Organic LETTERS

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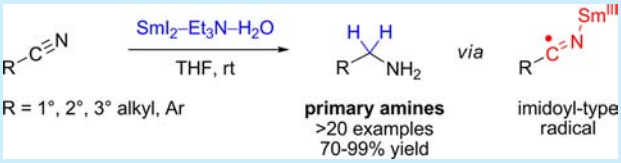
Electron Transfer Reduction of Nitriles Using SmI_2–Et_3N–H_2O: Synthetic Utility and Mechanism

Michal Szostak,* Brice Sautier, Malcolm Spain, and David J. Procter*

School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, U.K.

Supporting Information

ABSTRACT: The first general reduction of nitriles to primary amines under single electron transfer conditions is demonstrated using SmI_2 (Kagan's reagent) activated with Lewis bases. The reaction features excellent functional group tolerance and represents an attractive alternative to the use of pyrophoric alkali metal hydrides. Notably, the electron transfer from Sm(II) to CN functional groups generates imidoyl-type radicals from bench stable nitrile precursors.



Primary aliphatic amines are abundant structural motifs in biologically active molecules and pharmacophores, including life-saving drugs and important neurotransmitters (Figure 1).[1] In this regard, the reduction of nitriles by hydrogenation

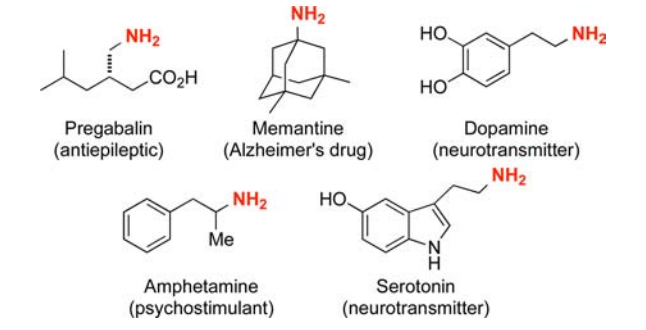


Figure 1. Examples of biologically active primary amines.

and alkali metal hydrides represents one of the most valuable processes for the synthesis of primary amines.[2,3] Although the reduction of nitriles via open-shell reaction pathways would constitute a highly attractive alternative for the direct synthesis of primary amines from readily available precursors, such a process involving mild conditions remains unknown.[4]

Very few examples of the efficient electron transfer reduction of nitriles have been reported.[4] This is primarily due to several challenges, which include (1) high redox potential of nitriles compared to other carboxylic acid derivatives; (2) low C–CN bond dissociation energy, which leads to undesired reductive decyanation side reactions via fragmentation to alkyl radicals and cyanide anions; and (3) instability of imine/iminium intermediates to the reaction conditions, which results in alcoholysis, transimination or reductive polymerization pathways.[5]

Since its introduction to the organic chemistry laboratory by Kagan in 1977, SmI_2 (samarium(II) iodide, Kagan's reagent) has gained status as one of the most chemoselective electron transfer reagents available to synthetic chemists.[6] Of particular note is the ability of SmI_2 to operate via complementary one- and two-electron pathways, which proceed under conditions fully orthogonal to other reagents.[7]

Over the past 35 years, SmI_2 has been successfully utilized to generate ketyl-type radicals from an impressive range of carbonyl precursors; however, efficient and general reduction of nitriles with SmI_2 has not been reported to date due to the prohibitive redox potential of these substrates, which prevents productive electron transfer from Sm(II) (Figure 2).[8−11]

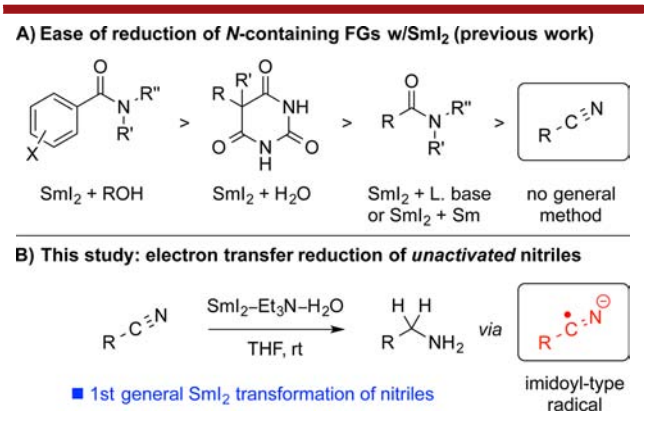


Figure 2. (a) Ease of reduction of functional groups using SmI_2. (b) This work: electron transfer reduction of unactivated nitriles.

The lack of mild, general and reliable methods to reduce nitriles under single electron transfer conditions came to our attention during our recent studies on the effect of protic and Lewis basic additives on the reactivity of lanthanide(II) reagents in transformations proceeding via non-classical open-shell intermediates derived from carboxylic acid derivatives.[12,13]

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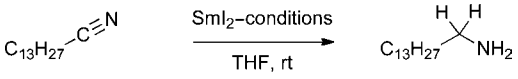
On the basis of these observations, we hypothesized that a suitably activated Sm(II) reagent would be capable of transferring single electrons to unactivated nitriles.[14]

Importantly, we recognized that if successful, this process would have two significant implications: (1) it would provide the first general method for the reduction of nitriles via open-shell pathways for the synthesis of primary amines for the pharmaceutical industry under conditions orthogonal to hydride-based methods;[1−3] (2) it would furnish imidoyl-type radicals from bench stable nitrile feedstock materials for their use in cross-coupling reactions under mild conditions.[15]

We began our study by screening a variety of activating ligands for Sm(II) in the reduction of tetradecanenitrile (Table 1 and Supporting Information). As expected, when standard Sm(II) systems were utilized, including the *separate* use of Lewis basic and protic additives (entries 1−4), the reduction was not observed. These results are consistent with inefficient electron transfer to the CN group from these Sm(II) reductants. We were pleased to discover that a combination of a Lewis basic and protic additive promoted the reduction of tetradecanenitrile in excellent yield (entry 5). Remarkably, reductive fragmentation, hydrolysis and ionic polymerization were not observed, demonstrating the mild reaction conditions enabled by the Sm(II) reagent. The lack of fragmentation of the intermediate imidoyl-type radical is consistent with its rapid reduction to the anion. Subsequent optimization studies revealed that H_2O is the protic additive of choice (entries 5−8). A broad range of amines could be used to trigger the reduction; however, triethylamine was optimal in terms of yield and selectivity (entries 9−14). Stoichiometry studies revealed that increasing the concentration of water diminishes the reaction efficiency (entries 15−17), which is consistent with the lower stability of the iminium intermediate under protic conditions (see Supporting Information). Finally, we demonstrated that the reduction can be efficiently carried out using in situ generated solutions of SmI_2[16] (entry 18), which should greatly facilitate the broad application of the current protocol.

With the optimal conditions identified, the scope of the nitrile reduction was examined (Table 2). A wide range of nitriles can be successfully employed as substrates for the Sm(II)-mediated reduction to furnish the corresponding amines in good to excellent yields, including aliphatic and aromatic primary, secondary, and tertiary nitriles (entries 1−7). Notably, activated benzylic groups bearing electronically diverse substituents were well tolerated (entries 8−14). Aryl ethers and trifluoromethyl groups did not interfere with the reaction conditions (entries 10−11). Importantly, a variety of halogens are compatible with the reaction conditions, providing synthetic

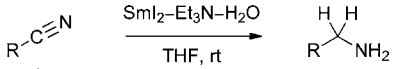
Table 1. Effect of Additives on Reduction of Nitriles with SmI_2[a]

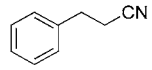
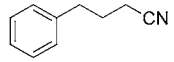
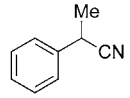
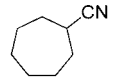
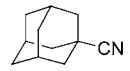
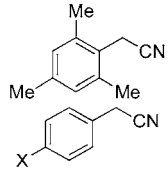
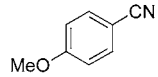
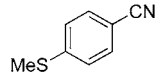
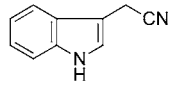
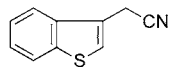


entry	proton source	amine	proton source (equiv)	amine (equiv)	yield[b] (%)
1	–	–	–	–	<2
2	H_2O	–	36	–	<2
3	H_2O	–	800	–	<2
4	–	Et_3N	–	36	<2
5	H_2O	Et_3N	36	36	94
6	MeOH	Et_3N	36	36	<2
7	*t*-BuOH	Et_3N	18	36	<2
8	EG	Et_3N	18	36	36
9	H_2O	pyrrolidine	36	36	71
10	H_2O	*n*-$BuNH_2$	36	36	51
11	H_2O	DIPA	36	36	86
12[c]	H_2O	$EtN(Me)_2$	36	36	89
13[c]	H_2O	$MeNH_2$	36	94	84
14	H_2O	NH_3	36	166	74
15[d]	H_2O	Et_3N	36	36	95
16	H_2O	Et_3N	144	36	84
17	H_2O	Et_3N	800	36	69
18[e]	H_2O	Et_3N	36	36	92

[a]Conditions: SmI_2, THF, 5 min−24 h. See Supporting Information for full details. [b]Determined by ^1H NMR and/or GC. [c]Dodecanenitrile used as a substrate. [d]Reverse addition. [e]SmI_2 prepared in situ.

Table 2. Effect of Structure on Reduction of Unactivated Nitriles with SmI_2−Et_3N−H_2O



entry	1	nitrile	yield (%)
1	**1a**	$C_{11}H_{23}$–CN	93
2	**1b**	$C_{13}H_{27}$–CN	94
3	**1c**		89
4	**1d**		84
5	**1e**		98
6	**1f**		99
7	**1g**		80
8	**1h**		70
9	**1i**	X = H	84
10	**1j**	X = MeO	89
11[a]	**1k**	X = CF_3	74
12[a]	**1l**	X = F	79
13[a]	**1m**	X = Cl	86
14[b]	**1n**	X = Br	83
15	**1o**		92
16	**1p**		81
17	**1q**		74
18	**1r**		90

[a]Dehalogenation not observed. [b]84:16 ratio of **2n** to 2-phenylethanamine formed in the reaction. See Supporting Information for full details.

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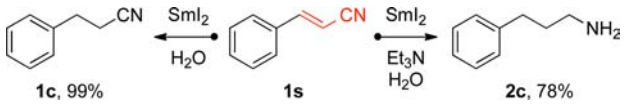
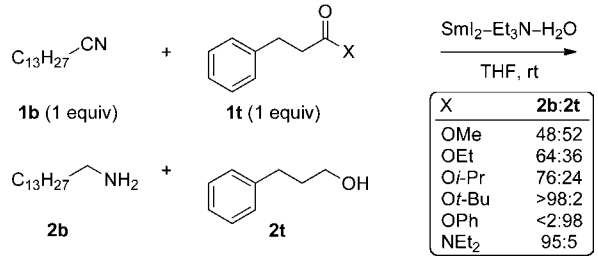
handles for further elaboration (entries 12−14). Moreover, the reaction could be readily extended to aromatic nitriles (entries 15−16) and electron-rich heterocycles such as indoles and benzothiophenes (entries 17−18). In several cases, the obtained products are isosteric with biologically active drugs and neurotransmitters (entry 7, cf. memantine, Figure 1; entry 5, cf. amphetamine; entry 17, cf. serotonin).

One of the attractive features of SmI_2 is the ability to fine-tune the redox properties of the lanthanide(II) by coordinating ligands. For example, the reduction of α,β-unsaturated nitriles with SmI_2−amine−H_2O results in full reduction, while the SmI_2−H_2O system selectively furnishes the saturated nitrile (Scheme 1).[17]

Scheme 1. Divergent Selectivity in the Reduction of α,β-Unsaturated Nitriles Using SmI_2−ROH Complexes



Scheme 2. Competition Experiments between Nitriles and Derivatives of Carboxylic Acids Using SmI_2−Amine−H_2O

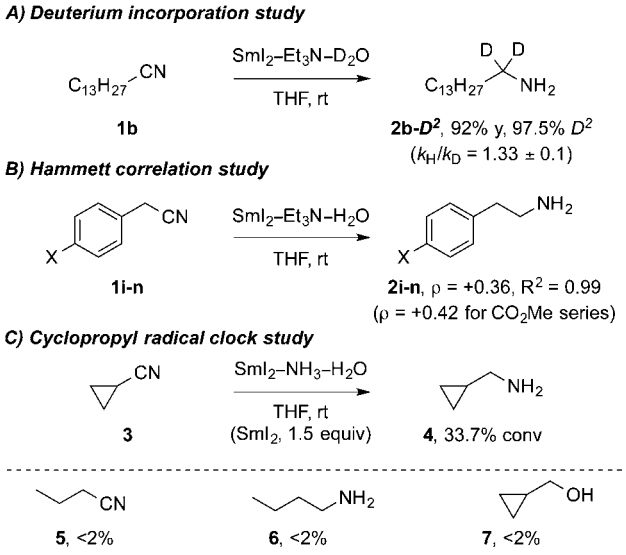


X	2b:2t
OMe	48:52
OEt	64:36
O*i*-Pr	76:24
O*t*-Bu	>98:2
OPh	<2:98
NEt_2	95:5

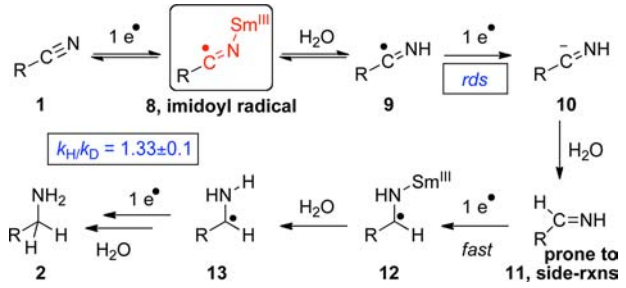
We conducted a number of competition studies between nitriles and carboxylic acid derivatives (Scheme 2 and Supporting Information for additional examples). These studies indicate that the reduction of nitriles proceeds at a similar rate to the reduction of aliphatic esters; however, high levels of selectivity are possible with electronically and sterically activated substrates. The remarkable selectivity obtained with several amide and ester substrates is orthogonal to the reduction of nitriles mediated by hydride reagents.

Several studies were conducted to gain insight into the reaction mechanism (Scheme 3 and Supporting Information). (1) The reduction of tetradecanenitrile with SmI_2/D_2O/amine (97.5% D^2; k_H/k_D = 1.33 ± 0.1) suggests that anions are generated and protonated by H_2O in a series of electron transfer steps and that proton transfer to carbon is not involved in the rate-determining step.[12b] (2) A Hammett study performed using a series of 4-substituted phenylacetonitriles showed a large positive ρ-value of 0.36 (R^2 = 0.99), which can be compared with the ρ-value of 0.42 for the reduction of methyl esters of phenylacetic acid with $SmI_2/Et_3N/H_2O$. (3) The reduction of cyclopropane radical clock **3** (approximated unimolecular rate constant for alkyl radicals, k_{frag} = ca. 10^8 s^{-1} at 25 °C) resulted in rapid reduction to **4**. Opening of the cyclopropyl ring was not detected. (4) Selectivity studies demonstrate the following order of reactivity: aromatic > benzylic > 1° > 2° > 3° nitriles, with a rate difference of more than 2 orders of magnitude. (5) Studies on the stability of the iminium intermediate demonstrate a potential for transimination and/or hydrolysis depending on the steric and electronic

Scheme 3. Studies on the Mechanism



Scheme 4. Proposed Mechanism



properties of the Lewis base. A mechanism consistent with these observations is presented in Scheme 4.

In conclusion, we have demonstrated the first general reduction of nitriles to the corresponding primary amines under single electron transfer conditions using SmI_2. The reactions typically proceed with excellent selectivity, thus offering an attractive alternative to reductions mediated by pyrophoric alkali metal hydrides. Studies on the reductive cyclizations of imidoyl-type radicals and expansion of the scope to diverse nitrogen-containing substrates will be reported shortly.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: michal.szostak@manchester.ac.uk.
*E-mail: david.j.procter@manchester.ac.uk.

Notes

The authors declare no competing financial interest.

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