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Tripyrrolidinophosphoric Acid Triamide as an Activator in Samarium Diiodide Reductions

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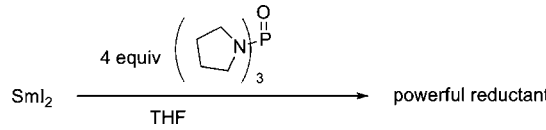
ABSTRACT



The electrochemical and spectrophotometric characterization of the complex formed from samarium diiodide and 4 equiv of tripyrrolidinophosphoric acid triamide (TPPA) is presented. Kinetic studies indicate that the SmI_2/TPPA complex possesses reactivity greater than the complex formed between samarium diiodide and 4 equiv of HMPA. Examples of the use of SmI_2/TPPA in synthesis are presented.

Samarium diiodide is a useful reagent for a broad range of organic reductions.[1] Inanaga reported that the addition of the electron-rich cosolvent HMPA greatly accelerates the reduction of alkyl halides by SmI_2.[2] Addition of HMPA to a deep blue THF solution of SmI_2 results in the formation of a purple soluble complex. X-ray analysis reveals the structure of the complex to possess four HMPA molecules bound to a central Sm^{2+} and two exceptionally long Sm−I bonds.[3] Conductivity measurements suggest that in solution the two iodides are displaced to the outer sphere by solvent, resulting in an ionic complex thought to be $[Sm(HMPA)_4(THF)_2]^{2+}2I^-$.[4,5] Current literature details numerous SmI_2 reductions promoted by HMPA.[6]

Unfortunately, HMPA has deleterious biological effects. It is reported to be both antispermatogenic (oral administration) and mutagenic, with rats developing nasal tumors from HMPA inhalation (50 ppb for one year).[7,8] Various additives have therefore been used in place of HMPA in SmI_2 reactions. *N*,*N*′-Dimethylpropyleneurea (DMPU) is the most commonly used alternative cosolvent for samarium diiodide.[9] Other electron-rich compounds such as 1,1,3,3-tetramethylguanidine (TMG), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[10] and hexamethyldisilazide[11] have been used with some success. We recently reported on the effectiveness of the dehydro dimer of HMPA (diHMPA) as an alternative to HMPA.[12] None of these substitutes appears to lead to

(1) Procter, D. J.; Flowers, R. A., II; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; Royal Society of Chemistry Publishing: UK, 2010.

(2) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485–1486.

(3) Hou, Z.; Wakatsuki, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 149–153.

(4) Enemærke, R.; Hertz, T.; Skrydstrup, T.; Daasbjberg, K. *Chem.—Eur. J.* **2000**, 3747–3754.

(5) For a review of mechanistic work done on various SmI_2 reductions, see: Flowers, R. A., II *Synlett* **2008**, 1427–1439.

(6) For current examples of the use of SmI_2/HMPA in the development of new synthetic methods, see: (a) Schöttner, E.; Wiechoczek, M.; Jones, P.; Lindel, T. *Org. Lett.* **2010**, *12*, 784–787. (b) Beemelmanns, C.; Reissig, H.-U. *Org. Biomol. Chem.* **2009**, *7*, 4475–4480. (c) Lam, K.; Markó, I. *Org. Lett.* **2008**, *10*, 2773–2776.

(7) Jackson, H.; Jones, A.; Cooper, E. *J. Reprod. Fert.* **1969**, *20*, 263–269.

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(9) Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008–5010.

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(11) Prasad, E.; Knettle, B.; Flowers, R. A. II. *J. Am. Chem. Soc.* **2002**, *124*, 14663–14667.

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complexes that can match the reactivity of the SmI_2/HMPA combination.[13,14]

It is interesting to note that the ethyl analogue of HMPA, hexaethylphosphoric acid triamide (HEPA, Figure 1), is not

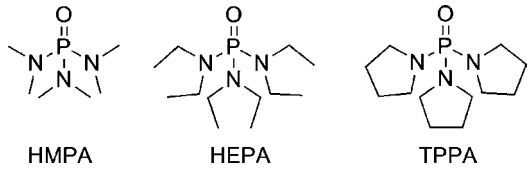

Figure 1. Phosphoramides investigated in SmI_2 reductions.

antispermatogenic.[7] HEPA is 300 times less mutagenic than HMPA in *Drosophila melanogaster*.[15] Although it has not been studied in detail, there is no evidence for toxicity or mutagenicity for the tricyclic analogue of HEPA, tripyrrolidinophosphoric acid triamide (TPPA). We therefore investigated the synthetic utility of complexes formed between SmI_2 and the two phosphoramides HEPA and TPPA.[16,17] TPPA is particularly intriguing as a ligand because it is known to be an excellent Lewis base. This ligand has a substantially higher exothermic heat of reaction with BF_3 than all of the other phosphoramides examined, including HMPA.[18] TPPA also has a higher dipole moment than all of the phosphoramides examined, including HMPA.[19]

Both HEPA and TPPA are readily accessible. The synthesis of TPPA can be accomplished in high yield by treating $POCl_3$ with excess pyrrolidine in ether.[20] HEPA is prepared by the oxidation of tris(diethylamino)phosphine with H_2O_2.[21]

Initial experiments to probe the reactivity of the SmI_2/HEPA and SmI_2/TPPA complexes were executed as follows. Purple soluble complexes were formed from SmI_2 and 4 equiv of each ligand. Ten minutes after the addition of 1-bromodecane and tetradecane (internal standard), an aliquot was removed and quenched with I_2.[22] Gas chromatographic yields of decane for SmI_2/HEPA (41%) and for SmI_2/TPPA (95%) were obtained. At 30 min of reaction time, the same process indicated a chromatographic yield of 98% decane using the HEPA complex. The rapidity and yield of the SmI_2/TPPA reduction is functionally equivalent to the results obtained by Inanaga with SmI_2/HMPA.[2,23]

The reactivities of the SmI_2 complexes with HMPA, HEPA, and TPPA were determined by measuring the rate constant during the reduction of 1-bromodecane. In each case, 1-bromodecane was added to a stirred 0.010 M solution of SmI_2 containing the indicated amounts of each ligand, 1-butanol and tetradecane. Sufficient quantities of SmI_2 and 1-butanol were included to ensure pseudofirst-order conditions. Aliquots were removed and immediately quenched with I_2. Gas chromatographic analyses of the resultant mixtures were performed.[24] Linear plots of reaction time vs ln[1-bromodecane] were obtained in the HMPA and TPPA cases allowing for the calculation of rate constants. The HEPA kinetic analysis revealed no diminution of the 1-bromodecane nor measurable formation of decane, so a rate constant could not be determined (Table 1). The SmI_2/TPPA complex is approximately three times more reactive than the corresponding SmI_2/HMPA complex. This is noteworthy because there is no previously reported evidence of an organic ligand which activates SmI_2 toward the reduction of alkyl halides to a greater extent than HMPA. The low reactivity of the SmI_2/HEPA complex indicates that HEPA does not activate SmI_2 sufficiently to be of synthetic value.

Table 1. Pseuofirst-Order Kinetic Study on the Effect of Ligand on the Reduction of 1-Bromodecane at 21 °C

entry	ligand	k_{obs} $(s^{-1})^a$
1	HMPA	$7.0 \times 10^{-4} \pm 0.3 \times 10^{-4}$
2	TPPA	$2.0 \times 10^{-3} \pm 0.3 \times 10^{-3}$
3	HEPA	–

[a] [1-bromodecane] = 0.0015 M, [SmI_2] = 0.010 M, [ligand] = 0.040 M, [1-butanol] = 0.020 M.

To assist in the characterization of the reactivity of the SmI_2/phosphoramide complexes, cyclic voltammetry was utilized. Previously, addition of up to 3 equiv of HMPA to SmI_2 caused a negative shift in standard potential.[4,25] A much larger decrease was observed for 4 equiv of HMPA (0.72 V), which greatly increases its ability to perform reductions. Because large excesses of HMPA (10 equiv) did not result in further decreases in standard potential, it was concluded that the species present under these conditions, $[Sm(HMPA)_6]^{2+}$,[3,4] exhibits reactivity toward organic functional groups similar to $[Sm(HMPA)_4(THF)_2]^{2+}$.[5] Recently, we observed that 2 equiv of diHMPA produced a decrease in standard potential of 0.68 V.[12]

Table 2 shows the standard potential of a series of SmI_2/HEPA complexes with varying equivalents of cosolvent. As

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(15) Zijlstra, J.; Brussee, J.; van der Gen, A.; Vogel, E. *Mutat. Res.* **1989**, *212*, 193–211.
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(21) Stuebe, C.; Lankelma, H. *J. Am. Chem. Soc.* **1956**, *78*, 976–977.
(22) Dahlén, A.; Hilmersson, G. *Chem.—Eur. J.* **2003**, *9*, 1123–1128.
(23) In the absence of phosphoramide ligands, SmI_2 reduces 1-bromodecane to decane in 4% yield after 10 min.
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(25) Shabangi, M.; Flowers, R. A.II. *Tetrahedron Lett.* **1997**, *38*, 1137–1140.

Table 2. Effect of HEPA on the Standard Potential of SmI_2[a]

entry	[ligand] to [SmI_2] ratio	standard potential (V vs Ag/$AgNO_3$)	ΔE relative to SmI_2 (V)
SmI_2:HEPA	0	-1.329 ± 0.005	0.00
SmI_2:HEPA	1	-1.39 ± 0.02	0.06
SmI_2:HEPA	2	-1.46 ± 0.05	0.13
SmI_2:HEPA	3	-1.68 ± 0.02	0.35
SmI_2:HEPA	4	-1.53 ± 0.04	0.20
SmI_2:HEPA	10	-1.65 ± 0.08	0.32
SmI_2:HMPA	4	-2.07 ± 0.01	0.74

[a] Cyclic voltammograms were recorded at 5 mM SmI_2 with n-Bu_4NPF_6 (0.100 M) and n-Bu_4NI (0.020 M) at 100 mV/s.

was observed with HMPA,[4,25] addition of even small quantities of cosolvent results in a decreased standard potential for the complex. In all voltammograms of SmI_2/HEPA complexes, quasi-reversible electron transfer is observed with $\Delta E_p \geq 1000$ mV. For HEPA, the standard potential decreases until 3 equiv haas been added and then remains constant at approximately -1.6 V vs Ag/Ag^+ or -0.3 V relative to uncomplexed SmI_2, even when 10 equiv of HEPA is utilized. Because the potential does not decrease substantially when more than 3 equiv of HEPA is utilized, it appears that SmI_2 is saturated with only three HEPA molecules. The standard potential of this complex is significantly more positive than that observed for HMPA and indicates that the reducing power of saturated SmI_2/HEPA is much lower than that of $[Sm(HMPA)_4(THF)_2]^{2+}$/$[Sm(HMPA)_6]^{2+}$. This is consistent with the observation that the use of HEPA as a cosolvent did not result in production of decane under the dilute conditions of the kinetic analysis.

TPPA, however, has electrochemical characteristics that are similar to those observed for HMPA. Table 3 contains

Table 3. Effect of TPPA on the Standard Potential of SmI_2[a]

entry	[ligand] to [SmI_2] ratio	standard potential (V vs Ag/$AgNO_3$)	ΔE relative to SmI_2 (V)
SmI_2:TPPA	0	-1.329 ± 0.005	0.00
SmI_2:TPPA	1	-1.40 ± 0.01	0.07
SmI_2:TPPA	2	-1.41 ± 0.02	0.08
SmI_2:TPPA	3	-1.6 ± 0.2	0.27
SmI_2:TPPA	4	-1.94 ± 0.05	0.61
SmI_2:TPPA	10	-2.05 ± 0.09	0.72
SmI_2:HMPA	4	-2.07 ± 0.01	0.74

[a] Cyclic voltammograms were recorded at 5 mM SmI_2 with n-Bu_4NPF_6 (0.100 M) and n-Bu_4NI (0.020 M) at 100 mV/s.

the measured standard potentials when varying equivalents of TPPA were complexed with SmI_2. The standard potential decreased significantly upon addition of 4 equiv of TPPA (-0.61 V) and was similar even when a large excess of TPPA was utilized (-0.72 V). At 4 equiv of TPPA and above, the voltammograms exhibited quasi-reversible electron transfer, while at lesser quantities of TPPA the reverse wave for the reduction of SmI_2^+/TPPA was diminished and the systems displayed characteristics of irreversible electron transfer. Both of these behaviors are similar to those previously observed for SmI_2/HMPA.[4,25,26] This suggests that SmI_2 is saturated with four TPPA molecules.

The SmI_2/TPPA complex was also characterized by visible spectroscopy. A 5 mM solution of SmI_2 in THF with 4 equiv of TPPA affords a peak at 540 nm, which is identical to the λ_{max} that was previously observed for $[Sm(HMPA)_4(THF)_2]^{2+}2I^-$.[4] The spectra are qualitatively similar over the range of the analysis (300 to 800 nm).

Because SmI_2 is also very useful in various reductions of carbonyl compounds, kinetic analyses of SmI_2/HMPA and SmI_2/TPPA reactions with 2-octanone were undertaken (Table 4). These experiments were executed in essentially

Table 4. Pseudofirst-Order Kinetics Study on the Effect of Ligard on the Reduction of 2-Octanone at 21 °C

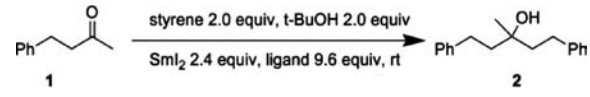
entry	ligand	k_{obs} (s^{-1})[a]
1	HMPA	$3.7 \times 10^{-4} \pm 0.3 \times 10^{-4}$
2	TPPA	$5.4 \times 10^{-3} \pm 0.6 \times 10^{-3}$

[a] [2-octanone] = 0.0015 M, [SmI_2] = 0.010 M, [phosphoramide] = 0.040 M, [1-butanol] = 0.020 M.

the same fashion as the 1-bromodecane kinetic analyses, and linear plots of reaction time vs ln[2-octanone] were obtained in both cases. The SmI_2/TPPA complex is substantially more reactive (by an order of magnitude) than the SmI_2/HMPA complex. There is no previously reported evidence of an organic ligand that activates SmI_2 for carbonyl reduction to a greater extent than HMPA.[27]

Three examples of the synthetic utility of the SmI_2/TPPA complex are shown, with explicit comparisons to both SmI_2/HMPA and SmI_2/DMPU. Samarium diiodide was added to a mixture of ketone **1**, styrene, and *t*-BuOH in the presence of various activating ligands (Table 5).[28] Both HMPA and

Table 5. Effect of Ligand Choice on the SmI_2-Mediated Addition of 4-Phenylbutanone to Styrene



1 **2**

entry	ligand	yield (%)[a]
1	HMPA	97[b]
2	TPPA	89
3	DMPU	52

[a] Isolated yield. [b] Ref 28.

TPPA facilitate the formation of alcohol **2** in an efficient manner. With DMPU a sluggish reaction occurs (as evi-

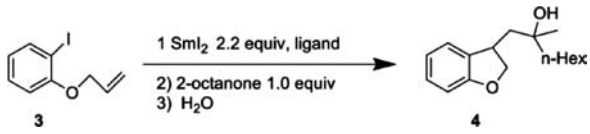
(26) Shabangi, M.; Kuhlman, M. L.; Flowers, R. A., II *Org. Lett.* **1999**, *1*, 2133–2135.

(27) Mixtures of water and various amines have been shown to greatly accelerate SmI_2 reductions of carbonyls; see ref 22.

denced by the slow rate of decolorization) to afford a modest yield of the product.[29]

Organosamarium species derived from radical cyclizations can be trapped with appropriate electrophiles.[30] The SmI_2-mediated cyclization of *O*-allyl-2-iodophenol followed by the addition of 2-octanone and an aqueous quench provides alcohol **4**. This reaction (Table 6) works very well with both

Table 6. Effect of Ligand Choice on the SmI_2-Mediated Cyclization and Trapping of *O*-Allyl-2-iodophenol



3 4

entry	ligand	yield (%)[a]
1	HMPA	80[b]
2	TPPA	76
3	DMPU	30

[a] Isolated yield. [b] Ref 30.

SmI_2/HMPA and SmI_2/TPPA. In contrast, SmI_2/DMPU produced a 30% yield of alcohol **4** with 55% recovered starting material.

Finally, alkyl chlorides are reluctant substrates for SmI_2/HMPA-mediated reductions.[31] The reduction of 1-chlorododecane (2.5 equiv of SmI_2 in THF with 5% HMPA) requires 8 h at 60 °C, whereas the corresponding alkyl bromide is reduced in 5 min at room temperature with the same reagents.[2] It is of interest to determine if the SmI_2/TPPA complex exhibits greater reactivity than SmI_2/HMPA toward a typical alkyl chloride such as 1-chlorodecane. As can be seen in Table 7, The SmI_2/TPPA complex is again significantly more reactive than the SmI_2/HMPA complex. The use of SmI_2/DMPU did not result in detectable formation of decane at the 10 min mark.

In conclusion, tripyrrolidinophosphoric acid triamide is an excellent alternative to HMPA for the activation of

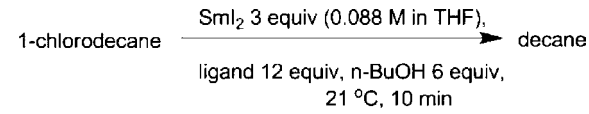
(28) Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2837–2840.

(29) A small percentage of alcohol **2** is formed in a complex mixture when HEPA is used as the ligand.

(30) Curran, D.; Totleben, M. *J. Am. Chem. Soc.* **1992**, *114*, 6050–6058.

(31) Girard, P.; Namy, J.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.

Table 7. Effect of Ligand Choice on the Reduction of 1-Chlorodecane



entry	ligand	yield (%)[a]
1	HMPA	4
2	TPPA	16
3	DMPU	0

[a] GC yield.

SmI_2. In contrast to HMPA, there is no evidence of untoward biological effects with TPPA. Spectral and electrochemical evidence suggests the complex formed between SmI_2 and 4 equiv of TPPA is structurally similar to $[Sm(HMPA)_4(THF)_2]^{2+}2I^-$. The SmI_2/TPPA complex has been shown to react more rapidly than the SmI_2/HMPA complex with an alkyl bromide, an alkyl chloride, and a ketone. Synthetically, the SmI_2/TPPA complex appears to be equivalent to $[Sm(HMPA)_4(THF)_2]^{2+}2I^-$ and clearly superior to the most common HMPA surrogate, DMPU. Hexaethylphosphoric acid triamide, however, is not a suitable replacement for HMPA. The electrochemical evidence presented here suggests that only three HEPA ligands coordinate to the SmI_2. We believe that three HEPA ligands do not provide sufficient electron density at the samarium center to lower the standard potential to the level observed for HMPA and TPPA.

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Supporting Information Available: Contains experimental procedures and NMR spectra for all compounds, all cyclic voltammograms, and the UV/Visible spectrum. This material is available free of charge via the Internet at http://pubs.acs.org.

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