Trimethylsilyl chloride-accelerated reduction and pinacol coupling of carbonyl compounds by means of samarium diiodide

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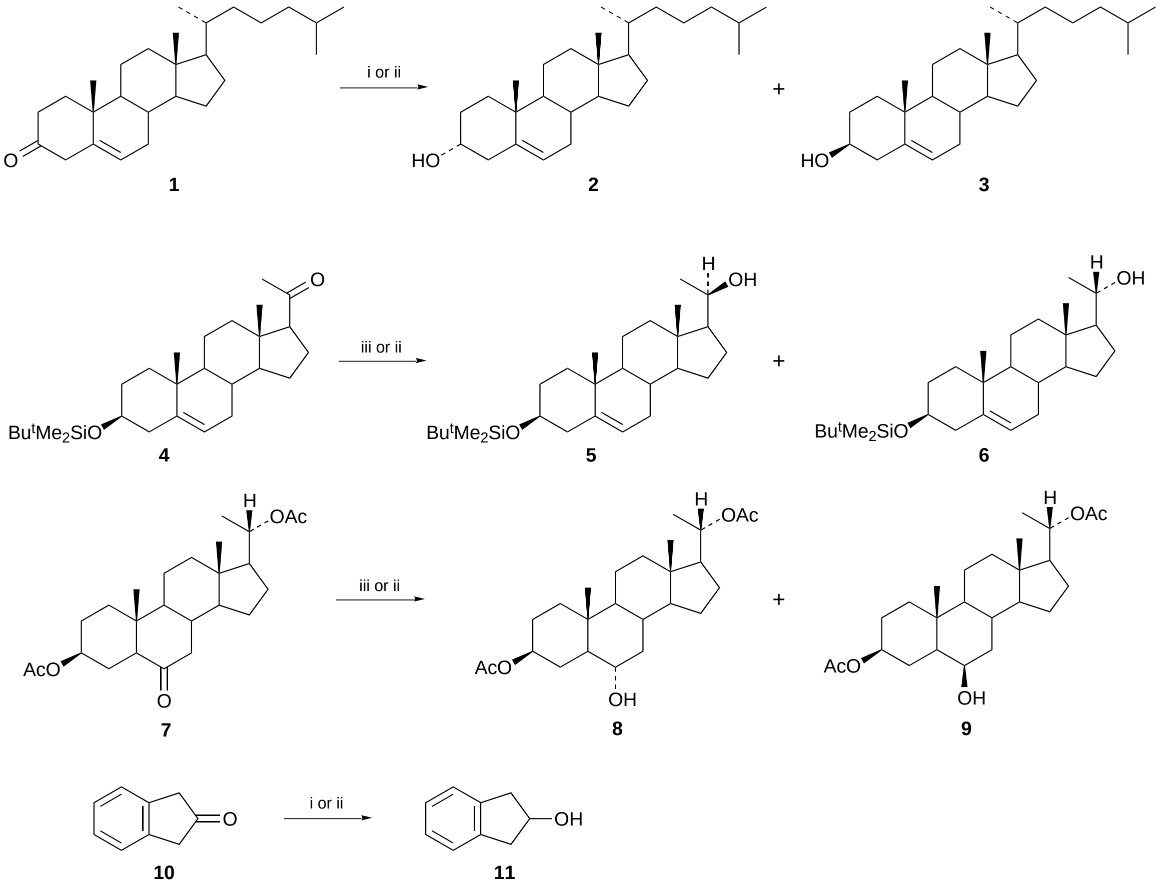
The combination of samarium diiodide (SmI_2) and trimethylsilyl chloride (Me_3SiCl) in THF–HMPA is found to accelerate the reduction of sterically hindered and enolisable ketones, and also to accelerate pinacolisation of the carbonyl compounds depending on the reaction conditions.

Samarium(ii) diiodide, originally introduced by Kagan and co-workers[1] into organic synthesis, has been established as a useful synthetic reagent and a number of interesting reactions have been developed by application of this reagent.[2] SmI_2 is a powerful one-electron reducing agent and serves as an effective reductant of carbonyl compounds. SmI_2-promoted reduction of carbonyl compounds usually proceeds quickly and completes within a few minutes when the reaction is carried out in the presence of a proton donor such as an alcohol or water in tetrahydrofuran to prevent the formation of the pinacol coupling product.[1–3] During the course of our work on the synthesis of physiologically active compounds employing SmI_2, we observed that the reduction of ketones with SmI_2 in THF–HMPA was accelerated in the presence of Me_3SiCl to give the corresponding alcohol(s) with Birch-type reduction stereochemistry in good yields.

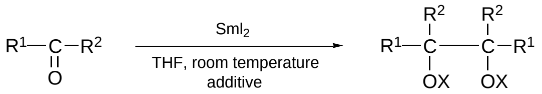
Treatment of the 3-keto steroid **1** with 3 equiv. of SmI_2 in the presence of 3 equiv. of Bu^{t}OH as a proton donor in THF–HMPA at ambient temperature for 10 min afforded the corresponding alcohols [**2** (3α) : **3** (3β) = 28 : 57%].† When this reduction was carried out in the presence of 3 equiv. of Me_3SiCl as an additive instead of Bu^{t}OH under the same reaction conditions, the yield improved to 90% [**2** (3α) : **3** (3β) = 30 : 60%].‡ Interestingly, reduction of the 20-keto steroid **4** with SmI_2 and Bu^{t}OH in THF–HMPA at room temperature required 6 h to afford the corresponding alcohols [**5** (20*S*) : **6** (20*R*) = 26 : 23%]. However, reduction of **4** under similar reaction conditions in the presence of Me_3SiCl proceeded within 10 min to provide the alcohols (**5** and **6**)‡ in 93% yield, in a ratio of 1 : 1. The reaction became significantly faster in the presence of Me_3SiCl. A dramatic change was observed in the reduction of 6-keto steroid **7**, which on treatment with SmI_2 in THF–HMPA gave none of the desired alcohol, although HMPA was recognised to increase the rate of the reaction of SmI_2.[4]



Scheme 1 *Reagents and conditions*: i, SmI_2, Bu^{t}OH, THF–HMPA, room temp., 10 min; ii, SmI_2, Me_3SiCl, THF–HMPA, room temp., 1 min, then Bu_4NF, THF, room temp.; iii, SmI_2, Bu^{t}OH, THF–HMPA, room temp., 6 h

However, reduction of **7** was carried out with $\mathrm{SmI_2}$ and $\mathrm{Bu^tOH}$ for 6 h to afford the alcohols [**8** (6α) : **9** (6β) = 39 : 22%) in moderate yields. Moreover treatment for 10 min of **7** with $\mathrm{SmI_2}$ in the presence of $\mathrm{Me_3SiCl}$ afforded **8** as the sole product‡ in 91% yield. These varied reaction times and yields are reflected by the steric hindrance of the carbonyl groups (6-keto > 20-keto > 3-keto) and the above results clearly suggest that $\mathrm{Me_3SiCl}$ accelerates the $\mathrm{SmI_2}$-mediated reduction of sterically hindered ketones, although it is premature to present a detailed mechanistic rationale at the present time. This type of reduction was found to be effective to the enolisable ketones. Thus, the reduction of indan-2-one **10** with $\mathrm{SmI_2}$ in THF–HMPA at ambient temperature in the presence of $\mathrm{Me_3SiCl}$ proceeded within 1 min to give indan-2-ol **11** in 79% yield, whereas similar reduction with $\mathrm{SmI_2}$ and $\mathrm{Bu^tOH}$ after 10 min afforded **11** in 66% yield. The reduction was typically carried out as follows—to a stirred solution of $\mathrm{SmI_2}$ in dry THF (7 $\mathrm{cm^3}$), prepared from samarium metal (0.76 mmol) and diiodoethane (0.69 mmol), under argon at room temperature, was added HMPA (0.9 $\mathrm{cm^3}$) and the resulting mixture was stirred for a further 15 min. After the successive addition of a solution of ketone (0.23 mmol) in THF (1 $\mathrm{cm^3}$) and $\mathrm{Me_3SiCl}$ (0.7 mmol), the mixture was stirred for the appropriate time and then treated with saturated aqueous sodium hydrogen carbonate. A stream of air was bubbled through the solution and an excess of Celite and $\mathrm{Et_2O}$ were added. The solution was filtered and the filtrate was extracted with ethyl acetate. Evaporation of the solvent followed by treatment of the residue with $\mathrm{Bu_4NF}$ (0.5 mmol) in THF (10 $\mathrm{cm^{-1}}$) at room temperature afforded the desired alcohol.

Table 1 Pinacol coupling of the ketones



	Starting material		Reaction conditions		Product	
Entry	R¹	R²	Additive	Time	X	Yield (%)[c]
1	$\mathrm{C_6H_{13}}$	Me	—	12 h	H	75
2	$\mathrm{C_6H_{13}}$	Me	$\mathrm{Me_3SiCl}$[a]	3 min	H	77
3	$\mathrm{C_6H_{13}}$	Me	—	24 h	H	80[d]
4	$\mathrm{C_7H_{15}}$	H	—	45 min	H	81
5	$\mathrm{C_7H_{15}}$	H	$\mathrm{Me_3SiCl}$[a]	1 min	H[b] $\mathrm{SiMe_3}$	37 45
6	$\mathrm{C_7H_{15}}$	H	—	3 h	H	85[d]
7	$\mathrm{PhCH_2CH_2}$	Me	—	10 h	H	78
8	$\mathrm{PhCH_2CH_2}$	Me	$\mathrm{Me_3SiCl}$[a]	5 min	H	78
9	$\mathrm{PhCH_2CH_2}$	H	—	1 h	H	65
10	$\mathrm{PhCH_2CH_2}$	H	$\mathrm{Me_3SiCl}$[a]	1 min	H[b] $\mathrm{SiMe_3}$	53 30

[a] 1.0 equiv. of starting material, 3.3 equiv. of $\mathrm{SmI_2}$ and 3.0 equiv. of $\mathrm{Me_3SiCl}$ were used. [b] A mixture of the alcohol and its trimethylsilyl ether was isolated. [c] Isolated yields. [d] This yield was based on the literature value (ref. 6).

The effectiveness of $\mathrm{Me_3SiCl}$ for $\mathrm{SmI_2}$-mediated pinacol coupling of the ketones in THF was also investigated. HMPA was used as co-solvent to reduce the formation of reduction products.[5] The results are summarised in Table 1 and indicate that the pinacol coupling of both aldehyde and ketone was also accelerated by the presence of $\mathrm{Me_3SiCl}$. For example, it was reported that the pinacol coupling of hexyl methyl ketone with $\mathrm{SmI_2}$ in THF–HMPA required 24 h to give the corresponding coupling product in 80% yield.[5] However, the same reaction in the presence of $\mathrm{Me_3SiCl}$ proceeded within 3 min to give the coupling product in 77% yield (entry 2). Similar results were also obtained (see entires 5, 8 and 10), clearly indicating that $\mathrm{Me_3SiCl}$ as an additive accelerated the pinacol coupling compared to the results previously reported.[5] A typical experimental procedure for the pinacol coupling is as follows—to a stirred solution of $\mathrm{SmI_2}$ (5.1 mmol) in dry THF (50 $\mathrm{cm^3}$), prepared from samarium metal and diiodoethane as above, were added a solution of ketone (1.55 mmol) in THF (2 $\mathrm{cm^3}$) and $\mathrm{Me_3SiCl}$ (4.7 mmol). The resulting solution was stirred for the appropriate time (see Table 1) under argon at room temperature. The mixture was worked-up as described above to give the coupling product.

In conclusion, we have found that $\mathrm{Me_3SiCl}$ is an effective additive for the $\mathrm{SmI_2}$-promoted reduction of ketones and also for pinacol coupling. Recently, Kagan and co-workers[6] reported the improved reactivity of $\mathrm{SmI_2}$ by catalysis with transition metal salts, in which Barbier-type reactions were found to be accelerated in the presence of such metal salts. $\mathrm{Me_3SiCl}$ in this work may play a similar role as the metal salts.

Footnotes

† The stereochemistry of the reduction products (**2, 3, 5, 6, 8** and **9**) were determined by comparison with authentic samples prepared according to literature procedures.

‡ The products from this reaction were trimethylsilyl ethers and the yields were obtained after their conversion into the corresponding alcohols by treatment with $\mathrm{Bu_4NF}$ in THF.

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