Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Mechanistic study of the samarium diiodide—*N*,*N*-dimethyl-2-aminoethanol reducing system

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ARTICLE INFO

Article history:
Received 25 November 2014
Revised 16 December 2014
Accepted 17 December 2014
Available online xxxx

This Letter is dedicated to the memory of Professor Harry Wasserman in deep appreciation for his seminal work on the chemistry of reactive intermediates and their use in the development of new synthetic methods

Keywords:
Samarium diiodide
Proton donor
Electron transfer
Reduction
DMAE

ABSTRACT

The impact of *N*,*N*-dimethyl-2-aminoethanol (DMAE) on the reactivity of SmI_2 is presented. The SmI_2–DMAE reagent system is capable of reducing a range of substrates including alkyl halides, ketones, lactones, and arenes. Mechanistic studies on anthracene reduction are consistent with a system that proceeds through a highly ordered, early transition state requiring 2 equiv of DMAE and 1 equiv of anthracene and Sm(II).

Samarium diiodide (SmI_2), first introduced by Kagan and co-workers is a versatile single electron reductant capable of reducing a range of functional groups under mild reaction conditions.[1,2] The majority of SmI_2-based reactions are carried out using SmI_2 in THF since the reagent is stable in this medium and is soluble up to 0.1 M. Initially considered a 'specialized' reagent, a range of studies have shown that SmI_2 is capable of efficiently initiating deoxygenations[3] and the reduction of a range of functional groups including but not limited to sulfoxides and sulfones,[4] organophosphates,[5] nitroalkanes[6] alkyl and aryl halides,[7] α-heterosubstituted ketones,[8] α,β -unsaturated carbonyls,[9] ketones,[10] esters, lactones and carboxylic acid derivatives,[11] nitriles,[12] and aromatics.[13] The rate by which SmI_2 reduces different functional groups varies significantly. As a consequence, SmI_2 can be used to selectively reduce a particular functional group in a multifunctional substrate for follow-up bond-forming reactions. This feature makes SmI_2 an attractive reagent for use in the synthesis of complex molecules.[14]

One of the unique features of SmI_2 is that the addition of additives can be used to alter its reactivity.[15] Significant changes in the rate, chemoselectivity, and stereoselectivity of bond-forming reactions initiated by SmI_2 can be achieved through the use of appropriate additives or cosolvents. In fact, many of the reductions cited above require the use of an additive to drive reductions to completion. Additives commonly employed in SmI_2-initiated reductions can be organized into three classes: (1) Lewis bases (HMPA and other electron donor ligands), (2) proton donors (water, alcohols, and glycols), and (3) inorganic additives (NiI_2, $FeCl_3$, etc.). Among Lewis bases, HMPA is the most widely employed and alters the reactivity by enhancing the reducing power of SmI_2, altering its coordination sphere, activating substrate bonds, and impacting post electron transfer events.[7a,16] Although HMPA is an exceptionally useful additive, its main drawback is its toxicity and suspected human carcinogenicity. In some instances, transition metal salts (Ni^{II}) can be employed as replacements for HMPA (i.e., samarium Barbier reactions), but it has been proposed that SmI_2 reduces Ni(II) and Ni(0) is the likely reactive species in the coupling of alkyl halides with ketones.[17] In addition to Lewis bases and transition metal salts, proton donors have played a prevalent role in the development of Sm(II)-initiated reductions and bond-forming reactions.[18] The most commonly utilized proton donors are alcohols, water, and glycols. Proton

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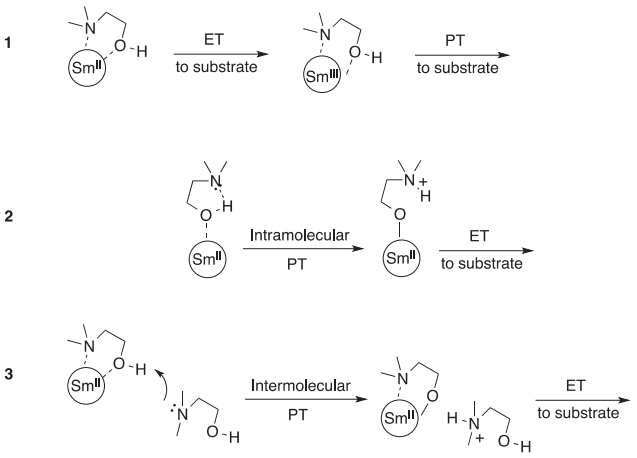
http://dx.doi.org/10.1016/j.tetlet.2014.12.095
0040-4039/

donors may coordinate to Sm(II) as well as donate a proton through heterolytic cleavage of the O–H bond and these processes may be coupled. As a consequence, proton donors are typically placed in two categories, those which form ground state complexes with SmI_2 (water, methanol, glycols) and those which do not (*t*-BuOH, and 2,2,2-trifluoroethanol, etc.).[10e,18]

Lewis bases can also be employed with coordinating proton donors.[11a] Seminal work in this area was carried out by Hilmersson who discovered that the combination of SmI_2 with water and amines produced a powerful reductant capable of reducing a wide range of functional groups.[19] Procter and co-workers have recently expanded on Hilmersson's work employing the reducing system for the reduction of a range of carboxylic acid derivatives.[20] During recent studies of this method, we considered a range of amines and approaches for mimicking the system with a common and inexpensive reagent. We were intrigued by the additive *N*,*N*-dimethyl-2-aminoethanol (DMAE) since it contained a proton donor and amine. In addition, we reasoned that it should have a high affinity as a chelating ligand and as a consequence have the potential for high reactivity at relatively low concentrations. Careful inspection of the literature shows that the additive has been employed in the selective opening of α,β-epoxy esters and 2-acylaziridines, aziridine-2-carboxylates, and aziridine-2-carboxamides to β-hydroxy esters and β-aminocarbonyls, respectively.[21] Interestingly, the additive worked significantly better than traditional proton donors in these reactions and could be used at lower concentrations. Given the unique reactivity displayed by SmI_2–DMAE, could this reagent system be used to reduce a range of substrates? If so, does it function like the SmI_2–water–amine system developed by Hilmersson?

To address these questions, a series of substrates containing representative functional groups were exposed to the SmI_2–DMAE system in THF as shown in Table 1. Interestingly, the reactions proceeded quickly and alkyl halides, a ketone, a model arene (anthracene), and lactone (decanolide) were readily reduced in good to excellent yields. A white precipitate formed in all reactions as they progressed to completion. Characterization of the precipitate revealed that it was the ammonium iodide salt of DMAE (DMAE.HI$^+$). A range of DMAE concentrations were explored, but we found that in the substrates examined, addition of 5–6 equiv of DMAE (relative to [SmI_2]) was best. Lower concentrations of DMAE led to slow or inefficient reductions. Large concentrations of the additive (over 20 equiv) led to oxidation of SmI_2 that likely proceeded through reduction of DMAE providing a poor yield of product.[22] In one case, the addition of more DMAE led to a slight increase in the time required for conversion to product, but impact on yield was modest. In the case of anthracene, doubling the amount of DMAE led to a decrease in the time for conversion although the yield decreased slightly.



Scheme 1.

In considering the possible mechanism of the reduction, there are several possibilities as displayed in Scheme 1: (1) DMAE is acting as a chelating proton donor (i.e., ethylene glycol) and electron transfer (ET) to substrate precedes proton transfer (PT), (2) DMAE coordinates to Sm(II) through oxygen and deprotonation of the O–H occurs through an intramolecular process followed by ET to substrate, or (3) DMAE chelates to Sm(II) and deprotonation occurs by another equivalent of additive followed by ET to substrate.

To obtain more insight into the mechanism of the reduction of substrate by SmI_2–DMAE, the rate of reduction of anthracene and rate orders for the components were determined under pseudo first order conditions by monitoring the decay of SmI_2 in THF at 25 °C. Anthracene was chosen as the substrate to simplify the analysis since it is unlikely to coordinate to Sm(II). The stability of SmI_2–DMAE under experimental conditions used in the rate studies was determined by measuring the decay of the reagent combination in the absence of anthracene. The natural decay was determined to be less than 1% of that obtained in the presence of anthracene (see Supplementary material). A representative decay for the reduction of anthracene by SmI_2–DMAE is shown in Figure 1. The decay of SmI_2 displayed first-order behavior over >4 half lives for all SmI_2–DMAE–anthracene combinations. The rate constant and rate orders for each component are contained in Table 2.

To acquire a more detailed insight into the electron transfer process for the reduction of anthracene by SmI_2–DMAE, rates were measured over a temperature range to obtain activation enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) from the linear form of the Eyring equation. The data obtained from this set of experiments are displayed in Table 3. The data show a small degree of bond reorganization and a high degree of order in the activated complex.

Table 1
Reaction of representative substrates with DMAE in THF at 25 °C

Substrate	Product	equiv DMAE relative to [SmI_2]	Time[c] (min)	Yield (%)
1-Iodododecane[a]	Dodecane	5	15	97 ± 1[d]
1-Bromododecane[a]	Dodecane	5	20	83 ± 1[d]
1-Bromododecane[a]	Dodecane	10	43	88 ± 1[d]
Anthracene[a]	9,10-Dihydroanthracene	5	100	99 ± 1[d]
Anthracene[a]	9,10-Dihydroanthracene	10	23	92 ± 1[d]
2-Heptanone[a]	2-Heptanol	6	30	99 ± 1[d]
5-Decanolide[b]	1,5-Decanediol	6	10	76[e]

[a] Conditions: 1 equiv substrate, 2.5 equiv SmI_2.
[b] Conditions: 1 equiv substrate, 7 equiv SmI_2.
[c] Time until solution decolorizes.
[d] GC yields.
[e] Isolated yield.

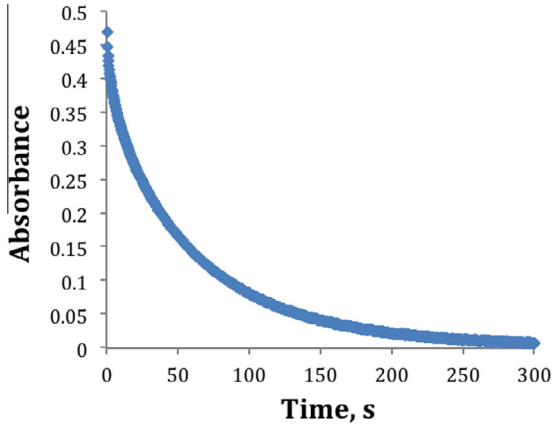


Figure 1. Representative stopped-flow trace showing the decay of 10 mM SmI_2 monitored at 555 nm in the presence of 100 mM DMAE and 120 mM anthracene at 25 °C.

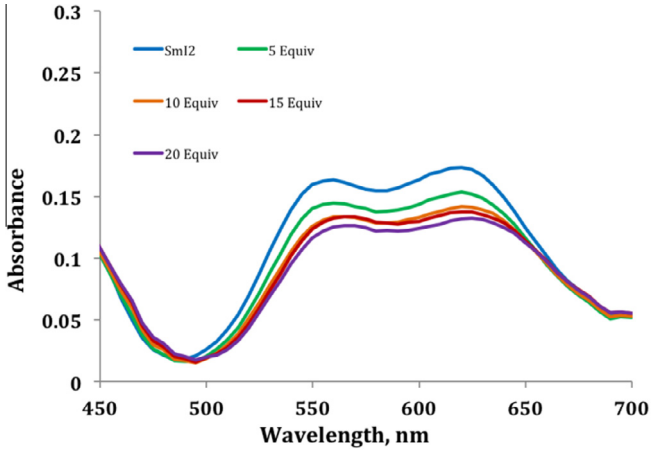


Figure 2. Representative UV–vis spectrum of 2 mM SmI_2 in THF with 5, 10, 15, and 20 equiv DMAE.

Table 2
Rate orders and rate constant for the reduction of anthracene by SmI_2–DMAE[a]

DMAE[b]	Anthracene[c]	SmI_2[d]	Rate constant (M^{-3}, s^{-1})
1.9 ± 0.1	1.0 ± 0.1	1	0.13 ± 0.03

[a] All rate studies were performed at 25 °C.
[b] Conditions: 10 mM SmI_2, 120 mM anthracene, 100–180 mM DMAE.
[c] Conditions: 10 mM SmI_2, 50 mM DMAE, 100–120 mM anthracene.
[d] Determined using fractional times method.

Table 3
Activation parameters for the reduction of anthracene by SmI_2–DMAE in THF[a]

$\Delta H^{\ddagger}$ (kcal/mol)[b]	$\Delta S^{\ddagger}$ (cal/mol, K)[b]	$\Delta G^{\ddagger}$ (kcal/mol)[c]
1.2 ± 0.4	−68 ± 1	21.1 ± 0.1

[a] Activation parameters are the average of three independent experiments and are reported as ±σ. Conditions: 10 mM SmI_2, 50 mM DMAE, 120 mM anthracene in THF monitored at 560 nm.
[b] Obtained from $\ln(k_{obs}h/kT) = -\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R$.
[c] Calculated from $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

Table 4
Observed rate constants for the reduction of anthracene by SmI_2–water–triethylamine and SmI_2–DMAE[a]

k_{obs} (s^{-1}) SmI_2–water–triethylamine[b]	k_{obs} (s^{-1}) SmI_2–DMAE[c]
$3.4 \pm 0.1 \times 10^{-2}$	$1.1 \pm 0.1 \times 10^{-2}$

[a] Rate experiments were performed at 25 °C.
[b] Conditions: 10 mM SmI_2, 120 mM anthracene, 50 mM water, 50 mM triethylamine.
[c] Conditions: 10 mM SmI_2, 120 mM anthracene, 50 mM DMAE.

To determine whether DMAE coordinates to SmI_2, UV–vis experiments were performed. The UV–vis spectrum of SmI_2 displays two distinct bands at 558 and 616 nm that broaden and shift upon complexation of ligands.[23] Figure 2 contains the UV–vis spectrum of SmI_2 with increasing amounts of DMAE. At higher concentrations of DMAE, the bands begin to coalesce and shift, a finding consistent with coordination of DMAE to SmI_2 in the ground state.[10e,22]

One interesting comparison is whether this system behaves like a traditional proton donor or the SmI_2–water–amine system. To examine this, the rate of reduction of anthracene by SmI_2–water–triethylamine was determined for each system under an identical set of conditions to examine the rates of substrate reduction. The data are displayed in Table 4. The observed rate of reduction for the SmI_2–water–triethylamine reagent system is three times faster than the SmI_2–DMAE reduction, but within the same order of magnitude. Water was examined as well since it is recognized to have a high affinity for Sm(II) and reduce substrates through a Sm(II)–water complex.[10e,18d] Addition of 5–10 equiv of water led to very slow reduction anthracene that was two orders of magnitude slower than SmI_2–DMAE or SmI_2–water–amine. Only higher concentrations of water (above 75 equiv) provided similar rates of reduction.

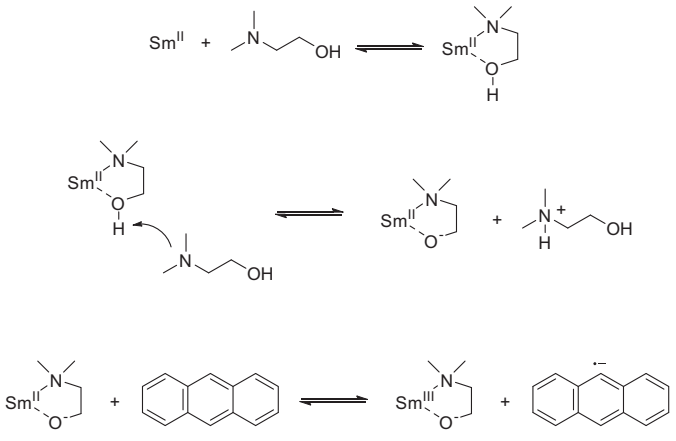
Taken together, the experiments described herein show the following: (1) The addition of DMAE to SmI_2 provides a reagent system capable of reducing a range of functional groups including alkyl halides, a model arene (anthracene), ketones, and a model lactone (decanolide). (2) Substrate reductions do not proceed, or proceed very slowly in the absence of DMAE. (3) The reaction of SmI_2–DMAE with anthracene is first order in substrate and SmI_2 and second order in DMAE. (4) Activation parameters for the reduction of anthracene show that the reaction occurs through a highly ordered activated complex with an early transition state (i.e., little bond-cleavage has occurred at the transition state). (5) SmI_2–DMAE reduces anthracene faster than SmI_2–water and at a rate of the same order of magnitude as the SmI_2–water–triethylamine reagent system.

On the basis of these studies, we propose the mechanism shown below in Scheme 2. In the first step, DMAE coordinates (or chelates) to SmI_2 in a manner similar to glycols.[22c,d] Coordination of the DMAE to the Lewis acidic Sm increases the acidity of the O–H significantly.[24] In the second step, another molecule of DMAE acts as a base to deprotonate the O–H bound to Sm(II). As the deprotonation occurs, the increasing electron density on the coordinated oxygen enhances the reducing power of the Sm(II) by producing a more powerful reductant[16a,b] or through stabilization of Sm(III).[16c,25] In the third step, the activated Sm(II) reduces anthracene. As this process occurs, insoluble DMAE·HI^{+} precipitates from solution leading to an irreversible process as described by Hilmersson for the SmI_2–water–amine system.[19c]

Overall, the process shown above is consistent with the first order in Sm and anthracene and the second order in DMAE as shown in the empirical rate law in Eq. 1:

$$\frac{-d[Sm^{II}]}{dt} = k_{obs}[Sm^{II}][DMAE]^2[anthracene] \quad (1)$$

In conclusion, the results shown herein describe insight into the possible general utility of DMAE as an additive in SmI_2-based reductions. While these studies provide some mechanistic details in the reduction of arenes by SmI_2–DMAE, it is probable that the



Scheme 2.

mechanism may be more complex for substrates capable of coordinating to Sm(II). In addition, it is likely that other amino alcohols may be useful as additives capable of accelerating reductions and reductive coupling reactions of SmI_2. We are currently exploring this supposition, and results from these studies will be reported in due course.

Acknowledgments

R.A.F. is grateful to the National Science Foundation – United States (CHE 1266333) for support of the work. We thank Dr. Lawrence Courtney, Dr. Kimberly Choquette and Ms. Niki Patel for helpful discussions and suggestions.

Supplementary data

Supplementary data (experimental, rate and spectroscopic data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.095.

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