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Facile Transformation of Benzocyclobutenones into 2,3-Benzodiazepines via 4π−8π Tandem Electrocyclic Reactions Involving Net Insertion of Diazomethylene Compounds

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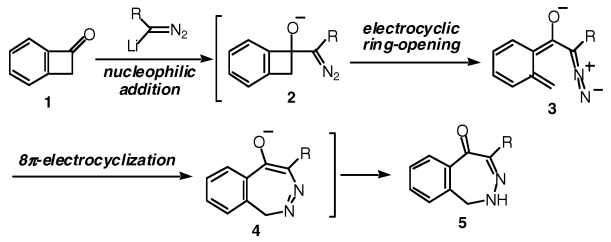
Benzocyclobutenes have been a powerful tool for organic synthesis and utilized for past decades, especially for construction of polycarbocyclic and heterocyclic systems.[1] Versatility of this class of compounds is mainly attributed to facile formation of highly reactive *o*-quinodimethane intermediates, which can participate in tandem pericyclic reactions in an inter- or intramolecular fashion such as electrocyclization and Diels−Alder reactions.[1a,b] Facility of the thermally allowed conrotatory 4π-electrocyclic ring opening of benzocyclobutenes has been known to highly depend on the electronic nature of the substituent(s) on the cyclobutene ring; in general, electron-donating substituents facilitate the quinodimethane formation with a strong outward torquoselectivity.[2,3] Particularly, the accelerating effect of an oxy-anion substituent is striking, which enforces the ring fission at temperatures even below 0 °C despite loss of the 6π aromatic stability of the benzene ring.[4] It is expected, reversely, that the second pericyclic reaction of the quinodimethane thus formed can proceed more easily than that of the usual diene compounds because of reconstruction of the stable 6π aromatic system involved. Although these sequential processes have been applied for various synthetic studies,[1a] it still remains to be developed for new ring system construction.[5] In this Communication, we wish to report a notably facile and mild transformation of benzocyclobutenones to 2,3-benzodiazepines, which is a biologically important heterocyclic core structure.[6] This transformation is accomplished through a nucleophilic addition of a diazomethylene anion followed by a cascade electrocyclic reaction sequence involving a formal and net diazomethylene insertion into the cyclobutene ring.

Our strategic outline is illustrated in Scheme 1, representing stepwise transformations with three running reactions. The initial nucleophilic addition of diazomethylene anion to benzocyclobutenone **1** provides an alkoxide **2**, which may easily undergo an oxy-anion-accelerated electrocyclic ring-opening reaction at low temperature to generate *o*-quinodimethane **3**. Strong preference for outward rotation of the oxide group can dictate the geometry of **3**, in which the diazo function lies at a favorable position for the next electrocyclization. Formal 8π electrocyclization of **3** will be promoted by the reconstruction of the stable benzene ring to furnish the 2,3-benzodiazepine derivative **5** via its enolate form **4** (Scheme 1).

Initially, lithiated (trimethylsilyl)diazomethane was examined as a nucleophile, and several substituted benzocyclobutenones (**1a**−**d**) were subjected for the reaction (Scheme 2). (Trimethylsilyl)-diazomethane was treated with *n*-BuLi in THF at −78 °C, and to the resulting solution, the benzocyclobutenone (**1**) was added at the same temperature. After that, a cooling bath was immediately removed to allow the reaction to warm to ambient temperature for 1 h. Gratifyingly, in all cases (substrates **1a**−**d**), clean conversion was observed to result in the formation of 2,3-benzodiazepin-5-ones (**5a**−**d**) in high isolated yields (Table 1, entries 1−4). Because

Scheme 1



Scheme 2

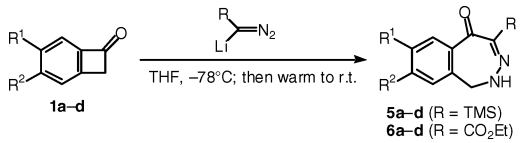


Table 1. Transformation of Benzocyclobutenones into 2,3-Benzodiazepines

entry	benzocyclobutenone	reagent	product	yield (%)[a]
1	**1a** ($R^1 = R^2 = H$)		**5a**	70
2	**1b** ($R^1 = H$, $R^2 = OMe$)	R = TMS[b]	**5b**	79
3	**1c** ($R^1 = OMe$, $R^2 = H$)		**5c**	72
4	**1d** ($R^1 = R^2 = OMe$)		**5d**	82
5	**1a**		**6a**	67
6	**1b**	R = CO_2Et[c]	**6b**	79
7	**1c**		**6c**	78
8	**1d**		**6d**	69

[a] Isolated yields. [b] The substrate was allowed to react with 3.6 equiv of the reagent in THF at −78 °C and then immediately warmed to room temperature for 1 h. [c] The substrate was allowed to react with 3.0 equiv of the reagent in THF at −78 °C for 15 min and then warmed to room temperature for 1 h.

precedent researches have suggested that the *o*-quinodimethane formation under the influence of the oxide group can be achieved at ca. −25 °C,[4] we consider that the present reaction proceeded through the tandem electrocyclic reactions depicted in Scheme 1.

Although there have been several reports on 1,2-diazepine synthesis, including benzodiazepines, via an analogous 1,7-electrocyclization of diazo compounds,[7] all of these require thermal activation and often suffer from predominant pyrazole formation via 1,5-cyclization.[8] In our reaction system, on the other hand, high reactivity and geometrical fixation of the quinodimethane intermediate are reason for the efficient transformation under the extraordinarily mild conditions, which have not been reported in the similar diazepine synthesis, to the best of our knowledge.

We expected that a simple adduct **7** could be isolated when the reaction of **1b** was stopped at −78 °C. This compound was, however, found to be so unstable in aqueous solvent at room temperature that degradation took place with loss of nitrogen during a workup process, to produce indanone derivatives (**8** and **9**) in

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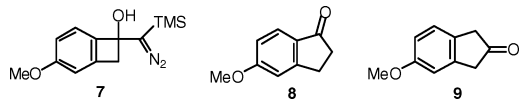
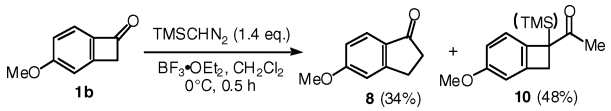
35% and 41% yields, respectively. This transformation is associated with one-carbon homologation of ketones, which has been frequently utilized in diazomethane chemistry as a carbenoid.[9]



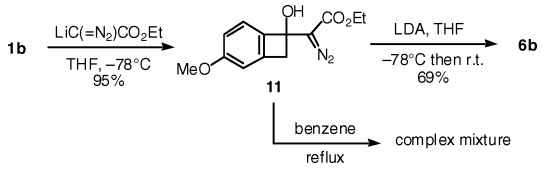
For comparison, the substrate **1b** was conducted to the reaction promoted by Lewis acid, which is a standard condition for such homologation reactions,[10] leading to the formation of the ring-expanded product (**8**) and acetyl derivatives (**10**, a mixture of silyl-containing and desilylated compounds) in a high total yield (Scheme 3).[11] These acid-promoted reactions are in good contrast with the anion-mediated diazepine-forming reaction, in which (trimethylsilyl)diazomethane acts as a C−N−N three-atom source.

Scheme 3



The other diazomethylene anion such as lithiated diazoacetate was demonstrated to work well for the diazepine-forming reaction as shown in Scheme 2 and Table 1 (entries 5−8). In every case, efficient transformation was achieved to afford 2,3-benzodiazepin-5-ones possessing a carboxylate functionality at the 4-positions. These results imply that a wide variety of α-diazocarbonyl compounds, which can generate a corresponding diazomethylene anion, may be applicable for the synthesis of functionalized 2,3-benzodiazepine derivatives. As shown in Scheme 4, when using diazoacetate with **1b**, a corresponding adduct alcohol **11** could be isolated in a high yield by quenching the reaction at −78 °C. In addition, this compound was confirmed to be a precursor of the diazepine product, because the alkoxide regenerated by treatment of **11** with LDA was cleanly converted to the diazepine **6b** after warm to room temperature.[12] On the other hand, thermal reaction of **11** in refluxing benzene resulted in a formation of a complicated mixture including ring-expanded compounds with loss of nitrogen, and the diazepine **6b** could not be detected. Thus, the oxide anion has a good effect on the benzodiazepine-forming reaction, keeping low reaction temperature to circumvent the thermal decomposition of the diazo group.

Scheme 4



In summary, we have described a remarkably facile and mild transformation of benzocyclobutenones into 2,3-benzodiazepines based on anion-accelerated successive electrocyclic reactions. This reaction has the following advantages: (1) the oxy-anion formed by the nucleophilic addition extremely facilitates the first electrocyclic ring-opening, (2) the exclusive outward torquoselectivity of the oxide group dictates geometry of the *o*-quinodimethane as required for the next electrocyclization, and (3) reconstruction of the stable 6π aromatic system facilitates the second 8π electrocyclization, involving a diazo group, which usually requires thermal activation. Further applications are in progress for the synthesis of various derivatives using *o*-quinodimethane chemistry.

CAUTION: Some of the diazo compounds may be explosive and should be handled with great care.

Supporting Information Available: Experimental procedures and characterization data for all new compounds (**5a**−**d**, **6a**−**d**, and **11**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Recently, a formal [4 + 3] cycloaddition of *o*-quinodimethane and alkynyl Fischer carbene complexes has been reported: Barluenga, J.; Garcia-Garcia, P.; Fernandez-Rodriguez, M. A.; Aguilar, E.; Merino, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 5875−5878. For a similar approach for constructing carbocycles using nonbenzo-type cyclobutenones, see Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1624−1625.
(6) For example, see (a) Zappala, M.; Postorino, G.; Micale, N.; Caccamese, S.; Parrinello, N.; Grazioso, G.; Roda, G.; Menniti, F. S.; De Sarro, G.; Grasso, S. *J. Med. Chem.*. **2006**, *49*, 575−581. (b) Elger, B.; Huth, A.; Neuhaus, R.; Ottow, E.; Schneider, H.; Seilheimer, B.; Turski, L. *J. Med. Chem.* **2005**, *48*, 4618−4627.
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(9) For a review, see Gutsche, C. D. *Org. React.* **1954**, *8*, 364−429.
(10) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 119−124.
(11) The latter products (**10**) were probably formed via epoxide formation, acid-catalyzed isomerization to form aldehyde, and further one-carbon homologation.
(12) A retroreaction to release the diazomethylene anion is responsible for the somewhat lower yield of **6b** (69%) than that expected, which is supported by the isolation of the ketone **1b** (30% yield) from the reaction medium. This implies that the initial nucleophilic addition step is in equilibrium, and therefore, 3.0 equiv of lithiodiazoacetate was used to increase the adduct form.

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