

# Sulfate Radical Anions ( $\text{SO}_4^{\bullet-}$ ) as Donor of Atomic Oxygen in Anionic Transannular, Self-Terminating, Oxidative Radical Cyclizations

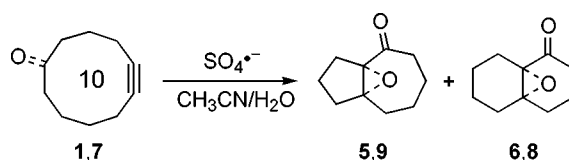
Uta Wille

Institut für Organische Chemie der Universität Kiel, Olshausenstrasse 40,  
24098 Kiel, Germany

uville@oc.uni-kiel.de

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## ABSTRACT



$\text{SO}_4^{\bullet-}$  generated by the Fenton redox system  $\text{S}_2\text{O}_8^{2-} - \text{Fe}^{2+}$  induces a novel anionic, transannular, self-terminating, oxidative radical cyclization in the reactions with the ten-membered cycloalkyne **1** and the cycloalkynone **7**, yielding the bicyclic ketones **5** and **6** or the  $\alpha,\beta$ -epoxy ketones **8** and **9**, respectively. In these reactions  $\text{SO}_4^{\bullet-}$  acts as an oxygen transfer reagent and can thus be considered as a donor of atomic oxygen in solution.

During the past two decades, radical cyclizations with their generally excellent stereoselectivities have become a very important tool in organic chemistry, especially for the synthesis of natural products.<sup>1,2</sup> However, one serious drawback with respect to their application in industrial procedures is the fact that most of these reactions still require toxic heavy metal compounds to initiate and maintain the radical chain, e.g., tin hydrides. Therefore, the development of alternative, nontoxic radical reaction conditions is a field of active research.

In recent publications we reported the reaction of various medium-sized cycloalkynes, cycloalkynones, and also open chain alkynes with the electrophilic nitrate radical (nitrooxydanyl,  $\text{NO}_3^{\bullet}$ ). This radical was generated on a preparative scale in situ from nontoxic precursors by either anodic oxidation of inorganic nitrates or by photolysis of  $\text{Ce}^{4+}$  nitrates. In these reactions isomeric ketones are formed in good yields through a transannular or intramolecular radical

cyclization process.<sup>3</sup> In the case of the medium-sized cycloalkynes, it was suggested that the strongly oxidizing  $\text{NO}_3^{\bullet}$  adds to the  $\text{C}\equiv\text{C}$  triple bond in the first step, leading to a vinyl radical **2** (see Scheme 1,  $\text{X} = \text{NO}_2$ ), which subsequently reacts via a transannular 1,5- or 1,6-hydrogen atom transfer (HAT).<sup>4,5</sup> The observed products are formed by 5-*exo*- or 6-*exo* cyclization of the resulting secondary alkyl radicals **3a,b** onto the site of the  $\text{C}=\text{C}$  double bond not bearing the nitrate substituent followed by fragmentation of **4a,b** into the respective ketones **5** and **6** and  $\text{NO}_2^{\bullet}$  by scission of the labile  $\text{O}-\text{NO}_2$  bond.<sup>6</sup> Thus, in these reactions  $\text{NO}_3^{\bullet}$  can be considered as a donor of atomic oxygen in solution. Because of the comparatively low reactivity of the released

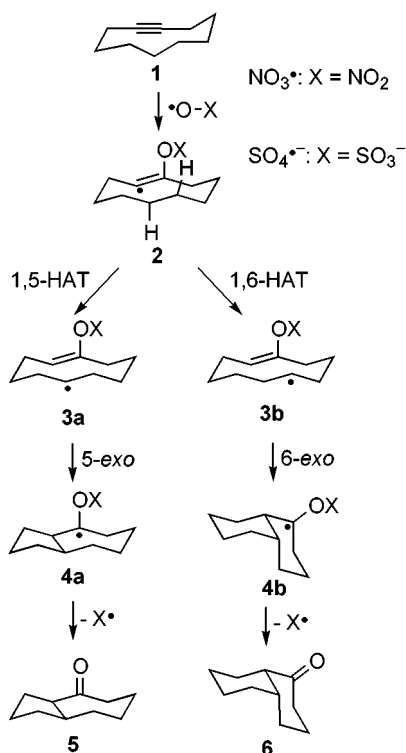
(3) (a) Wille, U.; Plath, C. *Liebigs Ann./Recueil* **1997**, 111–119. (b) Wille, U.; Lietzau, L. *Tetrahedron* **1999**, 55, 10119–10134. (c) Wille, U.; Lietzau, L. *Tetrahedron* **1999**, 55, 11469–11474.

(4) Correctly, by taking both possible directions of enumeration in the carbocyclic ring into account, the transannular 1,5-HAT of **2** to **3a** should be considered as a 1,5/1,7-HAT. For the sake of clarity, the nomenclature of these transannular radical reactions is based on the most probable process, e.g., 1,5- or 1,6-HAT, respectively: Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley-Masson: Chichester, New York, Brisbane, Toronto, Singapore, Paris, Milan, Barcelona, 1995; p 52.

(5) In the reactions of open-chain alkynes with  $\text{NO}_3^{\bullet}$ , the intramolecular HAT could be proved by deuteration experiments (ref 3b).

(1) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, New York, Basel, Cambridge, Tokyo, 1996.

(2) A recent compilation is given in the following: Linker, T.; Schmittel, M. *Radikale und Radikationen in der Organischen Synthese*; Wiley-VCH: Weinheim, New York, Chichester, Brisbane, Singapore, Toronto, 1998.

Scheme 1<sup>a</sup>

<sup>a</sup> For the sake of clarity, most of the hydrogen atoms are omitted.

NO<sub>2</sub>•, with respect to NO<sub>3</sub>•, this reaction has no radical chain character and is therefore termed as a self-terminating, oxidative radical cyclization cascade.

The finding of this novel radical oxidation sequence was a motivation to look for further radicals with properties similar to those of NO<sub>3</sub>•, e.g., having the unpaired electron predominantly located on the oxygen and possessing a labile O-heteroatom (O–X) bond, which may be cleaved after the radical cyclization cascade, thus terminating the whole sequence by release of an unreactive group X. The sulfate radical anion (SO<sub>4</sub>•<sup>-</sup>) could potentially be considered to fulfill these requirements, although the radical cyclization sequence shown in Scheme 1 had not yet been demonstrated.

SO<sub>4</sub>•<sup>-</sup> is known to be a very strong one-electron oxidant. Whereas the mechanistic aspects of the electron-transfer reactions of alkenes or aromatic compounds by SO<sub>4</sub>•<sup>-</sup> have been thoroughly investigated by various research groups,<sup>7</sup> SO<sub>4</sub>•<sup>-</sup> has not been used as an oxygen atom donor in synthetic radical addition reactions so far.

Because of their strong transannular interactions, medium-sized rings are appropriate substrates to study the scope of novel reactions, since subsequent reaction steps are preferred to proceed intramolecularly. In this paper the results of the reaction of SO<sub>4</sub>•<sup>-</sup> with two different ten-membered cyclic alkynes, e.g., cyclodecyne (**1**) and 5-cyclodecyne (**7**), are presented.<sup>8</sup>

Using the radical cyclization of cycloalkyne **1** as the test reaction system (according to Scheme 1 with X = SO<sub>3</sub><sup>-</sup>) different approaches were employed to generate SO<sub>4</sub>•<sup>-</sup> on a

preparative scale. In a first attempt, SO<sub>4</sub>•<sup>-</sup> was formed by photolysis of S<sub>2</sub>O<sub>8</sub><sup>2-</sup> in the presence of **1** (eq 1)<sup>7</sup> using acetone as a photosensitizer at both λ = 300 and 254 nm in either water and/or acetonitrile.



However, these conditions turned out to be unsatisfactory as the conversion of the persulfate was very slow and the starting cycloalkyne **1** decomposed during the irradiation. Thus, only traces of bicyclic ketones **5** and **6** were formed (Figure 1).<sup>9</sup>

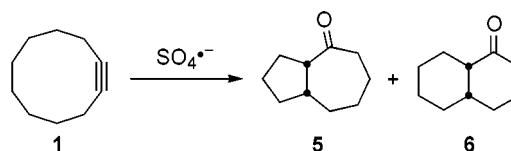


Figure 1. Reaction of SO<sub>4</sub>•<sup>-</sup> with cyclodecyne (**1**).

In an alternative approach, SO<sub>4</sub>•<sup>-</sup> was produced in the presence of **1** by the well-established Fenton redox process (eq 2) with M<sup>n+</sup> representing a transition metal ion (Fe<sup>2+</sup> or Ti<sup>3+</sup>). The success of the radical cyclization was significantly dependent on the reaction conditions. In Table 1 is compiled

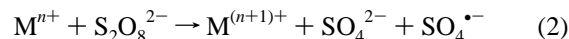


Table 1. Experimental Conditions for the Reaction of Fenton-Generated SO<sub>4</sub>•<sup>-</sup> with Cyclodecyne (**1**) According to Figure 1

entry	[ <b>1</b> ]/mmol	Fenton system/mmol	yield ( <b>5</b> + <b>6</b> )
1	1.2	Fe(EDTA)(SO <sub>4</sub> ) <sub>2</sub> ·4H <sub>2</sub> O: 2.3 (Bu <sub>4</sub> N) <sub>2</sub> S <sub>2</sub> O <sub>8</sub> : 1.9 <sup>a,b</sup>	no reaction
2	1.1	Fe(EDTA)(SO <sub>4</sub> ) <sub>2</sub> ·4H <sub>2</sub> O: 3.0 <sup>c,d</sup> K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> : 2.9	79% <sup>e</sup> <b>5</b> : <b>6</b> = 1.9:1
3	1.0	FeSO <sub>4</sub> ·7H <sub>2</sub> O: 3.1 K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> : 3.2 <sup>a,d</sup>	n.d. <sup>f,g</sup>
4	1.0	FeSO <sub>4</sub> ·1.5H <sub>2</sub> O: 2.3 (Bu <sub>4</sub> N) <sub>2</sub> S <sub>2</sub> O <sub>8</sub> : 3.0 <sup>c,h</sup>	56% <sup>e</sup> <b>5</b> : <b>6</b> = 1.9:1
5	1.0	FeSO <sub>4</sub> ·1.5H <sub>2</sub> O: 1.0 K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> : 1.0 <sup>c,d</sup>	n.d. <sup>g</sup>
6	1.0	TiCl <sub>3</sub> : 7.0 <sup>c,h,i</sup> K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> : 3.2	n.d. <sup>g</sup>

<sup>a</sup> Persulfate added as last component. <sup>b</sup> Solvent: CH<sub>3</sub>CN. <sup>c</sup> Metal ion added as last component. <sup>d</sup> Solvent: CH<sub>3</sub>CN/H<sub>2</sub>O 3:4. <sup>e</sup> Yield and ratio determined by GC. <sup>f</sup> n.d. = not determined. <sup>g</sup> Low conversion after 24 h. <sup>h</sup> Solvent: CH<sub>3</sub>CN/H<sub>2</sub>O 1:1. <sup>i</sup> Added in two portions.

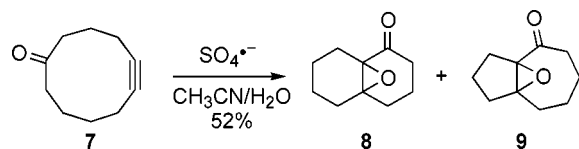
a selection of the different experimental conditions applied.

Four points seem to be essential: (i) The presence of water is essential for dissolving the metal salt (entry 1). Thus, a

persulfate which is soluble in organic solvents [e.g.  $(\text{Bu}_4\text{N})_2\text{S}_2\text{O}_8$ ]<sup>10</sup> is not required, and the commercially available potassium salt can be used. (ii) The Fenton system should be present in at least a 3-fold excess (entries 2 and 4 vs 5). (iii) For a fast and complete conversion of **1** within 15 min, the metal ion must be added as the last component to the heterogeneous mixture of the cycloalkyne and the persulfate (entry 2 vs 3). (iv)  $\text{Fe}^{2+}$  is preferable to  $\text{Ti}^{3+}$  as with the latter the conversion of **1** is not complete even after 24 h and even in the presence of a large excess of  $\text{Ti}^{3+}$  (entry 6). The nature of the counterion of the iron salt is only of importance with respect to the ease of the workup procedure, as the reaction mixtures containing the iron sulfate heptahydrate or the iron sulfate–EDTA complex do not give emulsions.<sup>11</sup>

These results demonstrate that the principle of a nonchain, self-terminating, oxidative radical cyclization cascade, which was discovered for reactions of  $\text{NO}_3^\bullet$  with (cyclic) alkynes, is clearly not limited to uncharged radicals. With the radical anion  $\text{SO}_4^{\bullet-}$ , an analogous anionic, oxidative radical cyclization takes place in excellent yield. The reaction sequence is terminated by release of  $\text{SO}_3^{\bullet-}$ , which is significantly less reactive than  $\text{SO}_4^{\bullet-}$ .<sup>12</sup> No evidence for an interfering reaction by  $\text{SO}_3^{\bullet-}$  has been observed.

Encouraged by this result the reaction of  $\text{SO}_4^{\bullet-}$  with 5-cyclodecyne (**7**) was also studied. In this cycloalkynone a methylene unit is replaced by a carbonyl group, which acts as a transannular radical acceptor for the initially formed vinylic radical. By treatment of **7** with  $\text{SO}_4^{\bullet-}$  according to the standard procedure,<sup>11</sup> a 1.2:1 mixture<sup>9,13</sup> of the  $\alpha,\beta$ -epoxy ketones **8** and **9** was isolated in 52% yield after column chromatography (Figure 2). The presumable mechanism



**Figure 2.** Reaction of  $\text{SO}_4^{\bullet-}$  with 5-cyclodecyne (**7**).

leading to these products is analogous to the reaction of  $\text{NO}_3^\bullet$  with **7**<sup>3a</sup> and is shown in Scheme 2.

Because of the asymmetry of the 5-cycloalkynone,  $\text{SO}_4^{\bullet-}$  attack at C-5 or C-6 of the alkyne bond in **7** leads to the two

(6) The exclusive formation of the *cis* fused bicyclic ketones **5** and **6** could be explained by the steric constraints in this medium-sized ring; see also refs 1 (p 69) and 3a.

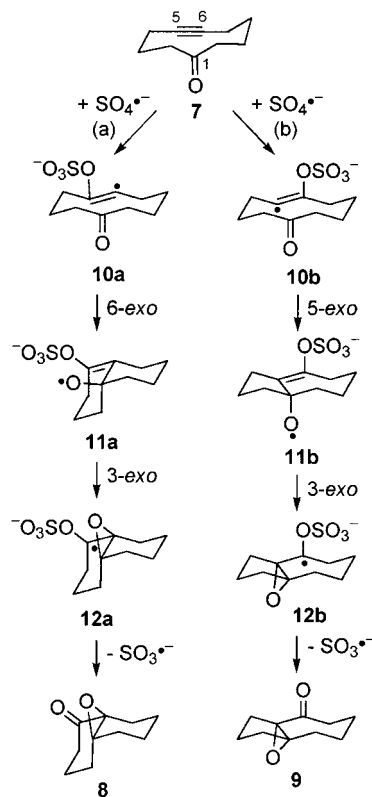
(7) See, for example: (a) Davies, M. J.; Gilbert, B. C. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1809–1815. (b) Niehaus, H.; Hildenbrand, K. *J. Chem. Soc., Perkin Trans. 2* **2000**, 947–952. (c) Walling, C.; Zhao, C.; El-Taliawi, G. M. *J. Org. Chem.* **1983**, *48*, 4910–4914. (d) Deeble, D. J.; Schuchmann, M. N.; Steenken, S.; von Sonntag, C. *J. Phys. Chem.* **1990**, *94*, 8186–8192. (e) Lomoth, R.; Naumov, S.; Brede, O. *J. Phys. Chem. A* **1999**, *103*, 6571–6579 and references therein.

(8) Cyclodecyne (**1**) and 5-cyclodecyne (**7**) were prepared according to literature procedures, see ref 3a.

(9) In all reactions under investigation, product identification was performed by comparing the NMR spectra with literature data (ref 3a).

(10)  $(\text{Bu}_4\text{N})_2\text{S}_2\text{O}_8$  was synthesized according to the following: Effenberger, F.; Kottmann, H. *Tetrahedron* **1985**, *41*, 171–182.

**Scheme 2.** Proposed Mechanism for the Reaction of 5-Cyclodecyne (**2**) with  $\text{SO}_4^{\bullet-}$ <sup>a</sup>



<sup>a</sup> Pathway a indicates primary radical attack at C-5, pathway b attack at C-6.

distinctive vinyl radical anions, **10a** and **10b**. A subsequent transannular 6-*exo* or 5-*exo* radical addition to the carbon atom of the carbonyl  $\pi$  system yields the allyloxy radical anions **11a** and **11b**, respectively. These intermediates undergo a further 3-*exo* cyclization to give the anionic oxiranyl radicals **12a,b**, which finally decompose into the observed  $\alpha,\beta$ -epoxy ketones **8** and **9** with expulsion of  $\text{SO}_3^{\bullet-}$ .

One aspect of the radical mechanism given in Scheme 2 is remarkable. Generally, both a radical cyclization onto a carbonyl group (**10**  $\rightarrow$  **11**) and also a 3-*exo* cyclization of an allyloxy radical to yield an oxiranyl radical (**11**  $\rightarrow$  **12**) are reversible reactions with the reverse ring opening being faster by several orders of magnitude.<sup>14</sup> In the reaction under

(11) **Representative experimental procedure:** 3 mmol of persulfate dissolved in 10 mL of water was added to a solution of 1 mmol of the cycloalkyne in 30 mL of acetonitrile. To this heterogeneous reaction mixture was added 3 mmol of  $\text{Fe}(\text{EDTA})(\text{SO}_4)_2 \cdot 4\text{H}_2\text{O}$  in 30 mL of water quickly under vigorous stirring through a dropping funnel. After thin-layer chromatography indicated complete consumption of the cycloalkyne (ca. 15 min), the mixture was diluted with water and extracted with ethyl acetate. The combined organic fractions were dried and evaporated. The residue was either analyzed by gas chromatography after filtration ( $\text{SiO}_2$ , ethyl acetate) using hexadecane as internal standard or purified by chromatography [ $\text{SiO}_2$ , diethyl ether/pentane (1:2)]. GC conditions: column OV 1701, 25 m; temperature program 100s  $\rightarrow$  200s, heating rate 5  $^\circ\text{C min}^{-1}$ .

(12) Muller, J. G.; Hickerson, R. P.; Perez, R. J.; Burrows, C. J. *J. Am. Chem. Soc.* **1997**, *119*, 1501–1506 and cited literature.

(13) The product ratio was determined by GC and  $^{13}\text{C}$  NMR using the *inverse gated decoupling* technique.

(14) (a) Reference 4, p 154. (b) Reference 1, p 26.

investigation, the obviously fast and irreversible fragmentation of the oxiranyl radical ions **12a,b** into  $\text{SO}_3^{\bullet-}$  with formation of the stable carbonyl group in the  $\alpha,\beta$ -epoxy ketones is the driving force of the whole sequence, which prevents the radical ion intermediates from undergoing a ring-opening reaction.

In conclusion, it is demonstrated that upon addition of  $\text{SO}_4^{\bullet-}$  to  $\text{C}\equiv\text{C}$  triple bonds in the 10-membered cycloalkyne **1** and cycloalkynone **7**, a nonchain, anionic, self-terminating radical cyclization cascade is induced. By these reactions the bicyclic ketones **5** and **6** or the  $\alpha,\beta$ -epoxy ketones **8** and **9** are formed in good to excellent yields. Because of the difficulty of oxidizing isolated triple bonds,<sup>15</sup>  $\text{SO}_4^{\bullet-}$  does not react as an electron-transfer reagent in these reactions but acts as a donor of atomic oxygen.

Together with  $\text{NO}_3^{\bullet}$ , there are now two inorganic radicals available for preparative synthesis, which can be considered

to be oxygen atom transfer reagents. This is of significant importance, as  $\text{SO}_4^{\bullet-}$  can be easily generated on a preparative scale by the Fenton redox reaction from inexpensive, nontoxic starting materials.

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(15) Isolated alkyne bonds are more easily reduced than oxidized: *Encyclopedia of Electrochemistry of the Elements: Organic Section*; Bard, A. J., Lund, H., Eds.; Marcel Dekker, Inc.: New York, 1978; Vol. XIV, p 74.