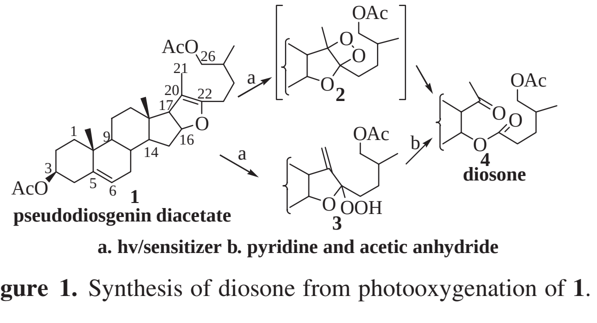
Application of the Criegee Rearrangement in Singlet Oxygen Reaction: A High Yield of Diosone from the Photooxygenation of Pseudodiosgenin Diacetate

Yan Zhang,[†,††] Zhang-Hua Zeng,[†,††] Yong-Yong Liu,[†] Xue-Xin Cheng,*[†] Xue-Song Wang,*[†] and Bao-Wen Zhang*[†]
[†]*Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100101, P. R. China*
[††]*Graduate School of Chinese Academy Sciences, Beijing 100039, P. R. China*

(Received November 22, 2004; CL-041403)

Photochemically generated singlet oxygen adds selectively to C_{20}–C_{22} rather than C_5–C_6 double bond of pseudodiosgenin diacetate **1** to give diosone **4**, an important intermediate for preparation of many steroidal drugs, and ene product **3** at room temperature. **3** was separated and characterized by ^{1}H and ^{13}C NMR as well as IR. When pyridine and acetic anhydride were presented, the Criegee rearrangement of **3** can yield **4**, as a result, leading to a high collection yield (80% in acetonitrile) of **4**.

Highly reactive singlet oxygen ($^1O_2$) generated photochemically can be quenched by many organic compounds either physically or by a chemical reaction. Alkenes are among the most reactive substrates for singlet oxygen leading to dioxetanes,[1] endoperoxides[2] or, in the presence of allylic hydrogens, to ene products.[3] Addition of $^1O_2$ to oxygen-substituted endocyclic double bond such as 2,3-dihydrofuran and dihydropyrans[4] have been reported to give dicarbonyl compounds and ene products in several solvents. The ene products are always unstable, which are prone to undergo many transformations.[5] In 1944, Criegee[6] observed that peroxy esters of *trans*-9-decalyl hydroperoxide rearranged to hemiacetalic esters and suggested a mechanism. In the following years the mechanism was tested and generalized,[7] and this rearrangement was used in the synthetic community though the cases were very limited.[8] One potential application of Criegee rearrangement in singlet oxygen reactions of alkenes is to transform the ene product allylic hydroperoxides to dicarbonyl compounds or carbonyl fragments, which generally results from the decomposition of [2+2]-cycloaddition product dioxetanes. On the basis of our investigations of the photooxygenation of endocyclic enol ethers,[4] we recently became interested in whether the steroidal pseudodiosgenin diacetate **1** (see Figure 1) bearing a five-mumbered ring of endocyclic enol would selectively react with singlet oxygen and form the desired oxygenated steroidal compound, diosone **4**, which is an important intermediate for preparation of steroidal drugs.[9] While environmentally toxic chromium oxidant was usually used to realize the conversion from **1** to **4**,[10] photochemical approach with $^1O_2$ is undoubtedly environmentally friendly. We found the dye-sensitized photooxygenation products of **1** contained not only desired diosone **4** most likely originating from the decomposition of dioxetane **2**, but also an ene product **3**, and the amount of **4** increased in the product distribution with the increased polarity of the solvents. Besides increasing the solvent polarity, we suppose the Criegee rearrangement may play a positive role in improving the isolated yield of desired diosone **4** by inducing the transformation of ene product.



a. hv/sensitizer b. pyridine and acetic anhydride

Figure 1. Synthesis of diosone from photooxygenation of **1**.

In this study, ene product was firstly separated and characterized and its conversion to the desired diosone **4** was investigated. It was found that the Criegee rearrangement of ene product **3** occurred in the presence of pyridine and acetic anhydride. The effect of polarity of solvent on this transformation was also studied.

When **1** was irradiated together with a catalytic amount of typical singlet oxygen sensitizers such as TPP in oxygen saturated benzene using the light above 380 nm at room temperature, photooxygenation reaction proceeded smoothly (see supporting information for detailed photoreaction condition). The disappearance of the starting material was detected by TLC to judge the end of the reaction and the mixture was detected to contain two main products by TLC. The photooxygenated mixture was purified immediately by silica gel flash chromatography yielding **4** and an unknown colorless oil product. The former was confirmed by mixed HPLC determination, and ^{1}H NMR and mass spectrum data by comparison with authentic sample. The latter was characterized by ^{1}H and ^{13}C NMR, IR spectral analysis. It should be firstly noted that both ^{1}H and ^{13}C NMR spectra of the unknown product show the unmodified double bond at C_5–C_6 position (^{1}H NMR signal at 5.37 (d, $J = 4.3$ Hz, 1H at C_6); ^{13}C NMR signals at 122.0 (C_6) and 139.9 (C_5)). The regioselectivity observed under the irradiation condition is probably due to the much more electron-rich feature of C_{20}–C_{22} double bond which possesses an enol ether structure. The ^{1}H NMR spectrum also shows that this compound should possess another double bond with the signals at 5.12 (d, $J = 1.6$ Hz, 1H) and 5.23 (d, $J = 1.9$ Hz, 1H). The ^{13}C NMR spectrum confirms the absence of the CH_3 group at 21-C position (signal at 11.0) and the presence of a CH_2 group of the double bond (signal at 109.4). In addition, the signal at 10.18 (s, 1H) in ^{1}H NMR spectrum is attributed to the OOH group, which is also confirmed by the corresponding FTIR spectrum (KBr; ν_{OH} 3360–3560 cm^{-1}). The unchanged signal at 3.78–3.94 (m, 2H at C_{26}) in ^{1}H NMR spectrum compared to pseudodiosgenin diacetate **1** indicates that the oxygen-containing heterocycle did not cleavage (otherwise H at C_{26} would be a doublet as in **4**). Besides, the FTIR spectrum of the unknown product also contains two peaks at 903 and 841 cm^{-1}, consistent with the presence of $=CH_2$ structure. Obviously, the ene product **3** is consistent with these spectrum data. Under above photooxygenation condition, dioxetane **2** intermediate was not obtained, which decomposed to **4** immediately. Other ene products were not detected. This is probably due to one point, namely, the $^1O_2$ tends to add on the same side as the alkoxy group, with the C–O bond forming preferentially at the carbon bearing the alkoxy group,[11] and another point, namely, there is preferential abstraction of those allylic hydrogens which are aligned perpendicular to the plan of the double bond.[12] In addition, it was found that no transformation between **3** and **4** occurred under the reaction conditions and even at higher temperature without catalyst. No significant degradation of pure **3** was identified after storing for 2 weeks under 0 °C.

Generally, ene products are not easily to be isolated at room temperature because of their instability, which are prone to undergo many transformations.[5] Fortunately, the relatively stable ene product **3** allowed us to conduct further study —to try to transfer it to the desired diosone **4**. When **3** (0.01 M) was treated with 2 equiv. of hydrochloric acid, pyridine or both acetic anhydride and pyridine in acetonitrile at 50 °C for 25 min, respectively, a moderate yield of **4** was obtained only in the system of **3**/acetic anhydride/pyridine, implying the occurrence of the Criegee rearrangement. The reactions were carried out in solvents of varied polarities, and the results were summarized in Table 1, which shows the yield of **4** is higher in polar solvent. We also found the reaction rate increased in polar solvent. The fact that this reaction is sensitive to solvent polarity agrees well with the general rules of solvent effect on the Criegee rearrangement.[8,13] Thus, the most likely mechanism is the Criegee rearrangement which should be considered to rationalize the present conversion from **3** to **4** (see Figure 2).[6,7,14] In this rearrangement, acetic anhydride and pyridine react to form a very effective acylating agent, with which **3** would give a peroxy ester at first so that the mechanism of forming a dioxetane intermediate should be ruled out. Then the heterolysis of the peroxy bond generates a positive oxygen fragment. The instability of the latter induces the migration of the group to the electron-deficient oxygen with concomitant rearrangement of the carbon skeleton. The migrating group in the case of allylic hydroperoxides is generally the vinyl group.[14] The cleavaged CH_3COO^- group combines with the oxycarbonium ion to form an ester which is attacked by pyridine to eliminate an acyl group and then rearrange to a dicarbonyl compound **4**. As a result, for $^1O_2$ reaction with pseudodiosgenin diacetate **1** in acetonitrile, the presence of a proper amount of acetic anhydride and pyridine promoted the isolated yield of **4** from 65 to 80%.

Table 1. Effect of solvents on the rearrangement of **3**[a]

Solvent	Acetonitrile	Acetone	Benzene	Hexane
diosone%	55	50	22	25

[a] $[3] = 1 \times 10^{-2}$ M; [pyridine] = [acetic anhydride] = 2×10^{-2} M.

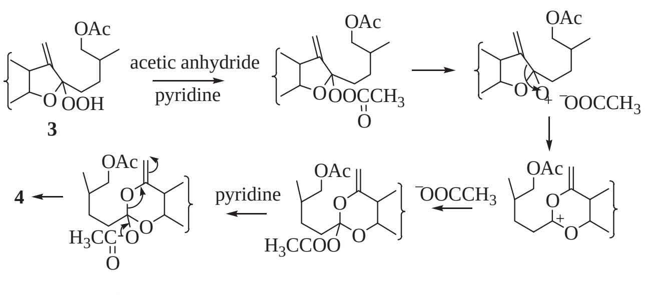


Figure 2. The Criegee Rearrangement of **3**.

In summary, our experiments demonstrate the formation of diosone **4** and a relatively stable ene product **3** in the photooxygenation of **1** at room temperature. Ene product **3** can be converted in moderate yield to **4** by way of the Criegee rearrangement in the presence of pyridine and acetic anhydride. The importance of this rearrangement is to facilitate the formation of dicarbonyl compounds in singlet oxygen reactions with alkenes, and in our case, **4** was obtained in an excellent yield of 80% with the help of this rearrangement. Extension of the Criegee rearrangement to the photooxygenations of other useful steroids are in progress in our laboratories.

References

1 A. L. Baumstark and A. Rodriguez, in "Handbook of Organic Photochemistry and Photobiology," ed. by W. M. Horspool and P.-S. Song, CRC Press, Boca Raton (1995), p 335.
2 W. Adam and A. G. Griesbeck, in "Handbook of Organic Photochemistry and Photobiology," ed. by W. M. Horspool and P.-S. Song, CRC Press, Boca Raton (1995), p 311.
3 A. G. Griesbeck, in "Handbook of Organic Photochemistry and Photobiology," ed. by W. M. Horspool and P.-S. Song, CRC Press, Boca Raton (1995), p 301.
4 K. Gollnick and K. K. Mies, *J. Org. Chem.*, **56**, 4017 (1991); W. Adam, A. G. Griesbeck, K. Gollnick, and K. K. Mies, *J. Org. Chem.*, **53**, 1492 (1988); Y. Y. Chan, X. Y. Li, C. Zhu, X. H. Liu, Y. D. Zhang, and H.-K. Leung, *J. Org. Chem.*, **55**, 5497 (1990); Y. Cao, B. W. Zhang, Y. F. Ming, and J. X. Chen, *J. Photochem.*, **38**, 131 (1987).
5 H. Hock and O. Schrader, *Angew. Chem.*, **49**, 595 (1936); A. A. Frimer and L. M. Stephenson, in "Singlet O_2," ed. by A. A. Frimer, CRC Press, Boca Raton (1985), Vol. 2, Chap. 3, p 73.
6 R. Criegee, *Chem. Ber.*, **77**, 722 (1944); R. Criegee, *Justus Liebigs Ann. Chem.*, **560**, 127 (1948).
7 M. S. Kharasch and J. G. Burt, *J. Org. Chem.*, **16**, 150 (1951); H. Hock and H. Kropf, *Angew. Chem.*, **69**, 313 (1957).
8 R. M. Goodman and Y. Kishi, *J. Org. Chem.*, **59**, 5125 (1994).
9 G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, **21**, 520 (1956); M. Cabeza, I. Heuze, E. Bratoeff, and R. Martinez, *Chem. Pharm. Bull.*, **49**, 525 (2001).
10 R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, W. D. J. Goldsmith, and C. H. Ruof, *J. Am. Chem. Soc.*, **69**, 2167 (1947); I. V. Micovic, M. D. Ivanovic, and D. M. Piatak, *Synthesis*, **1990**, 591.
11 Y. Y. Chan, C. Zhu, and H. K. Leung, *Tetrahedron Lett.*, **27**, 3737 (1986).
12 A. A. Frimer and L. M. Stephenson, in "Singlet O_2," ed. by A. A. Frimer, CRC Press, Boca Raton (1985), Vol. 2, Chap. 3, p 69.
13 J. B. Lee and B. C. Uff, *Q. Rev.*, **21**, 429 (1967).
14 A. A. Frimer, *Chem. Rev.*, **79**, 363 (1979).

Published on the web (Advance View) February 12, 2005; DOI 10.1246/cl.2005.368