Instantaneous SmI$_2$–H$_2$O-mediated reduction of dialkyl ketones induced by amines in THF

Anders Dahlén and Göran Hilmersson*

Organic Chemistry, Department of Chemistry, Göteborg University, SE-412 96 Göteborg, Sweden

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Abstract—Reduction of various ketones to their corresponding alcohols is shown to be instantaneous, i.e. completed in less than 10 s, by samarium diiodide (2.5 equiv.) in the presence of water (6.25 equiv.) and an amine (5 equiv.) in THF. The rates of reduction of ketones in this mixture exceed by far the rates determined by an amine or water alone. Rate enhancement is at least 100 000 compared to the reduction without a proton source, or at least 100 times faster than the rate of the widely used HMPA/alcohol accelerated reductions. This new method is therefore suggested to be an excellent replacement of the toxic HMPA/alcohol method. © 2002 Elsevier Science Ltd. All rights reserved.

The chemistry of samarium diiodide (SmI$_2$) in THF has developed rapidly during recent years to become a reagent of particular importance as a mild reducing reagent.[1] The popularity of SmI$_2$ as a selective reducing reagent has been largely dependent on the increased reactivity found upon addition of HMPA.[2] It has been shown that HMPA increases the oxidation potential of SmI$_2$ from −1.33 to −2.05 V.[3] The accelerations of ketone reductions are reported to result in reaction times of about 10–30 min instead of days.[1a] However, it would be desirable to avoid the use of the carcinogenic compound HMPA.

Earlier studies of SmI$_2$-mediated reductions have shown that an amine[3] or water[4] alone can be used to enhance the rates. However, there are no reports on the combination of these two additives, which bring about a remarkable increase in rate. The rate is far beyond the expected, i.e. the sum of the rates of water and amine, respectively.

Proton sources such as methanol or *t*-butanol are known to facilitate SmI$_2$-mediated reductions.[5] Recently we reported on the SmI$_2$-mediated reduction of 3-heptanone accelerated by diols with coordinating ethereal groups.[6] We showed that the rate of reduction of the ketone was accelerated some 255 times upon the addition of diglycol, a diol with three oxygens, capable of coordinating to samarium. The proton transfer was found to be rate determining with a primary kinetic isotope effect (k^H/k^D) of 2.

* Corresponding author. Tel.: 46 31 772 2904; fax: 46 31 772 3840; e-mail: hilmers@organic.gu.se

The initial step in SmI$_2$-mediated reductions of ketones is believed to be the transfer of one electron yielding a ketyl radical. The fast equilibrium between ketone and ketyl radical is believed to be lying on the left side, based on reported mechanistic evidence (Fig. 1).[7,8] Our idea is to drive the equilibrium forward by means of precipitation of by-products, e.g. the ions Sm^{3+} and I$^-$. Herein we wish to report the use of amine/water mixtures in the SmI$_2$-mediated reduction of ketones into alcohols.
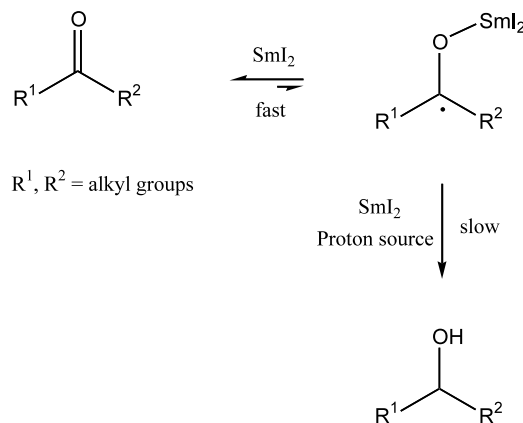

Figure 1. General mechanism for conversion of a ketone into an alcohol in SmI$_2$-mediated reductions.[7,8]

During our kinetic studies using various proton donors we were concerned with the difficulty of completely removing all traces of water from the additives, there-

fore several experiments with deliberate addition of water were performed. Water alone gave only a small rate enhancement (less than a factor of 10) compared to the SmI_2-mediated reduction in THF without any proton source. Tertiary amines appear to retard the reduction. To our surprise we observed rate enhancements considerably larger for a triethylamine/H_2O mixture than expected, i.e. the sum of the water and the amine accelerated SmI_2-mediated reductions, respectively. The reduction of 3-heptanone was complete in just a few seconds.[†] To investigate further this interesting discovery various amines were used as additives together with water. In organoalkali chemistry the diamine N,N,N',N'-tetramethylethylenediamine (TMEDA) is often used to enhance the rate of metallation reactions.[9] Since samarium(II) is regarded as a rather hard Lewis acid it was a natural choice to investigate the effect of TMEDA on the SmI_2–H_2O-mediated reduction of 3-heptanone. We observed that TMEDA/H_2O mixtures also gave a very large rate enhancement. In our previous report on diol accelerated reduction of 3-heptanone we could evaluate the different alcohols by comparing the initial rates of reduction.[6] However, with the amine/water mixtures we observed that the reductions were instantaneous and the initial rates could not be determined. Instead a qualitative measurement of the reaction rate was obtained from the analysis of the reaction mixture after 1 min. By analogy with our earlier results of the alcohols and diols we also investigated the triamine, N,N,N',N'',N''-pentamethyldiethylenetriamine (PMDTA) in the SmI_2–H_2O-mediated reduction. Again 100% of the alcohol was obtained after less than 1 min of reaction time (Table 1). To ensure complete reduction excess water (14 equiv.) was used in combination with the amine.

The effect of alcohol addition in place of water in combination with the amine did not give these extraordinary rate enhancements (entry 4). We therefore conclude that the rate enhancement for the SmI_2-mediated reduction must be a cooperativity effect of both amine and water (Scheme 1).
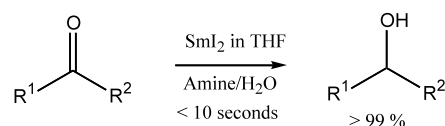
Scheme 1.

The extremely fast reactions (entries 6, 8 and 9 in Table 1) were also investigated after 10 s, which is the shortest time to allow mixing of the reagents in the Schlenk tube. Only the alcohol was detected even after this short reaction time for entries 8 and 9 indicating that the mixing of H_2O, amine, SmI_2 and ketone is rate limiting. A rough estimate of the rate based on this indicates at least 10% yield in less than 1 s, provided a linear dependence of yield versus time over the whole range from 0 to 100%. The initial rate is larger as the rate must fall off towards completion. However, this estimation corresponds to a rate enhancement of more than 100 000 in comparison with the SmI_2-mediated reaction in the absence of a proton donor. SmI_2-mediated reduction of ketones induced by HMPA/alcohol is reported to give 95% yield in 10–30 min in comparison, i.e. at least 700–1000 times faster than that without additives.[1,2] This means that our amine/H_2O method is more than 100 times faster than the HMPA/alcohol method.

We observed that a minimum of 2.5 equiv. of commercial purchased 0.1 M SmI_2 in THF was needed in order

Table 1. Different proton donors and additives together with the respective yield (determined by GC) of 3-heptanol in the SmI_2 (7 equiv.)-mediated reduction of 3-heptanone (1 equiv.) in THF after 1 min of reaction time

Entry	Proton source (equiv.)	Ligand (equiv.)	Yield (%)	Relative rate[a]
1	–	–	0.007[6]	1
2	H_2O (7)	–	0.018[6]	2.6
3	Diglycol (7)	–	1.7[6]	255
4	MeOH (14)	Et_3N (7)	0.7	100
5	–	Et_3N (7)	0.006[b]	0.9
6	H_2O (14)	Et_3N (7)	>99	>100 000[c]
7	–	TMEDA (7)	0.003[d]	0.4
8	H_2O (14)	TMEDA (7)	>99	>100 000[c]
9	H_2O (14)	PMDTA (7)	>99	>100 000[c]

[a] Based on initial rates.
[b] Estimated value, based on the yield (1.5%) after 3 h.
[c] Initial rate could not be determined, due to 100% yield in 10 s.
[d] Estimated value, based on the yield (0.6%) after 3 h.

[†] In a standard procedure, SmI_2 in THF (5.0 ml, 0.1 M, Aldrich) was added to a dry Schlenk tube, fitted with a septum and containing a magnetic stirrer bar, inside a glove box with nitrogen atmosphere. The proton donor, i.e. H_2O, and the amine was added under stirring. To this mixture was then added the ketone, e.g. 3-heptanone (10 μl, 0.14 equiv.), at 20.0°C. Small portions of the mixture (100 μl) was removed via a syringe and quenched with I_2 in n-hexane (0.1 M, 0.1 ml) including 1-hexanol (0.016 M) as internal standard. To the quenched solution was added diethyl ether (1 ml) and HCl (0.12 M, 0.1 ml) to dissolve the inorganic salts and finally $Na_2S_2O_3$ to remove excess iodine. The organic layer was transferred to a vial and analyzed by GC. All products were analyzed by ^1H NMR, GC/MS and also compared with references on GC.
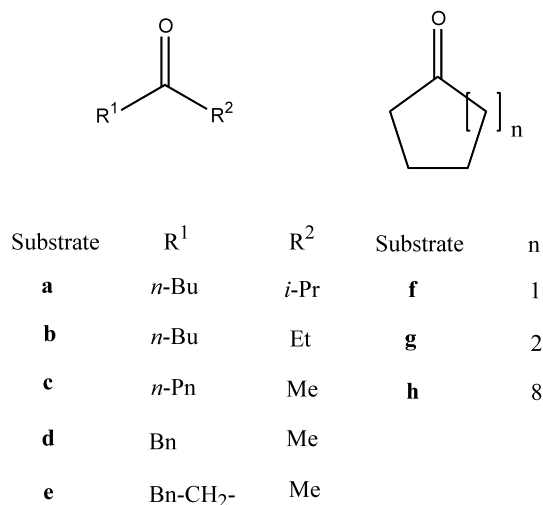
to obtain quantitative yield of 3-heptanol. Adding the amine and H_2O in portions proved that 2 equiv. of Et_3N and 3 equiv. of H_2O for each molecule of reacted SmI_2 must be used in order to obtain 100% yield in the reduction (Table 2). The reaction appears to be instantaneous based on the colour change from blue to white, reflecting the oxidation of Sm(II) to Sm(III). A clear, colourless solution and a white precipitate was obtained in less than 10 s. It was also demonstrated that these ratios of SmI_2, H_2O and amine were optimal using the bi- and tridentate amines. However, as the diamines have two amino functions only 1 equiv. of diamine for each SmI_2 was required. For the triamine only 0.7 equiv. for each SmI_2 was necessary.

Table 2. Evaluation of the required amount of water and amine together with the respective yields (determined by GC) of 3-heptanol in the SmI_2 (2.5 equiv.)-mediated reduction of 3-heptanone (1 equiv.) in THF[a]

| Entry	Proton source (equiv.)	Amine (equiv.)	Yield (%)
1	H_2O (5.0)	Et_3N (2.5)	42
2	H_2O (2.5)	Et_3N (5.0)	41
3	H_2O (5.0)	Et_3N (5.0)	86
4	H_2O (6.25)	Et_3N (5.0)	>99
5	H_2O (6.25)	TMEDA (2.5)	>99
6	H_2O (6.25)	PMDTA (1.7)	>99

[a] Entries 1–3 stopped at this yield and did not go to completion.

A number of experiments were performed on other dialkyl ketones (**a–h** in Scheme 2) to verify that this method is general. As a general procedure SmI_2 (2.5 equiv.), TMEDA (2.5 equiv.) and ketone (1 equiv.) were mixed followed by the addition of H_2O (6.25 equiv.). The reduction of all of these substrates was clean and instantaneous, i.e. completed in less than 10 s.


Substrate	R^1	R^2	Substrate	n
a	*n*-Bu	*i*-Pr	**f**	1
b	*n*-Bu	Et	**g**	2
c	*n*-Pn	Me	**h**	8
d	Bn	Me		
e	Bn-CH$_2$-	Me		

Scheme 2. Various dialkyl ketones examined in the SmI_2-mediated reduction induced by an amine and H_2O.

Based on our results we propose that samarium diiodide is coordinated by two nitrogens of one molecule of the diamine or two molecules of monoamine. Dimeric species of the type $[SmI_2(R_3N)_2(OH)_2]_2$ or $[SmI_2-(TMEDA)(OH)_2]_2$ may be key species in solution. It appears that the presence of H_2O and amine promote rapid precipitation of insoluble salts, for instance $Sm(OH)_3$ and $R_3N\cdot HI$.[‡] Our results also confirmed that it is not sufficient to precipitate only one of the two proposed insoluble salts of Sm^{3+} and I^- formed to obtain the maximum rate and yield. This was also verified in Table 2.
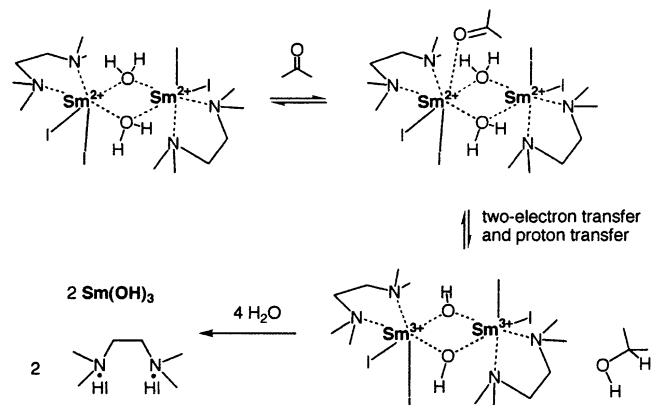
Figure 2. Suggested mechanism for the reduction of ketones mediated by SmI_2, amine and H_2O.

A potential mechanism for the SmI_2–H_2O-mediated reduction of ketones catalyzed by a bidentate amine is also presented above (Fig. 2). The exceptionally fast reaction indicates that it proceeds within one complex, most likely a dimer of SmI_2 since two electrons are required for the reduction of a ketone. The balanced equation below describes the reduction.

$$R_2C=O+2SmI_2+6H_2O+4R_3N \rightleftharpoons R_2CHOH+$$
$$2Sm(OH)_3+4R_3N\cdot HI$$
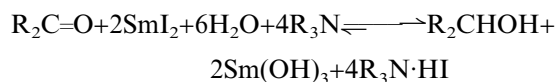
We have not examined the composition of these samarium and amine salts, which means that other salts may also be present. However, only trace amounts of amine could be found in the THF solution indicating that the amine is existing in the precipitate. Addition of NaOH (1 M) followed by extraction into diethyl ether (DEE) showed that the amine could be isolated from the salts, leaving a white precipitate of water and DEE insoluble samarium-salts. The work-up of the SmI_2-mediated reductions of ketones can thus be simplified to filtration of the salts and evaporation of THF.

The large rate enhancement found for the amine catalysis of the SmI_2–H_2O-mediated reduction of ketones is proposed to be a result of one or several factors:

[‡] Only trace amounts of the amine were detected in the supernatant after the SmI_2-mediated H_2O- and amine-catalyzed reactions were complete.

(1) SmI_2 is oxidized and in the presence of water and amine there is a rapid formation of $Sm(OH)_3$ and a quaternary ammonium salt $R_3N\cdot HI$. Rapid precipitation of these salts drives the equilibrium forward. Only trace amounts of the amine were detected in the supernatant after the SmI_2-mediated H_2O and amine-catalyzed reactions were completed.

(2) The increased reducing power of amine coordinated SmI_2, in analogy with additives such as HMPA, DBU or TMU.[3]

In conclusion, we have found that amines are effective additives for the SmI_2–H_2O-mediated reduction of ketones. Mono-, bi- and tridentate amines, such as Et_3N, TMEDA and PMDTA, respectively, accelerate the SmI_2–H_2O-mediated reduction of ketones; the rates can be increased more than 100 000 times. The reaction appears to be instantaneous, i.e. the mixing of the reagents is rate limiting. This impressive effect now sets the stage for a new era in SmI_2-mediated reductions. The mixture of water and amine is clearly superior to the widely used HMPA/alcohol mixtures. The use of amines in the SmI_2–H_2O-mediated reduction of ketones is advantageous because of the impressive rate of reduction. In addition, the work-up is extraordinarily simple as all reagents and SmI_2 by-products precipitate, leaving a clean, colourless THF solution with the product alcohol as the only compound in solution, based on GC and ^1H NMR analysis. These results also indicate that chiral diamines may be promising additives for asymmetric reduction reactions using SmI_2 since diamines catalyze the SmI_2–H_2O-mediated reduction of ketones. Use of different chiral amines in asymmetric reduction reactions mediated by SmI_2–H_2O are currently under investigation in our laboratory. Further studies including other functional groups and additives are also under investigation along with mechanistic studies on the catalytic reaction.

Acknowledgements

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