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Reductive Dehalogenation of Aliphatic *vic*-Dihalides with Metallic Samarium in a Methanolic Medium

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Abstract: In the title reaction, eight *vic*-dibromides and three vinylene dibromides gave the corresponding debromination products (alkenes and alkynes) at room temperature under neutral condition and an argon atmosphere. 2,3-Dibromosuccinic acid derivatives gave overreduction products or an unusual coupling dimer. Copyright © 1996 Elsevier Science Ltd

The chemistry of samarium(II) iodide (SmI_2) is of current interest in organic synthesis. SmI_2 has been developed as a mild, neutral, and ether-soluble one-electron reductant and many examples have been reported 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, 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 convenient and cheaper Sm directly as a reductant instead of SmI_2. There are some reports on the direct use of samarium metal in organic synthesis.[2] We have reported 1,4-reduction of α,β-unsaturated carboxylic acid derivatives[3] and deacylation of protected alcohols and lactams with Sm and I_2 under neutral condition without Sm activation.[4]

Debromination of *vic*-dibromide to alkene is important in organic synthesis as a deprotection step and many methods have been developed in this regard.[5] Previously, we examined the reductive debromination of aromatic *vic*-dibromides to alkenes in THF with SmI_2, Sm, or Sm and a catalytic amount of acid.[6] In these reactions, we observed that the activity of Sm alone is much lower than that of the others, that aliphatic *vic*-dibromides were usually inert, and that, as an exceptional case, cholesterol dibromide was debrominated after prolonged reaction time. We report here that the reductive dehalogenation of *vic*-dihalides to alkenes with Sm is accelerated in a methanolic medium[7] and that even aliphatic *vic*-dihalides can give alkenes under neutral conditions.

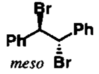
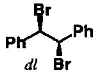
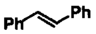
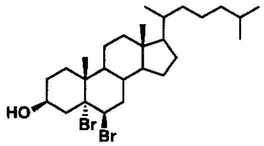
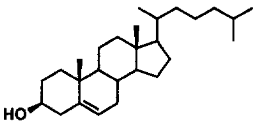
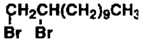
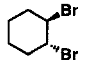
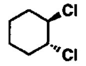
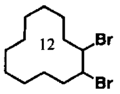
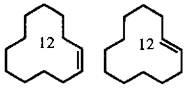
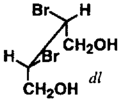
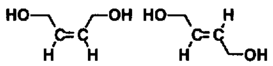
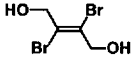
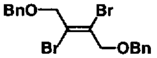
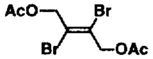
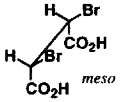
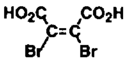
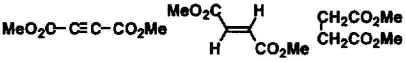
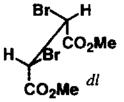
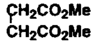
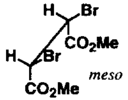
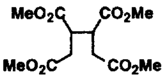
The general procedure is as follows. A mixture of *vic*-dihalide (0.25 mmol) and Sm (0.40 mmol) in methanol (2 ml) (when dissolution of *vic*-dihalide was difficult, methanol-THF was used as a solvent) was stirred vigorously at room temperature under an argon atmosphere. The reaction was slightly exothermic and the colour of the solution turned to dark blue after 2 min with hydrogen evolution. Dehalogenation seemed to finish within 10 min though the colour of the reaction mixture continued for about 1 h because of the excess Sm (2.4 times of the theoretical value).[8] After the colour changed to yellow-brown, the reaction mixture was evaporated to *ca.* 0.5 ml and poured into 0.1 *N* hydrochloric acid. The product was extracted with ethyl acetate and purified by short silica-gel column chromatography.

Table 1 summarizes the results. The reaction of *meso*-1,2-dibromo-1,2-diphenylethane in methanol-THF gave *trans*-stilbene quantitatively within 1 h (Entry 1). Previously, THF alone was used as the solvent, it gave *trans*-stilbene in 93 % yield after 5 h. It shows that methanol accelerates the reaction. The acceleration was observed when *dl*-1,2-dibromo-1,2-diphenylethane was used as a substrate (Entry 2). Its reaction in methanol- THF gave *trans*-stilbene in 98 % yield within 1 h. The reaction in THF alone gave *trans*-stilbene in 95 % yield after 40 h. If debromination occurs by *trans*-elimination, *meso*- or *dl*-*vic*-dibromide would give *trans*- or *cis*-alkene, respectively. It is therefore suggested that the reaction occurs via a relatively stable radical or anion intermediate because *trans*-stilbene is produced from both *meso*- and *dl*-1,2-dibromo-1,2-diphenylethane. The acceleration with methanol was observed during the debromination of aliphatic *vic*-dibromides. Cholesterol dibromide in methanol-THF gave cholesterol in 96 % within 1h (Entry 3). Its reaction in THF needed 8 h (95 %). Though other aliphatic *vic*-dibromides examined were inert in THF, their reactions in a methanolic medium proceeded smoothly to alkenes in high yield. 1,2-Dibromododecane or *trans*-1,2-dibromocyclohexane in methanol gave 1-dodecene in 95 % yield or cyclohexene quantitatively within 1 h, respectively (Entries 4 and 5). In the case of *trans*-1,2-dichlorocyclohexane, more Sm (3.2 mole times) and longer reaction time (1 day) were needed to obtain cyclohexene (91 % yield) (Entry 6). 1,2-Dibromocyclododecane, prepared from commercially available cyclododecene (*cis/trans*= 2.3), gave cyclododecene (cis/trans= 1.4) (Entry 7).[9] *dl*-2,3-Dibromo-1,4-butanediol gave 2-butene-1,4-diol (*cis/trans*= 1.6) in 99 % yield (Entry 8). It shows that the radical or anion intermediate of aliphatic *vic*-dibromide is less stable than that of the aromatic compound (Entry 2) and is transferred to alkene before the rotation around the carbon carbon bond has completed. Another possibility is that two hydroxy groups of *dl*-2,3-dibromo-1,4-butanediol coordinate to the samarium active species, favouring retention of *cis* configuration. The active species in the methanolic medium may be $SmX_n(OMe)_{2-n}$ but the details regarding this aspect have not been clarified. *vic*-Dibromides bounded to the double bond produced alkynes in high yields (Entries 9-11). 2,3-Dibromo-2-butene-1,4-diol and 1,4-bis(benzyloxy)-2,3-dibromo-2-butene gave the corresponding alkynes quantitatively. Debromination of 2,3-dibromo-2-butenylene diacetate accompanied deacylation[4] under the reaction conditions (Entry 11).

When 2,3-dibromo-1,4-dioic acid derivatives were used as substrates, overreduction[3] of the produced alkene or an unusual coupling reaction was found. The reaction of *meso*-2,3-dibromosuccinic acid with 1.6 mole times of Sm afforded a mixture of fumaric acid and succinic acid (1:10) in 98 % yield after 1 h (Entry 12). The products were isolated as the methyl esters by adding *conc.* H_2SO_4 to the reaction mixture followed by heating. The reaction with 3.2 mole times of Sm gave only succinic acid after 1 day. It shows that succinic acid is an overreduction product of fumaric acid. The reaction of 2,3-dibromomaleic acid with 1.6 mole times of Sm afforded a mixture of 2-butyne-1,4-dioic acid, fumaric acid, and succinic acid (2:1:1, isolated as methyl ester) after 1 day (Entry 13). The reaction with 3.2 mole times of Sm gave only succinic acid. These results show that the reaction produces 2-butyne-1,4-dioic acid as the first product, then the overreduction product, fumaric acid, and finally succinic acid. The reaction of dimethyl *dl*-2,3-dibromosuccinate with 1.6 mole times of Sm gave dimethyl succinate, an overreduction product, within 1 h quantitatively (Entry 14). However, dimethyl *meso*-2,3-dibromosuccinate yielded dimethyl 3,4-bis(methoxycarbonyl)adipate (*meso*:*dl*= 1:1) quantitatively (Entry 15). It is thought to be a dimer which may be produced from the radical intermediate. The reactions of Entries 14 and 15 are reproducible. Though details have not yet been clarified, these results are interesting and similar examples have been reported by others. Inanaga *et al.* reported that the reaction of α,β-unsaturated esters with SmI_2 in THF produced the 1,4-reduction product in the presence of *N,N*-dimethylacetamide as additive[10] and that the system gave only a dimerization product in the presence of hexamethylphosphoramide (HMPA) as additive.[11] On the other hand, Alper *et al.* reported that a similar system gave only the 1,4-reduction product in the presence of HMPA as additive.[12] These findings show that a small difference in reaction conditions with a samarium compound influences the results seriously. So far, a general mechanism to explain these results has not been reported.

In conclusion, reductive dehalogenation of aliphatic and aromatic *vic*-dihalides[9] to alkenes or alkynes with Sm in a methanolic medium proceeded in high yield under mild conditions. This reaction is rapid and the procedure is simple. It does not need the strict anaerobic condition which is required in reactions with SmI_2. This method may open a new way for using metallic samarium instead of SmI_2 in organic synthesis.

Table 1. Reductive debromination of *vic*-dibromides.

Entry	Substrate	Sm[a]	Reaction Time (h)	Product	Yield (%)
1[b]		1.6	1		quant.
2[b]		1.6	1		98
3[b]		1.6	1		96
4	 $CH_2CH(CH_2)_9CH_3$ with Br, Br	1.6	1	$CH_2{=}CH(CH_2)_9CH_3$	95
5[c]		1.6	1		(100)
6[c]		3.2	24		(91)
7		1.6	1	 1.4 : 1	quant.
8		1.6	1	 1.6 : 1	99
9		1.6	1	$HOH_2C{-}C{\equiv}C{-}CH_2OH$	quant.
10[d]		1.6	1	$BnOH_2C{-}C{\equiv}C{-}CH_2OBn$	quant.
11		1.6	1	$HOH_2C{-}C{\equiv}C{-}CH_2OH$	94
12[e]		1.6 3.2	1 24	 1 : 10 0 : 1	98
13[e]		1.6 3.2	24 24	 2 : 1 : 1 0 : 0 : 1	92
14		1.6	1	 CH_2CO_2Me / CH_2CO_2Me	quant.
15		1.6	1		quant.

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[a] Mole ratio of Sm/*vic*-dibromide.

[b] MeOH-THF (1:2) was used as solvent instead of MeOH to dissolve *vic*-dibromide.

[c] CD_3OD was used as solvent. The number in parentheses is the yield calculated by NMR.

[d] MeOH-THF (2:1) was used as solvent instead of MeOH to dissolve *vic*-dibromide.

[e] The product was isolated as methyl ester.

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9. Because bromination proceeds by *trans* addition mechanism (*dl* from *cis* and *meso* from *trans*), the ratio of *dl*- and *meso*-1,2-dibromocyclododecane may be 2.3:1 the same as that of the starting cyclododecene, but such ratios could not be elucidated. The debromination product was a mixture of *cis*- and *trans*-dodecene (1.4:1). The increase in the *trans*-dodecene ratio suggests that a part of *dl*-1,2-dibromododecane gives *trans*-dodecene via a radical or anion intermediate.
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