Diastereoselective and Regioselective Photooxygenation of a Chiral Allylic Amine and Its Acyl Derivatives: Stereochemical Evidence for a Steering Effect by the Amino Group in the Ene Reaction of Singlet Oxygen

Waldemar Adam* and Hans-Günter Brünker[1]

Institute of Organic Chemistry
University of Würzburg, Am Hubland
D-8700 Würzburg, Germany

Received December 21, 1992

The ene reaction of singlet oxygen ($^1O_2$) and olefinic substrates constitutes a convenient synthetic methodology for the oxyfunctionalization at allylic positions. Through the cis effect[2] this reaction may exhibit high regioselectivity and even diastereoselectivity, provided that steering groups such as carbonyl functionalities[3] or silyl[4] substituents are attached at the olefinic carbon atoms or that silyloxy[5] and hydroxy[6] groups are located at an allylic chirality center. Of these, particularly the directing effect of the hydroxy group in chiral allylic alcohols is of preparative value because it enables the introduction of oxygen functionalities adjacent to the hydroxy-directing center in a regiocontrolled and threo-selective manner.[6] Unquestionably, such an oxyfunctionalization would be of synthetic value for chiral allylic amines. Besides the well-established fact that amines[7] efficiently quench $^1O_2$ and that the quenching rates for primary amines are on the order of 10^5 M^{-1} s^{-1}, it is also well-known that the reaction rates for the $^1O_2$ ene reaction of olefins bearing three alkyl groups[8] are on the order of 10^6 M^{-1} s^{-1}. Therefore, the oxidation should be competetive with quenching. We herein present our novel results on the photooxygenation of the chiral allylic amine 2-amino-4-methyl-3-pentene (**1a**) and its acetyl and phthalimide derivatives **1b,c**.

As demonstrated *in* Scheme I, photooxygenation of the chiral amine **1a** with the necessary precautions, i.e., by operating at −20 °C and with subsequent triphenylphosphine reduction, afforded *threo*-2-amino-4-methyl-4-penten-3-ol (**3a**)[9,10] (Table I). To our knowledge this transformation not only represents the first successful ene reaction of $^1O_2$ with a primary amine but it also establishes the hitherto unprecedented steering effect of the nucleophilic amino group for the $^1O_2$ ene reaction, which guides the incoming electrophilic $^1O_2$ enophile threo-selectively. Photooxygenation of the acetyl and the phthalimide derivatives[11] **1b,c** gave under erythro control[12] the stable, isolable allylic hydroperoxides **2b,c**[9] (Scheme I, Table I).

Scheme I

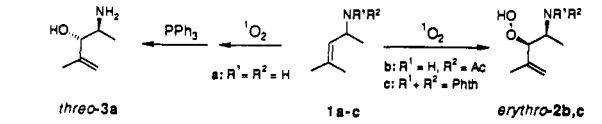
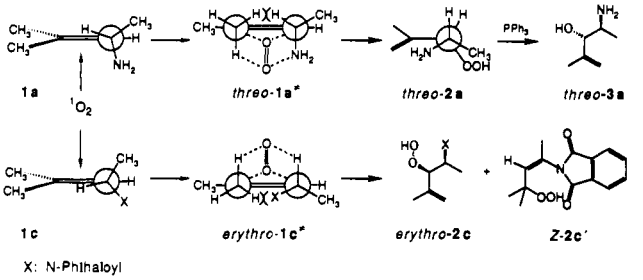


Table I. Product Studies in the Photooxygenation of the Chiral Allylic Amine **1a** and its Derivatives **1b,c**

entry	substrate	R^1, R^2	solvent[a]	t (°C)	T (h)	yield[b] (%)	ratio[b,c] threo	erythro
1	**1a**	H, H	CD_3OD	−35	4	87	85	15
2[d]	**1a**	H, H	CCl_4	−20	2	87	>95	<5
3	**1b**	H, Ac	CD_3OD	−35	4	90	29	71
4	**1b**	H, Ac	CCl_4	−15	4	93	28	72
5	**1c**	Phth[e]	CD_3OD	−15	4	90[f]	15	85
6	**1c**	Phth[e]	CCl_4	−15	4	90[f]	11	89

[a] Tetraphenylporphine (CCl_4), Rose Bengal (CD_3OD). [b] By ^1H NMR analysis directly on the crude product mixtures, within ca. 5% error of the stated values. [c] For the hydroperoxide **2b,c** and alcohol **3a**. [d] 20 mol % 2,6-di-*tert*-butyl-4-methylphenol as radical scavenger. [e] Phthaloyl (Phth). [f] Additionally, 10% of the regioisomeric product *Z*-**2c'** was formed.

Scheme II



As the above stereochemical results are mechanistically rationalized in Scheme II. Like for the nucleophilic hydroxy group in chiral allylic alcohols,[6] the still more nucleophilic primary amino group in the chiral allylic amine coordinates with the electrophilic $^1O_2$, and the latter approaches preferentially from that side for which 1,3-allylic strain[13] is minimized, namely by way of the *threo*-**1a**‡ transition state. This steering effect of the amino group is more effective in the nonpolar CCl_4 than in the polar methanol (compare entries 1 and 2 in Table I).

The situation is distinct for the acylated derivatives **1b,c** in that for these the nucleophilicity of the nitrogen atom is so drastically reduced that other factors dominate the stereocontrol (Scheme II). By taking the more interesting case of the phthalimide **1c**, approach of the singlet oxygen from the side opposite to the phthalimide group presumably is decisive rather than the resulting 1,3-allylic strain with the olefinic (*Z*)-methyl group in the cis-coordinated transition state *erythro*-**1c**‡. In addition, the exclusive formation of the erythro-type regioisomeric product (*Z*)-**2c'**, i.e., H abstraction from the olefinic (*Z*)-methyl group, speaks for *erythro*-**1c**‡ as a common activated complex for these regioisomers. Analogous transition states were postulated for allylic alcohols and acetates.[6]

In summary, for the first time has a chiral primary allylic amine, namely **1a**, been successfully oxyfunctionalized with singlet oxygen. This regio- and diastereoselective ene reaction makes available, after reduction with triphenylphosphine, the amino alcohol *threo*-**3a**. The high stereocontrol (diastereomeric ratio

(1) Diplomarbeit, University of Würzburg, September 1992.
(2) (a) Schulte-Elte, K. H.; Rautenstrauch, V. *J. Am. Chem. Soc.* **1980**, *102*, 1738. (b) Stephenson, L. M.; Grdina, M. J.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, *13*, 419.
(3) (a) Ensley, H. E.; Carr, R. V. C.; Martin, R. S.; Pierce, T. E. *J. Am. Chem. Soc.* **1980**, *102*, 2836. (b) Adam, W.; Griesbeck, A. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1070. (c) Orfanopoulos, M.; Foote, C. S. *Tetrahedron Lett.* **1985**, *26*, 5991.
(4) (a) Fristad, W. E.; Bailey, T. R.; Paquette, L. A.; Gleiter, R.; Böhm, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4420. (b) Adam, W.; Richter, M. *Tetrahedron Lett.* **1992**, *33*, 3461.
(5) Adam, W.; Catalani, L. H.; Griesbeck, A. *J. Org. Chem.* **1986**, *51*, 5494.
(6) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1992**, *114*, 6549.
(7) (a) Bellus, D. *Adv. Photochem.* **1979**, *11*, 105. (b) Monroe, B. M. In *Singlet Oxygen*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; Vol. 1, p 194.
(8) Monroe, B. M. In *Singlet Oxygen*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; Vol. 1, p 203.
(9) All stable new compounds were fully characterized, which includes satisfactory ($\Delta < 0.5\%$) elemental analysis and appropriate IR and ^1H and ^{13}C NMR spectral data.
(10) The stereochemical assignment of the amino alcohol **3a** was accomplished by chemical correlation of **3a** to *threo*-2-amino-4-methyl-3-pentanol, which was independently prepared from *cis*-4-methyl-2-pentene through *m*-CPBA epoxidation to the cis-epoxide and subsequent amination.
(11) In the case of the phthalimide **1c**, in addition also 10% of the regioisomer (*Z*)-**2c'** was obtained.
(12) The stereochemical assignment of **3b,c** was accomplished by chemical correlation to **3a** through reduction with PPh_3, followed by deprotection of the amino functionality.
(13) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

0002-7863/93/1515-3008$04.00/0

> 95:5) in this novel photooxygenation is proposed to be derived from the joint effort of steering by the nucleophilic primary amino functionality through association with the electrophilic $^1O_2$ and minimization of 1,3-allylic strain between the methyl group at the allylic chirality center and the olefinic (*Z*)-methyl group. Inverted stereochemistry can be achieved by photooxygenation of the phthalimide derivative **1c**. For this substrate the bulky phthalamide obliges the $^1O_2$ to approach preferentially from the opposite side. Such profound stereochemical control by the amino group and its acylated derivatives has not been previously observed in $^1O_2$ ene reactions and constitutes a novel synthetic tool in the design of complex, oxyfunctionalized, chiral molecules.

Acknowledgment. We are grateful for the generous financing by the Deutsche Forschungsgemeinschaft (SFB 347 "Selektive Reaktionen Metall-aktivierter Moleküle) and the Fonds der Chemischen Industrie.