in the reduction/acetylation of oximes.[2a] Under these conditions, the *N*-hydroxypyrrolidine **6** was converted into the amide **17** (identical to the product obtained by direct acetylation of **13**) in 60% yield (eq 1), which compares well with that obtained in the single reduction step (Table 2, entry 4). Indeed, this procedure may be convenient in some cases not only for performing the reduction with protection of the amine in a single synthetic step but also for facilitating the recovery of amine from the reaction medium.



(1)

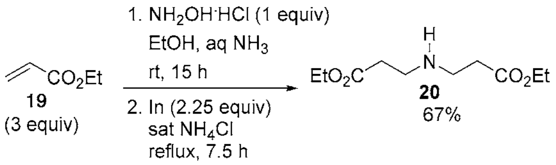
Two one-pot procedures, where hydroxylamines are formed as intermediates in the first step, were then studied. The first involves a nucleophilic addition of a Grignard reagent to a nitrone, followed by In reduction (eq 2).



(2)

C-Phenyl-*N*-methylnitrone (**18**) has been chosen as starting material. Addition of phenyl or vinylmagnesium bromide followed by in situ reduction of the intermediate hydroxylamine (**3** and **4**, respectively) provided directly amines **10** and **11** in good yields.

The second procedure we decided to address consisted of a double conjugate addition of hydroxylamine to ethyl acrylate (**19**)[20] followed by reduction with In (eq 3). The amino diester **20** was directly isolated in 67% yield by reduction of the corresponding intermediate disubstituted hydroxylamine.



(3)

The above examples clearly illustrate the virtue of this new method. However, its acceptance for application to large-scale preparations is prevented by the high cost of In(0),[21] used in stoichiometric amount. Therefore, the possible use of In(0) as a catalyst in conjunction with much less expensive metals as the stoichiometric reducing agents for the same hydroxylamine to amine transformation has been investigated (Table 3). Although catalytic In-based reactions have been reported in the case of Barbier−Grignard allylations in some occasions,[22] In catalysis in reduction reactions is unprecedented, to the best of our knowledge. Inexpensive

Table 3. In(0)-Catalyzed Reduction of **1** to **2**

entry	M (mol equiv)	In (mol %)	t (h)	conv (%)[a]	yield (%)[b]
1	Al (2.0)		8	16	nd
2	Sn (2.0)		8.5	25	nd
3	Zn (2.5)		6	24	nd
4	Al (2.0)	5	5	100	100
5	Sn (2.0)	5	8.5	49	44
6	Zn (2.5)	10	4.5	100	100
7	Zn (2.0)	5	5	100	100
8	Zn (2.0)	2	5.5	100	100

[a] Based on integration of ^1H NMR spectra of the crude reaction mixtures. [b] Isolated yields of products (nd = not determined).

reducing metals, such as Al, Zn, and Sn, were tested as stoichiometric reagents in the reduction of *N*,*N*-dibenzylhydroxylamine (**1**) to the corresponding dibenzylamine (**2**) under the same optimal reaction conditions found for the reduction with In. The results reported in Table 3 show that all of these metals were only moderately active, affording the amine with only modest conversions, even after longer reaction time (entries 1−3). When a catalytic amount of In was added (entries 4−6), the conversions increased significantly in all cases, indicating that a catalytic cycle was effective. However, only Al and Zn were able to convert the hydroxylamine completely, and reduction with Sn was not efficient enough (entry 5). This result is in agreement with the more negative redox potential of the former metals. In the reduction with Zn, the effect of a decrease in the amount of In used has been studied (entries 6−8). The reduction was still efficient by using as little as 2 mol % of In with respect to **1** (entry 8), only requiring a small increase in reaction time in order to go to completion. As in the case of reductions with stoichiometric In, the workup of the reaction mixtures was simple and straightforward. Filtration over Celite of the metal salts followed by extraction with ethyl acetate from a Na_2CO_3 aqueous solution and concentration of the solvent afforded the amine directly.

In conclusion, a new simple method for accomplishing the reductive cleavage of N−O bonds in *N*,*N*-disubstituted hydroxylamines has been developed. This method resulted in more satisfying and chemoselective reductions of sensitive substrates in comparison with the most commonly used methods. Notably, its use in one-pot procedures was employed successfully, affording secondary amines directly in good yields. The usefulness of the method has been significantly expanded, demonstrating its viability in catalytic conditions utilizing Zn or Al as stoichiometric reducing agents, which represents the first example of an In-catalyzed reduction. Studies are currently underway in our laboratory in order to extend the In-catalyzed reduction to other substrates and functional groups and to define the effective scope and usefulness of In reductions in organic synthesis.

Acknowledgment. We are grateful to the *Ministry of Instruction, University and Scientific Research* (MIUR), Italy, for financial support (Cofin 2002). J.R. was the recipient of a fellowship under the Socrates/Erasmus student exchange program (Firenze-Zaragoza).

Supporting Information Available: Experimental procedures, spectral data of amines, and analytical and spectroscopical characterization of compounds **8** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034434L

---

(11) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351−3354.

(12) Dhavale, D. D.; Gentilucci, L.; Piazza, M. G.; Trombini, C. *Liebigs Ann. Chem.* **1992**, 1289−1295.

(13) Westermann, B.; Walter, A.; Flörke, U.; Altenbach, H.-J. *Org. Lett.* **2001**, *3*, 1375−1378.

(14) Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Kodera, Y. *Tetrahedron Lett.* **1988**, *29*, 2973−2976.

(15) (a) Murahashi, S.-I.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 6469−6472. (b) Murahashi, S.-I.; Sun, J.; Tsuda, T. *Tetrahedron Lett.* **1993**, *34*, 2645−2648.

(16) (a) Murahashi, S.-I.; Kodera, Y. *Tetrahedron Lett.* **1985**, *26*, 4633−4636. (b) Kodera, Y.; Watanabe, S.; Imada, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2542−2549.

(17) Merino, P.; Anoro, S.; Franco, S.; Gascon, J. M.; Martin, V.; Merchan, F. L.; Revuelta, J.; Tejero, T.; Tunon, V. *Synth. Commun.* **2000**, *30*, 2989−3021.

(18) Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1981**, *29*, 1159−1161.

(19) **General Procedure.** The hydroxylamine (1 mmol) is dissolved into a 2:1 solution of EtOH and saturated aqueous NH_4Cl (6 mL) in a 25-mL round-bottomed flask equipped with a Claisen condenser and a magnetic stirring bar. The appropriate amount of In powder (see Tables) is then added, and the mixture is heated under reflux. After completion of the reaction (TLC control), the mixture is cooled, filtered over Celite, and concentrated. Then, a saturated Na_2CO_3 solution (15 mL) is added, and the product is extracted with ethyl acetate (3 × 15 mL). The organic phase is dried over anhydrous Na_2SO_4, filtered, and concentrated to afford the desired amine. When necessary, the amine has been purified by flash column chromatography.

(20) Baldwin, J. E.; Harwood, L. M.; Lombard, M. J. *Tetrahedron* **1984**, *40*, 4363−4370.

(21) Compare, for example, the following prices (Euros/mol) of In and other commonly used reducing metals, extracted from the Aldrich 2003 catalogue: In, 1332; Sn, 36; Zn, 6; Al, 3.

(22) (a) Araki, S.; Jin, S.-J.; Idou, Y.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1736−1738. (b) Augé, J.; Lubin-Germain, N.; Thiaw-Woaye, A. *Tetrahedron Lett.* **1999**, *40*, 9245−9247. (c) Steurer, S.; Podlech, J. *Adv. Synth. Catal.* **2001**, *343*, 251−254. (d) Lombardo, M.; Girotti, R.; Morganti, S.; Trombini, C. *Org. Lett.* **2001**, *3*, 2981−2983. (e) Gordon, C. M.; Ritchie, C. *Green Chem.* **2002**, *4*, 124−128.