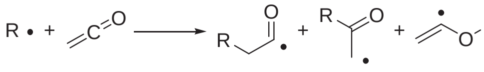
Radical Addition of Alkyl Halides to 2-Methylene-1,3-dithiane Monoxide as a Ketene Equivalent

Suguru Yoshida, Hideki Yorimitsu,* and Koichiro Oshima*
Department of Material Chemistry, Graduate School of Engineering, Kyoto University,
Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510

(Received December 22, 2008; CL-081198; E-mail: yori@orgrxn.mbox.media.kyoto-u.ac.jp,
oshima@orgrxn.mbox.media.kyoto-u.ac.jp)

Radical addition reaction of alkyl halides with ketene dithioacetal monoxide in the presence of tributyltin hydride and a catalytic amount of 2,2′-azobis(isobutyronitrile) (AIBN) proceeds smoothly to provide the corresponding adducts in moderate to high yields.

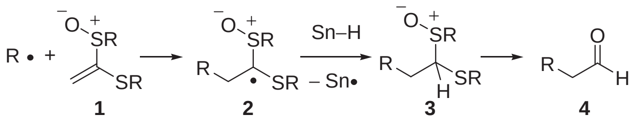
Ketene is one of the most important building blocks for synthesis of carbonyl compounds.[1,2] However, few radical reactions using ketene have been reported,[3] because of the difficulty to control the regiochemistry in the addition of radicals to ketene[4] (eq 1). Radical addition to ketene equivalents, instead of ketene itself, has also been limited,[5] although the reaction provides us with an alternative route to various carbonyl compounds via radical pathways. Therefore, development of new methods for the radical addition reaction to a novel ketene equivalent as a radical acceptor would provide a powerful synthetic tool.



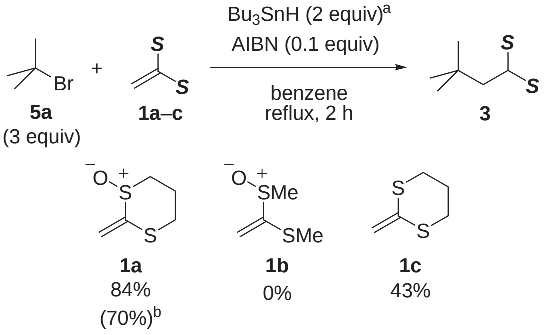
(1)

Recently, we have been pursuing the synthetic utility of ketene dithioacetal monoxides as ketene equivalents.[6] Ketene dithioacetal monoxides should be good candidates for a radical acceptor because radical intermediate **2**, generated by the addition of alkyl radical to ketene dithioacetal monoxide **1**, would be well-stabilized by both sulfanyl and sulfinyl groups due to captodative effect[7] (Scheme 1). The stability of intermediate **2** could prevent undesired side reactions such as polymerization. Here, we report radical addition of alkyl halides to ketene dithioacetal monoxide **1** as a ketene equivalent.

Tributyltin hydride (2.0 equiv) was added to a mixture of *tert*-butyl bromide (**5a**) (3.0 equiv) and a ketene dithioacetal derivative **1a**, **1b**, or **1c** (1.0 equiv) over 1 h in the presence of 0.1 equiv of 2,2′-azobis(isobutyronitrile) (AIBN) as a radical initiator in boiling benzene (Scheme 2).[8] Among three ketene dithioacetal derivatives, 2-methylene-1,3-dithiane 1-oxide (**1a**) was found to be the best radical acceptor. The reaction of **5a** with **1a** afforded **3a** in 84% yield. To our surprise, the reaction with acyclic reagent **1b** failed to afford the corresponding adduct, instead yielding a complex mixture. Treatment of **5a** with 2-methylene-1,3-dithiane (**1c**) provided the desired product **3c** in only 43% yield. It is worth noting that sulfoxide **3a** could be separated by silica-gel column purification without contamination by tin residues due to the high polarity of **3a**.



Scheme 1.



[a] Slow addition over 1 h.
[b] **5a** (1.0 equiv), **1a** (1.2 equiv), AIBN (0.2 equiv), Ph_3SnH (2.0 equiv, slow addition over 1 h), benzene, reflux, 2 h.

Scheme 2.

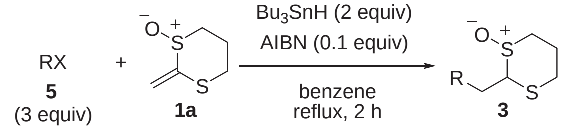
The use of triphenyltin hydride instead of tributyltin hydride could decrease the amount of alkyl halide. Thus, the reaction of *tert*-butyl bromide (**5a**) (1.0 equiv) with ketene dithioacetal monoxide **1a** (1.2 equiv) in the presence of triphenyltin hydride (2.0 equiv) and AIBN (0.2 equiv) gave the corresponding adduct **3a** in 70% yield.[9]

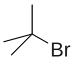
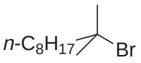
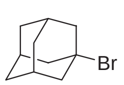
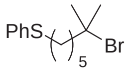
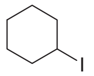
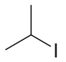
Then, we examined the scope of alkyl halides (Table 1). In the case of tertiary alkyl bromides (Entries 1–4), desired products were obtained in high yields. The phenylsulfanyl group was tolerated under the reaction conditions (Entry 4). Secondary and primary alkyl halides also underwent the radical reaction smoothly with **1a** (Entries 5–7). Secondary alkyl iodides **5e** and **5f** were converted to the corresponding adducts in good yields in the reactions with **1a**, although the products were mixtures of two diastereomers. Primary alkyl iodide **5g** reacted with **1a** to provide **3g** in moderate yield.

We next examined the utility of the products (Scheme 3). The dithioacetal monoxide moiety could be removed smoothly without using toxic mercury reagents. Treatment of sulfoxide **3b** with a catalytic amount of sulfuric acid in hot toluene afforded aldehyde **6** in almost quantitative yield. In addition, sulfoxide **3b** could be reduced easily into 1,3-dithiane.[10] Treatment of sulfoxide **3b** with trifluoroacetic anhydride and sodium iodide gave 1,3-dithiane **7** in high yield.

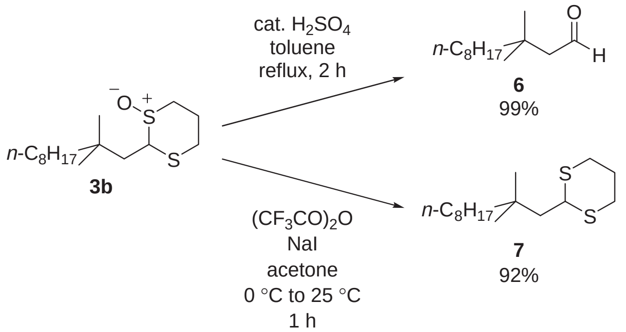
In order to develop the further utility of the radical addition products of ketene dithioacetal monoxide, tertiary alkyl bromide **8** bearing an amide moiety[11] was subjected to the reaction with **1a** (Scheme 4). The reaction proceeded efficiently to give desired adduct **9** in high yield. Then, the product **9** was treated with hydrochloric acid followed by an addition of benzoyl chloride to

Table 1. Reactions of alkyl halides with sulfoxide **1a** in the presence of tributyltin hydride and a catalytic amount of AIBN

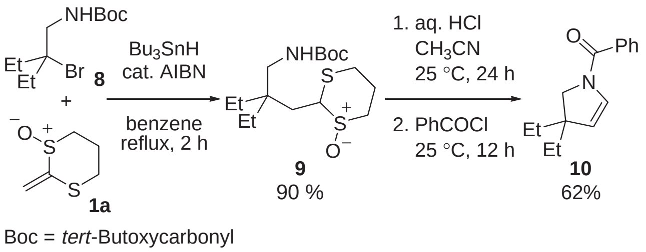


Entry	RX	5	3	Yield/%[a]
1		**5a**	**3a**	84
2		**5b**	**3b**	84
3		**5c**	**3c**	91 (d.r. = 17:1)
4		**5d**	**3d**	67
5		**5e**	**3e**	75[b] (d.r. = 8:1)
6		**5f**	**3f**	80[b] (d.r. = 6:1)
7	*n*-$C_6H_{13}I$	**5g**	**3g**	58[b] (d.r. = 3:1)

[a]Isolated yields. [b]AIBN (0.2 equiv).



Scheme 3.



Scheme 4.

provide dihydropyrrole **10** bearing a quaternary carbon atom in good yield. This result shows that the radical addition reaction would be useful for the synthesis of heterocycles bearing such a quaternary carbon moiety.

In conclusion, we have developed radical addition of alkyl halides to 2-methylene-1,3-dithiane 1-oxide as a ketene equivalent in the presence of tributyltin hydride and a catalytic amount of AIBN. The reaction afforded alkanal equivalents protected as dithioacetal monoxide, which can be removed easily with sulfuric acid. The products could be subjected to a variety of organic transformations.

This work was supported by Grants-in-Aid for Scientific Research, COE Research, and Global COE Research from JSPS. S.Y. acknowledges JSPS for financial support.

References and Notes

1 For recent review, see: T. T. Tidwell, *Eur. J. Org. Chem.* **2006**, 563.

2 Selected examples: a) H. Staudinger, *Justus Liebigs Ann. Chem.* **1907**, *356*, 51. b) H. Wynberg, E. G. J. Staring, *J. Am. Chem. Soc.* **1982**, *104*, 166. c) H. Wynberg, E. G. J. Staring, *J. Org. Chem.* **1985**, *50*, 1977. d) T. Machiguchi, J. Okamoto, J. Takachi, T. Hasegawa, S. Yamabe, T. Minato, *J. Am. Chem. Soc.* **2003**, *125*, 14446.

3 W. Huang, H. Henry-Riyad, T. T. Tidwell, *J. Am. Chem. Soc.* **1999**, *121*, 3939.

4 K. Sung, T. T. Tidwell, *J. Org. Chem.* **1998**, *63*, 9690.

5 K. Ogura, N. Sumitani, A. Kayano, H. Iguchi, M. Fujita, *Chem. Lett.* **1992**, 1487.

6 a) S. Yoshida, H. Yorimitsu, K. Oshima, *J. Organomet. Chem.* **2007**, *692*, 3110. b) S. Yoshida, H. Yorimitsu, K. Oshima, *Synlett* **2007**, 1622. c) S. Yoshida, H. Yorimitsu, K. Oshima, *Org. Lett.* **2007**, *9*, 5573. d) S. Yoshida, H. Yorimitsu, K. Oshima, *Chem. Lett.* **2008**, *37*, 786. e) S. Yoshida, H. Yorimitsu, K. Oshima, *Heterocycles* **2008**, *76*, 679.

7 H. G. Viehe, Z. Janousek, R. Merenyi, *Acc. Chem. Res.* **1985**, *18*, 148.

8 Experimental procedure: A benzene (1.0 mL) solution of 2-methylene-1,3-dithiane 1-oxide (**1a**, 49.4 mg, 0.33 mmol), 2-bromo-2-methylpropane (0.11 mL, 0.99 mmol), and 2,2′-azobis(isobutyronitrile) (5.0 mg, 0.030 mmol) was placed in a flask under an atmosphere of argon. Then, a benzene (1.0 mL) solution of tributyltin hydride (0.18 mL, 0.66 mmol) was added over 1 h with a syringe pump at reflux. After the addition was completed, the mixture was stirred for an additional 1 h at the same temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by chromatography on silica gel (hexane/AcOEt = 1/2) provided 2-(2,2-dimethylpropyl)-1,3-dithiane 1-oxide (**3a**, 58.0 mg, 84%).

9 Smooth hydrogen abstraction from triphenyltin hydride would increase the efficiency of the reaction, because of the weaker Sn–H bond of triphenyltin hydride. See: C. Chatgilialoglu, M. Newcomb, *Adv. Organomet. Chem.* **1999**, *44*, 67.

10 M. deGreef, S. Z. Zard, *Tetrahedron* **2004**, *60*, 7781.

11 A. Sliwinska, A. Zwierzak, *Tetrahedron* **2003**, *59*, 5927.