Extension of the Criegee Rearrangement: Synthesis of Enol Ethers from Secondary Allylic Hydroperoxides

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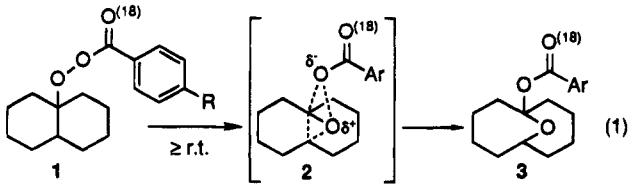
Summary: The Criegee rearrangement has been extended to secondary allylic hydroperoxides, allowing for the selective synthesis of cyclic and acyclic enol ethers; the effect of base and electrophilic agent was studied.

In 1944, Criegee observed[1] that acetate and benzoate esters of *trans*-9-decalyl hydroperoxide slowly rearranged to isomeric ester–ketals (eq 1). This discovery inspired

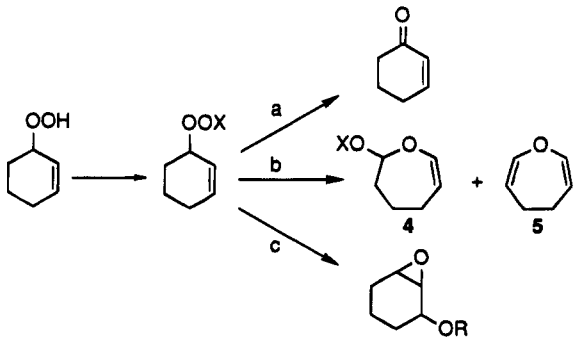


relative rate: R = NO_2 > Br > H > Me > OMe (60-80%, R=H)

a series of mechanistic investigations during the 1940's and 1950's which helped to elucidate some of the controlling factors of this rearrangement.[2] It was found that the rate of rearrangement was accelerated by increasing the ionizing power of solvent and the electron-deficient nature of the acyl moiety in the peroxy ester. Other studies[3] with aromatic esters derived from tertiary aralkyl hydroperoxides indicated that the *migratory aptitude* is strongly influenced by the electron-donating ability of the migrating group. This was further illustrated by the reactions of Schenck,[4] Treibs,[5] and Schreiber,[6] which, along with Criegee's work, constitute the foremost examples of the Criegee rearrangement.[7] Although the above results indicated an ionic mechanism, Denney showed that when the carbonyl oxygen of **1** was labeled with O^{18}, 98% of the label remained in the carbonyl oxygen of the rearranged product **3**.[8] This classic work demonstrated a high degree of concertedness to the reaction and led Denney to propose **2** as the intermediate/transition-state.

Despite these and related mechanistic studies, the Criegee rearrangement has received limited attention from the synthetic community.[6,9] In terms of electrophiles and hydroperoxide substrates, its scope and limitations have remained largely unexamined. During

Scheme 1



synthetic studies on several natural products, we noticed potential use of the rearrangement, but our demands necessitated further development of the reaction. Of particular interest to us was the possibility of using secondary allylic hydroperoxides in the Criegee rearrangement. In theory, there are three main pathways by which a system like cyclohexenyl hydroperoxide could react (Scheme 1). The desired pathway (path b) proceeds via vinyl migration, leading to the oxepin enol ether of type **4**, conceivably along with the eliminated product **5**.[10] On the other hand, path a would lead to the generation of the stable enone derivative either via hydrogen migration[11] or E2 elimination.[12] The last option, path c, is reminiscent of known lipid chemistry,[13] but has not generally been observed otherwise. The literature holds only a few examples where secondary hydroperoxides have been subjected to conditions of acylating agent and base; to the best of our knowledge, all cases led to ketone[14] or epoxide[13b,c] formation. Thus, we were interested in finding conditions that would allow for selective vinyl migration and at the same time shed more light on the mechanistic aspects of this rearrangement.

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(1) (a) Criegee, R. *Chem. Ber.* **1944**, *77*, 722. (b) Criegee, R.; Kaspar, R. *Liebigs Ann. Chem.* **1948**, *560*, 127.

(2) For selected reviews, see: (a) *Methoden der org. Chem.*; Georg Thieme Verlag: Stuttgart, 1988; Vol. E13, p 1095–1102. (b) Lee, J. B.; Uff, B. C. *Quart. Rev.* **1967**, *21*, 429–457. (c) Plesnicar, B. In *The Chemistry of Peroxides*; Patai, S., Ed.; John Wiley & Sons: New York, 1983; Chapter 17. (d) *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1970. Although no problems were encountered during the course of this research, peroxides were handled with caution, as described in these references.

(3) Hedaya, E.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1661.

(4) Schenck, G. O.; Schulte-Elte, K.-H. *Liebigs Ann. Chem.* **1958**, *618*, 185.

(5) Treibs, W.; Heyner, E. *Chem. Ber.* **1957**, *90*, 2285.

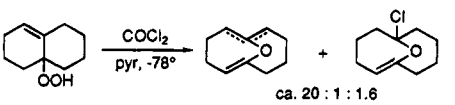
(6) Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363.

(7) Tertiary hydroperoxides were used in all studies by earlier researchers.

(8) (a) Denney, D. B. *J. Am. Chem. Soc.* **1955**, *77*, 1706. (b) Denney, D. B.; Denney, D. G. *J. Am. Chem. Soc.* **1957**, *79*, 4806.

(9) Cope used Criegee's reaction of decalyl hydroperoxide to prepare cyclodecane derivatives; see: Cope, A. C.; Holzman, G. *J. Am. Chem. Soc.* **1950**, *72*, 3062.

(10) Our preliminary studies on Schenck's hydroperoxide indicated that such eliminated products could be produced by altering the electronics of the electrophile:



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Here, apparently loss of CO_2 facilitates departure (and hampers capture) of the migrating anion. For another example, see: Koser, S.; Hoffmann, H. M. R. *J. Org. Chem.* **1993**, *58*, 6163.

(11) Literature on the related Baeyer–Villiger reaction indicates a potentially high migratory aptitude for hydrogen.

(12) Secondary hydroperoxides are known to eliminate to ketones upon exposure to weak base or simply over time. See ref 2 and: Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880.

(13) (a) Hamberg, M; Gotthammar, B. *Lipids* **1973**, *8*, 737. (b) Corey, E. J.; Marfat, A.; Goto, G. *J. Am. Chem. Soc.* **1980**, *102*, 6607. (c) Corey, E. J.; Su, W.-g.; Mehrotra, M. M. *Tetrahedron Lett.* **1984**, *25*, 5123.

(14) (a) Benzoate ester of tetralin hydroperoxide, as discussed in ref 1b. (b) Wieland, H.; Maier, J. *Chem. Ber.* **1931**, *64*, 1205. (c) Rousseau, G.; Le Perchec, P.; Conia, J. M. *Synthesis* **1978**, 67. (d) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

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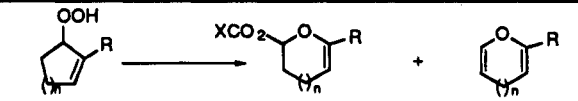
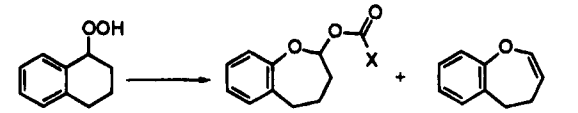
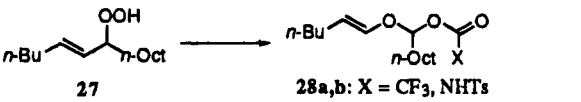
When vinylstannane and silane hydroperoxides **8**[15] and **10**[16] were treated with just over 1 equiv of trifluoroacetic anhydride (TFAA), along with 2.4 equiv of pyridine in CH_2Cl_2 at 0 °C, instantaneous conversion to the oxepin enol ethers **9a** and **11a** took place; little or no enone products were detected by crude ^1H NMR. Likewise, treatment with TsNCO in CH_2Cl_2 at 0 °C gave the rearranged oxepin products **9b** and **11b**, also uncontaminated by any enone. Other electrophiles gave mixtures of rearranged and enone products (*p*-NO_2PhCOCl, methyl oxalyl chloride) or else exclusively enone (MsCl, $SOCl_2$, phosgene, $ClSO_2NCO$).

When unsubstituted cyclohexenyl hydroperoxide **12** was subjected to a wide variety of electrophiles in the presence of 2.2 equiv of pyridine, enone formation was exclusive or nearly exclusive in almost every case. Even TFAA was found to give a mixture of enone, rearranged oxepin **13a**, and dihydrooxepin **14** in a 2.5:2:1 ratio.[17] The greater reluctance of the unsubstituted cyclohexenyl substrate to give vinyl migration can presumably be attributed to the more electron-deficient nature of the olefin with respect to the vinylstannane and silane derivatives. Despite this, treatment with TsNCO again gave extremely clean rearrangement, yielding **13b** and **14** in an 8:1 ratio.

The fact that TsNCO was consistently the only reagent to affect clean rearrangement highlighted the need to examine the influence of the added base on the reaction. In fact, when 2.2 equiv of pyridine was added to the reaction with TsNCO, only enone was formed! Cyclohexenyl hydroperoxide was therefore subjected to the TFAA reaction with a series of added bases, varying in steric and electronic nature, and the ratio of products obtained was analyzed by NMR (Table 2). The results clearly imply that enone is in fact generated via a direct E2-type elimination on the intermediate acylperoxide. Interestingly, the 2:1 ratio of rearranged oxepin to eliminated dihydrooxepin remains constant throughout the series, until the pK_a (aqueous) of the conjugate acid of the base reaches a point near that of TFA. In the extreme, when no base is added, no eliminated product is formed, and the rearranged acetal is produced cleanly.[18]

Having successfully obtained selective ring expansion for the cyclohexenyl system, it was logical to apply the reaction to ring systems of other sizes. Given the significant lack of general methodology for the construction of medium- and large-size cyclic ethers, extending the generality of the Criegee reaction in this sense would obviously be of substantial use. The allylic hydroperoxides **15**, **18**, and **21** of cycloheptene, cyclooctene, and cyclodecene were all readily prepared via photooxygenation. When allowed to react with TsNCO in $CDCl_3$, all gave the expanded rearranged cyclic enol ethers cleanly, with no enone detectable by NMR; the only other visible products were the eliminated compounds **17** (<10%), **20** (trace), and **23** (trace), respectively.[19] Similarly, exposure

Table 1. Substrates Studied for the Criegee Rearrangement[a]

substrate	products		method
			
n=1 **6**: R=H	**7a,b**: R=H, X=Me, *i*-Pr		C
n=2 **8**: R=$SnBu_3$	**9a,b**: R=$SnBu_3$, X=CF_3, NHTs		A,B
10: R=$SiMe_3$	**11a,b**: R=$SiMe_3$, X=CF_3, NHTs		A,B
12: R=H	**13a,b,c**: R=H, X=CF_3, NHTs, Me	**14**: R=H	A,B,C
n=3 **15**: R=H	**16a,b**: R=H, X=CF_3, NHTs	**17**: R=H	A,B
n=4 **18**: R=H	**19a,b**: R=H, X=CF_3, NHTs	**20**: R=H	A,B
n=6 **21**: R=H	**22a,b**: R=H, X=CF_3, NHTs	**23**: R=H	A,B
			
24	**25a,b**: X = CF_3, NHTs	**26**	A,B
			
27	**28a,b**: X = CF_3, NHTs		B

[a] Method A: substrate is treated at 0 °C with the appropriate base, followed immediately by TFAA. Method B: substrate is treated at 0 °C with a slight excess of TsNCO or TFAA, without added base. Method C: substrate is treated at 0 °C with the appropriate anhydride (1.4 equiv) and then 6 mol % DMAP. A catalytic amount of BF_3·Et_2O is added at 0 °C and the reaction mixture is allowed to warm to room temperature; the rearrangement is complete within 30 min.

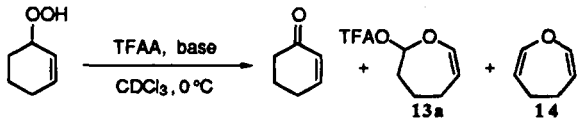
to a slight excess of TFAA in the presence of 2,6-dichloropyridine at 0 °C gave instant conversion to the rearranged trifluoroacetates **16a**, **19a**, and **22a** cleanly. In contrast, if pyridine is present, enone is either the only or the predominant product of the reactions. Since we estimate the conjugate pK_a of 2,6-dichloropyridine to be below that of TFA, it would *a priori* seem unlikely that its presence has an effect on the reaction. Indeed, some of the above TFAA reactions proceeded cleanly in the absence of any base. However, the reaction of **21** without base produced an unacceptable amount of hydrolyzed aldehyde and other undesirable products; when 2,6-dichloropyridine was present, every reaction was extremely clean.

The rearrangements also proceeded smoothly for an acyclic allylic hydroperoxide **27**,[20] as well as the historical tetralin hydroperoxide **24**. With TFAA, the rearranged product **25a** was formed exclusively if no base was present, but **25a** and eliminated **26** could be produced in about a 6:1 ratio, with <4% enone, if 2,6-di-*tert*-butylpyridine (2.2 equiv) was present.

All the reactions in our study to this point involved electrophiles active enough to induce rearrangement without stopping at the intermediate acylperoxide. It was hoped that, if the hydroperoxides could be acylated with a less active electrophile, we might intercept such an intermediate and further examine Bartlett's demonstration[21] of acid catalysis for the rearrangement. The problem, however, was lack of a method to acylate the

(15) Adam, W.; Klug, P. *J. Org. Chem.* **1993**, *58*, 3416.
(16) Fristad, W. E.; Bailey, T. R.; Paquette, L. A. *J. Org. Chem.* **1980**, *45*, 3028.
(17) Due to the volatile and sometimes sensitive nature of some products, reactions were generally performed in deuterated solvents (usually $CDCl_3$) and analyzed by monitoring directly in an NMR tube.
(18) The effect of solvent was also evaluated for the TFAA and TsNCO reactions (C_6D_6, CD_3CN, CD_3NO_2, d_6-acetone, d_8-dioxane, d_7-DMF). Although no clear pattern appears evident, the TsNCO reaction in DMF yielded only enone product.
(19) In one run, 70 mg of cyclooctenyl derivative **18** was dissolved in $CHCl_3$ (3 mL) and treated with TsNCO until TLC showed disappearance of **18**. Isolation by size-exclusion column chromatography gave cyclic enol ether **19b** in 86% yield.
(20) Synthesized from the corresponding allylic chloride via a modification of the Frimer reaction (*J. Org. Chem.* **1977**, *42*, 3194). We have found that anhydrous H_2O_2 can be conveniently generated *in situ* by treatment of bis(trimethylsilyl)peroxide with HF–pyridine. For a simple preparation of bis(trimethylsilyl)peroxide, see: Taddei, M; Ricci, A. *Synthesis* **1986**, 633. Matsubara, S.; Okazoe, T.; Oshima, K.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 844.
(21) Bartlett, P. D.; Kice, J. L. *J. Am. Chem. Soc.* **1953**, *75*, 5591.

Table 2. Effect of Base on the Criegee Rearrangement of a Secondary Allylic Hydroperoxide[a]



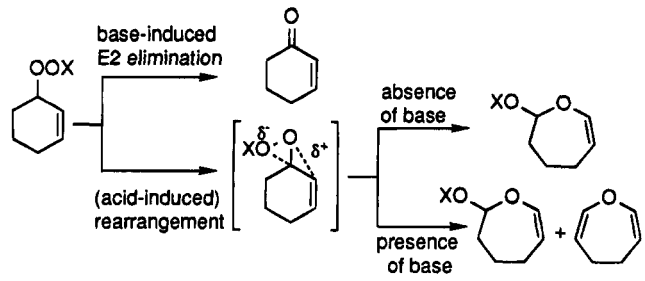
base (approx pK_a)	approx ratio enone:(**13a** + **14**)[b]
proton sponge (12.3)	73:27
quinoline (4.9)	65:35
5-nitroquinoline (2.7)	8:92
pyridine-d_5 (5.2)	45:55
(+3 equiv of pyridinium trifluoroacetate)	40:60
(1.1 equiv of base)	17:83
(5 equiv of base)	75:25
4-picoline (6.1)	55:45
2-picoline (6.0)	50:50
2,6-lutidine (6.7)	40:60
2,6-diethylpyridine[c] (NA)	12:88
2,6-dicyclohexylpyridine[d] (NA)	10:90
2,6-diisopropylpyridine[d] (6.3, *5.34*[e])	6:94
2,6-di-*tert*-butylpyridine (4.5, *3.58*[e])	2:98
(rt)	same
(0°, 1.4 equiv)	same
2,6-di-*tert*-butyl-4-methylpyridine (NA, >4.5)	6:94
2-chloro-6-cyclohexylpyridine[d] (NA)	0:67:33[f]
2-chloropyridine (0.7)	<1:71:28[f]
2,6-dichloropyridine (NA, ca. −1.5)	only **13a**
$NaHCO_3$	only **13a**
no added base	only **13a**

[a] Unless otherwise stated, reactions run at 0 °C with approximately 2.2 equiv of base. [b] Unless otherwise noted, the ratio of **13a** to **14** = 2:1. [c] Prepared via Kumada coupling of 2,6-dichloropyridine and EtMgBr with cat. $NiCl_2$dppp (yield = 50%). [d] Prepared via the modified Kumada coupling ($ZnCl_2$ and cat. $PdCl_2$dppf) (diisopropylpyridine yield = 90%). [e] Lit. pK_a value in 50% aqueous EtOH. In comparing known experimental pK_a values of compounds in 50% aqueous EtOH with aqueous values, the aqueous values are typically 0.8−1 pK_a unit larger. Therefore, the first value is a rough adjusted value. [f] Ratio of enone:**13a**:**14**.

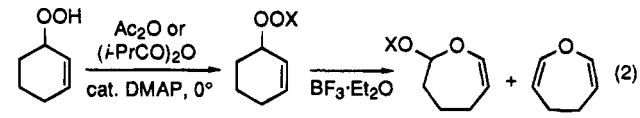
hydroperoxides under conditions neutral enough to avoid any E2-type elimination.[7] Indeed, initial attempts to acylate cyclohexenyl hydroperoxide with Ac_2O or acetyl chloride, using a variety of pyridine bases, all met with failure; either enone was generated immediately or else the acylation was too slow in comparison with the following elimination step.[22] Nevertheless, it was found that when the hydroperoxide is treated with a slight excess of Ac_2O in chloroform at 0 °C, followed by addition of a catalytic amount of dimethylaminopyridine (DMAP, 6 mol %), the hydroperoxide is immediately acylated, with

(22) Diphenylketene (Taylor, E. C.; McKillop, A.; Hawks, G. H. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 549), which may be considered a carbon analog of TsNCO, gave a complex mixture of products when reacted with the hydroperoxide.

Scheme 2



no enone generated; isobutyric anhydride also reacted equally cleanly and quickly (eq 2). As expected, when



cyclohexenyl acetylperoxide was reacted with a standard set of Lewis and protic acids, rearrangement did occur. Best results were obtained with catalytic BF_3·Et_2O (−30 °C → rt, 30 min), which cleanly produced a 3−3.5:1 ratio of rearranged acetate oxepin **13c** to dihydrooxepin **14**.

The importance of this new method for rearrangement was further demonstrated by conversion of cyclopentenyl hydroperoxide **6** into the corresponding rearranged pyran. Previous attempts to induce rearrangement in the cyclopentene system, using the methods described earlier, all met with complete failure.[23] Gratifyingly, the acylation/Lewis acid one-pot method was found to proceed well for the synthesis of the pyran systems **7a** and **7b**.[24]

Scheme 2 shows a diagrammatic mechanistic view of the reaction for electrophiles of low- and mid-range activity. Further studies on this rearrangement and its application toward total syntheses are in progress in our laboratories.

Acknowledgment. Financial support from the National Institutes of Health (NS 12108) and the National Science Foundation (CHE 89-09762) is gratefully acknowledged. R.M.G. thanks ONR/ASEE for providing a predoctoral fellowship.

Supplementary Material Available: ^1H NMR spectra for all new compounds (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(23) All reactions gave cyclopentenone as the only product or else complex mixtures with enone as the major product.

(24) Although both products are chromatographable, their volatility prevented an accurate determination of yields. The expansions of the cyclopentenyl system were not as clean (NMR) as the other systems evaluated in this study.