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Rapid Stereoselective Reduction of Thermally Labile 2-Aminonitroalkanes.

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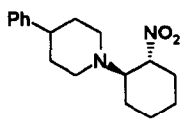
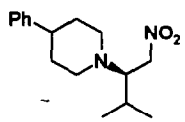
Abstract: Samarium diiodide may be employed in the stereoselective reduction of thermally unstable 2-aminonitroalkanes to give a range of useful 1,2-diamines.

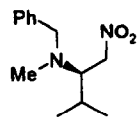
The 2-aminonitroalkane subunit is potentially an extremely versatile synthon. However, with the exception of Hydrogen bond stabilized species, e.g. aminonitrosugars, the employment of such species in modern synthetic chemistry is often handicapped by their chemical and stereochemical instability.[1] The ultimate goal of most applications of nitroalkane chemistry involves the degradation of the nitro unit, most commonly by reduction to give the primary amine. The majority of such reductive procedures involve transition metal catalysts, usually palladium, and a source of hydrogen, usually hydrogen gas.[2] Unfortunately these reductions usually proceed slowly, thereby allowing competing loss of stereochemical integrity and degradation of the substrate. All literature examples of such catalytic reductions have utilized stable aminonitroalkanes.



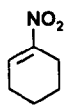
(±) 1a

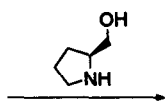


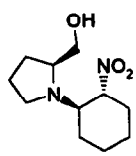
(±) 2a



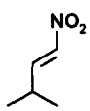
(±) 4a







3a



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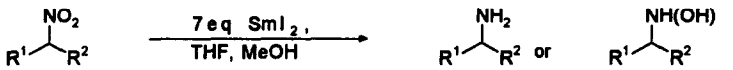
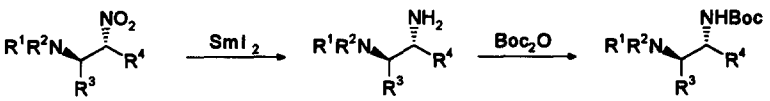
An alternative procedure, utilizing stannous chloride[3,4] as the active reductant, employs an aqueous acidic medium. However, highly hydrophobic substrates such as 1a and 2a are not soluble under such conditions. Our initial efforts have revealed that in such cases acid catalyzed degradation of the substrate is the primary pathway observed, with only minimal amounts of the reduction products being observed. In additional to the solubility problem, we were concerned regarding the potential intramolecular Nef hydrolysis of substrates such as 3a to give the corresponding

aminoketones. *In situ* reduction of these by-products would generate the corresponding aminoalcohols, which we felt may be difficult to remove from the desired diamine products. Of these species only **3a** was reduced under the standard $SnCl_2$ conditions. However, even in this case the subsequent aqueous work up and extraction of the diaminoalcohol was not inconsequential. On a more general note, the use of highly acidic reaction conditions greatly limits the choice of functionality present in the remainder of the molecule. We were therefore intrigued by the possibilities of examining other potential reagents, and of performing such a transformation under complementary non-acidic conditions.

We have been interested in the use of 2-aminonitroalkanes in the preparation of complex and unusual 1,2-diamines and related species. Recently we had cause to explore the reduction of a series of nitroalkanes that were both stereochemically labile as well as chemically labile. 2-Aminonitroalkane **3a** could be readily prepared in an almost stereospecific manner by simply mixing prolinol and 1-nitrocyclohexene in CH_2Cl_2 at room temperature.[5] The related species **2a** and **4a** were prepared by mixing the corresponding amine with 3-methyl-1-nitrobut-1-ene[6] **5** in CH_2Cl_2. Purification by kugelruhr distillation gave the pure adducts. All three of these delicate aminonitroalkanes slowly underwent retroaddition at rt. The 3-methyl-1-nitrobut-1-ene derived species also underwent slow loss of nitromethane upon standing. Furthermore, these degradation products reacted to give a series of highly complex mixtures under the standard reductive conditions outlined above.



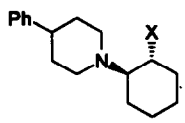
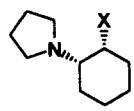
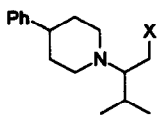
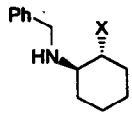
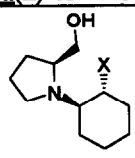
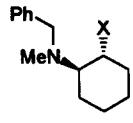
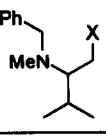
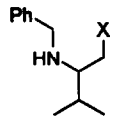
Kende[7] has recently shown that SmI_2 may be employed as an electron source in the reduction of nitroalkanes to give either the corresponding hydroxylamine or primary amine. Although a number of the substrates employed in this work contained oxygen functionalities at the β-carbon, none of the substrates exhibited either relative or absolute stereochemistry at the nitrocenter. We felt that the very fast rate of reduction (~10mins) of the nitro unit to the stereochemically stable hydroxylamine could be employed to retain the stereochemical integrity of our substrates, and thus generate the corresponding stereochemically defined diamines. In the reported procedure, methanol was used as the proton source. Our primary concern was as to whether the methoxide generated during the reduction would cause a significant loss of stereochemical integrity at the nitrocenter. We were also concerned that the more interactive solvent, THF, may hasten the degradation of these adducts.[8] We report here that neither of these concerns are prohibitive.



The three unstable nitroalkanes **2a**, **3a** and **4a** may be cleanly reduced under our modified conditions without significant loss of integrity or degradation (Table 1).[9] Furthermore, the hydrophobic substrate **1a** was cleanly reduced to the corresponding diamine **1b**. Although the chemical yield of **1b** is very good, there has been a slight erosion of the stereochemical purity of the nitroalkane. The *cis* and *trans* isomers may however be readily separated by chromatography on silica gel. The diamines may be readily characterized after purification by either distillation or silica gel chromatography. Nitroalkane **6a** is an interesting example of the kinetic product of addition of an amine to a nitroalkene. This species epimerized to give predominantly the *trans* adduct on standing. Reduction of **6a** (*cis*:*trans* 4.7:1) (entry 5) gave the corresponding diamine **6b** (*cis*:*trans* 4:1), which was not isolated after filtration of the samarium salts, but was derivatized as the N-Boc species[10] **6c**. Careful kugelruhr distillation of the protected diamine under reduced pressure (125°C @ 0.03mm Hg) lead to a *cis*: *trans* ratio of 7:1 (68% from 1-nitrocyclohexene). Entries 6-8 illustrate the potential of this procedure in the preparation of simple protected 1,2-diamines. In these cases the original amine residue retains the benzyl group, which is often employed to differentiate two similar nitrogen units. Such

a situation is clearly not compatible with the standard catalytic reduction protocols. Catalytic reductive procedures would have resulted in the loss of this unit in addition to reduction of the nitro unit.

Although, a slight loss of stereochemical integrity was observed for these substrates, in most cases the desired diamines may be easily purified by further recrystallization or chromatography. Although we feel that the samarium methoxide generated during the early stages of the reduction may be partially responsible for this phenomenon, it should be stressed that epimerization of these substrates in quite facile in polar H-bonding solvents such as THF and MeOH even in the absence of additional basic species.

Entry	Substrate	Yield*	Entry	Substrate	Yield*
1.		95% *trans:cis* 6:1 (0%)	5.		68%** *cis:trans* 4:1 (61%**)
	1a(±) X = NO_2	**1b** X = NH_2		**6a**(±) X = NO_2 *cis:trans* 4.7:1	**6b** X = NH_2 **6c** X = NHBoc
2.		66% (0%)	6.		56% <5% *cis* (53%)
	2a(±) X = NO_2	**2b** X = NH_2		**4a**(±) X = NO_2	**4b** X = NH_2
3.		90% (88%)	7.		65% (78%)
	3a X = NO_2	**3b** X = NH_2		**5a**(±) X = NO_2	**5b** X = NH_2
4.		71% (53%)	8.		66% (46%)
	4a(±) X = NO_2	**4b** X = NH_2		**6a**(±) X = NO_2	**6b** X = NH_2

* Yields in parenthesizes are the best yield attained employing $SnCl_2$/conc. $HCl_{(aq)}$

** Isolated as the N-Boc derivative (see procedure)

TABLE 1

This procedure should greatly enhance the variety of 2-aminonitroalkanes that may be employed as precursors of 1,2-diamines. Diamines of this type may be valuable intermediates in the preparation of σ and κ brain receptor antagonists.[11] In addition, such a sequence has allowed the trapping of unstable amine/nitroalkene adducts. Inasmuch, this procedure has allowed us to trap stereochemically labile 2-aminonitroalkanes and at the same assess the initial kinetic products of addition of amines to nitroalkenes. We are currently employing such a sequence to evaluate the interaction of chiral amines with achiral nitroalkenes.

Whilst our basic experimental procedure is similar to that employed previously,[7] a modification has been developed which greatly simplifies the final work up. Although, this procedure requires the use of 7eq of a relatively

expensive reagent, precipitation of the samarium(III) by-products as the oxalate salts facilitates the removal of the inorganic components, and in principle would allow for the recovery and regeneration of the reductant. Furthermore, a recent report[12] of the Sm(III) catalyzed electrochemical reductive allylation of ketones, wherein Sm(II) salts were formed *in situ*, suggests that in principle only catalytic amounts of reductant may be necessary. We are presently investigating this possibility. Additionally as demonstrated in the case of **6b**, the crude reduction mixture, after filtration to remove the majority of the inorganic salts is suitable for further derivatization of the diamines. Such further manipulations greatly enhance the extractive isolation of the product. A full comparative study of the relative merits of this procedure and those of the complementary $SnCl_2$ reduction protocol will be published at a later date.

Typical Procedure : Samarium (9eq.) and 1,2-diiodoethane (7eq.) were placed in a flask equipped with a reflux condenser, and the glassware was thoroughly flushed with Ar via an evacuate/fill triple sequence. THF (5mL) was added and the suspension was stirred for 30mins at rt., after this time a further portion of THF (14mL) was added and the mixture was stirred overnight. The aminonitroalkane (0.5mMol) was dissolved in 1:1 THF/MeOH (2mL) and added dropwise to the samarium diiodide solution at rt. The mixture was stirred for 24hr. Oxalic acid (12eq.) in water (10mL) was added to quench the reaction and precipitate the samarium salts. The resulting suspension was diluted with water (40mL) and filtered through celite. Removal of the organic solvent by rotary evaporator gave an aqueous solution of the oxalate salt. Neutralization with NaOH (24eq.) and extraction with ethyl acetate (5X100mL) gave the crude diamine, which was usually >90% pure. Further purification was achieved by either distillation or chromatography on silica gel (5-10% MeOH in CH_2Cl_2). Alternatively, neutralization of the oxalate salt with the same quantity of NaOH, addition of $CHCl_3$ (10mL), and di-tert-butyldicarbonate (1.5eq.), and stirring this mixture at 60°C for 2hrs gave the crude N-Boc derivative. Separation of the organic layer and washing the aqueous layer with $CHCl_3$ (2X10mL) gave the desired crude diamine derivative. Distillation of this material gave the N-Boc derivative **6c**.

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References :

1. The presence of both a basic nitrogen and a stereogenic acidic carbon-hydrogen bond usually results in either eliminative degradation and/or loss of stereochemical integrity.
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8. Although the degradation of these aminonitroalkanes could be retarded by the employment of non-polar solvent systems such as benzene, in more polar solvents (especially those capable of H-bond donation and/or acceptance) the rate of decomposition and/or epimerization was substantially increased.
9. All new compounds gave satisfactory spectral (^1H, ^{13}C, ir) and mass spectral (EI and HREI) analysis.
10. The protection was carried out using a modification of the procedure of Tarbell; D.S. Tarbell, Y. Yamamoto, B.M. Pope Proc. Natl. Acad. Sci. USA **1972**, *69*, 730.
11. See for example, L. Radesca, W.D. Bowen, L.D. Paolo, B.R. deCosta J. Med. Chem. **1991**, *34*, 3058; C. Dominguez, B. deCosta, X. He, J.T. Linders, W. Williams, W. Bowen 205th National A.C.S. Meeting, Denver CO, 1993, Abstract # MEDI 70; B.R. deCosta, C. Dominguez, X.S. He, W. Williams, L. Radesca, W. Bowen J. Med. Chem. **1992**, *35*, 4334.
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