Pergamon

Tetrahedron Letters, Vol. 38, No. 18, pp. 3271-3274, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00600-X

Reductive Coupling of Carbonyl Compounds to Pinacols by Using Sm-I_2-MeOH or Sm-I_2-Ti(O^iPr)$_4$-MeOH Systems

Reiko Yanada* and Nobuyuki Negoro

Faculty of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-01, Japan

Kazuo Yanada and Tetsuro Fujita

Faculty of Pharmaceutical Sciences, Setsunan University, Nagaotoge-cho, Hirakata, Osaka 573-01, Japan

Abstract: The coupling reaction of aromatic carbonyl compounds was performed with Sm-I_2 or Sm-I_2-Ti(O^iPr)$_4$ in methanol. *Meso* isomer was mainly produced in the presence of Ti(O^iPr)$_4$.
© 1997 Elsevier Science Ltd.

The chemistry of samarium(II) iodide (SmI_2) is of a current interest in organic synthesis. SmI_2 has been developed as a mild, neutral, and ether-soluble one-electron reductant and there have been many examples of its use in the reduction of various functional groups.[1] However, some problems are incurred when it is used as a reductant. Though SmI_2 is a useful reagent, storage is difficult because it is very sensitive to air oxidation. On the other hand, samarium metal (Sm) is stable in air and has strong reducing power (Sm^{3+}/ Sm=-2.41V) similar to that of magnesium (Mg^{2+}/ Mg=-2.37V). These properties prompted us to use the more convenient and cheaper Sm directly as a reductant instead of SmI_2. There are some reports on the direct use of Sm in organic synthesis.[2] We have reported 1,4-reduction of α,β-unsaturated carboxylic acid derivatives,[3] deacylation of protected alcohols and lactams,[4] and reductive dehalogenation of aliphatic *vic*-dihalides to alkenes[5] under neutral conditions without Sm activation.

It has been known that aldehydes and ketones are transformed into pinacols with SmI_2 in THF in the absence of alcohols or water.[6] If there is a small amount of a protic solvent, the obtained products are only the corresponding alcohols.[6,7] We report here that pinacol coupling reactions occur in a protic solvent, methanol, with Sm and I_2 or Sm, I_2, and titanium tetraisopropoxide (Ti(O^iPr)$_4$).

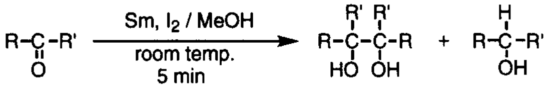
Table 1 shows that aromatic aldehydes and ketone are reduced with Sm and I_2 in methanol to give pinacol coupling products (diol) in moderate yields with a trace amount of alcohols (Entries 1-3). These results show that steric hinderance around the carbonyl group affects the yield of diol. The colour change of the reaction mixture (footnote to Table 1) suggests that the active species is an Sm^{2+} compound (probably $SmI_n(OMe)_{2-n}$).[5] The *dl/meso* ratio[8] of diols is 1.0-1.5 and is similar to that with SmI_2.[9] Because the reaction of SmI_2 usually proceeds via a radical mechanism, the formation of pinacols in this reaction probably proceeds via radical-radical coupling. Aliphatic aldehydes gave only alcohols (Entries 4 and 5). When cyclopentanone was used as a substrate, the starting material was recovered in 66 % with cyclopentanol (29 %). Aliphatic ketones such as camphor and menthone were inert, and the starting materials were recovered.[10] Kagan reported that the reduction of aldehydes or ketones with SmI_2 gave alcohols in the presence of a small amount of a protic solvent and the formation of pinacol is frequently negligible.[6] It is interesting that the pinacol coupling reaction of aromatic aldehydes and ketone described here was performed in a protic solvent, methanol.

The addition of $Ti(O^iPr)_4$ to this reaction increases the ratio of *meso*-diol. Generally, a mixture of Sm (0.85 mmol), I_2 (0.50 mmol) and $Ti(O^iPr)_4$ in methanol (3 ml) was stirred under an argon atmosphere for 3 min at room temperature, then the reaction mixture was cooled for 2 min at -78 °C. *o*-Anisaldehyde (0.50 mmol) in methanol (1 ml) was added to the solution, and the reaction mixture was stirred for 1 h at -78 °C. The resulting reaction mixture was worked up as usual. When 0.85, 0.5, or 0.25 mmol of $Ti(O^iPr)_4$ was used, diol was produced in 89 % (*meso/dl*= 5.8) with alcohol (9 %), 90 % (*meso/dl*= 8.8) with alcohol (8 %), or 35 % (*meso/dl*= 11.7) with alcohol (2 %) and recovery of the starting material (62 %), respectively. No diol was obtained without $Ti(O^iPr)_4$ (alcohol (8 %) and recovery of starting material (90 %)). These results show that $Ti(O^iPr)_4$ plays an important role and a stoichiometric amount is needed in this reaction. It may be reduced to a titanium(III) active species with Sm-I_2-methanol system and then reacts with the substrate. The produced complex including the titanium(IV) ion and/or samarium(III) ion would no longer react with the Sm-I_2-methanol system. Though the reason has not been clarified, 0.5 mmol of $Ti(O^iPr)_4$ (same molar to substrate) is most effective in the yield of diol and more $Ti(O^iPr)_4$ gives a lower ratio of *meso*-diol. The additive is sometimes used in samarium chemistry to affect the reactivity of SmI_2. Inanaga reported that benzaldehyde gave diol (*dl/meso*= 11) with SmI_2 in THF in the presence of Cp_2TiCl_2,[11] but it was inert in this reaction. These results imply that the reaction mechanism of our reaction may be different from that of Inanaga's reaction.

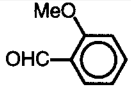
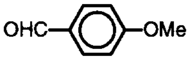
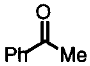
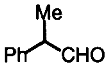
The coupling reaction of other substituted benzaldehydes proceeded with Sm, I_2, and $Ti(O^iPr)_4$ in methanol in 90-98 % yield (Table 2, Entries 1-8). *Meso*-diols were mainly produced except in the case of 2,6-dimethoxybenzaldehyde (Entry 8). Basically, the electron-releasing group increased *meso*-diol (Entries 1-7). When *p*-substituted benzaldehydes were used, the ratio of *meso*- to *dl*-pinacols followed a Hammet correlation with σ para values[12] of the *p*-substituents (CN, Cl, OMe, and Me) in the phenyl ring (correlation coefficient, γ=0.996, ρ=-4.127) (Entries 1-4). Benzaldehyde gave a higher ratio of *meso*-diol than other *p*-substituted benzaldehydes (Entry 5), and the reason has not been clarified. *Meso*-diol selectivity is also affected by the steric hinderance around the formyl group. Though *o*-anisaldehyde gave mainly *meso*-diol, 2,6-dimethoxybenzaldehyde gave *meso*- and *dl*-diols equally (Entries 7 and 8). The phenolic OH prevented the reaction. When *o*-hydroxybenzaldehyde was used instead of *o*-anisaldehyde under the same reaction conditions, the starting material was recovered in 54 %. The acidic hydrogen of phenolic OH may be reduced to H_2 competitively in this case. When twice the amount of reagent was used, the reaction proceeded completely, but the coupling reaction was suppressed and the reduction to alcohol occurred mainly (Entry 9).[13] The steric hinderance around the carbonyl group inhibits the coupling reaction. An aromatic ketone such as acetophenone gave the starting material mainly in 82 % with diol (5 %) and α-phenethyl alcohol (7 %). When benzophenone was used as a substrate, a trace of pinacol and 18 % yield of alcohol was produced. It is known that sterically crowded radicals predominantly yield *meso* dimers, while other radicals afford equal amounts of both dimers.[14] *dl*-Isomer was mostly produced because of chelation control by the interaction of the metal ion and the pinacol coupling intermediate. It is known that titanium(III) chloride in methanol-30 % NaOH solution as a reductant gives *dl*-diol more than *meso*-diol because of the chelation control between the titanium ion and two oxygens in the reaction intermediate.[14] The present reaction is rare because *meso*-diols were selectively produced though a titanium compound was used.

In conclusion, we have demonstrated Sm-I_2-MeOH or Sm-I_2-Ti($O^iPr)_4$-MeOH system can be used for pinacol coupling reactions of aromatic aldehydes and/or ketone. The experimental simplicity, mild reaction conditions and high product yield provides a new way for using Sm in organic synthesis. The results described here are interesting not only in synthetic chemistry but also in the chemistry of lanthanoids.

Table 1. Coupling of carbonyl compounds with Sm and I_2.

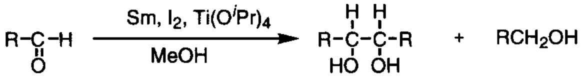


$$R-C(=O)-R' \xrightarrow[\text{room temp., 5 min}]{\text{Sm, } I_2 \text{ / MeOH}} R-C(R')(OH)-C(R')(OH)-R + R-CH(OH)-R'$$

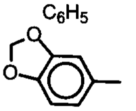
Entry	Carbonyl Compound	Diol (%)	Ratio (*dl/meso*)	Alcohol (%)
1		74	1.4	22
2		91	1.0	–
3		71	1.5	24
4	$PhCH_2CH_2CHO$	–	–	94
5		–	–	95

A mixture of carbonyl compound (0.50 mmol), Sm (0.85 mmol), and I_2 (0.50 mmol) in methanol (4 ml) was stirred vigorously at room temperature under an argon atmosphere. The reaction was exothermic and the colour of the solution turned to dark blue immediately, then to brown, and to yellow-brown after 5 min. The reaction mixture was worked up as usual. In all cases the recovery of the starting material was in a trace amount or not determined.

Table 2. Coupling of aromatic aldehydes with Sm, I_2, and Ti($O^iPr)_4$.[a]



$$R-C(=O)-H \xrightarrow[\text{MeOH}]{\text{Sm, } I_2\text{, Ti}(O^iPr)_4} R-CH(OH)-CH(OH)-R + RCH_2OH$$

Entry	R	Diol (%)	Ratio (*meso/dl*)	Alcohol (%)
1	*p*-CN-C_6H_4	92	2.9	trace
2	*p*-Cl-C_6H_4	92	4.6	7
3	*p*-MeO-C_6H_4	91	6.2	-
4	*p*-Me-C_6H_4	95	6.4	trace
5	C_6H_5	91	10.5	-
6		98	11.5	-
7	*o*-MeO-C_6H_4	90	8.8	8
8	2,6-$(MeO)_2$-C_6H_3	96	1.0	trace
9[b]	*o*-HO-C_6H_4	10	0.3	88

[a] Generally, a mixture of Sm (0.85 mmol), I_2 (0.50 mmol) and Ti($O^iPr)_4$ in methanol (3 ml) was stirred under an argon atmosphere for 3 min at room temperature, then the reaction mixture was cooled for 2 min at -78 °C. Substrate (0.50 mmol) in methanol (1 ml) was added to the solution, and the reaction mixture was stirred for 1 h at -78 °C.

[b] Substrate (0.5 mmol), Sm (1.7 mmol), I_2 (1.0 mmol) and Ti($O^iPr)_4$ (1.0 mmol) were used.

REFERENCES AND NOTES

1. Kagan, H. B.; Namy, J. L. *Tetrahedron*, **1986**, *42*, 6573-6614. Kagan, H. B. *Nouv. J. Chim.*, **1990**, *14*, 453-460. Molander, G. A. *Chem. Rev.*, **1992**, *92*, 29-68. Molander, G. A. *Organic Reactions*, **1994**, *46*, 211-367. Molander, G. A.; Harris, C. R. *Chem. Rev.*, **1996**, *96*, 307-338.
2. Yamazaki, T.; Lin, J. T.; Takeda, M.; Kitazume, T. *Tetrahedron; Asymmetry,* **1990**, *1*, 351-354. Ogawa, A.; Nanke, T.; Takami, N.; Sumino, Y.; Ryu, I.; Sonoda, N. *Chem. Lett.*, **1994**, 379-380. Kamochi, Y.; Kudo, T. *Chem. Pharm. Bull.*, **1994**, *42*, 402-404. Taniguchi, Y.; Fujii, N.; Takaki, K.; Fujiwara, Y. *J. Organomet. Chem.*, **1995**, *491*, 173-179. Kamochi, Y.; Kudo, T. *Chem. Pharm. Bull.*, **1995**, *43*, 1422-1424. Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.*, **1995**, *60*, 2474-2487 and references cited therein.
3. Yanada, R.; Bessho, K.; Yanada, K. *Synlett*, **1995**, 443-444.
4. Yanada, R.; Negoro, N.; Bessho, K.; Yanada, K. *Synlett*, **1995**, 1261-1263.
5. Yanada, R.; Negoro, N.; Yanada, K.; Fujita, T. *Tetrahedron Lett.*, **1996**, *37*, 9313-9316.
6. Namy, J. L.; Kagan, H. B. *Tetrahedron Lett.*, **1983**, *24*, 765-766.
7. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.*, **1980**, *102*, 2693-2698.
8. The ratio of *dl /meso* was determined by ^{1}H-NMR (270 MHz) analysis. The proton α to the hydroxy group in *dl*-isomer appears at ca. 0.1-0.2 ppm higher field than the one in *meso*-isomer. Handa, Y.; Inanaga, J. *Tetrahedron Lett.*, **1987**, *28*, 5717-5718.
9. a) The *dl/meso* ratio is 1.3 in the reaction of PhCHO with SmI$_2$ in THF. Ref. 6. b) The *dl/meso* ratio is 1.0 in the reaction of PhCOCH$_3$ with TMSCl/NaI/Sm/CH$_3$CN. Akane, N; Kanagawa, Y; Nishiyama, Y; Ishii, Y. *Chem. Lett.*, **1992**, 2431-2434, Akane, N.; Hatano, T; Kusui, H; Nishiyama, Y; Ishii, Y. *J. Org. Chem.*, **1994**, *59*, 7902-7907. c) Other pinacol coupling reactions with low-valent lanthanide reagents were reported. SmBr$_2$: Lebrun, A.; Namy, J. L.; Kagan, H. B.*Tetrahedron Lett.*, **1993**, *34*, 2311-2314. Sm and Yb: Hou, Z.; Takamine, K.; Aoki, O.; Shiraishi, H.; Fujiwara, Y.; Taniguchi, H. *J. Org. Chem.*, **1988**, *53*, 6077-6084. Ce/I$_2$: Imamoto, T.; Kusumoto, T.; Hatanaka, Y.; Yokoyama, M. *Tetrahedron Lett.*, **1982**, *23*, 1353-1356. Sm(OTf)$_2$: Hanamoto, T.; Sugimoto, Y.; Sugino, A.; Inanaga, J. *Synlett*, **1994**, 377-378. Fukuzawa, S.; Tsuchimoto, T.; Kanai, T. *Chem Lett.*, **1994**, 1981-1984. SmCl$_3$ catalyzed electrochemical coupling: Léonard, E.; Duñach, E.; Périchon, J. *J. Chem. Soc., Chem. Commun.*, **1989**, 276-277.
10. Probably this results may be attributed to the difference in stability between the radical intermediates. Because a benzyl radical intermediate from an aromatic carbonyl compound is stabilized by the neighboring aromatic ring, it has enough time to react with another radical intermediate to give diol. The less stable radical intermediate from the aliphatic one may abstract the hydrogen radical from the solvent methanol more rapidly than react with another radical intermediate.
11. Ref. 8. Recently *dl* selectivity was reported in the coupling reaction of aldehydes with Cp$_2$TiCl in THF-H$_2$O and of aromatic aldehydes with TiCl$_3$ in CH$_2$Cl$_2$. Barden, M. C.; Schwartz, J. *J. Am. Chem. Soc.*, **1996**, *118*, 5484-5485, Clerici, A; Clerici, L.; Porta, O. *Tetrahedron Lett.*, **1996**, *37*, 3035-3038.
12. Cary, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, 3rd Ed., Part A, Plenum Press, New York and London*, **1990**, 201.
13. Alcohol was formed mainly in the presence of an excess of Sm. Olivier, H.; Chauvin, Y.; Saussine, L. *Tetrahedron*, **1989**, *45*, 165-169.
14. Clerici, A.; Porta, O. *J. Org. Chem.*, **1985**, *50*, 76-81.

(*Received in Japan* 20 *February* 1997; *revised* 21 *March* 1997; *accepted* 26 *March* 1997)