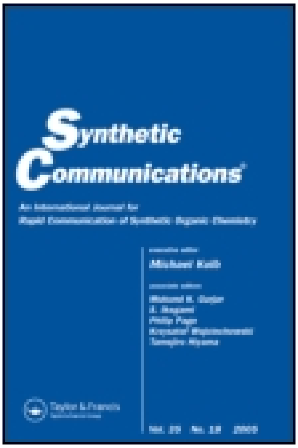

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Water Effects on SmI_2 Reductions: A Novel Method for the Synthesis of Alkyl Thiols by SmI_2-Promoted Reductions of Sodium Alkyl Thiosulfates and Alkyl Thiocyanates

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ABSTRACT

Water as a cosolvent has significant improving effect on the reductivity of SmI_2 in the reduction of sodium alkyl thiosulfates and alkyl thiocyanates. A new method for synthesis of alkyl thiols by SmI_2/THF/H_2O system has been developed.

Key Words: Alky thiol; Cosolvent; Water; Reduction; Samarium diiodide.

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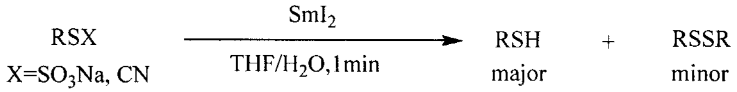
Samarium diiodide as a single-electron transfer reagent has become one of the most popular reducing agents in organic synthesis, because it is easy to prepare and reasonably soluble in many organic solvents and it cleanly reduces a wide range of functional groups.[1] An important aspect concerning the reactivity of SmI_2 is that the addition of cosolvents increases the reducing power of SmI_2. Reactions utilizing SmI_2-cosolvent mixtures generally proceed at accelerated rates compared to reductions without cosolvents.[2] The cosolvent HMPA is the most widely utilized; DMPU and 1,1,3,3-tetramethyl urea have also been employed in reactions of SmI_2.[3]

Recently, Hilmersson examined water/amine as cosolvents and found that they accelerate the reduction of ketones, imines, and α, β-unsaturated esters mediated by SmI_2.[4] Water/DBU and water/1,1-3,3-tetramethylguanidine have been utilized in concert with SmI_2 to accelerate the cyclization of aryl radicals,[5] but little work has been carried out on water alone as a cosolvent. Water has been thought to be served only to protonate basic organometallic intermediates.[6] Although addition of water to the SmI_2/THF system is reported to enhance the reductive potential,[3a] that is not supported by a recent report.[7] To pursue the further proof that water improves the reacting ability of SmI_2, we investigated the reduction of alkyl thiocyanates and sodium alkyl thiosulfates by SmI_2 in aqueous and anhydrous media. The experiments show that water has significant improving effect on the reactivity of SmI_2 and that as a cosolvent, water promoted the conversion from sodium alkyl thiosulfates and alkyl thiocyanates not to the reductive intermediate product alkyl disulfides but all the way to the final reductive product alkyl thiols. Table 1 summarizes the results of all the experiments that we conducted.



$$\underset{X=SO_3Na,\ CN}{RSX} \xrightarrow[THF/H_2O,1\,min]{SmI_2} \underset{major}{RSH} + \underset{minor}{RSSR}$$

In general, to the substrates with and without water, HMPA or absolute methanol was added 0.1 *M* SmI_2 in THF (2.2 equiv.), the reaction was quenched after 1 min.[a] The reactions were very clean and the product mixtures

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[a] General procedure: To the N_2-prepurged substrate (0.5 mmol) was added water (0.3 mL, 16.5 mmol) or HMPA (2.87 mL, 16.5 mmol) or absolute methanol (0.67 mL, 16.5 mmol) or no additive, and then 0.1 *M* SmI_2 in THF (11 mL, 1.1 mmol). The mixture was stirred for 1 min followed by bubbling of air and the subsequent addition of saturated NH_4Cl. The mixture was extracted with ether and the extract was washed with saturated brine and dried with Na_2SO_4. The ^1H NMR analysis of the crude products was performed. The crude product was purified by column chromatography over silica gel (petroleum ether as eluent).

Table 1. Reduction of $RSSO_3Na$ and RSCN by SmI_2 with and without water, HMPA, or MeOH.[a]

Entry	Substrate	Reaction medium	Ratio of RSH : RSSR[b]	Yield of RSH[f]
1	n-$C_8H_{17}SSO_3Na$	THF[d]	<1 : >99	—
2	n-$C_{10}H_{21}SSO_3Na$	THF[d]	<1 : >99	—
3	n-$C_{12}H_{25}SSO_3Na$	THF[d]	<1 : >99	—
4	n-$C_{16}H_{33}SSO_3Na$	THF[d]	<1 : >99	—
5	n-$C_8H_{17}SSO_3Na$	THF/H_2O[e]	92 : 8	78%
6	n-$C_{10}H_{21}SSO_3Na$	THF/H_2O[e]	96 : 4	82%
7	n-$C_{12}H_{25}SSO_3Na$	THF/H_2O[e]	96 : 4	86%
8	n-$C_{16}H_{33}SSO_3Na$	THF/H_2O[e]	95 : 5	86%
9	n-$C_{12}H_{25}SSO_3Na$	THF/MeOH[d]	<1 : >99	—
10	n-$C_{16}H_{33}SSO_3Na$	THF/MeOH[d]	<1 : >99	—
11	n-$C_{12}H_{25}SSO_3Na$	THF/HMPA[e]	98 : 2	89%
12	n-$C_{16}H_{33}SSO_3Na$	THF/HMPA[e]	99 : 1	92%
13	n-$C_8H_{17}SCN$	THF[c,d]	81 : 19	55%
14	n-$C_{10}H_{21}SCN$	THF[c,d]	86 : 14	53%
15	n-$C_{12}H_{25}SCN$	THF[c,d]	84 : 16	63%
16	n-$C_{16}H_{33}SCN$	THF[c,d]	87 : 13	60%
17	n-$C_8H_{17}SCN$	THF/H_2O[e]	>99 : <1	81%
18	n-$C_{10}H_{21}SCN$	THF/H_2O[e]	>99 : <1	84%
19	n-$C_{12}H_{25}SCN$	THF/H_2O[e]	>99 : <1	92%
20	n-$C_{16}H_{33}SCN$	THF/H_2O[e]	>99 : <1	90%
21	n-$C_{12}H_{25}SCN$	THF/HMPA[e]	92 : 8	81%
22	n-$C_{16}H_{33}SCN$	THF/HMPA[e]	94 : 6	85%

[a] Substrates/SmI_2/additive = 1 : 2.2 : 33.

[b] Determined by ^1H NMR.

[c] About 20%–30% unreacted substrates recovered.

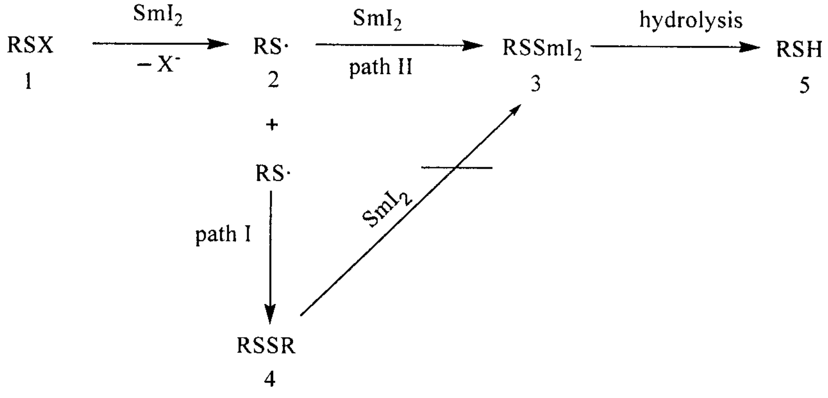
[d] The dark blue in the system still persisted after 1 min.

[e] The color of blue faded after 1 min.

[f] Isolated yield.

only consisted of alkyl disulfides and alkyl thiols. From Table 1, it can be seen that reduction of sodium alkyl thiosulfates mediated by SmI_2/THF/H_2O led predominantly to alkyl thiols (entries 5–8) compared to the complete conversion to the coupling products alkyl disulfides in the absence of water (entries 1–4). Methanol as a cosolvent proved ineffective in promoting the formation of alkyl thiols from the reduction of sodium alkyl thiosulfates and only alkyl disulfides were obtained (entries 9–10). Meanwhile, the addition of HMPA as a cosolvent favored the formation of alkyl thiols (entries 11–12). Similar results were obtained in the reduction of alkyl thiocyanates in aqueous media (entries 17–20). However, although alkyl thiocyanate reductions mediated by SmI_2 in anhydrous conditions predominantly provided alkyl thiols, 20%–30% of starting materials were recovered (entries 13–16). Also, HMPA can promote the formation of alkyl thiols but it has a little less promoting effect than water in the reduction of alkyl thiocyantates (entries 21–22).

Based on the nature of SmI_2 as a single-electron transfer reagent and the results in our experiment, Sch. 1 illustrates the proposed mechanism for the reduction of substrates. Note that **1** reacts with SmI_2 in a single-electron transfer producing radical species **2**. Subsequently, there are two possible scenarios: In path I, the formation of disulfides **4** by the coupling of radical **2**, by path II, the reduction of the radical **2** to samarium alkyl thiolate **3**. Path I is competitive with path II. Although **3** can be hydrolyzed into alkyl thiols **5**, this protonation cannot influence the overall rate of path II. Furthermore, alkyl disulfide **4** cannot be reduced to **3**, which is proved in our experiments. For sodium alkyl thiosulfates, we speculate that path I should be almost exclusive in dry conditions so almost only **4** was found and the amount of alkyl thiols **5** is trace, and in the presence of water, path II predominates and provides a majority of **5** and very little of **4**. Hence, we believe that water increases the reducing power of SmI_2 and strongly pushes the process of path II. HMPA plays a role similar to that of water in the reduction of sodium alkyl thiosulfates. Methanol, however, has no such promoting effect on the reduction of sodium alkyl thiosulfates and only provided alkyl disulfides similar to the results observed in none-additive condition. Based on the fact that water and HMPA promoted the reduction to final reductive product alkyl thiols, but methanol didn't, we proposed that just like HMPA,



Scheme 1.

it is as an additive, which provides prominent enhancement of reactivity of SmI_2, rather than as a proton source that water drives the reduction forward to alkyl thiols.

As for alkyl thiocyanates, when the reactions were quenched within 1 min, 20%–30% of starting materials were recovered from the reduction without any additives compared to the complete consumption of starting materials with water or HMPA as additives. The results show that water and HMPA accelerate these reductions and drive the reactions to completion instantly. As cosolvents, water and HMPA helped to increase the proportion of alkyl thiol (entries 17–22). This also indicates that these additives push the rate of path II.

Our experiments indicated that alkyl disulfides cannot be reduced to $RSSmI_2$ by SmI_2. Deep blue color of the reaction systems in entries 1–4, 9–10, and 13–16 still persisted after 1 min, which shows that there are plenty of Sm^{2+} cations. However, alkyl disulfide could not be converted to $RSSmI_2$, even if reaction time was prolonged. Hence, water and HMPA are essential to the preparation of alkyl thiols using sodium alkyl thiosulfates and alkyl thiocyanates as starting materials and SmI_2 as reductive reagent. Although HMPA can effectively promote the reactivity of SmI_2, it's carcinogenic. Hence, water is more advantageous with regard to environmental concerns.

The experiments described in this paper show that water can promote certain classes of SmI_2 reductions and has underrecognized potential as a free and healthy additive for improving SmI_2 reductions. The reduction of sodium alkyl thiosulfates and alkyl thiocyanates mediated by SmI_2 using water as a cosolvent provides a novel method for synthesis of alkyl thiols.

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