Tandem Oxidative Ring Cleavage–Cyclisation Reactions of Cyclopropylsulfides: A Novel Synthesis of Cyclic Ethers

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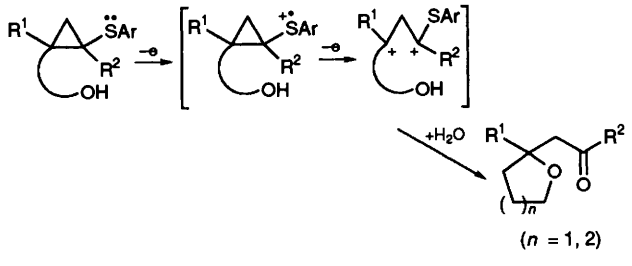
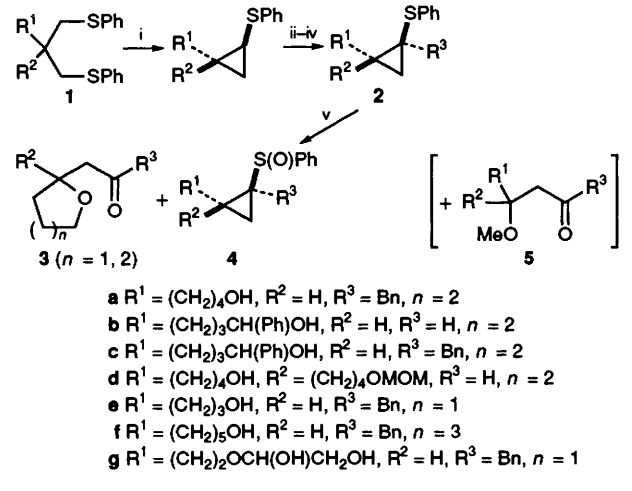
Treatment of cyclopropylsulfides bearing a hydroxy group in the side chain with ceric ammonium nitrate in methanol gives five- or six-membered cyclic ethers *via* a tandem cation radical ring cleavage–cyclisation sequence.

Although organosulfur cation radicals have been studied mostly in the area of heterocyclic chemistry such as phenothiazine, thianthrene and phenoxathiin,[1] recently much effort has been directed to their use for carbon–heteroatom[2] or carbon–carbon bond formation.[3] In the former case, there are many papers on single electron transfer (SET) oxidation of the α-substituted sulfides by group 14 elements to give the corresponding acetals or thioethers.[2] However, the SET oxidation of cyclopropylsulfides as substrates has remained unexplored,[4] although that of cyclopropanol derivatives to construct carbon–carbon bonds has been actively examined.[5,6] An important aspect of the oxidation of cyclopropylsulfides is their availability as α,γ-dication synthons. In particular, we are interested in intramolecular etherification of cyclopropylsulfides that bear a hydroxy group in the side chain to provide cyclic ethers (Scheme 1).[7] In this paper, we describe the tandem oxidative ring cleavage–cyclisation reactions of cyclopropylsulfides with ceric ammonium nitrate (CAN) as a chemical oxidant.

Several types of cyclopropylsulfides **2**† were prepared from 1,3-bis(phenylthio)propane derivatives **1** according to Tanaka's method[8] (Scheme 2). In the initial approach, we examined the several conditions for CAN oxidation to yield the desired tetrahydropyran **3a** in good yield from 2,2-disubstituted cyclopropylsulfide **2a**.‡ These experiments revealed the following interesting points: (*i*) methanol (MeOH) is crucial as a solvent to yield the desired cyclic ether **3a** in good yield (73%); (*ii*) the cyclopropyl bond between the sulfur substituted carbon and more substituted carbon should be cleaved; (*iii*) addition of molecular sieves and potassium carbonate (K_2CO_3) tends to depress the formation of sulfoxide **4a**.[9] In order to investigate the scope and limitation of the tandem oxidative ring cleavage–cyclisation reactions, other cyclopropylsulfides **2b–g** were subjected to the same reaction conditions as **2a**. Some results are shown in Table 1. Although 2-monosubstituted cyclopropylsulfide **2b** gave predominantly the corresponding sulfoxide **4b** (22%) along with the expected tetrahydropyran derivative **3b** (12%: *cis*:*trans* = 1.5:1) as a minor product, 1,2- or 2,2-disubstituted cyclopropylsulfides **2c** and **2d** afforded the desired tetrahydropyrans (**3c** and **3d**) as a major product, respectively. These results suggest that efficient cyclisation requires an increase of steric hindrance and/or electron density of cyclopropyl bond to enhance oxidation potential of the cyclopropane ring. Table 1 also indicates that the tandem oxidative ring cleavage–cyclisation reaction affords the 2,5-substituted tetrahydrofurans (**2e** → **3e**) but not the seven-membered cyclic ether (**2f** → **3f**). Furthermore, intramolecular etherification of the diol **2g** proceeded *via* five-membered ring closure, not six-membered one as in SET oxidation, to provide 2,5-substituted tetrahydrofuran **3g** in 61% yield without tetrahydropyran deriva-



Scheme 1



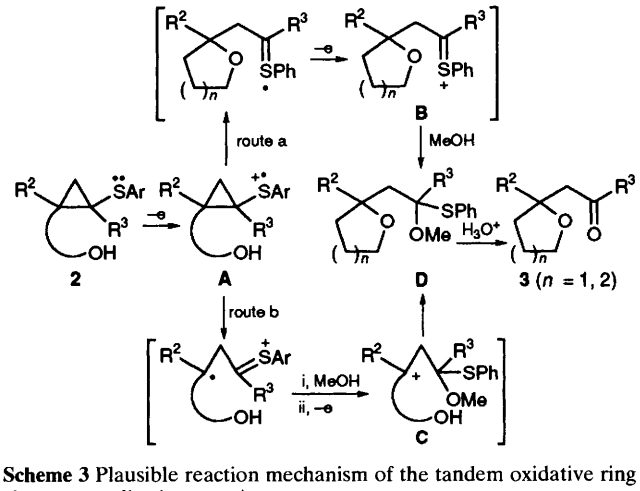
a $R^1 = (CH_2)_4OH$, $R^2 = H$, $R^3 = Bn$, $n = 2$
b $R^1 = (CH_2)_3CH(Ph)OH$, $R^2 = H$, $R^3 = H$, $n = 2$
c $R^1 = (CH_2)_3CH(Ph)OH$, $R^2 = H$, $R^3 = Bn$, $n = 2$
d $R^1 = (CH_2)_4OH$, $R^2 = (CH_2)_4OMOM$, $R^3 = H$, $n = 2$
e $R^1 = (CH_2)_3OH$, $R^2 = H$, $R^3 = Bn$, $n = 1$
f $R^1 = (CH_2)_5OH$, $R^2 = H$, $R^3 = Bn$, $n = 3$
g $R^1 = (CH_2)_2OCH(OH)CH_2OH$, $R^2 = H$, $R^3 = Bn$, $n = 1$

Scheme 2 *Reagents*: i, ref. 8; ii, *m*-CPBA; iii, Bu^nLi, R^3Br; iv, DIBAL; v, CAN

Table 1 Synthesis of cyclic ethers **3** from cyclopropylsulfides **2** by CAN oxidation

	Yield[a] (%)		
2	Cyclic ether **3**	Sulfoxide **4**	Methyl ether **5**
a	73	8	17
b	12 (1.5:1)[b]	22	6
c	48 (2:1)[c]	Trace	Trace
d	72	7	8
e	60	6	11
f	Trace	6	40
g	61 (1:1)[c]	4	13

[a] Isolated yields. [b] *cis*:*trans* ratio calculated from isolated yields. [c] *cis*:*trans* ratio deduced from ^1H NMR.



Scheme 3 Plausible reaction mechanism of the tandem oxidative ring cleavage–cyclisation reaction

tives.[10] In all reactions except those of **2b** and **2f**, cyclic ethers could be obtained in preference to the sulfoxides **4** and methanol addition products **5**.

From the products formed, the mechanism of the tandem oxidative ring cleavage–cyclisation reaction is proposed as follows (Scheme 3). The SET oxidation of **2** initially generates the cation radical intermediate **A**, which might follow two pathways. One is concerted process (route a), in which nucleophilic attack on the more hindered β-carbon by the hydroxy group followed by another SET oxidation and termination by nucleophilic addition of methanol to the resulting sulfonium cation **B**, affords **D**. The other is initial ring-opening process (route b) *via* carbocation **C**. The ring-opening leading to the carboradical would be followed successively by nucleophilic addition of the solvent, SET oxidation and then cyclisation of **C** into the desired cyclic ether **D**. Finally, in both cases, **D** is solvolysed by methanol or water to produce the dimethyl acetal or ketone **3**.

In conclusion, we demonstrated herein that (*i*) cyclopropylsulfides can be used as α,γ-dication equivalents by means of the SET oxidation with CAN and (*ii*) various cyclic ethers can be synthesised by the tandem oxidative ring cleavage–cyclisation reaction of the ω-hydroxycyclopropylsulfides in good yields. Further applications of cyclopropylsulfides are underway in our laboratory.

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Footnotes

† The α-substituted cyclopropylsulfides (R^3 = Bn: **2a**, **c**, **e–g**) were prepared by alkylation and sequential reduction of the corresponding sulfones (R^3 = H). All new compounds have been characterised by spectroscopic and analytical methods.

‡ CAN promoted reactions were conducted by slow addition of a solution of cyclopropylsulfides **2** in dry methanol to a suspension of CAN (5.0 equiv.) and K_2CO_3 (5.0 equiv.) in dry methanol in the presence of molecular sieves 3Å at 0 °C.

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