Peri-selectivity in Thermolysis of Acyloxybenzocyclobutenes Possessing α,β-Unsaturated Carbonyl Group: Synthesis of 2-Benzoxocin Derivatives

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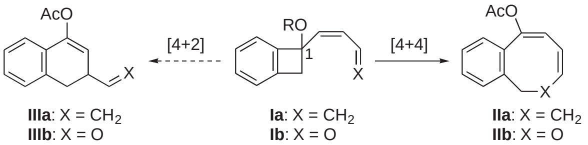
1-Acyloxybenzocyclobutenes, having an α,β-unsaturated carbonyl group at C1 position, undergo the periselective thermal ring expansion to give 2-benzoxocin derivatives in high yields.

We previously reported a selective approach to benzocyclooctene **IIa** via four-carbon ring expansion of dienylbenzocyclobutenol derivative **Ia** (Scheme 1).[1] By analogy, we became interested in the corresponding reactions of the oxo-analogue **Ib**, 1-acyloxybenzocyclobutene possessing an α,β-unsaturated carbonyl group on the four-membered ring, which is reported in this communication.

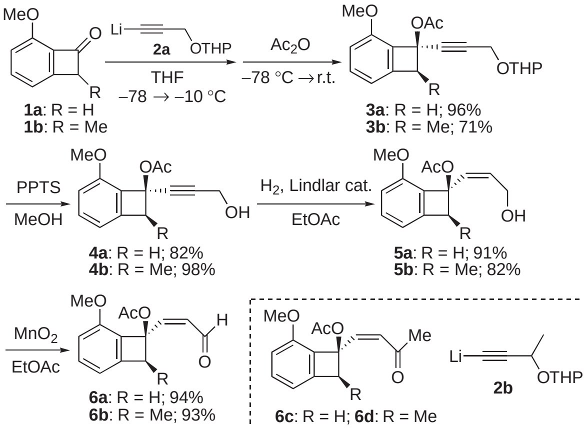
Particularly notable is the high *peri*-selectivity in that the four-atom ring expansion of **Ib** normally predominates over the corresponding two-carbon ring expansion, providing a facile access to eight-membered ethers **IIb**.[2]



Scheme 1.

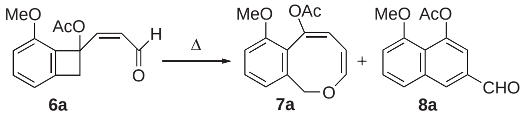
Scheme 2 illustrates preparation of the starting material **6** from benzocyclobutenones **1a** and **1b**, which, in turn, were easily prepared by the regioselective $[2 + 2]$ cycloaddition of α-alkoxybenzyne and ketene silyl acetals.[3]

For example, treatment of **1a** with alkynyllithium **2a** followed by trapping of the resulting lithium alkoxide in situ with Ac_2O gave the product **3a** in 96% yield. Removal of the THP group in **3a** gave propargyl alcohol **4a**, and half-reduction of its triple bond followed by oxidation furnished enal **6a**.



Scheme 2.

Table 1.



Entry	Conditions	Product (Yield/%)	
		7a	**8a**
1	toluene, 110 °C, 3 h	74	22
2	1,4-dioxane, 100 °C, 4 h	73	22
3	1-butanol, 110 °C, 3 h	60	23
4	DMF, 110 °C, 2 h	40	34

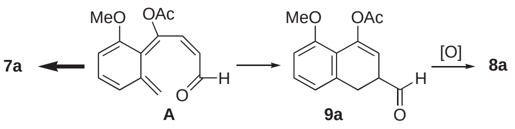


Figure 1.

Similar sequence of reactions starting from **1b** afforded **6b** as a single product in high yield. The relationship of the acyloxy group and methyl group on the four-membered ring was determined by NOE study.

In a similar manner, enones **6c** and **6d** were obtained by alkynyllithium **2b** and the benzocyclobutenones **1a** or **1b**.

After screening of various cyclization conditions, it turned out that simple heating in toluene (110 °C, 3 h) effected the skeletal change of enal **6a**, giving benzoxocin **7a** in 74% yield (Table 1).[4] In this case, however, a considerable amount (22% yield) of naphthalene **8a** was obtained, which could be rationalized by the 6π-electrocyclization of the quinodimethane intermediate **A** followed by air-oxidation of the resulting dihydronaphthalene **9a** (Figure 1). 1,4-Dioxane was also the solvent of choice in terms of the *peri*-selectivity, giving **7a** and **8a** in 73% and 22% yields, respectively (Entry 2). On the other hand, the use of 1-butanol and DMF as the solvent gave lower yields of eight-membered ring ether **7a** (Entries 3 and 4).

Application of the protocol to other substrates is summarized in Table 2. Enal **6b**, having a methyl group on the four-membered ring, rearranged to give ether **7b** in 82% yield without forming the 6π-cyclization product (Entry 1). Careful crystallization of **7b** (hexane–EtOAc) gave single crystals suitable for X-ray analysis,[5] which revealed a characteristic feature in the eight-membered ring, i.e. a non-planer, twist-boat conformation of the 1,3,5-cyclooctatriene moiety (Figure 2).[6]

The thermal reaction was also applied to enones **6c** and **6d** to achieve clean ring expansion to give the corresponding cyclized products **7c** and **7d** in 78% and 83% yields, respectively. In the former case, however, the 6π cyclization was observed as a side reaction.

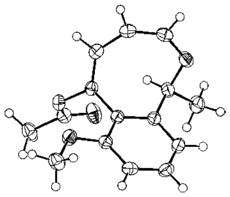
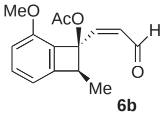
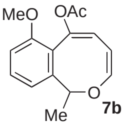
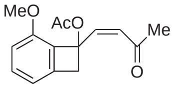
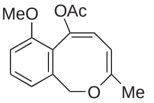
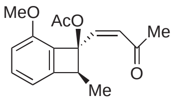
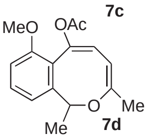


Figure 2. ORTEP drawing of compound **7b**.

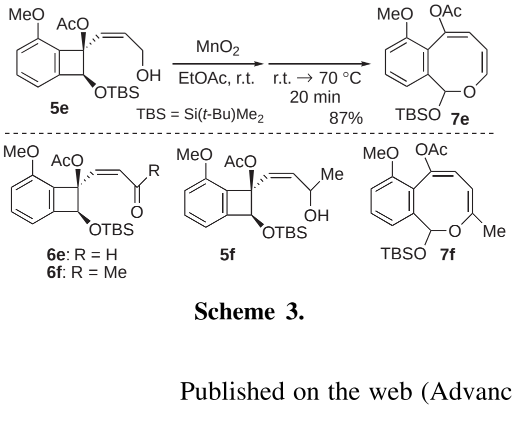
Table 2.

Entry	Substrate	Time^a	Product^b	Yield/%
1	 **6b**	2.5 h	 **7b**	82
2	 **6c**	3 h	 **7c**	78 (17)^c
3	 **6d**	4 h	 **7d**	83

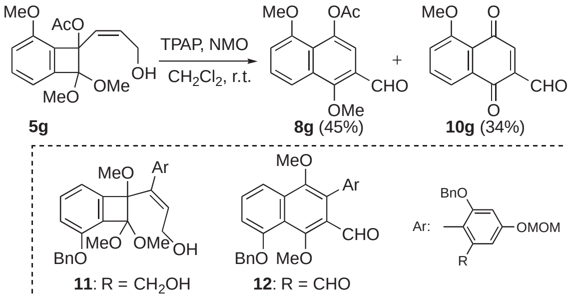
^{a}110 °C, toluene. ^{b}All new compounds were fully characterized by spectroscopic means and combustion analysis. ^{c}The corresponding naphthalene based on the 6π cyclization was obtained.

Furthermore, the eight-membered ring formation was even prominent for the reaction of more oxygenated compound **6e** with a siloxy group (TBSO) on the four-memberded ring. Upon treatment of allyl alcohol **5e**[7] with MnO_2 in EtOAc at room temperature, the starting material **5e** was quickly consumed to give enal **6e**, including a small amount of eight-membered ether **7e**. This result suggested that the ring expansion could be executed in one pot simply by warming the reaction mixture. Indeed, the reaction mixture was warmed to 70 °C (20 min), the product **7e** was solely obtained in 87% yield (Scheme 3). Similarly, oxidation of allyl alcohol **5f** (TPAP, NMO, CH_2Cl_2, room temp.)[8,9] gave ketone **6f**, which was warmed to 70 °C (toluene, 10 min) after separation of the oxidizing agent from the reaction mixture, affording the eight-membered ether **7f** in 83% yield.

Although the eight-membered ring formation was the major path in these α,β-unsaturated carbonyl systems, a different *peri*-selectivity was observed for *gem*-dimethoxy congener **5g**. Upon oxidation of **5g** (TPAP, NMO, CH_2Cl_2), rapid two-carbon ring expansion occurred at room temperature to give naphthalene **8g** and quinone **10g** in 45 and 34% yields, respectively (Scheme 4). Similar periselective reaction of *gem*-dimethoxy derivative **11** under Swern oxidation was recently exploited for the total synthesis of TAN-1085, which also gave the exclusive 6π-cyclized product **12** in high yield.[10]



Scheme 3.



Scheme 4.

In summary, we have described the periselective thermal reaction of acyloxybenzocyclobutenes possessing α,β-unsaturated carbonyl group on the four-membered ring. Further studies on the origin of *peri*-selectivity including the theoretical calculation and the reactivities of the eight-membered ethers are currently underway in our laboratories.

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References and Notes

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2 For syntheses of eight-membered ethers, see: a) E. Alvarez, M. L. Candenas, R. Pérez, J. L. Ravelo, J. D. Martin, *Chem. Rev.* **1995**, *95*, 1953. Also, see: b) N. Ortega, T. Martin, V. S. Martin, *Org. Lett.* **2006**, *8*, 871, and references cited therein.

3 a) T. Hosoya, T. Hamura, Y. Kuriyama, T. Matsumoto, K. Suzuki, *Synlett* **2000**, 520. b) T. Hamura, T. Hosoya, H. Yamaguchi, Y. Kuriyama, M. Tanabe, M. Miyamoto, Y. Yasui, T. Matsumoto, K. Suzuki, *Helv. Chim. Acta* **2002**, *85*, 3589.

4 Related reactions of 1-acylbenzocyclobutene into 6-membered cycle have been noted. a) K. Shishido, M. Ito, S. Shimada, K. Fukumoto, T. Kametani, *Chem. Lett.* **1984**, 1943. b) K. Shishido, E. Shitara, K. Fukumoto, T. Kametani, *J. Am. Chem. Soc.* **1985**, *107*, 5810.

5 Crystallographic data reported in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-606337. Copies of the data can be obtained free of charge on application to CCDC, 12, Unions Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

6 *Conformational Analysis of Medium-Sized Heterocycles*, ed. by R. S. Glass, VCH, Weinheim, **1988**.

7 Allyl alcohol **5e** was prepared via alkynylation of the benzocyclobutenone having a siloxy group on the four-membered ring. See Ref. 3.

8 MnO_2 was less effective for this oxidation.

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