Video Article

Preparation and Use of Samarium Diiodide (SmI_2) in Organic Synthesis: The Mechanistic Role of HMPA and Ni(II) Salts in the Samarium Barbier Reaction

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Abstract

Although initially considered an esoteric reagent, SmI_2 has become a common tool for synthetic organic chemists. SmI_2 is generated through the addition of molecular iodine to samarium metal in THF.[1,2-3] It is a mild and selective single electron reductant and its versatility is a result of its ability to initiate a wide range of reductions including C-C bond-forming and cascade or sequential reactions. SmI_2 can reduce a variety of functional groups including sulfoxides and sulfones, phosphine oxides, epoxides, alkyl and aryl halides, carbonyls, and conjugated double bonds.[2-12] One of the fascinating features of SmI_{-2}-mediated reactions is the ability to manipulate the outcome of reactions through the selective use of cosolvents or additives. In most instances, additives are essential in controlling the rate of reduction and the chemo- or stereoselectivity of reactions.[13-14] Additives commonly utilized to fine tune the reactivity of SmI_2 can be classified into three major groups: (1) Lewis bases (HMPA, other electron-donor ligands, chelating ethers, etc.), (2) proton sources (alcohols, water etc.), and (3) inorganic additives ($Ni(acac)_2$, $FeCl_3$, etc).[3]

Understanding the mechanism of SmI_2 reactions and the role of the additives enables utilization of the full potential of the reagent in organic synthesis. The Sm-Barbier reaction is chosen to illustrate the synthetic importance and mechanistic role of two common additives: HMPA and Ni(II) in this reaction. The Sm-Barbier reaction is similar to the traditional Grignard reaction with the only difference being that the alkyl halide, carbonyl, and Sm reductant are mixed simultaneously in one pot.[1,15] Examples of Sm-mediated Barbier reactions with a range of coupling partners have been reported,[1,3,7,10,12] and have been utilized in key steps of the synthesis of large natural products.[16,17] Previous studies on the effect of additives on SmI_2 reactions have shown that HMPA enhances the reduction potential of SmI_2 by coordinating to the samarium metal center, producing a more powerful,[13-14,18] sterically encumbered reductant[19-21] and in some cases playing an integral role in post electron-transfer steps facilitating subsequent bond-forming events.[22] In the Sm-Barbier reaction, HMPA has been shown to additionally activate the alkyl halide by forming a complex in a pre-equilibrium step.[23]

Ni(II) salts are a catalytic additive used frequently in Sm-mediated transformations.[24-27] Though critical for success, the mechanistic role of Ni(II) was not known in these reactions. Recently it has been shown that SmI_2 reduces Ni(II) to Ni(0), and the reaction is then carried out through organometallic Ni(0) chemistry.[28]

These mechanistic studies highlight that although the same Barbier product is obtained, the use of different additives in the SmI_2 reaction drastically alters the mechanistic pathway of the reaction. The protocol for running these SmI_2-initiated reactions is described.

Video Link

The video component of this article can be found at https://www.jove.com/video/4323/

Protocol

1. Synthesis of SmI_2 (0.1 M)

1. Flame dry a 50 ml round bottomed flask and flush it with argon. Add a stir bar and cover the flask with septa. Weigh out samarium metal (0.2 g, 1.3 mmol) and add to flask, again flushing the flask with argon.
2. Add 10 ml dry, thoroughly degassed tetrahydrofuran (THF) followed by iodine crystals (0.254 g, 2.0 mmol). Add an argon balloon through the septum; this keeps a positive pressure of Ar atmosphere on the reaction.
3. Stir the solution vigorously at room temperature for over 3 hr. As SmI_2 is generated the solution passes through a variety of color changes; orange followed by yellow (45 min), and green (1 hr) which eventually turns into blue.
4. The final navy blue color is indication that singly ionized samarium has formed. In order to ensure full conversion, stir the solution for at least 3 hr before using SmI_2 in synthesis.

2. Samarium Barbier Reaction-hexamethylphosphoramide (HMPA) Addition

1. To make the SmI_2-HMPA complex, take the freshly prepared SmI_2 under argon (10 ml, 0.1 M, 1.0 mmol) and add 1.75 ml of HMPA (10 equiv., 10 mmol) through a syringe, dropwise, under argon. A deep purple color forms.
2. Separately in a clean, dry vial under argon, add iodododecane (0.45 mmol, 110 µl), 3-pentanone (0.45 mmol, 48 µl) and 2 ml of dried THF.
3. Add the substrate solution mixture dropwise to the SmI_2/HMPA complex.
4. Within 5 min of stirring, the purple color will start to look cloudy, indicating the end of the reaction.
5. After the reaction is complete, expose the solution to air to quench it; upon stirring the color further changes to yellow.
6. The reaction is then worked up by washing with saturated aqueous ammonium chloride. Add the solution to a separatory funnel and add diethylether (5 ml). After vigorous shaking remove the top organic layer, add more diethyl ether. Extract from the aqueous layer two more times and then combine all of the organic layers.
7. Wash the organic layer with a saturated solution of aqueous sodium thiosulfate. Remove the bottom aqueous layer, followed by wash with water and then final wash with brine. Obtain the top organic layer and add magnesium sulfate to soak up any last amount of water present in the solution.
8. Pass the solution through a plug of Florisil in order to remove excess HMPA.
9. Concentrate the solution on a rotary evaporator to obtain Barbier product. The product was identified by GCMS and ^{1}H NMR.[23]

3. Samarium Barbier Reaction-Ni(acac)$_2$ Catalyst

1. Weigh out $Ni(acac)_2$ (1 mol%, 0.01 mmol, 0.0026 g) and add to a clean, dry vial containing 3 ml of degassed THF, under argon. Add the $Ni(acac)_2$ solution through a syringe to a freshly prepared solution of 0.1 M SmI_2 (1.0 mmol, 10 ml).
2. Separately in a clean, dry vial under argon, add iodododecane (0.45 mmol, 110 µl), 3-pentanone (0.45 mmol, 48 µl) and 2 ml of dried THF.
3. Add the substrate solution dropwise to the SmI_2/Ni mixture.
4. Within fifteen minutes of stirring, the blue color will dissipate to form a yellow-green color indicating the end of the reaction.
5. After the reaction is complete, expose the solution to air to quench it; upon stirring the color further changes to yellow. Work up the reaction by washing with 0.1 M aq. Hydrochloric acid (3 ml). Add the solution to a separatory funnel and add diethylether (5 ml).
6. Wash the organic layer using the protocol described previously with an aqueous solution of sodium thiosulfate, water and brine, and then dry over magnesium sulfate. Concentrate the solution to obtain Barbier product. The product can be identified by GCMS and ^{1}H NMR.[28]

Representative Results

Figure 1 illustrates the samarium Barbier reaction. With no additives the Sm-mediated reaction takes 72 hr; yielding 69% of the desired product with the remaining being starting materials. With the addition of 10 or more equiv. of HMPA the reaction is nearly quantitative and complete within a few minutes.[15,23] With the addition of 1 mol% $Ni(acac)_2$, the reaction is complete within 15 min, with a 97% yield.[28]

When HMPA is added to SmI_2, the cosolvent displaces the coordinated THF to form SmI_2-$(HMPA)_4$. With the addition of even more HMPA (6-10 equiv.), the iodide ions are displaced to the outer sphere (**Figure 2**).[19-21] Mechanistic studies indicate that when HMPA is used in the Sm-Barbier reaction the cosolvent also interacts with the alkyl halide substrate forming a complex which elongates the carbon-halide bond, activating the species making it more susceptible to reduction by Sm (**Figure 3**). Through this detailed understanding of the roles of HMPA, a mechanism for the Sm-Barbier reaction with HMPA was proposed (**Figure 4**).[23] The alkyl halide-HMPA complex formed in a pre-equilibrium step is reduced by Sm/HMPA to form the radical in the rate determining step. The radical undergoes further reduction to form an organosamarium species which couples with the carbonyl and upon protonation yields the final product.

In the case of Ni(II) additive, SmI_2 initially reduces Ni(II) to Ni(0) preferentially over reduction of either of the substrates. Based on kinetic and mechanistic studies the following mechanism was proposed (**Figure 5**).[28] After reduction by SmI_2, the soluble Ni(0) species inserts into the alkyl halide bond forming an organonickel species. Driven by the highly oxophilic nature of Sm(III), transmetallation to form an organosamarium intermediate releases Ni(II) back into the catalytic cycle. The organosamarium then couples with the carbonyl, and upon protonation forms the desired tertiary alcohol. It was also observed that Ni(0) nanoparticles are formed through Sm-mediated reduction of Ni(II), however these particles were found to be inactive and the source of deactivation of the catalyst.

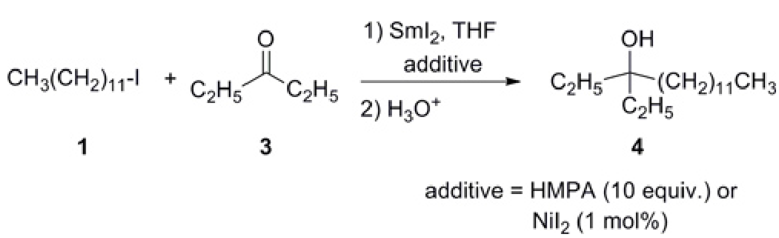

Figure 1. Samarium Barbier reaction with iodododecane and 3-pentanone.

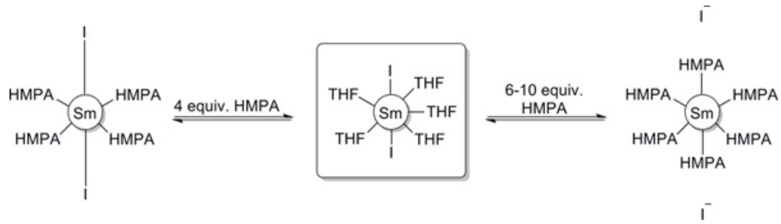

Figure 2. SmI_2-HMPA complex.

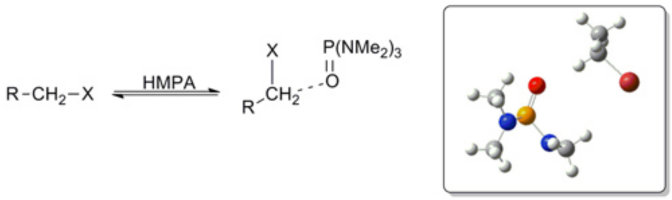

Figure 3. HMPA and alkyl iodide complex.

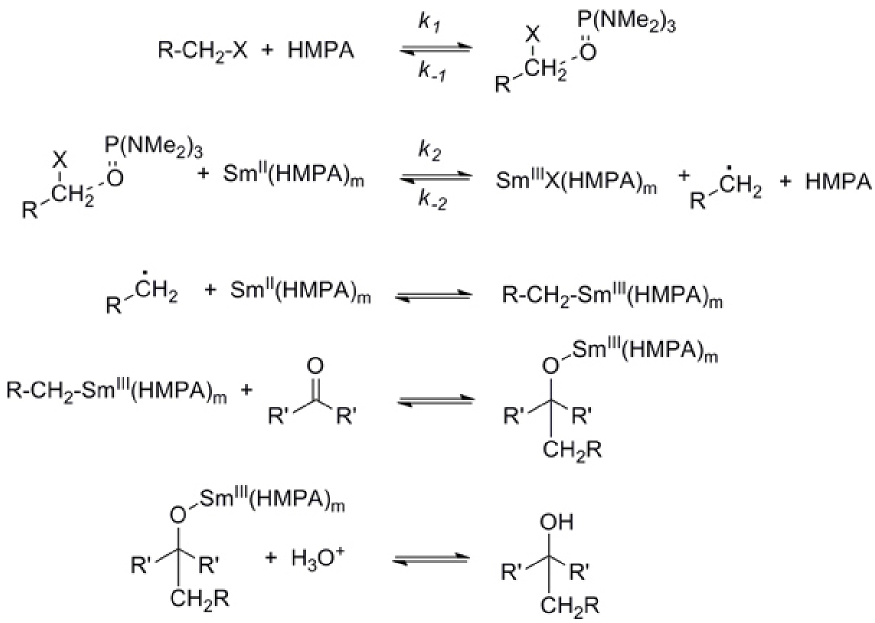

Figure 4. Proposed mechanism for the samarium Barbier reaction with excess HMPA.

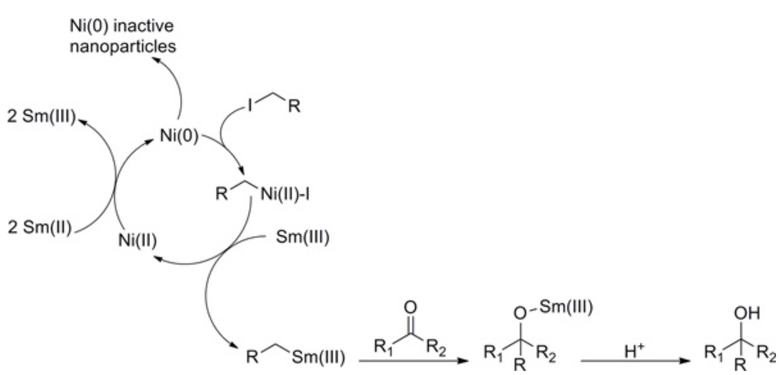

Figure 5. Proposed mechanism for the samarium Barbier reaction containing catalytic Ni(II).

Discussion

A straightforward procedure for generating SmI_2 solution and its application in organic synthesis using two of the most common additives is presented here. The two examples described portray the importance of mechanistic understanding of the reaction to fine tune the reactivity of SmI_2. Knowledge of the underpinning of the reaction mechanism allows the use of this reagent to be adapted by synthetic chemists as per the requirements of their reaction.

This single electron homogeneous reductant is easy to handle and can be purchased from commercial sources. While the above protocol is straight forward when done under inert conditions, some of the common troubleshooting procedures are: (a) make sure the THF is properly degassed and dry, (b) if Sm metal has had prolonged exposure to air it could have an oxidized outside layer, grind the metal with a mortar and pestal to expose the clean metal surface, (c) flame-dry all glassware and cool under argon, (d) argon is preferred inert atmosphere over Nitrogen, as the later has been shown to interact with the metal, (e) The presence of excess Sm-metal helps to maintain the concentration of SmI_2, (f) resublime the iodine crystals.

Disclosures

No conflicts of interest declared.

Acknowledgements

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