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Instantaneous SmI_2/H_2O/amine mediated reduction of nitroalkanes and α,β-unsaturated nitroalkenes

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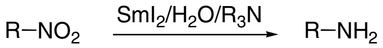
Abstract—A rapid method for efficient reduction of nitroalkanes and α,β-unsaturated nitroalkenes using SmI_2/H_2O/amine has been developed.

The discovery and development of new methods for the efficient synthesis of amines continues to play an important role in organic chemistry. The amine functional group is ubiquitous in natural products, pharmaceuticals, dyes and fine chemicals. For this reason, a number of important methods are available for the synthesis of aliphatic amines.[1] This is generally accomplished with a suitable hydride or hydrogen source, for example, lithium aluminium hydride ($LiAlH_4$),[2] sodium borohydride ($NaBH_4$) in conjunction with a Lewis acid,[3] or hydrogenation catalyzed by palladium,[4] platinum[5] or Raney-Ni.[6]

The single electron transfer reagent SmI_2, introduced in organic chemistry by Kagan,[7] has become a popular reagent for selective radical coupling reactions and reduction reactions.[8] In pioneering experiments, reported by Zhang and Lin in 1987, it was observed that nitrobenzene was reduced to aniline using SmI_2 and methanol in almost quantitative yield at room temperature.[9] More recently, Banik et al. reported the use of SmI_2 for the reduction of various aromatic nitro compounds.[10] There have also been a few reports on the reduction of nitroalkanes with SmI_2,[11] but these reductions are generally slow. Yacovan and Hoz reported that SmI_2 mediates the reduction of 1,1-diphenyl-2,2-dinitroethane.[12] However, the reaction gave a complex mixture of coupling products and various reduced compounds. In contrast, Hu and co-workers have shown that Sm(0) mediates chemoselective reduction of aromatic nitro groups in the presence of aliphatic nitro groups.[13] The use of $Sm[NSi(Me_3)]_2$ as reducing agent for the reduction of aromatic nitro compounds to primary amines has been explored by Brady and co-workers. They showed that the reduction occurs via a complex reaction mechanism involving several intermediates, for example, hydroxylamine,[14] however, using excess Sm(II) they obtained the amines as the sole product.

A few years ago we discovered that the SmI_2/H_2O/amine mixture, in THF, mediates instantaneous reduction of ketones.[15] Later studies in our laboratory showed that SmI_2/H_2O/amine is a particularly powerful reducing agent, which mediates rapid and selective reduction of alkyl and aryl halides,[16] α,β-unsaturated esters,[17] conjugated olefins,[18] β-hydroxyketones,[19] imines[20] and allyl ethers[21] in up to quantitative yields. Although SmI_2/H_2O/amine appears to be a poor reagent for radical coupling reactions, it is an efficient reagent for pinacol couplings of aryl ketones and aryl imines and for aryl halide-olefine cyclization.[22] We report our results on the reduction of nitroalkanes and nitroalkenes with SmI_2/H_2O/amine, Scheme 1. The α,β-unsaturated nitro substrates were easily synthesized via the Henry reaction,[23] and the aliphatic nitro substrates were obtained by subsequent $NaBH_4$ reduction of the corresponding nitroalkene.

Initial experiments revealed that addition of a dilute solution (0.1 M) of the nitro compound to a premixed THF solution of SmI_2 (0.1 M), isopropylamine (0.3 M)



$$R{-}NO_2 \xrightarrow{SmI_2/H_2O/R_3N} R{-}NH_2$$

Scheme 1.

Keywords: Reduction; SmI_2; Amine; Nitroalkane; Nitroalkene.

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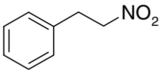
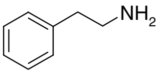
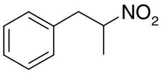
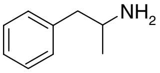
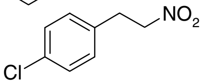
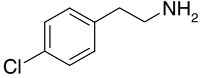
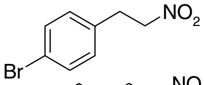
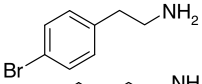
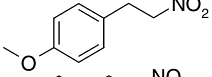
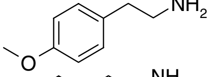
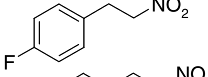
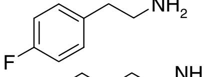
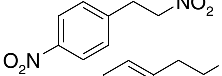
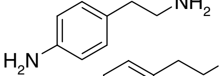
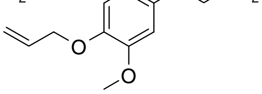
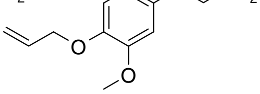
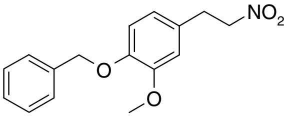
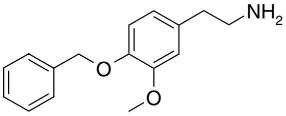
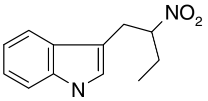
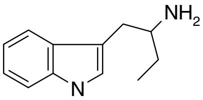
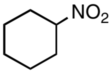
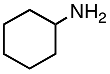
and water (0.6 M) gave a clean and almost quantitative conversion of aliphatic nitro compounds to the respective amines, Table 1.[24] All the reactions were instantaneous, thus the workup procedure was initiated immediately after complete mixing of the reagents. Prolonged reaction times did not influence the chemical yield. Substrates containing halides (entries 3,4,6), ethers (entries 5,8,9), an allyl ether (entry 8), a benzyl group (entry 9), and indole (entry 10), that is, many groups that would not survive treatment with, for example, Pd/H_2, were examined. Unfortunately, we observed no selectivity between the nitro group attached to an aryl or an alkyl group (entry 7). The chemoselectivity between the aryl bromide and the nitro group was low for the brominated nitro substrate (entry 4) resulting in a (60:40) mixture of products. Thus the reactivity difference for the nitro group and the aryl bromo group is not large enough to allow practical use in synthesis, but for all the other nitro substrates we observed clean reduction and high yields of the corresponding amines (85% or higher isolated yields). The reduction of nitro groups to amines is known to involve various intermediates, which may result in complex product mixtures. The most common by-product in these reductions are hydroxylamines.[15] However, we did not observe any formation of hydroxylamines using SmI_2, amine and water.

As a result of the successful reduction of the nitro group, the possibility to reduce α,β-unsaturated nitroalkenes directly to amines using the SmI_2/H_2O/amine reagent was investigated. GC analysis indicated clean and instantaneous conversion to saturated amines. However, the isolated yields after workup were only 22–75%, see Table 2.[25] The dimethoxy derivative (entry 6) and the aliphatic α,β-unsaturated nitroalkene (entry 8) were isolated in fairly high chemical yields (75% and 70%, respectively). Again, the competing reduction of the aryl bromide was observed with the aryl bromide substrate (entry 4). Nitrobenzene (entry 9) was also instantly reduced to aniline.

Careful workup and analysis by HPLC and NMR showed that the reaction also generates some byproducts of polymeric and dimeric character. Therefore, it is most likely that there is a competing side reaction involving a benzyl radical intermediate. This possible side reaction was explored further and, interestingly, it was shown that nitrostyrene undergoes almost

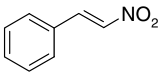
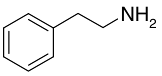
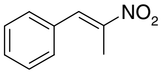
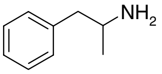
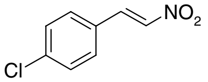
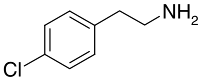
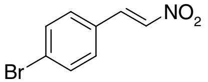
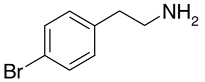
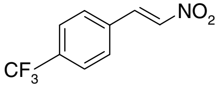
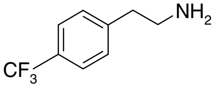
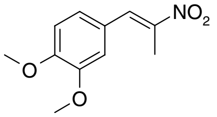
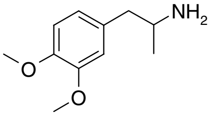
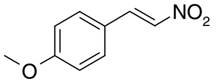
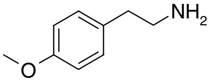
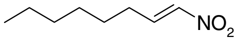
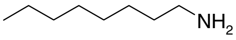
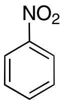
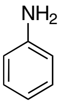
Table 1. Instantaneous reduction of various nitroalkanes with a mixture of SmI_2, isopropylamine and water in THF[a]

Entry	Starting material	Product	Isolated yield (chemical yield, GC) (%)
1			(99)
2			92 (99)
3			95
4			60
5			96
6			87
7			86
8			85
9			94
10			99
11			>95[b]

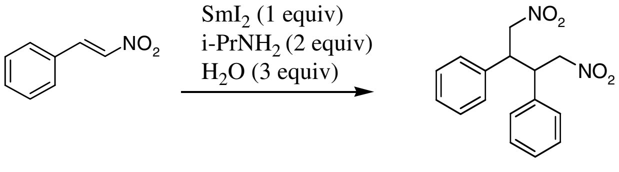
[a] The reactions are complete directly after the addition of substrate (1:10) in THF at room temperature. Each mol of substrate requires 6 mol of SmI_2, 12 mol of isopropylamine and 60 mol of water for completion.

[b] Chemical yield determined by GC with 3-phenylpropylamine as internal standard.

Table 2. Reduction of α,β-unsaturated nitroalkenes to saturated amines[a]

Entry	Starting material	Product	Isolated yield (%)
1			60
2			52
3			47
4			22
5			45
6			75
7			36
8			70
9			90

[a] The reactions are complete directly after the addition of substrate (1:10) in THF at room temperature. Each mol of substrate requires 8–10 mol of SmI_2, 16–20 mol of isopropylamine and 80–100 mol of water for completion.



100% (>95%) d.e.

Scheme 2.

quantitative reductive dimerization in the reaction with 1 M equiv of SmI_2. Analysis showed that the product was obtained with high diastereoselectivity (>95% de), Scheme 2.

In conclusion, The SmI_2/H_2O/amine reagent mediates a simple and very fast reaction for efficient conversion of nitroalkenes to primary amines. Based on our results, particularly the observation of coupling products, it appears that the conjugated C–C double bond in the nitrostyrenes is reduced faster than the isolated nitro group.

Acknowledgement

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24. Representative procedure for the reduction of aliphatic nitro compounds to amines: To a stirred solution of SmI_2 (0.1 M, 20 ml, 2.0 mmol, 6 equiv) in THF under a nitrogen atmosphere, isopropylamine (4.0 mmol, 0.342 ml, 12 equiv) and water (20 mmol, 0.36 ml, 60 equiv) were added followed by dropwise addition of the nitro compound dissolved in THF (0.33 mmol, 3.3 ml, 0.1 M, 1 equiv). After the addition the reaction was quenched with diethyl ether (20 ml). The reaction mixture was treated with a solution of potassium carbonate and sodium potassium tartrate in water (10% w/v, 20 ml). The aqueous phase was extracted with diethyl ether (2×10 ml). The combined organic extracts were dried and concentrated to afford the amines as colourless oils or crystals.
25. The workup used in the reduction of unsaturated nitro compounds was slightly modified and employed acidic workup of the post reaction mixture with 1 M HCl. This was washed once with dichloromethane before treatment with a saturated solution of sodium potassium tartrate and basification with KOH. Repeated extraction of the aqueous phase with dichloromethane yielded the amine in the yields specified in Table 2.