Selenium-catalysed Debromination of *vic*-Dibromides to Alkenes with Cysteine or Glutathione

Kazuo Yanada,* Reiko Yanada, and Haruo Meguri

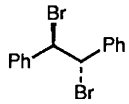
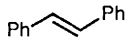
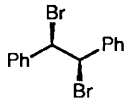
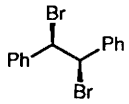
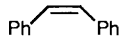
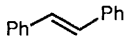
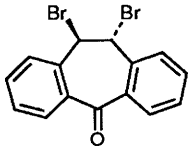
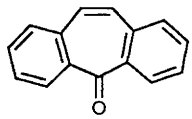
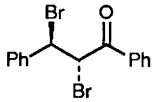
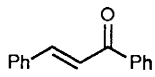
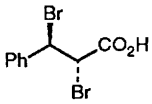
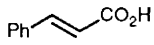
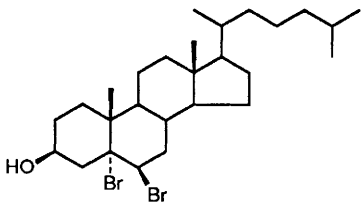
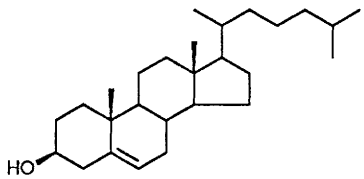
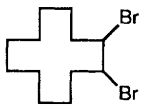
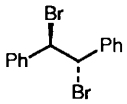
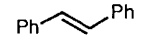
Faculty of Pharmaceutical Sciences, Setsunan University, Nagaotoge-cho, Hirakata, Osaka 573-01, Japan

Sodium selenite catalyses, under mild conditions, the reductive debromination of *vic*-dibromides [*e.g.*, *meso*- or (±)-1,2-dibromo-1,2-diphenylethane, *trans*-10,11-dibromodibenzosuberone, 2,3-dibromo-1,3-diphenyl-1-propanone, α,β-dibromobenzenepropanoic acid, and cholesterol dibromide] to alkenes in the presence of the thiols cysteine or glutathione.

Selenium, one of the essential trace elements, has been recognized to function as an electron transfer catalyst in certain enzymes such as glutathione peroxidase.[1] It is also known that the inorganic salt, sodium selenite (Na_2SeO_3), catalyses the reduction of cytochrome c and methaemoglobin *in vitro* in the presence of a thiol such as glutathione (GSH) or cysteine (CysSH).[2]

Organohalides are widely used in industry, agriculture, and medicine. It is known that some *vic*-dihalides are toxic, mutagenic, or carcinogenic.[3] It has been reported that NaHSe or Na_2Se reduces *vic*-dibromides to alkenes.[4] However, to the best of our knowledge, there has been no attempt reported in which a selenium compound has been used as a catalyst during the debromination of *vic*-dibromide. As part of our continuing

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

Entry	Dibromide	*T* / °C	*t* / min	Alkene	Yield / %
1		0	5		98
2		0	5	—	0
3[a]		0	1	 	91 8
4		0	5		99
5		0	5		95
6		0	30		98
7		0	60		98
8		0	30	—	0
9[b]		25	30		quant.

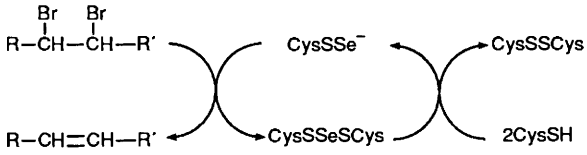
[a] DMSO was used instead of THF. [b] GSH was used with Na_2CO_3 instead of CysSH.

$H_2SeO_3 + 4GSH \longrightarrow GSSeSG + GSSG + 3H_2O$

$GSSeSG + GSH \longrightarrow GSSeH + GSSG$

$GSSeH + GSH \longrightarrow H_2Se + GSSG$

Scheme 1



Scheme 2

study of the catalytic properties of selenium for organic synthesis,[5] we report here that the reductive debromination of *vic*-dibromides may be achieved with Na_2SeO_3 and thiol (CysSH or GSH) and that it proceeds catalytically with respect to Na_2SeO_3.

General procedure is as follows: CysSH (3 mmol) and Na_2SeO_3 (0.3 mmol) in water (10 ml) were stirred at 0 °C under an argon atmosphere. The colour of the solution turned to red immediately. Dibromide (0.3 mmol) in tetrahydrofuran (THF) (40 ml) was added to the red solution and stirred at 0 °C. When the colour of the reaction mixture turned grey (probably due to the formation of metallic selenium), the reaction mixture was diluted with water (10 ml), and then extracted with ether. The crude product was purified by chromatography on a short silica-gel column.

Table 1 shows the results concerning the debromination of *vic*-dibromides. *trans*-Stilbene was produced from *meso*-1,2-dibromo-1,2-diphenylethane in a high yield (entry 1). No reaction occurred with only CysSH (without Na_2SeO_3). The debromination of (±)-1,2-dibromo-1,2-diphenylethane did not occur in THF–water (entry 2) but it proceeded smoothly in dimethyl sulphoxide (DMSO)–water to give a ratio of *cis* : *trans* stilbene of 11 : 1 (entry 3). The observed stereoselectivities for the eliminations are consistent with a concerted *anti*-elimination process. The other benzylic *vic*-dibromides similarly gave the corresponding alkenes in a high yield (entries 4—6). Cholesterol dibromide underwent smooth debromination whereas 1,2-dibromocyclododecane was inert. The *trans* diaxial arrangement of the bromine substituents in the former facilitates elimination; such an arrangement is difficult to achieve in the latter dibromide. When GSH was used as reductant instead of CysSH, debromination in water (10 ml) and THF (40 ml) of *meso*-1,2,dibromo-1,2-diphenylethane scarcely occurred, but the reaction in water (20 ml) and THF (30 ml) proceeded in the presence of Na_2CO_3 (5 equiv.) (entry 9). The reaction mixture with GSH was more acidic than that with CysSH owing to the glutamic acid residue of GSH. This shows that the pH of the reaction mixture and the solubility of GSH are important for this reaction.

The catalytic debromination of *vic*-dibromides was examined with *meso*-1,2-dibromo-1,2-diphenylethane as substrate. When 0.1 equiv. of Na_2SeO_3 was used with CysSH (10 equiv.), the reaction did not proceed to completion, but did proceed quantitatively to give *trans*-stilbene within 5 min in the presence of Na_2CO_3 (5 equiv.). Presumably the hydrobromic acid produced during the debromination prevents further reaction. This reaction proceeded quantitatively with only 0.01 equiv. of Na_2SeO_3 catalyst for 40 min in the presence of CysSH and Na_2CO_3, but the reaction scarcely occurred without Na_2SeO_3 for 40 min (yield 4%). Na_2SeO_3 is therefore essential to the reaction.

It has been reported that selenite reacts with GSH to form the seleno-trisulphide (GSSeSG) and that GSSeSG reacts with further GSH forming a seleno-persulphide ($GSSe^-$) at the physiological pH in the presence of excess GSH (Scheme 1).[6] Scheme 2 shows one of the possible mechanisms for reductive debromination. However, because further reduction of $GSSe^-$ to H_2Se occurs to some degree, the possibility of the involvement of H_2Se (or HSe^- or Se^{2-}) as the active reductant could not be ruled out.

In conclusion, it has been demonstrated that *vic*-dibromides can be converted to alkenes in good yields with Na_2SeO_3–CysSH or GSH. This reaction proceeds catalytically with respect to Na_2SeO_3 in the presence of Na_2CO_3. The debromination of *vic*-dibromides to alkenes is important in synthesis as a deprotection method[7] and this procedure should be an attractive addition to existing methodology. This system is inexpensive, easy to handle, and produces little smell. The reaction is very rapid under mild conditions and good yields of alkenes are obtained. Furthermore, this reaction is interesting from a biological standpoint. It is known that selenium may act as an anticarcinogen (for example, selenium acts as a chemopreventative agent against mammary carcinogenesis).[8] Though there is no example in which selenium inhibits the carcinogenic property of *vic*-dibromide, the catalytic debromination may be interesting if it is thought that similar reactions may occur in biological systems.

Received, 19th February 1990; Com. 0/00762E

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