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Metal-Free Reduction of Aromatic and Aliphatic Nitro Compounds to Amines: A $HSiCl_3$-Mediated Reaction of Wide General Applicability

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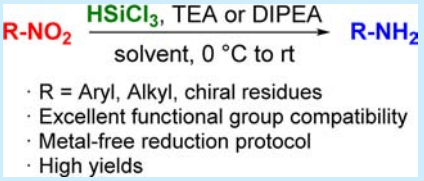
Supporting Information

ABSTRACT: A new, mild, metal-free, $HSiCl_3$-mediated reduction of both aromatic and aliphatic nitro groups to amines that is of wide general applicability, tolerant of many functional groups, and respectful of the stereochemical integrity of stereocenters is reported.

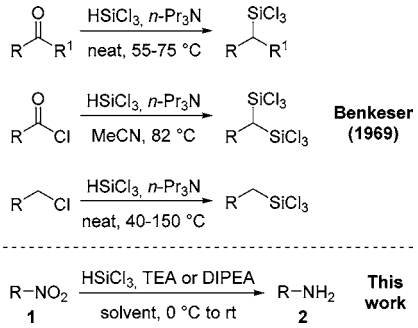


Reduction of nitro groups represents one of the most straightforward entries to aliphatic or aromatic amines.[1] Among the numerous available methodologies, reductions via hydrogenation with classical or revisited protocols (Pd/C, PtO_2, Raney nickel, or transition-metal catalysts)[2] or under transfer hydrogenation conditions[3] are largely employed. However, these protocols sometimes lack functional group compatibility, often requiring high-pressure equipment, and may suffer from the use of hazardous reagents (e.g., hydrazine) or the presence of potentially toxic transition metals. Similar considerations can be made for reductions with $SnCl_2$[4] or for metal-dissolving reductions involving Zn, Fe, In, or Sm,[5−7] which were reported to be poorly compatible with the presence of halogen atoms.[8] Efforts have been made to discover new green methodologies that would avoid the use of metal catalysts, but only few new protocols have been reported to date. Some representative examples of metal-free transfer hydrogenations, limited to reduction of nitroarenes, include the use of 9,10-dihydroanthracene,[9] 1,4-dihydropyridines,[10] thiols,[11] (2-pyridyl)phenylmethanol,[12] and vasicine.[13] However, a real application is hampered by the formation of difficult-to-remove organic byproducts. An alternative is provided by the use of sodium dithionite, $Na_2S_2O_4$.[14] Despite the fact that its use on a large scale results in highly exothermic reactions,[15] this reagent has been used for the synthesis of benzimidazoles via reductive cyclization of 2-nitroanilines on a multigram scale.[16] However, the reaction scope is restricted to the synthesis of aromatic amines only.

Hence, a green, efficient, mild, and widely general methodology for the nitro-to-amine conversion is still strongly required. Here we report an innovative metal-free reduction of both aliphatic and aromatic nitro derivatives to the corresponding amines that is efficient, chemoselective, and compatible with a plethora of functional groups.

$HSiCl_3$ is a green, cheap waste byproduct of the silicon industry that may be activated as a reducing agent in combination with Lewis bases[17] and employed in enantioselective catalytic reductions of ketoimines.[18] However, it is likewise known that when $HSiCl_3$ is used in combination with a tertiary amine, a formally nucleophilic silicon species is generated,[19] which was demonstrated to be reactive toward carbonyls,[20] alkyl halides,[21] and acid chlorides, typically under harsh reaction conditions (Scheme 1).[22] Here we report that

Scheme 1. Use of the $HSiCl_3/R_3N$ Mixture in Reduction Reactions



the combination of $HSiCl_3$ and a tertiary amine allows efficient reduction of both aliphatic and aromatic nitro compounds using a simple experimental protocol under mild reaction conditions (Scheme 1).[23]

The reduction of 4-nitrotoluene was selected as a model reaction and was performed in the presence of 3.5 equiv of $HSiCl_3$ and 5 equiv of a tertiary amine. The solvent of choice appeared to be either dichloromethane or acetonitrile, providing the reduction of **1a** in full conversion (see Table S1 in the Supporting Information). Among the screened tertiary amines, the aliphatic ones provided optimum results (Table S1). It is noteworthy that in the presence of Lewis bases such as pyridines, DABCO, and DMF, the reaction did not occur.[24]

The scope of the reaction was then explored (Scheme 2). In most cases, complete conversion of the nitro derivative into the corresponding amine was observed. Isolated yields after a quick chromatographic purification were in good agreement with the

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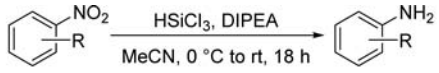
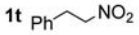
Scheme 2. Scope of the Reaction[a]



Substrate		yield (%)	Substrate		yield (%)
1a	4-Me	>98 (91)	**1o**	4-Cl	>98 (97)
1b	4-CH_2OH	>98 (95)	**1p**	4-Br	>98 (97)
1c	4-OAll	>98 (98)	**1q**	4-I	>98 (98)
1d	2-OAll	>98 (91)			
1e	4-OBn	>98 (95)	**1r**		96 (94)
1f	2-OBn	98 (93)			
1g	3-NHBn	n.d. (88)	**1s**		>98 (90)
1h	4-CN	93 (89)			
1i	4-NHAc	92 (90)			
1j	4-Ac	70 (70)	**1t**		>98 (98)
1k	4-Bz	>98 (93)			
1l	3-CO_2H	60 (57)	**1u**		>98 (90)
1m	4-CO_2H	70 (65)			
1n	3-$CONBn_2$	>98 (95)	**1v**	*n*-Hex NO_2	>98 (93)

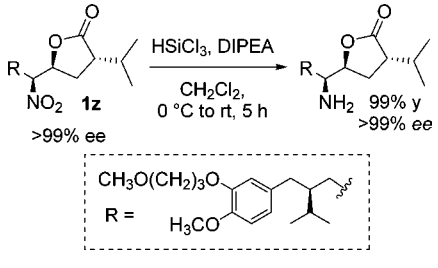
[a]Standard reaction conditions: to a solution of the nitro compound (0.7 mmol) and the base (5 equiv) in acetonitrile (7 mL) was added $HSiCl_3$ (3.5 equiv) at 0 °C; the reaction mixture was then allowed to warm to rt in 18 h. The yield column shows the reaction conversion based on the ^1H NMR spectrum of the crude mixture, with the isolated yield in parentheses.

^1H NMR-determined conversions. Allylic and benzylic protecting groups on both O and N atoms survived the reduction reaction conditions (**1c–g** and **1n**). Moreover, cyanides, amides, ketones, alcohols, and carboxylic moieties were tolerated (**1h–n**). Nitropyridines can be efficiently reduced (**1r–s**), as well as nitroalkanes (**1t–v**); remarkably, halogenated nitro compounds can be converted to amines without any detectable traces of dehalogenated products (**1o–q** and **1s**).

Furthermore, the metal-free reduction protocol was successfully employed in the reduction of nitrolactone **1z** in the total synthesis of aliskiren. The very mild procedure afforded the enantiopure aminolactone in 99% isolated yield without altering the stereochemical integrity of the four stereocenters of the molecule (Scheme 3).[25] Indeed, the new metal-free reduction methodology allowed the development of a novel and straightforward route for the synthesis of this important pharmaceutical product.

The first studies reporting the use of $HSiCl_3$ in combination with a tertiary amine date back to 1969.[19] On the basis of NMR experiments, it was hypothesized that the combination of $HSiCl_3$ with a base could lead to the formation of the R_3NH^+/Cl_3Si^- ion pair (Scheme 4). Almost 30 years later, Karsch proposed that this equilibrium may further evolve toward the formation of dichlorosilylene, $SiCl_2$ (Scheme 4).[26] More recently it was reported that the reaction of $HSiCl_3$ with an organic base may generate $SiCl_2$ *in situ*.[27]

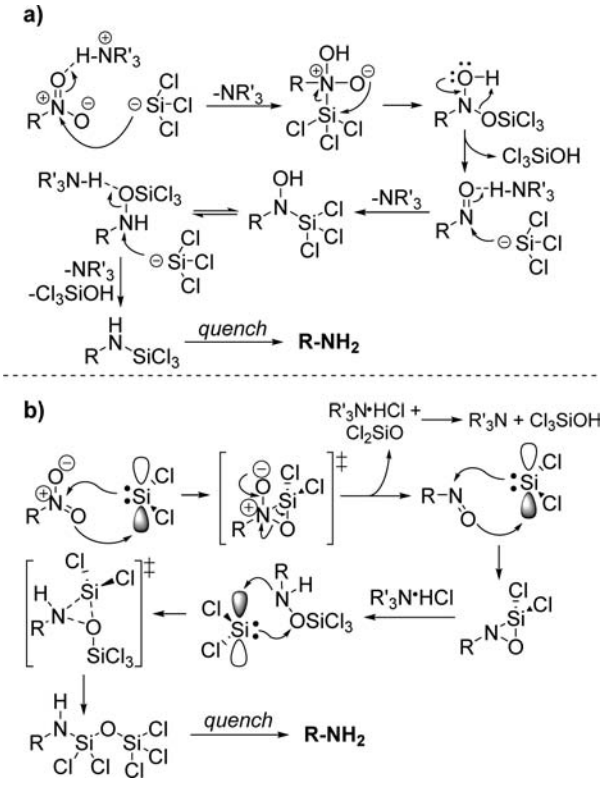
Scheme 3. Metal-Free Reduction of a Functionalized Chiral Nitro Derivative



Scheme 4. Generation of $SiCl_3^-$ and $SiCl_2$ from $HSiCl_3$ in the Presence of Tertiary Amines

In proposing a plausible mechanism for the reaction, it should be considered that either $SiCl_3^-$ or $SiCl_2$ may be the effective reducing agent. While the former, an anionic species, might act as a nucleophile toward the electrophilic nitrogen atom, $SiCl_2$ could react with N=O bonds through a cheletropic mechanism. The two mechanistic hypotheses are depicted in Scheme 5. In Scheme 5a, $SiCl_3^-$ is involved, while in Scheme 5b, $SiCl_2$ behaves as the reducing species. It is important to point out that the proposals offer only a general picture and that variations are possible; for example, although the mechanism involving a naked $SiCl_2$ is reported here for simplicity, this reacting species likely could be stabilized by an amine molecule.[28] Further studies devoted to the determination of the correct reaction mechanism are ongoing in our laboratories.[29]

Scheme 5. Hypothesized Mechanisms Involving $SiCl_3^-$ or $SiCl_2$



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In conclusion, we have reported a new $HSiCl_3$-mediated reduction of both aromatic and aliphatic nitro groups to amines. The methodology has several positive features, as it is of general applicability, chemoselective, tolerant of many functional groups, and respectful of the stereochemical integrity of stereocenters. Moreover, the reduction protocol relies on the use of inexpensive and nonhazardous chemicals, features a simple experimental procedure, and is performed under mild conditions. Since the new method will offer the opportunity to redesign ex novo the synthetic plans of several important molecules or key intermediates, it is expected that the metal-free protocol could possibly find useful applications also in industrially relevant processes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01698.

Experimental procedures for both nitro reduction reactions and mechanistic studies, ^{1}H and ^{29}Si NMR spectra, and theoretical details (PDF)

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Notes

The authors declare no competing financial interest.

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(28) We warmly thank one referee for a real meaningful discussion and valuable suggestions in the mechanism proposal.

(29) Preliminary DFT computational studies did not allow the preferred mechanistic pathway to be firmly established (see the Supporting Information for details on these explorative results). Further experimental and computational works are currently underway and will be reported in due course.

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