CHEMISTRY LETTERS, pp. 1457−1460, 1991.

Synthesis of γ-Lactones by the Intramolecular Radical Cyclization of 2-Bromo-3,3-bis(methylthio)propionates. A Useful Ketene Radical Synthon

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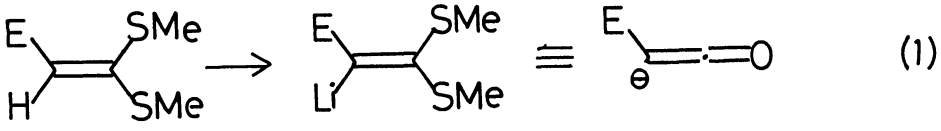
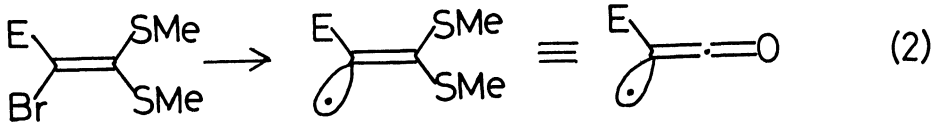
The first example of intramolecular radical cyclization of ketene radical synthon is presented. Intramolecular radical cyclization of 2-bromo-ketene-S,S-acetals proceeded highly regioselectively to give the corresponding 5-exo-trig cyclized γ-lactones.

Synthetic applications of ketene-S,S-acetals substituted with electron withdrawing groups at C(2)-position have been well studied to construct a variety of heterocyclic systems.[1] The advantage of this method is that acetal can be easily prepared by the known procedure[2] and the C(2) carbon atom is highly activated by the effect, generally known as push-pull or donor-acceptor effect. Thus an anion or a radical can be generated at this position by the effective stabilization. In previous studies, we demonstrated the preparation of ketene enolate anions from ketene-S,S-acetals and its synthetic utility (Eq. 1).[3] In this paper, our interest has been focused on the generation of the radical version of ketene radical synthon (Eq. 2).



(1)

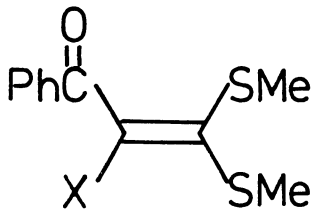


(2)

E = electron-withdrawing group

This is a unique concept since radicals have never been accounted to be utilized as ketene radical synthon.[4] Exposure of ketene-S,S-acetals to a radical reaction would result in a nasty reaction, because carbon-sulfur bonds are believed to be fragile under those conditions.[5] We looked for a possibility to create a hitherto unknown type of ketene radical synthon and we reported here the successful preparation of ketene radical synthon and its intramolecular radical cyclization reaction assisted by tri-n-butyltin hydride.[6]

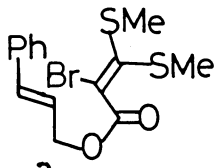
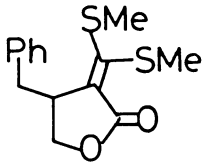
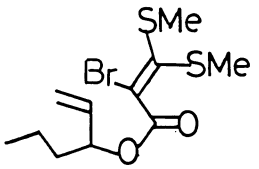
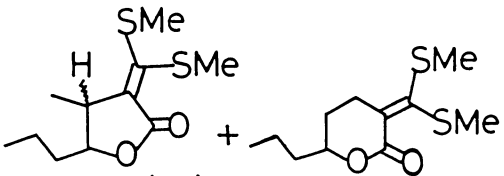
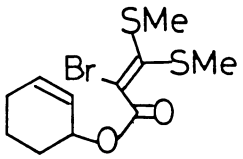
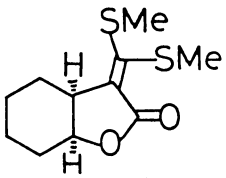
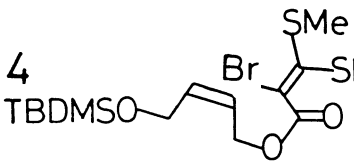
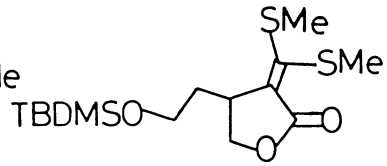
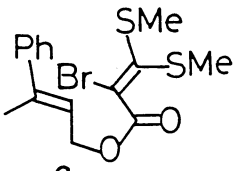
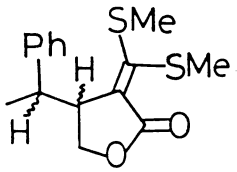
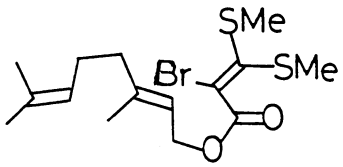
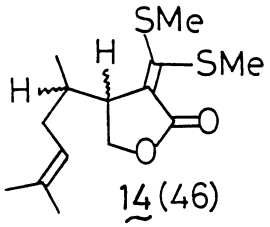
At first, we found that ketene-S,S-acetal unit as a protecting group was stable under the standard radical reaction condition.[7] The ketene radical precursor was prepared via an introduction of bromine at C(2) position by the reaction of ketene-S,S-acetals with N-bromosuccinimide (NBS) in CCl_4 at room temperature.[8] 2-Benzoyl-2-bromo-ketene-S,S-acetal (1b) obtained was reduced efficiently to 2-benzoyl-ketene-S,S-acetal (1a) by treating with tri-n-butyltin hydride and azobisisobutyronitrile (AIBN) at 80 °C in dry toluene.



1a : X = H
1b : X = Br

Since the S,S-dimethyl acetal group was inactive under the above mentioned radical reaction conditions, we attempted an intramolecular radical cyclization using this synthon. The results are shown in Table 1.[9] The radical cyclization proceeded highly regioselectively to give 5-exo-trig cyclized γ-lactones with ketene-S,S-acetals at α-position (in entries 1, 3, 4, 5,and 6). In the case of entry 2, 5-exo-trig cyclized compound 9 and thermodynamically stable product 10 were obtained in the ratio of 1:1 respectively.[10] In entries 5 and 6, the stereoselectivity of the radical cyclization was almost 1:1.[11] However, in cyclic system, the radical cyclization of the ketene radical synthon showed high regio and stereoselectivity (entry 3). The obtained cyclized ketene-S,S-acetals 8—14 could be converted to the corresponding γ-lactones with carboalkoxy group at α-position.

Table 1. Intramolecular Radical Cyclizations of Ketene Radical Synthon

Entry	Ketene-S,S-acetals	Products (Yield/%) [a]	syn:anti [b]
1	 2	 8 (71)	
2	 3	 9 (23) + 10 (45)	
3	 4	 11 (53)	(>99:1)
4	 5	 12 (68)	
5	 6	 13 (69)	(1:1)
6	 7	 14 (46)	(1:1)

a) Isolated yield. b) Determined by 270 MHz ^{1}H-NMR analysis.

References

1) For recent reviews, see M. Yokoyama, and Y. Tominaga, Yuki Gosei Kagaku Kyokaishi, 47, 413 (1989); H. Junjappa, H. Ila, and C.W. Asokan, Tetrahedron, 46, 5423 (1990) and references therein.

2) R. K. Dieter, J. Org. Chem., 46, 5031 (1981).

3) M. Yamamoto, T. Takemori, S. Iwasa, S. Kohmoto, and K. Yamada, J. Org. Chem., 54, 1457 (1989).

4) For acyl radical synthon; A. Nishida, M. Nishida, and O.Yonemitu, Tetrahedron Lett., 31, 7035 (1990).

5) J. M. McIntosh and C. K. Scharm, Can. J. Chem., 55, 3755 (1977); G. G. Gutierrez, R. A. Stringham, T. Nitasaka, and K. G. Glasscock, J. Org. Chem., 45, 3393 (1980); G. G. Gutierrez, and L. R. Summerhays, ibid., 49, 5206 (1984).

6) For reviews see B. Giese, "Radicals in Organic Synthesis, Formation of Carbon-Carbon Bonds," Pergamon Press, Oxford (1986), and references therein.

7) Dithioacetal 1a was found to be inert under heating at 80°C in toluene with tri-n-butyltin hydride and AIBN.

8) G. Singh, H. Ila, and H. Junjappa, Synthesis, 1985, 165.

9) General Procedure: Intramolecular Radical Cyclization of 2b; A mixture of 2b (0.1100 g, 0.30 mmol), tri-n-butyltin hydride (0.1050 g, 0.36 mmol), and catalytic amount of azobisisobutyronitrile (AIBN) (0.0050 g, 0.1 equiv.) in dry and degassed benzene (150 mL) (0.002 M) was heated at 80°C under an argon for 2 h. The mixture was purified by flash column chromatography on silica gel using benzene as an eluent to give cyclized product, γ-lactone 8 in 71%. 8; IR (neat) 1740, 1560, 1210, 1090 cm^{-1} ^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.49 (s, 3H), 2.52 (s, 3H), 2.65 (dd, 1H, J = 13.9 and 10.8 Hz), 3.12 (dd, 1H, J = 13.9 and 4.2 Hz), 3.66 (dddd, 1H, J = 10.8, 4.2, 4.2, and 4.2 Hz), 4.20 (d, 2H, J = 4.2 Hz), 7.18-7.36 (m, 5H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ (INEPT) 17.79 (CH_3), 18.37 (CH_3), 39.03 (CH_2), 45.15 (CH), 68.34 (CH_2), 126.80 (CH), 128.40 (C), 128.69 (CH), 129.15 (CH), 138.31 (C), 153.13 (C), 167.21 (C). HRMS M^+, found m/z 280.0590 calcd for $C_{14}H_{16}O_2S_2$ M^+ 280.0549.

10) The determination of the ratio and separation of the diastereomers were carried out with a Hitachi L-6000 HPLC system using a 250X10 mm column packed with Merck Lichrosorb Si 60.

11) Reference 6, p. 147 in Chap. 4.

(Received May 30, 1991)