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Regioselective radical elimination of *o*-(bromoaryl)sulfides

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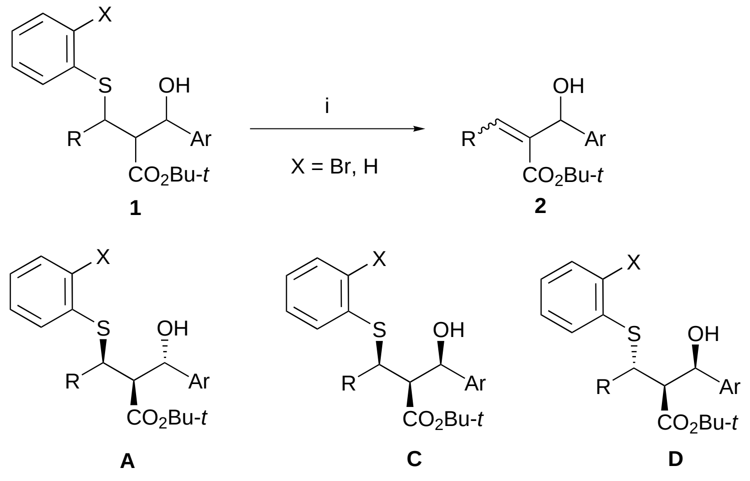
Abstract—Treatment of *o*-(bromophenyl)sulfides with Bu_3SnH or $(Bu_3Sn)_2$ resulted in the regioselective elimination of thiol to give internal or terminal alkenes, which depend on radical conditions initiated thermally or photochemically, respectively. © 2001 Elsevier Science Ltd. All rights reserved.

Although β-elimination from hydrogen halides or analogues is regarded as a fundamental reaction in organic chemistry as well as providing a useful procedure to introduce an alkene unit in a molecule, a problem regarding the regiochemistry is sometimes incurred.[1] If hydrogen atoms, for example, exist in only one carbon adjacent to the carbon bearing the leaving group, the β-elimination takes place in only one way to give a single alkene selectively. On the other hand, the elimination from the molecules containing two or more carbons bearing the hydrogen atoms to be abstracted results in the formation of a mixture of regioisomers of alkenes. This classic problem, known as controlling the Zaitsev and Hofmann elimination, has been discussed and rationalized in terms of steric, thermodynamic or electronic factors. From the point of view of molecular construction, however, it often spoils the synthetic potential of the β-elimination, and many alternative routes to generate carbon–carbon double bonds have been developed so far.[2] Conversion of sulfides or selenides to alkene is, for example, readily accomplished through thermal treatment of sulfoxides or selenoxides.[3] Although its synthetic utility has been firmly established, application of these procedures to a



1a; X = H, Ar = Ph, R = Me
1b; X = Br, Ar = Ph. R = Me
1c; X = Br, Ar = 1-naphthyl, R = Me
1d; X = Br, Ar = Ph, R = C_3H_7-

Scheme 1. *Reagents and conditions*: (i) Bu_3SnH, AIBN, toluene, 80°C, 1 h.

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molecule containing this problem usually gives a mixture of regioisomeric alkenes.[4] During the course of our investigation on the development of tandem Michael/aldol strategy,[5,6] we were interested in the hydrogen-transfer-type radical elimination of the arylthio group from *o*-bromosulfides.[7] In this paper, we describe that the radical elimination of arylthiol is effectively controlled by the choice of thermal or photochemical reaction conditions, and almost complete switching of the orientation of the elimination is achieved. Additionally, highly stereospecific *syn*-elimination is clearly observed in an open-chain system.

The starting materials, β-arylthio-α-(hydroxyalkyl)-esters **1**, were prepared through our tandem Michael/aldol methodology.[5d] Due to the presence of three contiguous stereogenic centers in **1**, there was a possibility that four diastereomers occurred, but three out of the four isomers, **A**, **C** and **D**, were prepared in a diastereomerically pure form or as a mixture of two diastereomers, the ratio of which was determined by HPLC or NMR analyses. With these starting materials **1** in hand, the radical elimination reaction was examined (Scheme 1). The results are summarized in Table 1.

In the absence of an *o*-bromo group, no reaction took place (entry 1). Treatment of *o*-bromo derivative **1b-A** with Bu_3SnH in the presence of AIBN at 80°C, however, resulted in smooth disappearance of **1b-A** and α,β-unsaturated ester **2b** was isolated in 72% yield, in which the *E*/*Z* ratio was found to be 96/4 (entry 2). A mixture of **1b-C** and **1b-D** (38/60, containing 2% of **1b-A**) also underwent the radical elimination to give a mixture of *E*- and *Z*-**2b** in the ratio of 37/63 (entry 3). These results suggest that the *E*/*Z* ratio of **2b** almost reflects the diastereomeric ratio of **1b**; the elimination from **1b-A** and **1b-C** gives *E*-**2b** and diastereomers **B** and **D** afford *Z*-**2b**. Thus, the present radical elimination occurs mainly through a stereospecific *syn*-elimination process. Similar stereospecificity was observed in the radical elimination of **1c** and **1d** (entry 4 and 5). The configuration of *E*- or *Z*-**2** was determined by the NMR spectrum. Due to an anisotropic effect from the ester carbonyl group, the vinyl proton in *E*-**2b**, for example, appeared at 6.97 ppm, which was down field of 6.21 ppm where the corresponding vinyl proton in *Z*-**2b** appeared.

Although the present stereospecific elimination provides a useful alternative procedure to convert sulfides to alkenes, this conversion destroys two out of three seterogenic centers in **1**. Switching of the orientation of the elimination to give a terminal vinyl unit would enhance its synthetic potential because the two stereogenic centers which were generated in the tandem Michael/aldol reaction survive after the conversion. To the best of our knowledge, however, so far there have been no practical examples to introduce a double bond in the β,γ-position of the esters using sulfoxide or selenoxide chemistry. We examined the same reaction at low temperature, expecting change in the orientation of the elimination to give β,γ-unsaturated esters preferentially. UV irradiation was employed for the initiation of the radical elimination (Scheme 2). The results are summarized in Table 2.

UV irradiation to a mixture of Bu_3SnH (1.1 equiv.) and **1b-A** in toluene at 0°C triggered the reaction smoothly, giving a mixture of four fragmented products, **3**, **4**, *E*- and *Z*-**2b**, in 87% of total yield, the ratio of which was found to be 51/30/11/8 (entry 1). The structure of the products was determined on the basis of NMR and HPLC comparison of authentic samples. The first trial, giving the desired β,γ-unsaturated ester **3** as a major product, encouraged us to improve the reaction condi-

Table 1. Thermal elimination of thiophenol from **1**[a]

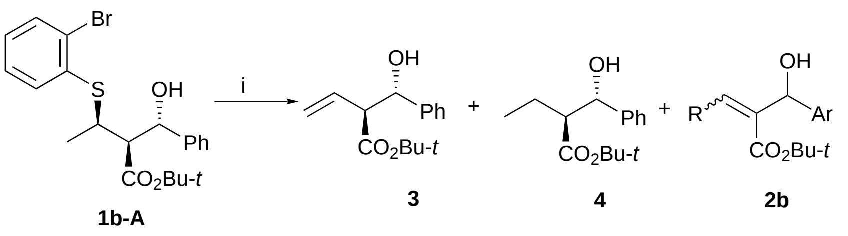
Entry	R	Ar	X	**A**/**B**/**C**/**D**	**2**	Yield (%)[b]	*E*/*Z*[c]
1	Me	Ph	H	100/0/0/0	**2a**	0	–
2	Me	Ph	Br	100/0/0/0	**2b**	72	96/4
3	Me	Ph	Br	2/0/38/60	**2b**	98	37/63
4	Me	1-$C_{10}H_7$-[d]	Br	0/0/17/83	**2c**	63	16/84
5	C_3H_7-	Ph	Br	3/0/38/59	**2d**	81	34/66

[a] Reaction conditions: **1** (0.5 mmol), Bu_3SnH (1 mmol), AIBN (0.01 mmol), toluene (75 mL), 80°C.

[b] Isolated yield.

[c] Determined by ^1H NMR analyses.

[d] 1-Naphthyl.



Scheme 2. *Reagents and conditions*: (i) Bu_3SnH or $Bu_3SnSnBu_3$, AIBN, toluene or benzene, 0°C, *hv*.

Table 2. Photochemically initiated elimination of thiophenol from **1b**-**A**

Entry	Solvent	Reagent	Time (h)	Yield (%)[a]	**3**/**4**/**2b**/**1a**[b,c]	$\beta,\gamma/\alpha,\beta$
1	Toluene	Bu_3SnH	1	87	51/30/19(56/44)/0	86/14
2	Toluene	Bu_3SnH	12[d]	72	62/24/14(51/49)/0	86/14
3	Toluene	$Bu_3SnSnBu_3$	1	90	70/11/19(73/27)/0	81/19
4	Toluene	$Bu_3SnSnBu_3$	3[e]	85	67/0/4(100/0)/28	94/6
5	Benzene	$Bu_3SnSnBu_3$	3[e]	97	70/0/2(100/0)/20	97/3

[a] Isolated yield.

[b] Determined by ^1H NMR analyses.

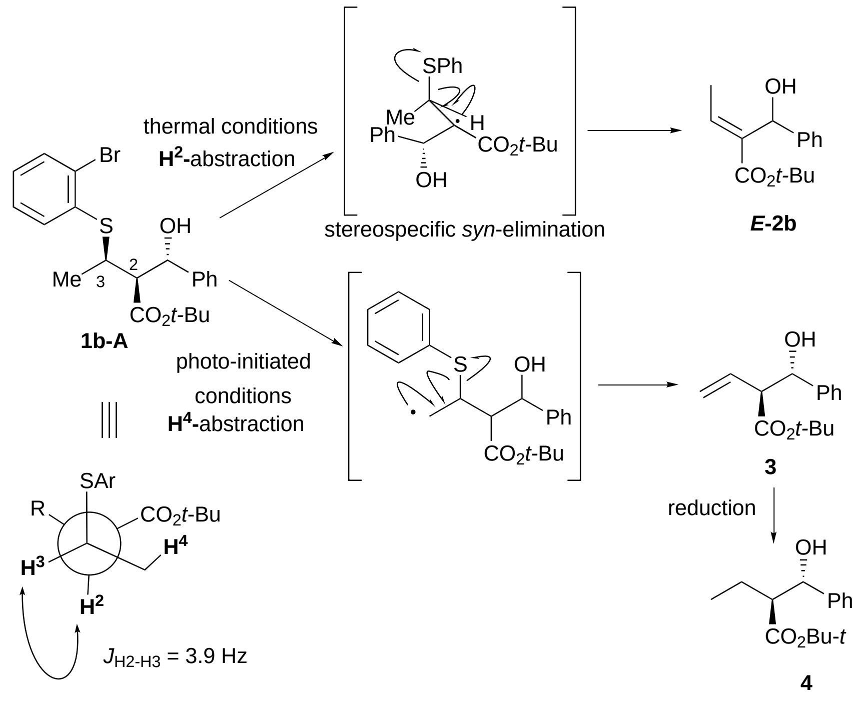
[c] *E*/*Z* ratio for **2b** in parentheses.

[d] Tin reagent was slowly added over 12 h.

[e] Tin reagent was slowly added over 2 h.

tions. Since no diastereomer of **4** was observed in the reaction mixture, we suspected that **4** should be formed from the reduction of **3** in the presence Bu_3SnH. To suppress the formation of **4**, Bu_3SnH solution was added slowly over 12 h to control its concentration as low as possible (entry 2). As we expected, formation of **4** decreased to some extent, but not completely. The $\beta,\gamma/\alpha,\beta$ ratio, representing regioselectivity of the elimination, did not change very much. From the point of view of the reaction mechanism, when the elimination completes, the parent molecule releases a thiyl radical, which then abstracts hydrogen from Bu_3SnH to give thiophenol, which might act as a potential reducing source to convert **3** to **4**. Accordingly, we used $(Bu_3Sn)_2$ instead of Bu_3SnH to remove any hydride source from the reaction mixture (entry 3 and 4). No trace amounts of **4** were detected in the NMR spectra of the reaction mixture under the conditions of slow addition of $(Bu_3Sn)_2$, although there was accompanying formation of a small amount of simple debrominated product **1a** (entry 4). The regioselectivity of the elimination was improved to 94/6 under these conditions. The reaction carried out in benzene provided the best result in which the desired **3** was produced in a good regioselective manner (entry 5). Thus, we achieved almost complete switching of the orientation of the radical elimination under the photochemically initiated radical elimination at low temperature.[8]

Scheme 3 depicts a plausible reaction pathway of the elimination: at first, the bromine atom at the ortho position in **1** is abstracted by the tributylstannyl radical to give an aryl radical, which then abstracts a hydrogen affording a (β-phenylthio)alkyl radical. Subsequent fragmentation of the (β-phenylthio)alkyl radical gives a thiyl radical and an alkene **2** or **3**.[9] High stereospecificity observed under the thermal elimination conditions suggests that formation of **2** should mainly come from the direct elimination from **1**, not by the isomerization of **3**. Thus, the orientation of the elimination should be determined in the step of hydrogen abstraction. The abstraction from the terminal methyl group, for exam-



Scheme 3.

ple, results in the formation of **3** and that from the tertiary carbon gives **2**. The latter hydrogen should be favored to be abstracted under the thermal conditions so that α,β-unsaturated ester **2** was prepared predominantly. Additionally, stereochemical elucidation supports that **1** undergoes a high level of stereospecific *syn*-elimination. On the other hand, at low temperature, hydrogen abstraction from the terminal methyl group was preferred. In the ^{1}H NMR spectrum for **1b-A**, coupling constant between H^2 and H^3 was measured to be 3.9 Hz, which suggests that these two protons locate in a *gauche* conformation.[10] Thus, the arylthio group and the tertiary hydrogen occupy *anti*-periplanar positions so that abstraction of the tertiary hydrogen becomes difficult. As a result, the aryl radical abstracts a hydrogen atom from the terminal C4-methyl group selectively and β,γ-unsaturated ester **3** is obtained as the main product. Overreduction of **3** to give **4** happens if a hydrogen source such as Bu_3SnH or thiophenol exists in the reaction mixture.

In conclusion, the present hydrogen atom-transfer-type radical elimination from *o*-(bromophenyl)sulfides can be controlled regiochemically by the choice of the reaction conditions. Further studies on this chemistry are underway in our laboratory.

Acknowledgements

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8. Photoreaction from a mixture of **1b-C** and **1b-D** also gave β,γ-unsaturated ester in good yield, but the product was contaminated with α,β-unsaturated ester.
9. Comparison of BDE between Ar–H and C–H shows that this abstraction exclusively happens to give an alkyl radical. See: Isaacs, N. S. *Physical Organic Chemistry*, 2nd ed.; Longman Scientific and Technical, 1995; p. 43.
10. This *gauche* conformation is also observed in the X-ray analysis in the analogous compound. See: Ref. 5c.